# INSTITUTIONAL REVIEW BOARDS: A SYSTEM IN JEOPARDY

## HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RESOURCES

OF THE

## COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

SECOND SESSION

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# INSTITUTIONAL REVIEW BOARDS: A SYSTEM IN JEOPARDY

THURSDAY, JUNE 11, 1998

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RESOURCES,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
*Washington, DC.*

The subcommittee met, pursuant to notice, at 9:30 a.m., in room 2154, Rayburn House Office Building, Hon. Christopher Shays (chairman of the subcommittee) presiding.

Present: Representatives Shays, Snowbarger, Pappas, Burton, Towns, Barrett, and Kucinich.

Staff present: Lawrence J. Halloran, staff director and counsel; Anne Marie Finley and Robert Newman, professional staff members; Jesse S. Bushman, clerk; and Cherri Branson, minority counsel.

Mr. SHAYS. I call this hearing to order and welcome our witnesses and our guests.

The history of human subject protection follows a fitful journey between trust and tragedy: from the Hippocratic Oath to the Holocaust, from the Nuremberg Code to Tuskegee, from the common rule to the irresponsible administration of pyridostigmine bromide, PB, to United States troops in the Gulf war.

The bond of trust between researcher and subject, between doctor and patient, between Government and the governed, demands we heed warning signs before, not after, another tragic chapter in that history must be written.

Today, the Department of Health and Human Services [HHS], Inspector General [IG], sounds such a warning. Institutional Review Boards [IRBs], the local committees responsible for protecting the safety and dignity of persons participating in clinical research, are in jeopardy of being overwhelmed by the weight and complexity of their work. As a result, the 25-year-old system of review and oversight intended to ensure ethical design and implementation of research protocols is in need of structural reforms.

These important findings and recommendations by the HHS Inspector General confirm and amplify testimony we heard in May 1997, that the safety net to protect human research subjects was showing signs of age and disrepair even then. In this hearing, we ask what steps must be taken to strengthen Institutional Review Boards before the system is strained to the breaking point.

A quarter century ago, most biomedical research was conducted at an academic medical center or hospital by a single investigator studying a small number of subjects. The scientific merit, inherent

risks, research protocol, and informed consent materials were reviewed, approved, and monitored by local review board members who knew the community, the patients, the doctors, and the procedures involved.

But today's research environment has changed dramatically. Institutional Review Boards have not.

Large, multi-site studies involving thousands of participants challenge both the concept and practice of local IRB control. Increasingly sophisticated studies, involving biochemical and genetic concepts, considered scientific fiction just a few years ago, demand time and expertise IRBs often lack. Complex science can pose subtle, yet profound, ethical questions about risk assessment and the ability of subjects to consent; questions often beyond the capacity of altruistic, overworked, but ill-trained, IRB members.

Examples of systemic weaknesses in subject protections are readily available. I know Mr. Towns, the ranking member of this subcommittee, is particularly concerned about IRB approval of inequitable subject selection and lax informed consent procedures in a "fenfluramine challenge" study of childhood aggression conducted by the New York Psychiatric Institute.

And today, the entire membership of this subcommittee joins in introducing legislation to make sure U.S. soldiers will never again be required to take an experimental drug without first being given basic information, in writing, about the drug, the reasons for its use, known side effects, and possible interactions.

In both these instances, giving fenfluramine to children and giving PB to U.S. soldiers, the current system of bioethical review failed miserably.

To remain effective in an era of entrepreneurial research and managed health care, IRBs need greater expertise, broader representation, more resources, and effective Federal oversight. Many of these reforms are within the power of the IRB sponsors and administrators to implement immediately. The IG found promising approaches to IRB training, workload management, performance evaluation and broadened membership already being implemented.

Still lacking, however, is the basic coordination needed to transform isolated innovation into systemic reform. Incredibly, Federal regulators know more about lab animals than they do about the human beings who subject themselves to medical research. The IG, and others testifying today, support central registration of IRBs to capture empirical data about practices and trends now discerned only through anecdotal evidence. We ask our witnesses today to discuss the feasibility and efficacy of this modest proposal.

When the footings of a highway bridge show signs of structural stress, we close the road and make repairs. While the IRB system continues in the main to perform admirably, a structure built on the fragile foundation of trust will not be repaired by self-congratulation or statistical quibbles about the extent of the problem. We look to all our witnesses today for your help in sustaining and strengthening Institutional Review Boards, and recommend any other ways to protect those who participate in medical research.

Again, I welcome our witnesses and I look forward to our testimony.

At this time, I'd like to recognize the chairman of the full committee, Mr. Burton. And it's a real pleasure to have you here, Mr. Burton.

Mr. BURTON. Thank you, Mr. Chairman. I really appreciate the opportunity to be with you.

On April 22nd of this year, the full committee held a hearing focusing on the FDA's responsibility to oversee and protect clinical trial participants. It was apparent to me then, as a result of some compelling witnesses' testimony, that a real problem exists within the scientific community in providing meaningful protections to clinical trial subjects.

Several problems were discussed in the context of clinical trials. One was the use of placebos and/or wash-out phases in clinical trials which place subjects at high-risk for relapse in the case of psychiatric patients and for irreversible physical damage in the case of patients with heart disease and hypertension. Another was the non-beneficial experimentation on young minority children in New York City by several prestigious medical centers of the drug fenfluramine, which has been banned by the FDA as unsafe for use in adults. And that was very troubling.

The subject of meaningful oversight by Institutional Review Boards was also discussed and the experts who testified, as well as many members, expressed serious concerns over the conflicts of interest that exist among members of IRBs and the overload of protocols that they must review and approve. Thus, it is not surprising to me that the HHS IG, Inspector General, has determined in her draft report that IRBs are not living up to the standard of protection required by Government regulation. Of course, within Health and Human Services, the National Institutes of Health, including the Office of Protection Against Research Risks, as well as the Food and Drug Administration, are charged with the responsibility to oversee these review boards. And when I questioned the FDA about this, there was a lot of finger pointing and shifting of the blame to somebody else.

Thus, I'm pleased to see that some representatives of other potentially responsible parties are here today. I am concerned that the head of the FDA is not present, nor is the Director of NIH, nor HHS. I certainly hope that after this hearing, critical followup will be done to make sure that those agency heads are involved in the sharing of responsibility for this very serious and potentially growing problem.

And I thank you, Mr. Chairman.

Mr. SHAYS. I thank the chairman of the full committee, and assure him that this will not be our only hearing and that we will have the FDA, HHS, and NIH here.

Thank you very much.

At this time, the Chair would recognize the ranking member of this committee, a full partner in all our investigations and not only a tremendous friend but a wonderful Member of Congress.

Mr. TOWNS. Thank you very much, Mr. Chairman. Thank you for your kind words. I want to thank you for holding this hearing today. The report of the Department of Health and Human Services' Inspector General raises serious issues concerning the oversight these boards exercise in reviewing and approving research

study applications. The IRBs play an important role in approval of federally funded research. However, where research is privately funded, the IRBs are the only safety net protecting the human volunteer from unnecessary risks or harm.

In the course of preparing for this hearing, we have reviewed a New York case which is very, very disturbing. The research plan specifically included only African American or Hispanic male children between the ages of 6 and 10. The research plan excluded white children. In a document dated February 18, 1994, the researchers informed the IRB that all of the children have been selected for the study. Two weeks later, in a document dated March 2, 1994, the IRBs told the researchers to "reformat" the criteria to eliminate previous references to race or ethnicity. At this point, the researchers had spent 2 years selecting the children for the study. All evidence points to the conclusion that these selections were based on the original research plan. The institution has repeatedly stated that these selections were based on chance. Today, we know that those assertions are false. I would like to enter into the record the research plan and these memos. They provide clear proof that these children were chosen by design, not by chance. They were selected because of the color of their skin and the actions of their siblings.

Additionally, Mr. Chairman, let me add there are serious questions about the voluntariness of the participants, of the parents and the children. Government employees were used to interview the parents and enlist the children. The use of Government employees would give anyone the idea that the Government had condoned this experiment or that failing to comply could bring serious consequences.

Mr. Chairman, you and I know we would be foolish to refuse an invitation from the IRS. These parents would have been foolish to decline this invitation from the State government and officials.

Furthermore, there are problems about the payment mechanisms. The researchers provided separate payments for each test. This created an economic incentive for the parents and children to participate in as many tests as possible.

Finally, there is something very shameful here about compensation received by the children. Here, the children received gift certificates for food and toys as compensation for their participation. Mr. Chairman, these researchers have taken the purest innocent motivation of children, a desire to help, and have transformed it into a snare for the unwary.

Given all of these problems, the IRB voted unanimously to approve the study. The Inspector General's report finds that the IRB process needs reform. Well, I'd like to help it. If this case is indicative of the IRB's process, it needs to be torn down, rebuilt from scratch. Reforming is not enough.

It has been 20 years since a horrified Nation learned of the Tuskegee syphilis experiments. The IRB process was designed to assure that there would never, never, never be another Tuskegee situation. Yet, we are here today to listen to testimony about nontherapeutic, non-beneficial, medical experiments that involved only African-Americans and Hispanic male children. I'm left with a feel-

ing of déjà vu all over again, and I'm saddened that we have again arrived at this point.

Finally, Mr. Chairman, following this hearing, we must—and I say we must—take strong and decisive action to assure that the Federal oversight process holds researchers and the IRB accountable, especially where experiments are improperly racially motivated or place children at risk without any possible benefit.

Thank you for holding this hearing, and I look forward to working very closely with you in the days ahead to be able to clean up this situation.

Mr. SHAYS. I thank the gentleman. Mr. Pappas, do you have an opening statement?

Mr. PAPPAS. No, Mr. Chairman.

Mr. SHAYS. Let me just get some housekeeping out of the way and ask unanimous consent that all members of the subcommittee be permitted to place any opening statement in the record, and that the record remain open for 3 days for that purpose. Without objection, so ordered. I ask further unanimous consent that all witnesses be permitted to include their written statements in the record. And without objection, so ordered.

And also you, Mr. Towns, want to submit for the record a document. Is that the document right there?

Mr. TOWNS. That's correct.

Mr. SHAYS. And without objection, we'll submit that for the record.

[The information referred to follows:]

ATTACHMENT 1 p.3 IRB

III. RESEARCH PLAN

A. HYPOTHESES TO BE TESTED (If there are no specific hypotheses, summarize study goals).

Study goals are two-fold: 1) to identify predisposing medical, neurobiological, neurological, neuropsychological, psychiatric and behavioral factors in a population at risk for the development of antisocial behavior; 2) to implement prevention procedures in this high-risk population.

B. PROCEDURES

NOTE: WHERE APPROPRIATE, PROVIDE A FLOW CHART (DIAGRAM) OF STUDY PROCEDURES.

1. Subjects (specify sample sizes, age range, diagnostic group and other characteristics as relevant). If subjects from other studies are to be asked to participate, list studies with their IRB #, principal investigator and title.

N = 100 Age range 6-10 year old male siblings

Diagnostic groups: Male siblings of male delinquents identified through NYC Department of Probation, Bronx County

2. Study Inclusion and Exclusion Criteria (list in outline form)

| CRITERION | METHOD OF ASCERTAINMENT |
|---|---|
| Inclusion | |
| 1. Male sibling | Sex |
| 2. Age 6-10 | Date of birth |
| 3. Older sibling is juvenile offender | NYC Department of Probation Bronx County |
| 4. Parent or Guardian Agrees | Signed consent |
| 5. African-American or Hispanic | Ethnicity |
| Exclusion | |
| 1. Subject has been placed in non-family foster care | Current living arrangement |
| 2. Physical or mental condition likely to overwhelm the predictive power of other influences (PDD, mental retardation) | Assessment on DISC<br>Known medical history |
| 3. Child has not begun school at 7 or 8 | Status - in school |
| 4. Only 1 child from any given family | Enrollment of other siblings |
| 5. White | Ethnicity |

ATTACHMENT 2A



C. PROCEDURES

NOTE: WHERE APPROPRIATE, PROVIDE A FLOW CHART (DIAGRAM) OF STUDY PROCEDURES.

**Provide details of all procedures including credentials (R.N., M.D.) of person(s) conducting each procedure including interviews.**

**If medication is to be used, specify drug and dose schedule. For more complex designs, flow diagrams are helpful.**

1. **Recruitment Methods (attach to this form any letters to be sent, texts of advertisements etc., if available now. If not available now, they must be submitted to the IRB before recruitment begins.**

All potential participants for this study will have participated in an already approved larger study (protocol 2283 - Prediction Study; Dr. Wasserman) examining younger brothers of adjudicated delinquents. Only subjects who have already participated will be eligible for this protocol. Center staff members will have already informed potential subjects that they will be asked to visit the Center for this study. Center staff member will again discuss the medical and neurological assessment which is to be done following completion of the Prediction Study (Dr. Wasserman's study). If the subject and his parent/guardian agree at this time, an appointment will be set up to come to N.Y.S.P.I. for the medical and neurological assessment. The informed consent for these studies will be obtained on the day of the work-ups.

2. Experimental Procedures

**Provide details of all experimental procedures. Indicate methods of group assignment, sequence of procedures, length of each session, duration of study, etc.; if medication is to be used, specify dose and dose schedule.**

Subjects after being assessed by the Behavioral Assessment Core of Lowenstein Center (Prediction Study - Dr. Wassermann) will be referred for a Neurobiological Assessment. This assessment will consist of:

1. Medical history will be obtained by a physician. In addition, this physician will assess:
   a) presence of prenatal/perinatal factors which may exert effects upon the central nervous system
   b) abnormal development history by use of the Denver Developmental Screening Test
   c) evidence of organic disorders
   d) history of lead poisoning, malnutrition
   e) family history of learning disabilities, psychiatric and/or medical disorders

2. Medical examination will be the standard pediatric examination supplemented by measurement of muscularity and strength, and examination for the 18 minor physical anomalies typically assessed.

   Portions of the medical history and examination will be repeated no more than once per year.

3. Routine lab work: Chem screen, CBC, urinalysis, lead levels and EKG.

4. Neurological History: will assess the presence of head injury (date), loss of consciousness (number, duration), epilepsy, febrile seizures, meningoencephalitis or other symptoms listed in the medical and neurological history form in the appendix). Further assessment of possible temporolimbic excitability, inter-ictal temporal lobe epilepsy behavior, frontal lobe syndromes (e.g., orbito frontal or dorsolateral) will be conducted.

ATTACHMENT 3

New York State
Psychiatric Institute

**MEMORANDUM**

March 2, 1994

TO: Dr. Gail Wasserman

FROM: Dr. B. Timothy Walsh and Dr. John Rainer, Co-Chairmen, IRB

SUBJECT: Protocol #2282: MEDICAL AND NEUROLOGICAL ASSESSMENT IN A POPULATION AT RISK FOR ANTISOCIAL BEHAVIOR

---

The Child Psychiatry Subcommittee reviewed the modification of the above protocol, including your reply to the February 2, 1994 memo. Some additional concerns were raised and after these are addressed, approval will be given. Please send 2 copies of the revised material.

1. Delete Mt. Sinai as a site from the IRB Protocol Summary Form face sheet.

2. Approval of the MRI component will be given after Drs. Nicolson and Alderson have approved this procedure for this protocol.

3. When and by whom is the family history obtained?

4. The Fenfluramine procedure requires that youngsters do not eat or drink for a long time prior to and on the day of the procedure: Please describe in the Consent Form. Are you getting blood sugars?

5. Inclusion and Exclusion:

   A. Reformat the listing of the inclusion criteria so that item #4 for the Fenfluramine procedure is the last item.
   B. Make explicit that youngsters are recruited from the main study.

6. Please clarify the number of times children will be asked to do these studies (every year?) and revise the Consent Form accordingly. If separate Consent Forms are given each time, please submit these for review.

cont'd

Mr. SHAYS. At this time, I recognize our witnesses before swearing them in, just introduce them: George F. Grob, Deputy Inspector General for Evaluation and Inspections, U.S. Department of Health and Human Services, accompanied by Dr. Mark R. Yessian, Regional Inspector General for Evaluation and Inspections. A second testifier will be Dr. Eric Meslin, Executive Director of National Bioethics Advisory Committee, U.S. Department of Health and Human Services; and Dr. Gary Ellis, Director, Office of Protection from Research Risks, Office of Extramural Research, National Institutes of Health.

[Witnesses sworn.]

Mr. SHAYS. Note for the record that all our witnesses responded in the affirmative.

And let me just say, before recognizing you, Mr. Grob, we have before us four reports done by your office, the Office of Inspector General. One is entitled "Institutional Review Boards: The Emergence of Independent Boards." Another is "Institutional Review Boards: Their Role in Reviewing Approved Research." Another is "The Institutional Review Boards—Promising Approaches." And another is "Institutional Review Boards," titled now, "A Time for Reform." It's original draft was "A System in Jeopardy."

And I would like to say that while I believe these are very balanced reports, if anything, I think they understate the concern we have about the IRBs.

Mr. Grob.

**STATEMENTS OF GEORGE F. GROB, DEPUTY INSPECTOR GENERAL FOR EVALUATION AND INSPECTIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY MARK R. YESSIAN, PH.D., REGIONAL INSPECTOR GENERAL FOR EVALUATION AND INSPECTIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; ERIC MESLIN, PH.D., EXECUTIVE DIRECTOR, NATIONAL BIOETHICS ADVISORY COMMITTEE, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; GARY B. ELLIS, PH.D., DIRECTOR, OFFICE OF PROTECTION FROM RESEARCH RISKS, OFFICE OF EXTRAMURAL RESEARCH, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Mr. GROB. Thank you, Mr. Chairman, and members of the committee. Again, I would like to introduce Dr. Mark Yessian, who is our regional director in Boston, and it was he and his team that prepared these reports that we're discussing here today.

Mr. Shays, I think you did an excellent job of summarizing the findings of our report, that it will make it a little easier for me to deal with the reports in the brief time I have for my oral testimony. Perhaps, I can supplement what you have said by providing a little bit more background about their origin and their implications. And, perhaps, I could begin by addressing the question you raised in the change in title. The original title was "A System in Jeopardy," and we did change it because some of our reviewers, while not disagreeing with what we found, felt that they might have been too alarmist. And it was our feeling that it would be better to concentrate our discussions on what should be done about the problem than on the particular language that was used in the

title. So we were more than happy to change the title for that reason so we could get down to the business of making the repairs that we think are made.

We do come before you with a feeling that we need to give you a warning that the system that we have relied on for many years to protect human research subjects may not be adequate to the job now, and perhaps even less in the future. I myself would liken it to a shield, which has been hardy in the past but may be outdated now. It is brittle, strained, and, I think, even cracked. We certainly need a better one.

The four reports that you highlighted before are the ones primarily on which our testimony is based. But I think that it is worthwhile to recall an earlier report that we did 3 years ago. This report, "Investigational Devices For Case Studies," was actually the origin of our work here. We prepared this at the request of the Food and Drug Administration who were concerned about the way trials were being conducted for investigational devices and particularly their premature commercial application. So we worked with them to review four case studies, and I think a brief summary of what we found there would be in order here.

We found in one of the trials, or in one of the research centers, that there were three times as many patients that had implanted in their bodies a device that was a device for testing, three times more than were approved in the research protocol. We found another research site that continued to conduct the research on a device 6 weeks after the IRB had asked them to halt. We found another one in which the researchers did not make the changes to the informed consent forms that the IRB had asked them to make. And, generally, we found some missing or problematic consent forms for some of the research subjects.

It was these findings of these particular problems that led us to do the broader study that is the subject of our hearing today. The things we found there are just not supposed to happen. So we thought well let us take a look then at the system under which that did happen.

The system is one that was built for a research world that largely does not exist anymore. Originally when it was designed, it was for research conducted at a single site by a single investigator with small cohorts of subjects under Government-funding and primarily at a university or teaching hospital. Today, research tends to be multi-site trials, across the country, some even across the world, involving tens or hundreds of researchers, thousands of research subjects. We see an increased use of commercial sponsors of the research and we see research done in new sites, such as doctors' offices, managed care organizations, in-vitro fertilization clinics, and diet and weight loss centers. We see, as well, an increase in interest in the research subjects wanting to participate in the research, wanting to get drugs that are available, perhaps wanting to make some money to help them through school. And we see new types of research that are coming to the fore.

The IRBs are faced with these research challenges. They are also faced with a great increase in the amount of research that is being conducted in this country, and perhaps at a pace that has outpaced their ability to deal with them.

Perhaps one of the strongest findings we have is what we consider an inadequacy in the role of continuing to review the research protocols, as opposed to the initial approval of the protocols. We identified threats to the independence of the boards, a lack of training, and a lack of evaluation and oversight.

In response, Mr. Shays, to your request that we try to deal with coming to grips with the problem, we concentrated in the reports on offering a framework for solution. In this report we offer, I think, a lot more recommendations than we usually do in our reports; and we tried to present them in a framework that the research community could use to consider some of the problems that we raised in the report. I won't repeat them now because they are in the report and they respond to the findings that we have here.

Mr. SHAYS. Let me just say to you, I'm going to roll over the clock, and just expect that you'll stop between the 5 and 10 minute framework.

Mr. GROB. OK. I think I can summarize now, perhaps, if you will allow me to put things in perspective.

In the most recent reports, we did not attempt to systematically identify the extent of the problem that was out there. We thought that the problems that we had found earlier were enough to warrant a look at the system itself and that's where we concentrated our efforts. In this report, we don't claim that the research abuses are particularly widespread. We just haven't done enough random studies to know that that is the case. And we recognize very much the dedicated and conscientious board members often working long hours as volunteers to deal with these problems. In fact, we even went out of our way to produce one report that showed innovations and promising approaches that these IRBs themselves were developing to improve the way that research is done.

Nevertheless, we end with a feeling that this is the time for the reform of this system; and we would urge action to be taken as soon as possible.

Thank you very much.

[The prepared statement of Mr. Grob follows:]

Good morning. I am George Grob, Deputy Inspector General for Evaluation and Inspections in the U.S. Department of Health and Human Services (HHS). I am pleased to testify at today's hearing on Institutional Review Boards (IRBs). With me is Dr. Mark Yessian, Regional Inspector General for Evaluation and Inspections in our Boston office.

Mr. Chairman, the IRB system, which has provided important protections for human subjects for so many years, needs to be reformed. While I bring you no evidence of widespread harm to research subjects at this time, I do feel obligated to call your attention to weaknesses inherent in the system that was designed to protect them.

Research and medicine have changed dramatically in the past decade. However, our system for ensuring human-subject protections has not kept pace with these changes. Its shortcomings could become more apparent and significant in light of future developments. These include plans to increase the Federal investment in cancer and other biomedical research and a number of recent proposals recommending greater responsibilities for IRBs in the areas of genetics and patient confidentiality.

My testimony is based on more than a year of inquiry into the work of IRBs that we have just completed and on an earlier study performed by our office. Today we are releasing four reports that describe the results of our recent work. Our total effort reveals a brittle system

and even a few cracks. I call these to your attention now in the hopes of preventing more serious problems in the future.

**Background on Our Inquiry**

We initiated the broad, systemic review in response to concerns raised in a prior Office of Inspector General study. In that study, we examined clinical trials involving four investigational medical devices, and, in each case, discovered limitations related to IRB review. These concerned serious matters such as the implantation of a device in three times the number of human subjects specified in the IRB-approved research protocol, the initiation of a research effort without the changes called for in the informed consent document, and the continuation of a research project for six weeks beyond when the IRB had suspended it.

We were also aware of concerns about the IRB system raised by others. For instance, in its 1995 report, the Advisory Committee on Human Radiation Experiments questioned the adequacy of the IRB review process and the effectiveness of Federal oversight. In that same year, the General Accounting Office issued a report identifying numerous factors inhibiting IRB performance.

In our most recent inquiry, we conducted a broad-based analysis of the IRB system in order to gain an in-depth understanding of (1) the challenges facing IRBs and (2) how the IRBs and the Federal government were meeting these challenges. Toward that end, we developed a multi-faceted methodology drawing on many sources. These included analyses of Federal records; an extensive literature review; site visits to IRBs in 6 academic health centers; additional site visits accompanying FDA inspectors; a survey on the electronic e-mail forum for those associated with IRBs; and the systematic gathering of data from representatives of about 75 IRBs.

**IRB Role: Trust but Verify**

The IRB review system is rooted in trust. IRBs work closely and collaboratively with researchers, assuming the best of intentions on their part. This is one of the traditional strengths of the system.

At the same time, IRBs have important responsibilities and authorities for verifying that the intended human-subject protections are, in fact, being provided. In the 1970s, the national commission whose work established the foundation for Federal IRB regulations elaborated at some length on the kind of verification efforts that IRBs might undertake. The Federal regulations established in the 1970s and 1980s recognized the importance of such verification by giving IRBs the authority "to observe or have a third party observe the consent process and

the research." Further, it required IRBs to conduct continuing reviews of approved research "at intervals appropriate to the degree of risk, but not less than once a year." The National Institutes of Health has informed IRBs that these reviews must be "substantive and meaningful."

Other groups such as clinical audit teams, clinical trials coordinators and research sponsors themselves have responsibilities in overseeing the research process. However, IRBs are the sole bodies whose central mission is the protection of human subjects. This fact emphasizes the importance of IRBs' role in verification. (For further background information on IRBs, see the primer attached at the end.)

## MAJOR FINDINGS

Our overriding finding is that the system of protections that has been so carefully developed over the years is in need of reform. We base this conclusion on six main findings that we present below.

### 1. IRBs Face Major Changes in the Research Environment.

As I mentioned, Federal IRB regulations were established during the 1970s and early 1980s. At that time, most human-subjects research took place under government funding in a

university teaching hospital with established controls. The research itself was most often carried out by a single investigator with a small cohort of subjects at a single site. There was a considerable awareness of the risks of participating in research in the wake of several highly-publicized incidents involving the abuse of human subjects. IRB workloads were more limited and allowed ample time for deliberations over proposals.

Times have changed over the past 20 years and the changes have significant implications for IRBs. Medical institutions and particularly academic medical centers, where a large portion of clinical research takes place, are subject to increasing cost pressures due to the rise of managed care and capitated payments. A greater proportion of research is funded by commercial sponsors. IRBs feel pressure to accommodate these sponsors who are looking for quick turnaround of their research and for whom time is money. Many research protocols are now multi-center trials involving thousands of subjects, numerous investigators and institutions spread out across the country or even the world. Each institution has little knowledge of what is occurring at other sites, if problems have arisen, or even if other IRBs have called for changes in the protocol. Advances in biomedical research in areas such as gene testing or gene therapy raise many new and difficult ethical issues. Patients and consumers now demand access to research trials in the hopes of some benefit or treatment for life-threatening illnesses. IRBs must consider and ensure the equitable recruitment of subjects and, more importantly, ensure that subjects understand the distinction between research and treatment.

**2. IRBs Conduct Minimal Continuing Review of Approved Research.**

The IRBs' ongoing review of research after it has begun can serve as an important safety net for human subjects. This safety net may be more important now as individuals who consent in writing to participate do not necessarily understand the implications of their decision to participate. The 1995 Advisory Commission on Human Radiation Experiments found in their interviews with actual research subjects that few realized they were participants in research and many had little understanding of the informed consent forms they signed.

However, continuing review has become a low priority at many IRBs. For example, at one meeting we observed, several annual reviews and amendments were approved within the last 15 minutes of a 2 ½ hour meeting. One IRB member told us that he reviews the continuing review summaries during the board meeting to see if a patient has died. If no patient has died, then he generally will not raise questions.

Continuing review is also limited to a paper-based review at most IRBs. Board members and officials we spoke with reported that they seldom left the board room to visit the research site. In addition, although many IRBs would like to, few oversee the consent process or solicit feedback from subjects. Research investigators are relied upon to provide timely, accurate reports to the IRB. Several IRB members we spoke with are uncomfortable with this degree of reliance on self-reported data and would like to do more continuing review.

Continuing review is further limited by the inadequate information IRBs receive from outside sources. There is little communication between the Data Safety Monitoring Boards, which are created by research sponsors to oversee many of the large-scale trials, and the IRB. The adverse-event reports that the IRBs receive from sponsors arrive without sufficient contextual information to make them meaningful. When FDA issues a warning letter to a clinical investigator, it typically does not inform the IRB. And, when a sponsor or investigator submits a research plan, it may not inform the IRB of any prior review of that plan by another IRB.

In an effort to improve continuing review, the National Institutes of Health (NIH) and their Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA) have issued interpretations of Federal requirements in the forms of Dear Colleague letters and Information Sheets. However, from the perspective of the IRBs, some of these have served only to reduce IRB flexibility and add to their burdens.

**3. IRBs Review Too Much, Too Quickly, with Too Little Expertise.**

IRBs across the country are inundated with protocols. We found average increases of 42 percent in initial reviews during the past 5 years at the sites we visited. Some of them are now reviewing more than 2,000 protocols annually. These IRBs are also being flooded with adverse-event reports from the multi-center trials they oversee. One IRB reported receiving an average of 200 such reports a month. These problems are not found only in large IRBs; even

smaller IRBs are suffering. Several small IRB representatives told us that while the number of proposals they review is substantially fewer than at the large institutions, they often have only one staff member who is responsible for coordinating all IRB activities.

The increased workload, coupled with resource constraints, causes problems for IRBs and threatens the adequacy of their reviews. In an effort to cope, many are forced to rely on a pre-assigned reviewer to examine and summarize research plans. In some IRBs, unless one of the assigned reviewers raises a question or concern about the research, the board engages in little or no discussion at its meeting. Some IRBs have been able to increase the length of their meetings, but many others are forced to squeeze more reviews into a fixed block of time.

Science is becoming increasingly complex and many IRBs find that they lack sufficient scientific expertise on their boards or staffs to adequately assess protocols. This is particularly evident for protocols involving advanced biomedical techniques--such as gene testing--that raise scientific issues as well as moral and ethical questions that may not be apparent to the untrained eye. From time to time, IRBs will use consultants to fill the gap, but this can be costly and can bog down an already overburdened review process.

**4. Neither IRBs nor HHS Devote Much Emphasis to Evaluating IRB Effectiveness.**

IRBs have little basis for knowing how well they are accomplishing their mission of protecting

human subjects. Illustratively, when we asked one dean of a medical school how he knows when the IRB is doing a good job, he replied, "when I don't hear about them." Seldom, we found, do the IRBs seek out feedback from human subjects or their families. Nor do they often examine the complaints that they do receive to determine if they reflect broader, system problems or inquire as to how well the informed consent process is actually working. Independent, outside parties conducting such evaluations are even less frequent.

Federal oversight does not compensate for these deficiencies as it, too, is not geared to evaluating effectiveness. The OPRR's oversight is limited almost entirely to an upfront assurance process. The assurance is a document stating an institution's commitment to adhere to Federal requirements and is considered by most IRB staff we spoke with to have little impact on IRB functioning. The OPRR generally goes on-site only in instances of alleged breakdowns in IRB protections. Some of their reviews represent the most probing and results-focused inquires we have found of IRB performance, resulting in strong recommendations to the IRBs. But because of resource shortages, they are infrequent. Between April 1997 and May 1998, OPRR conducted only one for-cause visit.

The FDA oversight involves a more frequent on-site presence. However, their visits focus almost entirely on IRB compliance with the procedural requirements set forth in Federal regulations- such as attendance at review meetings, completeness of minutes, and a review of the informed consent document. Such matters can be important indicators of performance, but

they give FDA little direct feedback on the actual effectiveness of IRBs. For instance, in an information letter to IRBs, FDA requires IRBs to make certain that individuals understand what they are consenting to when they agree to participate in a research effort. Yet, FDA's inspection process does not extend beyond determining that informed consent forms contain all the appropriate elements and that they have been reviewed by the IRB.

**5. IRBs Face Conflicts that Threaten Their Independence.**

In fulfilling their mission of protecting human subjects, IRBs must keep the interests of its subjects central. But, we found that many IRBs we spoke with face conflicts that could lessen their objectivity.

Clinical research, particularly from commercial sponsors, is an important source of revenue and/or prestige for most institutions. For example, at one of the academic medical sites we visited, about 25 percent of the operating budget (nearly $200 million) derives from research activities. We found several examples of hospital IRBs that were housed in offices of grants and contracts or of clinical research programs, the very offices geared to bring in research dollars. Independent IRBs, which review primarily commercial research, are subject to similar pressures as several are owned by contract research organizations. Others may have

equity-owners as board members reviewing protocols. Such organizational placements, while not necessarily representing a conflict, certainly can accentuate pressures on IRBs to accommodate financial interests.

An important counterbalance to these sorts of pressures is the perspectives of certain IRB members whose concerns are primarily in nonscientific areas or who are not otherwise affiliated with the institution. However, Federal regulations require only one of each. We found few such "outside" members on the boards. It is not unusual for an IRB of 15 to 20 or more members to include only one or two noninstitutional members.

**6. IRBs and Their Institutions Provide Little Training for Investigators and Board Members.**

The review process can involve complicated ethical issues and scientific questions. Because of this, the education of board members, particularly "outside"members, is important. An understanding of these issues is also essential for research investigators who, themselves, initiate the informed consent process and interact directly with research subjects.

Nationally, in the context of the numbers of research investigators and the complexity of the ethical issues, such efforts are minimal. IRBs face significant obstacles which include not only insufficient resources, but the reluctance of many investigators to participate in training

sessions. For new IRB members, their orientation to the role is seldom much more than a stack of materials to read and on-the-job learning.

## RECOMMENDATIONS

We found the stresses on the IRB system to be significant enough for us to make a number of strong recommendations to NIH/OPRR and FDA. The thrust of our recommendations is for a more streamlined approach to providing human-subject protections, both at the local and Federal levels. At the same time, we call for a greater emphasis on accountability, performance, and results. Our recommendations include a number of actions, many of which, in the near-term, could help to address the vulnerabilities in the system. These are, among others:

- **Grant IRBs Greater Flexibility but Hold them More Accountable for Results**

If IRBs are to meet the significant challenges facing them in the years ahead, they must be relieved of unnecessary burdens. Thus, we call for eliminating, or at least loosening, a number of the procedural requirements that Federal regulations currently impose on IRBs. An example of this is the requirement that IRBs conduct full, annual reviews for all research plans, regardless of the level of risk the plan poses to human subjects. The IRBs would enhance their efficiency, and thus their effectiveness, if they could be more strategic in how they use their limited time and resources. This would allow them to concentrate on those research plans

involving substantial risks to human subjects. We expect that by giving IRBs greater flexibility we will nourish the creativity and innovation illustrated in our report on promising approaches.

But a quid pro quo for allowing IRBs greater flexibility is an increased emphasis on accountability. This accountability must be achieved in two basic ways. First, we recommend that all IRBs under NIH/OPRR's and FDA's purview undergo performance-focused evaluations to assess their effectiveness in achieving their core mission. The evaluation results should be made available to the public. Second, we recommend that there be more extensive representation on IRBs of nonscientific and noninstitutional members. The current policy, which requires that there be one noninstitutional and one nonscientific member, does not provide an adequate measure of public accountability.

- **Reengineer the Federal Oversight Process**

As it now functions, the Federal oversight of IRBs is not equipped to respond effectively to the issues we present in this testimony. We call for changes in the way that NIH/OPRR and FDA carry out their oversight responsibilities. We suggest reorienting the NIH/OPRR assurance process so that it rests essentially on an institutional attestation to conform to the IRB requirements set forth in Federal regulations. This attestation could be provided in a brief statement referencing the pertinent regulations. As a result, the scarce OPRR resources that are now devoted to reviewing and negotiating assurances could be freed up to conduct periodic

performance-based reviews and to provide education for investigators and IRB members. We also suggest that FDA search for ways of revamping its inspections, so that they focus less on narrow compliance matters and more on performance issues.

We particularly urge that FDA and NIH/OPRR incorporate into their oversight efforts specific lines of inquiry to determine how well IRBs are actually protecting human subjects. This would call for examining matters such as how the processes of recruiting, selecting, and gaining informed consent from human subjects actually work. It would also call for addressing verification effort to make sure that research plans are in fact submitted for review and that approved plans do not stray off course. The FDA and NIH/OPRR could enhance a performance focus by finding ways in which experienced IRB members and staff could play some on-site role in reviewing IRB performance.

- **Strengthen Continuing Protections for Research Subjects**

The IRBs need to be more aware of what is actually happening at the research sites under their jurisdiction. They need to move beyond reliance on a signed informed consent document to ensure the integrity of the consent process itself. In the current system, IRBs have no way of knowing whether those participating in research truly understand that they are research subjects, and that there may be risks associated with their participation. Further, IRBs should find mechanisms to assure themselves that the research under their purview is being conducted

as planned. As we reported in our prior OIG work, the information provided to IRBs is not always accurate. In making this recommendation we acknowledge that trust is an important element to the system; but we also feel that IRBs have a vital role in verifying the information presented to them.

Certainly, increased flexibility will help ease the burden on IRBs and will allow them to concentrate their time and resources on high-risk research. But if they are to conduct meaningful reviews of approved research, they need to receive continuous feedback from the various other players involved in overseeing research. Key among these are the Data Safety Monitoring Boards that oversee many of the large-scale trials. The role of these boards is to review the continued safety and efficacy of trials; yet rarely do they provide IRBs with meaningful and timely feedback. Doing so would not only enhance the efficiency of review but would allow IRBs to focus on what they know best, *i.e.*, the continued applicability of the research plan to the local environment. To complete the information loop, the FDA needs to provide IRBs with feedback on actions it takes against investigators that are engaged in research under their purview.

- **Enhance Education for Research Investigators and IRB Board Members**

In the final analysis, the most important continuing protection for human subjects is the presence of well-trained and sensitized investigators. Such research investigators can also

serve to minimize the need for regulatory intervention, be it by the Federal government or by IRBs themselves.

The NIH is well positioned to assume a leading role here since it funds a significant portion of the biomedical and behavioral research in the country. It should require that institutions which receive funds for human-subject research under the Public Health Service Act have a program to educate their investigators about human-subject protections. Simultaneously, investigators who receive money under this program should be required to provide a written attestation of their familiarity with, and commitment to upholding, Federal policies concerning the protection of human subjects. As identified in our report on promising approaches, a number of institutions have, of their own accord, begun to initiate educational programs for investigators. The Federal government should continue to foster these efforts by establishing model curricula, developing basic educational materials, and continuing to sponsor symposia and conferences.

Finally, IRBs should be required to provide an orientation program for new members and a continuing education program for all members. This would be especially relevant for noninstitutional and nonscientific members. Such a program should help to bring them up to a level where they can fully and actively participate on the IRBs to which they belong.

## CONCLUSION

In closing, Mr. Chairman, I would like to underscore that we do not document, nor do we suggest that, widespread harm is being done to human subjects. The current system of protections is supported by many conscientious researchers committed to protecting human subjects and by many dedicated IRB members and staff doing their best under trying circumstances.

But, I must reiterate our warning signal-- that the effectiveness of the current system of human-subject protections is in need of reform. IRBs are struggling under intense workload and resource constraints. This situation will only intensify if funding for research is increased and if IRBs are expected to take on additional responsibilities. We cannot afford to wait any longer to act. It is time for reform.

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.

## INSTITUTIONAL REVIEW BOARDS: THE BASICS

**What Do They Do?**

The responsibilities of IRBs fall into two main categories: initial review and continuing review of research involving human subjects.

**Initial Review:** IRBs review and approve a research plan before the research is carried out. This review encompasses the research protocol, the informed consent document to be signed by subjects, any advertisements to be used in recruiting subjects, and other relevant documents. In carrying out this review, the boards seek to ensure any risks subjects may incur are warranted in relation to the anticipated benefits, that informed consent documents clearly convey the risks and the true nature of research, advertisements are not misleading, and the selection of subjects is equitable and justified. IRBs focus much attention on the informed consent document as it is the vehicle for providing information to potential research subjects.

**Continuing Review:** The continuing review process is multifaceted and includes required reviews "at an interval appropriate to the degree of risk but not less than once per year." In addition to this continuing review, study amendments and reports of unexpected adverse experiences by subjects are received periodically and reviewed to ensure that the risk-benefit ratio of the research has not changed and remains acceptable.

**Why Were They Established?**

As public awareness and concern about the treatment of human subjects in research increased, the need for additional review mechanisms was evident. These concerns grew from stories of the abuse of subjects during the World War II trials at Nuremberg, the promotional distribution of thalidomide resulting in numerous children born with birth defects, the administration of cancer cells to chronically ill and senile patients at a hospital in New York, and others. A 1966 article by Henry Beecher brought prominent attention to human research abuses in medical schools and hospitals citing 22 cases involving highly questionable ethics. The formal requirements for the establishment of IRBs were outlined in regulations stemming from the National Research Act of 1974 and in FDA regulations issued in 1981.

**Where Are They Located?**

An estimated 3,000-5,000 IRBs can be found across the country. They are most commonly associated with hospitals and academic centers. Boards also exist in managed-care organizations, government agencies (such as the National Institutes of Health, the Centers for Disease Control, and State governments), or as for-profit entities that are independent of the institutions in which the research takes place.

**How Are They Organized?**

Federal regulations require that boards have at least five members with varying backgrounds. At least one member must have primarily scientific interests, one must have primarily nonscientific interests, and one must be otherwise unaffiliated with the institution in which the IRB resides. A quorum, with at least one member whose interests are primarily nonscientific present, is needed for voting.

**How Does the Department of Health and Human Services (HHS) Oversee Them?**

Two agencies within HHS share responsibility for IRB oversight: the Office for Protection from Research Risks (OPRR) in NIH and the FDA. The OPRR's main tool for oversight is the assurance document. Any institution that intends to conduct HHS-funded research must have an assurance on file with OPRR. The assurance is a written statement of an institution's requirements and procedures for its IRB and human subject protections. Institutions conducting multiple HHS-supported studies can apply for a multiple project assurance (MPA) which can be renewed every five years. Institutions with smaller HHS-funded workloads, however, use a single project assurance (SPA) for each such project it conducts. The OPRR also conducts a small number of site-visits. The FDA's main mechanism for IRB oversight is the inspection process. The FDA also inspects research sponsors and scientists (known as research investigators).

Mr. SHAYS. Thank you, Mr. Grob.

Dr. Meslin.

Mr. MESLIN. Thank you very much, Mr. Chairman. My name is Eric Meslin and I am the Executive Director of the National Bioethics Advisory Commission, or NBAC. I am pleased to have been invited to appear before you this morning to discuss issues in human subjects research and IRBs, issues which are at the center of NBAC's ongoing interest and, indeed, its mission.

We are pleased to know that the Office of the Inspector General has completed its report, and the Commission will look forward to studying it carefully in the weeks ahead.

Since I have already submitted written testimony, I'd simply like to summarize very briefly the points that I have raised there.

NBAC was established by Executive order, signed by President Clinton, and has been meeting on a regular basis since October 1996. It is charged with making recommendations to the National Science and Technology Council on issues relating principally to research involving human subjects. As a Federal advisory committee, the Commission takes seriously its role in informing and learning from the public, holding its meetings both within the Washington, DC, area and around the country, and utilizing a newly refurbished website. The Commission was directed by the President's Executive order as a first priority to examine issues in the protection of human subjects. As this subcommittee is aware, NBAC was requested by the President to provide advice on the issue of human cloning and once this report had been completed, NBAC returned to its original agenda.

Mr. Chairman, in May 1997, NBAC adopted unanimously the resolution that "No person in the United States should be enrolled in research without the twin protections of informed consent by an authorized person and independent review of the risks and benefits of that research." With this starting point, the Commission turned its attention to two important topics, both of which address Institutional Review Boards. I'm pleased to report that we are very close to completing these reports.

The first project is examining issues in research involving persons with mental disorders that may affect decisionmaking capacity. This population is felt by many to be vulnerable, not only because they lack the ability to consent to participate in research in some instances, but also because Federal regulations do not explicitly provide protections specific to their needs. The Commission has not developed its final recommendations on this subject, but we expect to release an interim report within the next 3 weeks on our website in order to solicit public and expert comment. We intend to issue the final report in the fall. However, in the most recent staff draft, several possible recommendations are being considered, none of which, I should emphasize, have been formally adopted by the Commission as yet. But two of them are worth noting this morning.

The first is that the common rule should be amended in certain ways. For example, to require that IRBs include at least two members who are familiar with the nature of these disorders and with the concerns of this population. Given that amending the common rule would take some time, the staff draft also proposes that this

recommendation, and several others, be adopted voluntarily by IRBs immediately. Two of these recommendations are that investigators should justify to IRBs the need for certain controversial study designs, such as symptom-provoking or challenge studies; and, second, that IRBs, and the institutions in which they work, utilize strategies of disclosure and audit. There are a number of other proposed recommendations and these are all contained in a staff draft on our website.

Mr. SHAYS. Excuse me?

Mr. MESLIN. Yes?

Mr. SHAYS. Would you just repeat the first one you said?

Mr. MESLIN. The first of what we hope to be immediate recommendations, if the Commission decides to go in this way, is that investigators justify the need to IRBs for the use of certain controversial or difficult to defend, in some instances, study designs. We have looked at the issue of challenge studies and wash-out studies. And the second is to utilize audit and disclosure.

A second project is looking at the use of human biological materials and this raises some similar issues with respect to IRBs, in particular, how IRBs assess the risks of non-physical harms, such as dignitary or psychosocial harms resulting from discrimination or stigmatization. We expect this report to be available in the late spring, or early summer, and hopefully finalized in the fall.

The Commission's research agenda includes two other projects, again, related to IRBs and the Federal system of protection. The first focuses on international research and specifically the rules that ought to apply when the United States conducts or supports research in other countries. The other project is a comprehensive assessment of the Federal system of oversight of human subjects protections. The first phase of this effort is almost complete. Staff has surveyed Federal agencies to determine the extent to which they are implementing the common rule and we will complete this analysis within the month.

Finally, Mr. Chairman, this report will assess various structural issues within the system, including the location and jurisdiction of oversight offices and whether any reforms may be necessary to the existing IRB system. We expect this report to be completed in the spring.

Thank you very much, Mr. Chairman.

[The prepared statement of Mr. Meslin follows:]

Mr. Chairman and Honorable Members of this Subcommittee,

I am Eric Meslin, Executive Director of the National Bioethics Advisory Commission, NBAC. I am pleased to have been invited to appear before you today to discuss NBAC's on-going work in the area of human subjects research. The subject of this hearing is very much in line with the NBAC's on-going interests in the structure and function of the federal system of overseeing human subjects research in this country, and we are pleased to know that the Office of the Inspector General has completed its report.

NBAC was established by President Clinton through Executive Order #12975, and met for the first time in October 1996. It is charged with advising and making recommendations to the National Science and Technology Council (NSTC), chaired by the President and to other appropriate government entities, regarding the appropriateness of governmental policies, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior.

The Commission also is charged with identifying broad principles to govern the ethical conduct of research. NBAC is not authorized to review or approve specific research projects. In addition to responding to requests for advice and recommendations from the NSTC, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. In this spirit, the Commission has held its regular meetings both in the Washington DC area and in other parts of the country. These meetings are announced in advance in accordance with the Federal

Advisory Committee Act. Public comments are invited at all Commission meetings and have proven to be very helpful. NBAC has established a website--www.bioethics.gov--which, as of Monday afternoon, had more than 32,000 visits since we first established the site in January of this year.

The Commission was directed by the President's Executive Order, as a first priority, to examine issues in the protection of human subjects. As this subcommittee is aware, the announcement in February 1997 of the birth of the apparently cloned sheep Dolly led the President to request that NBAC advise him within 90 days of the ethical, legal, and scientific issues arising from this technology. Once this report was completed, the Commission returned to its original agenda.

Mr. Chairman, NBAC's commitment to issues in human subjects research is evidenced in the resolution it adopted unanimously at its May 1997 meeting:

"No person in the United States should be enrolled in research without the twin protections of informed consent by an authorized person and independent review of the risks and benefits of the research."

In adopting this resolution, the Commission understood the opportunity it has to provide thoughtful and timely advice about a system that has been functioning for more than two decades. The Commission is currently completing two projects relating to human subjects research ethics, both of which address, in part, Institutional Review Boards. The first project is examining issues in research involving persons with mental disorders that may affect decision-making capacity. This population is felt by many to be doubly vulnerable: first, federal regulations do not explicitly provide protections

specific to the needs of these individuals; indeed, one of NBAC's historical relatives, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, recommended more than two decades ago that individuals institutionalized as mentally infirm be afforded particular protections in regulation. Second, given the importance for scientific and medical progress on diseases such as schizophrenia and Alzheimer's, some of these individuals are vulnerable to discrimination because they lack the capacity to give an informed consent to participate in research. NBAC has heard testimony from investigators, clinicians, subjects of research, federal and state officials and regulators.

Although the Commission has not issued its final report on this subject--it will be releasing an interim report within the next three weeks on its website in order to solicit public comment, and a final report is expected in the Fall--there are a number of issues that NBAC has considered during the course of its deliberations. In the most recent staff draft to the Commission, which I hasten to add has not been adopted by the Commission as yet, the following recommendations have been proposed:

(1) The Common Rule should be amended to address a number of issues concerning this vulnerable population, one of which is a requirement to include on IRBs at least two members who are familiar with the nature of these disorders and with the concerns of this population, one of whom shall be a member of this population, or a family member or representative of an advocacy organization for this population.
It has been proposed that, since it will take time to amend the Common Rule, the IRB system might adopt these recommendations on a voluntary basis.

(2) Other recommendations being considered for adoption by the Commission not related to the Common Rule include: the requirement that IRBs require of investigators that they justify the need for certain controversial study designs, for example, studies which provoke symptoms (challenge studies); that IRBs and the institutions in which they operate publicly disclose their policies and procedures that characterize key aspects of their work; that IRBs provide, on an annual basis, summary statistics regarding the overall scope and nature of their activities; and each institution with an IRB adopt appropriate internal audit procedures to assure itself that its IRB is complying with appropriate rules and regulations.

The Commission's second project underway is developing recommendations for the research use of human biological materials. Like the report on research involving persons with mental disorders, the study of human biological materials has raised important questions about the appropriateness of consent forms and the process used to obtain informed consent; and how institutional review boards assess the risks of non-physical harms, such as dignitary or psychosocial harms resulting from discrimination or stigmatization to individuals and groups. We expect this report to be available for public comment by early Fall.

The Commission's research agenda includes two other projects, both of which will involve consideration of human subjects issues generally, and IRB issues in particular. One of these focuses on international research, specifically the rules that ought to apply when the United States conducts or supports research in other countries. The other project is a comprehensive assessment of the federal system

of oversight of human subjects protections. We have already begun the first phase of this effort, by surveying federal agencies to determine the extent to which they are implementing the Common Rule. NBAC's report will also assess various structural aspects of the system, including the location and jurisdiction of oversight offices; whether reforms may be necessary to the existing IRB system; and whether the existing system should be extended to protect research subjects in non-federally funded research. This project is scheduled to be completed by the Spring of 1999.

Thank you very much, Mr. Chairman. I would be pleased to answer any questions you may have.

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Mr. SHAYS. Thank you very much, Dr. Meslin.

Dr. Ellis.

Mr. ELLIS. Thank you. My name is Gary Ellis, Director of the Office for Protection from Research Risks, OPRR, the NIH office that implements the Department of Health and Human Service's regulations for protection of human subjects. I also chair the Federal interagency human subjects coordinating committee.

Are IRBs in jeopardy? With Mr. Grob's testimony, we have the Inspector General's answer. One thing IRBs are not in is jeopardy. The Inspector General pointedly turned away from any use of the word jeopardy in developing her final report. So let us set aside any sense of peril, danger, hazard, or menace. Let us instead soberly address the need for reform, correction, revision, and improvement.

The seminal finding of this report for people who are today subjects in research is that the IG does not document, nor does the IG suggest—and those are her words not mine—that widespread harm is being done to human subjects. Our challenge is to ensure that today's finding remains true tomorrow and on into the future. We have a multi-layered system of protections designed to prevent physical injury, prevent psychological injury, and prevent harm to the dignity of research subjects as biomedical and behavioral scientists pursue new knowledge for the common good.

This system of protection of human subjects in research is based on a succession or chain of judgments made by people in the context of Federal regulations. Thoughtful people, often volunteering large amounts of their time, look at research protocols and weigh risks and potential benefits. There are at least half a dozen levels of protection in this system.

First and foremost, there's the interaction between the research volunteer and the research investigator. This is where the informed consent process takes place. The IRB has a minimum of five people, including at least one scientist, one non-scientist, and one person not otherwise affiliated with that institution. The local IRB at the research site is the cornerstone of our system of protection of human subjects. No research on human subjects may be initiated and no ongoing research may continue in the absence of an IRB approval.

IRB review is prospective and continuing review of proposed research by a group of individuals with no formal involvement in the research. Ideally, it is a local review by individuals who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and the likely subject population.

Downstream from the IRB are the executive official of the research site, for example, the dean or department chair; the scientific review group at the funding entity; and the program and administrative staff or executive officer of that funding entity. Each has the authority to express concerns about human subjects' issues. Exerting oversight over the whole process are OPRR, and when investigational drugs, devices, or biologics are involved, the FDA.

An additional layer of review that may be employed, especially in large studies, is an independent Data and Safety Monitoring

Board, appointed to oversee and to evaluate the research investigation. At periodic intervals during the course of the study, the Data and Safety Monitoring Board reviews the accumulated data and makes recommendations on the continuation or modification of the study.

While I have emphasized the multiple layers of protections inherent in the system, I know that you are most interested about the possibility that this system could somehow fail. What is the possibility of a catastrophic failure in human judgment running through six or more layers? I would characterize this possibility as slight. Protection of the rights and welfare of human subjects is particularly important when subjects are likely to be vulnerable to coercion or undue influence. Thus, IRBs watch out especially for research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

OPRR requires that each HHS agency and extramural research institution, that conducts research involving human subjects, sets forth the procedures it will use to protect those human subjects in a written statement called an assurance of compliance. The HHS assurance process, which was highly educational for institutions that submitted their initial assurances in the 1970's, 1980's, and early 1990's, is due for streamlining so that OPRR can devote more effort to working with institutions to better educate IRB members, IRB staff, and research staff. But OPRR will not abandon its current pre-emptive oversight procedures, that is, negotiation of written assurances to comply, before putting in place an education program for assuring competency-based compliance.

OPRR has increasingly made information that is useful to IRBs available on our website. We are committed to vigorous personal consultation with IRBs and institutional officials. We log 175 to 200 phone calls each day. OPRR and FDA are scheduled to meet with numerous IRB members and staff in seven regional conferences through the next 12 months, the continuation of an ongoing educational conference program that spans two decades. OPRR is currently recruiting for a senior professional to direct a new education branch. NIH is committed to enhancing fiscal year 1999 funding for this education branch, which will have responsibility for broad educational outreach.

I made reference to the core HHS regulations for protection of human subjects, that's Subpart A of 45 CFR Part 46. The regulations at Subpart A are the HHS manifestation of the common rule, the 1991 Federal Policy for the Protection of Human Subjects, shared by 16 other agencies. Because any proposal to revise the core HHS rules would require consideration and concurrence by the 16 other departments and agencies, we have asked that the IG convey today's report to her counterpart at each respective department and agency. Policy changes are best not imposed unilaterally and will need to be shaped by all of the departments and agencies that will also be affected.

Our collective goal is to continuously strengthen our system of human subjects' protection from the Federal side and from the institutional side as well. Many promising approaches that IRBs

might take are demonstrably already within their authority to take.

In the final analysis, Mr. Chairman and members of the subcommittee, research investigators, institutions, and we are the stewards of a trust agreement with the people who volunteer to be research subjects. We have a system in place that to the greatest degree possible minimizes the potential for harm, enables and protects individual autonomous choice, and promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow citizens who make a remarkable contribution to the common good by electing to volunteer for research studies. We owe them our best effort.

Thank you.

[The prepared statement of Mr. Ellis follows:]

Testimony of
Gary B. Ellis, Ph.D.
Director
Office for Protection from Research Risks,
Office of Extramural Research,
National Institutes of Health,
Department of Health and Human Services

Before the
Subcommittee on Human Resources
Committee on Government Reform and Oversight
United States House of Representatives

Thursday, June 11, 1998
Rayburn House Office Building, Room 2154
9:30 a.m.

Mr. Chairman and Members of the Subcommittee:

I am Gary Ellis, Director of the Office for Protection from Research Risks (OPRR), Office of Extramural Research, National Institutes of Health (NIH). I am pleased to appear before the Subcommittee to describe our well-developed, yet ever-evolving, system of protection of human research subjects. My testimony today thus describes a responsibility of enormous weight.

With the Inspector General (IG) of the Department of Health and Human Services (DHHS) releasing her final reports on Institutional Review Boards (IRBs) at this morning's hearing, I am pleased to address the system of protection of human research subjects that has been evaluated by the Inspector General and her staff.

This spring season marks the 24th anniversary of the formal promulgation on May 30, 1974 of the DHHS regulations for Protection of Human Subjects in research (Title 45 Code of Federal Regulations Part 46). This enduring and vigorous system of protections is designed to prevent physical injury, psychological injury, and harm to the dignity of research subjects, as biomedical and behavioral scientists pursue new knowledge for the common good. We are always interested in improving the system to make research as safe as it possibly can be.

This system of protection of human subjects in research is based on a succession, or chain, of judgments made by people in the context of federal regulations. Thoughtful people, often volunteering large amounts of their time, look at research protocols and weigh risks and potential benefits. There is no computer program for this; there is no generic formula. One size doesn't fit all. This is custom work.

Multiple Layers of Protection for Human Research Subjects

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection. First, and foremost, there is the interaction between the research volunteer and research investigator. This is where the informed consent process takes place. It must be an ongoing, dynamic process, as new information becomes available or is desired. The informed consent document, or form, is one component--the written component--of the informed consent process. I will describe the particulars of informed consent in a moment. There may also be other parties involved, such as nursing, scientific, or medical staff other than the principal investigator. There may be a consent auditor or monitor, or an advocate for the research subject.

The Institutional Review Board is, by federal regulation, to be established at the local level and has a minimum of five people, including at least one scientist, one nonscientist, and one person not otherwise affiliated with that institution. The nonscientist must be present to achieve a quorum. The local IRB at the research site is the cornerstone of our system of protection of human subjects. No human-subjects research may be initiated, and no ongoing research may continue, in the absence of an IRB approval. By regulation, DHHS and 16 other federal departments and agencies cannot provide funds for human subjects research unless an IRB approves the protocols for such studies.

IRB review is 1) prospective and 2) continuing review of proposed research by a group of individuals with no formal involvement in the research. Ideally, it is a local review, by individuals who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and likely subject population.

Once research is underway, the IRB must conduct continuing review of the research, at intervals appropriate to the degree of risk--in any event, at least once per year. I will return to the responsibilities of the IRB in a moment.

Downstream from the IRB are:

- the executive official of the research site (e.g., dean, department chair, chief financial officer);
- the scientific review group at the funding entity (e.g., one of the NIH Institutes or Centers); and
- the program and administrative staff (e.g., the executive official) of that funding entity.

Each has the authority to express concerns about human-subjects issues. Exerting oversight of the whole process are OPRR and, when investigational drugs, devices, or biologics are involved, the Food and Drug Administration (FDA).

An additional layer of review that may be employed, especially in large studies, is an independent Data and Safety Monitoring Board (DSMB), appointed to oversee and to evaluate the research investigation. DSMBs are usually appointed by, and report to, the funding organization--not the investigators or the institution doing the study. At periodic intervals during the course of the study, the DSMB reviews the accumulated data and makes recommendations on the continuation or modification of the study. A study can be stopped prematurely because of a toxic effect, or because a strong positive effect was seen and it would be unethical to continue with some subjects not receiving the intervention which has demonstrated benefit. When a study is stopped for such reasons, it is likely due to the action of a DSMB.

While I have emphasized the multiple layers of protection inherent in this system, I know you are most concerned about the possibility that this system could somehow fail. What is the possibility of a catastrophic failure in human judgment running through six or more layers? I would characterize that possibility as "slight."

It is OPRR's role to make sure that the IRB process works at institutions within OPRR's jurisdiction. To give you a sense of the kinds of problems that do occur and actions taken to address them, I will relate brief accounts of some actions taken by OPRR. In one well-publicized instance, the concern was the proper explanation of risks in the informed consent process for a study involving schizophrenia. OPRR 1) rebuked the Institutional Review Board for poor oversight of the informed consent process, 2) directed that the informed consent process be revised, and 3) instituted close monitoring of the institution's human-subjects activities. In a second instance, the concern was misuse of an expedited IRB review process. OPRR identified a failure of leadership within the Institutional Review Board, and the IRB Chairman subsequently resigned. At a third institution, the concern was whether or not the IRB was properly conducting the required continuing, annual review of research. The institution demonstrated to OPRR that some 2,000 research protocols involving human subjects had, indeed, received continuing review in accord with DHHS regulations.

Institutional Review Boards

Let me turn briefly to the specific responsibilities of the Institutional Review Board. IRB review assures that:

- risks are minimized;
- risks are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- there is proper informed consent; and
- the rights and welfare of subjects are maintained in other ways as well. This is

particularly important when subjects are likely to be vulnerable to coercion or undue influence.

What populations are judged to be vulnerable? IRBs watch out especially for research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

Federal regulations provide extra protection for vulnerable subjects in several ways. If an IRB regularly reviews research that involves a category of vulnerable subjects, consideration must be given to including as IRB members one or more individuals who are knowledgeable about, and experienced in working with, the vulnerable subjects. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, IRBs must see that additional safeguards are included in the study protocol. Specific, detailed protections are actually written into DHHS regulations pertaining to pregnant women, fetuses, human ova fertilized in vitro, prisoners, and children involved in research.

Once research is initiated, IRBs have continuing responsibilities. These include:

- The conduct of continuing review at intervals appropriate to the degree of risk, and in any event, not less than once per year.
- Authority to observe or have a third party observe the consent process and the research.
- Receipt of prompt reports from investigators of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the IRB's requirements or determination, or with the regulations.
- Authority to suspend or terminate IRB approval of research that is not being conducted in accord with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

Assurance of Compliance with Human Subjects Regulations

The DHHS regulations for Protection of Human Subjects are not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, this is a framework in which investigators, IRB members, and others can ensure that adequate efforts have been made to protect the rights and welfare of research subjects.

OPRR oversees implementation of the regulations in all DHHS facilities as well as domestic and foreign institutions or sites receiving DHHS funds. OPRR requires that each DHHS agency and extramural research institution that conducts research involving human subjects sets forth the procedures it will use to protect human subjects in a policy statement called an "Assurance" of compliance. At OPRR's discretion, institutions with a large volume of

research and demonstrated expertise in human subjects protection may be granted a Multiple Project Assurance. A Multiple Project Assurance, as the term implies, is an institution's pledge of full human subject protections for multiple projects at the institution. By federal regulation, OPRR has authority for approving an Assurance at DHHS-funded institutions for federal-wide use.

An Assurance statement is a formal, written commitment to: 1) widely held ethical principles; 2) the DHHS regulations for Protection of Human Subjects; and 3) institutional procedures adequate to safeguard the rights and welfare of human subjects. The terms of the institution's Assurance are negotiated with OPRR. The detailed, written Assurance statement becomes the instrument that OPRR uses to gauge an institution's compliance with human subject protections if there is a problem.

The DHHS assurance process--which was highly educational for institutions submitting their initial Assurances in the 1970s and 1980s--is due for streamlining, so that OPRR can devote more effort to working with institutions to better educate IRB members, IRB staff, and research staff. OPRR has been seriously considering a redirection of its intensive Assurance effort toward education, and performance-based reviews of IRBs. Please know that OPRR will not abandon its current preemptive oversight procedures (i.e., negotiation of institutional assurances to comply) before putting in place an education program for assuring competency-based compliance.

Informed Consent

All present today know how integral--how crucial--the process of informed consent is. Many have a general picture of informed consent, and it is useful to add higher resolution to that picture. DHHS regulations specify 14 elements of informed consent, 8 of which are required:

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2) A description of any reasonably foreseeable risks or discomforts to the subject.

3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A researcher who seeks to recruit an individual for research without conveying these elements of information in language understandable to the potential subject is not obtaining *informed* consent.

Research, Education, and Training

The specificity of Federal regulatory language on informed consent, its endurance through many years, and the enthusiasm with which we all adhere to it all belie the fact that little empirical work exists to document the degree of understanding achieved by research participants. There is a scarcity of data that bear upon, for example: 1) research subjects' comprehension of a study's methods and procedures; 2) subjects' understanding of relative risks and benefits of participation; 3) subjects' understanding of confidentiality and any exceptions to confidentiality; and 4) subjects' understanding of the implications of withdrawal from a study. Such data are needed to aid in designing informed consent procedures that are readily comprehended by prospective participants and, at the same time, impart all critical information.

NIH has recently taken major steps to bring improved understanding to informed consent, including the award in 1997 of fourteen, 3-year research grants to scientists who are studying informed consent. And, to further education and training, NIH has issued two solicitations for training initiatives in bioethics. One would provide postdoctoral training for individuals who seek a concentrated training experience. The other will support short-term institutional awards to make increased training in bioethics available to a larger number of scientists.

In the World Wide Web era, OPRR has increasingly made information that is useful to IRBs available on our website. We are also committed to vigorous personal consultation with IRBs and institutional officials. (OPRR logs 175 to 200 phone calls per day!) This level of consultation is instrumental in the development of meaningful performance measures for IRBs. OPRR and FDA are scheduled to meet with numerous IRB members and staff in regional conferences in Los Angeles, Rochester NY, New Orleans, San Diego, Salt Lake City, Kansas City MO, and Detroit in the next 12 months--the continuation of an ongoing educational

conference program that spans two decades. OPRR will participate in the FDA's upcoming National Forum on Human Subject Protection, which will present an opportunity to discuss with the IRB community some promising approaches in the education, orientation, management, and assessment of IRBs.

OPRR is currently recruiting for a senior professional to direct a new Education Branch in our Division of Human Subject Protections. NIH is committed to enhanced Fiscal Year 1999 funding for this Branch, which will have responsibility for: 1) developing and conducting an educational outreach program to provide clarification and guidance on ethical issues related to biomedical and behavioral research involving human subjects; 2) developing the content of human-subjects educational programs and guidance materials, including the OPRR's ongoing series of "Dear Colleague" letters, and extensive Web-based tutorials; 3) implementing a national program of 5 to 7 human-subjects education workshops per year, co-hosted by institutions conducting DHHS-supported human-subjects research; 4) initiating, coordinating, and conducting 12 to 24 educational and technical assistance site visits per year at institutions conducting DHHS-supported human-subjects research, through contact with institutional officials; IRB chairs, staff, and members; and research investigators; and 5) handling OPRR's large volume of Freedom of Information Act requests.

Consideration of Regulatory Change

As I noted, the requirements for IRB membership, function, operations, review of research, and recordkeeping are described by the core DHHS regulations for Protection of Human Subjects at Subpart A of 45 CFR Part 46. The regulations at Subpart A are the DHHS manifestation of a common rule, the 1991 Federal Policy for the Protection of Human Subjects. In addition to DHHS, the 1991 Federal Policy is shared by 16 other agencies.[1] Because any proposal to revise Subpart A of 45 CFR Part 46 would require consideration and concurrence by these 16 other departments and agencies, we have asked that the DHHS Inspector General convey the final versions of her four reports to her counterpart at each respective department and agency.

Also to further the broad appreciation of the recommendations of the DHHS IG, I will take her final reports to the Subcommittee on Human Subjects Research, Committee on Science, National Science and Technology Council, which I chair. The Subcommittee will have great interest in suggestions for any potential changes to the common 1991 Federal Policy for the Protection of Human Subjects, as it is responsible for the uniform implementation of those

[1]Agency for International Development; Central Intelligence Agency; Consumer Product Safety Commission; Department of Agriculture; Department of Commerce; Department of Defense; Department of Education; Department of Energy; Department of Housing and Urban Development; Department of Justice; Social Security Administration; Department of Transportation; Department of Veterans Affairs; Environmental Protection Agency; National Aeronautics and Space Administration; and National Science Foundation.

common regulations. Policy changes are best not imposed unilaterally and will need to be shaped by all of the departments and agencies that will also be affected.

Conclusion

Our collective goal is to continuously strengthen our system of human-subjects protection from the federal side and from the institutional side as well. Many promising approaches that IRBs might take are, demonstrably, already within their authority to take. In the final analysis, Mr. Chairman and Members of the Subcommittee, research investigators, institutions, and we are stewards of a trust agreement with the people who volunteer to be research subjects. We have a system in place that to the greatest degree possible 1) minimizes the potential for harm, 2) enables and protects individual, autonomous choice, and 3) promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow citizens who make a remarkable contribution to the common good by electing to volunteer for research studies. We owe them our best effort.

Thank you, Mr. Chairman. I am pleased to answer any questions about our system for safeguarding the rights and welfare of human research subjects.

Mr. SHAYS. Thank you very much, Dr. Ellis. At this time the Chair would recognize the chairman of the full committee, Mr. Burton.

Mr. BURTON. I thank you very much, Mr. Chairman. I have to leave for just a moment but I'll come back. And I would like to ask this panel just a couple of questions.

Dr. Ellis, your testimony, I listened to it intently and it sounded to me like there's no problem. We had a hearing on April 22nd, and we had a fellow named Joe Foster who was a participant in a clinical trial for a hypertension drug, and without his knowledge or consent, he was taken off his medication. He didn't know he was getting a placebo. And 6 days later, he had a heart attack and a stroke and the man is suffering severely today because of that. That was a particularly egregious case. And, as I said, many things went wrong.

You stated in your testimony that with so many layers of protection in place the possibility of a catastrophic failure in human judgment is slight. I don't think Joe Foster would agree with that. If at the very first layer, a researcher does not inform the subject, like Joe Foster, that he's taking a placebo and he was dropped out of the study because of a severe stroke and it was never reported. It was one of those wash-outs. How are all those layers going to protect him because nobody even knew about it until he brought it to the attention of the United States through our committee hearing?

And the other thing that I'd like for you to comment on is this case in New York. I just cannot understand how in the world there could be a series of research tests conducted on children from specific ethnic areas where the drug in question, fenfluramine, was going to hurt them. Specifically, one of the questions I have is that the use of fenfluramine on these children after the drug was banned last fall, when it was discovered to cause heart valve damage in adults. They continued on with the research with the kids even after they discovered that. Now, if you say all these layers of protection are there, how could that happen?

And then I would just like to ask one other, Mr. Chairman, and he can answer all three of them at once, and that is how can OPRR evaluate NIH, NIMH-approved research when the OPRR are subordinates of the NIH?

And with that, those are the only questions I have, Mr. Chairman?

Mr. ELLIS. Thank you for the questions. First, let no one take the impression that you had from my testimony that I would say that there's no problem in the system. I talked about a non-zero possibility of catastrophic failure and that's just what it is. It's not zero and I'm not saying there's no problem.

I, along with the IG, called for reform, correction, improvement, revision in our system of protections. Our files in OPRR are replete with unfortunate incidents gathered through the years. In calling attention to those incidents, I'm talking about the numerator of a ratio and in the denominator is a huge, huge volume of research activity as we pursue new knowledge in biomedical and behavioral research. I'm just trying to put the problems that we do see and that we're here to call attention to in some sort of perspective. I'm

not explaining them away by any means, nor would I want anyone to take away the impression that I'm here to say there's no problem.

With regard to the fenfluramine——

Mr. SHAYS. If the gentleman would suspend a second, I just want to make sure I understand. You say your files are replete with what?

Mr. ELLIS. Our files are replete with investigations of allegations about problems in human subjects research. Sometimes those allegations prove true in part or in whole and we take action.

Mr. SHAYS. How many onsite investigations have you had in the last year?

Mr. ELLIS. In the last year, we've done one onsite investigation.

Mr. SHAYS. Thank you.

Mr. ELLIS. With regard to the fenfluramine studies that were reported in the press in April and the topic of much discussion at the full committee's April hearing, our office is interested in the answers to the questions that you posed, that the distinguished ranking minority member posed at the outset. We are investigating at four institutions: the Research Foundation for Mental Hygiene, a component of which is the New York State Psychiatric Institution; Columbia University College of Physicians and Surgeons; the Mount Sinai School of Medicine; and the Research Foundation of the City University of New York, a component of which is Queens College, fenfluramine research with children. Our office received the first complaint, an allegation about this research in December, 1997 and we opened an investigation. We have, to date, eight separate complaints about a body of research in New York City under the auspices of these four institutions. It will be many months before we're able to conclude our investigation.

The third question, paraphrasing the chairman's question, how can OPRR properly oversee the protection of human subjects when my office's superiors are the people and the institutions that we would be criticizing? I think what you're really asking is what is the strongest foundation for the protection of human subjects in Government-sponsored research, intramurally or extramurally? And in current practice, our system of protections depends on the goodwill of the incumbents holding the position superior to my office.

Mr. SHAYS. I'm going to recognize Mr. Towns. But would you just explain what you mean by "the goodwill?"

Mr. ELLIS. By goodwill, I mean people discharging their authority and responsibility in an honorable way and recognizing that in those instances where the protection of human subjects may conflict with the mission of an agency or an office, society dictates that the protection of human subjects must come first, that the pursuit of new knowledge is optional and can be deferred. To quote philosophers and others who have gone before me, we have much more to lose by disregarding the dignity and rights and welfare of human subjects than by deferring new knowledge.

Mr. SHAYS. Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me begin by first asking the question, how many IRBs do we have in the United States?

Mr. GROB. Between about 3,000 and 5,000.

Mr. TOWNS. Between 3,000 and 5,000?

Mr. GROB. Yes, sir. Give or take.

Mr. GROB. Give or take. I guess another answer might be, nobody knows for sure.

Mr. TOWNS. Yes, yes. How many of these are certified?

Mr. GROB. I have to defer to NIH for that.

Mr. TOWNS. Now, you can understand why I don't like the word "reform." How many?

Mr. ELLIS. The Office for Protection from Research Risks does not certify Institutional Review Boards. We assure institutions—and part of that assurance is a roster with the names of the specific members. There's no question in my mind we know how many Institutional Review Boards there are under our area of authority. We have their names and addresses. We communicate with them regularly. Under our area of authority, there are let's say 3,700 IRBs or so. I can get you a precise number.

Mr. TOWNS. Let me ask——

Mr. ELLIS. Yes.

Mr. TOWNS [continuing]. If I say we do not know how many and we don't know how many are certified, I think that that would be a pretty accurate statement, wouldn't it?

Mr. ELLIS. If you're speaking about in the United States as a whole, that would be correct.

Mr. TOWNS. It's the United States we're talking about.

Mr. ELLIS. That's right.

Mr. TOWNS. These are the U.S. Members of Congress, do you know what I mean?

Mr. ELLIS. The Federal authorities over IRBs are partitioned in a most complex way. I was trying to go as long as I could without referring to this chart because it may send us spinning in confusion but my job is to make it clear. The universe of involvement of human subjects research is broad, and the outer limits are actually unknown. Within the universe of human subjects in research, there are two statutes that are especially pertinent: first, the Food, Drug and Cosmetic Act, and the Food and Drug Administration discharges its responsibility under that statute to protect human subjects when an investigational drug, device, or biologic is involved. Second, the Department of Health and Human Services, under the Public Health Service Act, discharges its responsibility when HHS funds or support are involved. And that's where my Office for Protection from Research Risks sits. And the jurisdiction of those two statutes overlap.

The Food and Drug Administration and the Department of Health and Human Services have overlapping jurisdiction. We share congruent regulations on informed consent and Institutional Review Boards. The Food and Drug Administration conducts numerous IRB inspections. Our office conducts very few site visits.

Now, I must also mention that the Department of Health and Human Services is formally yoked with 16 other departments and agencies. We are in lock-step. We share a common rule. And so that was the point in my testimony this morning that any change in regulation for protection of human subjects that we might talk

about at the Federal level must be agreed upon by 17 departments and agencies.

Beyond these domains of Federal protection of human subjects in research are numerous human subjects, an unknown number. Mr. Grob mentioned some of the research pursuits. Colleges and universities not receiving Federal research funds. He mentioned in-vitro fertilization clinics, there are some 300 around the country. At some of these sites, there's human subjects research going on; some weight loss or diet clinics; some physician offices; some dentist offices; some psychotherapist offices; some legal services clinics; some corporate or industrial health, safety, and fitness programs; some developers of genetic tests; and some websites.

So our files are also replete with examples of human subjects involved in research that are not formally protected by the twin protections of IRB review and informed consent. These are very frustrating cases for our office because our authority stops the moment we determine that there are no Federal funds involved. Now, there's nothing different about the human subjects that stand beyond the perimeter of current Federal authority. If there is, please tell me because I don't believe there is.

The NBAC, in its wisdom, the first thing out of the box, before any real analysis was done——

Mr. TOWNS. I'm going to have to stop you because——

Mr. ELLIS. Yes.

Mr. TOWNS [continuing]. You said all that to say we do not know. And I understand that we do not know how many. So I have to cut you off because the caution light is on there.

Let me just go to some others. We have a situation where the researcher was a State employee who worked at the New York Psychiatric Institute, a teacher at Columbia University, one of our finest institutions, and the board of a private organization that provided the research grant, would anyone on the panel like to comment on her possible conflict of interest and the actions the IRB should have taken in this situation? Anybody? Dr. Ellis, Meslin, Dr.—you know, let me——

Mr. ELLIS. I'll be pleased to respond.

Mr. TOWNS. I can't get any volunteers. That bothers me, Mr. Chairman.

Mr. ELLIS. I'll volunteer. This answer isn't what you're seeking at the moment. But one witness, myself, can't comment on this case because we're currently investigating, as I described, and I wouldn't want to compromise the integrity of the investigation to come. So I may not, I cannot volunteer an opinion on it.

Mr. TOWNS. But generally in a case like this, I know we don't know dates, and months, and that kind of thing, generally how long does an investigation like this take?

Mr. ELLIS. Well, we have one full-time professional person, a physician in the compliance business in our office. We currently have about 70 open investigations. This one is a complex one, four institutions, eight complaints. I have to give the estimate of many months.

Mr. TOWNS. Months. It is my understanding that the IRBs are required to have five members, with one non-medical member. I'm concerned about the proportions of such an arrangement. If Federal

law only requires one non-medical member, couldn't a board dilute that member's vote simply by expanding the numbers of other members? Shouldn't the number of non-medical members proportional to the number of medical members?

Mr. GROB. Mr. Towns, I'd like to answer that question and volunteer a partial answer to your previous question. One of the threats we found against the proper functioning of the IRBs are the conflicts of interest that are inherent on the boards. The point you're making is a very good one and, as a matter of fact, many boards do have more than the five members and those that may still only have one non-scientist member of the board are a very small number of those. And we found that as one of the weaknesses to be overcome in the board structure.

Something that is related to the point you raised previously is actually, I think, even broader than the point that you raised, which is, many members of the boards of the IRBs do have an association with the university they work for or the sponsoring organization. So whether they think of themselves as having a conflict of interest or not, whether they're conscious of it or not, the system is set up in such a way that there are, in fact, people on the board making decisions about research that will affect the institution they work for in terms of how much research funds it receives, things of this nature. So we see that as an inherent problem as well. The teacher you mentioned is just one particular example of it; it's actually a somewhat broader problem in our view.

Mr. TOWNS. Let me just sort of move very quickly. As a general matter, should there be special protection involved in medical research involving human subjects who cannot legally consent, such as children, mentally disabled, or incompetent individuals?

Mr. GROB. Absolutely, absolutely.

Mr. TOWNS. I want Dr. Meslin.

Mr. MESLIN. The Commission has been deliberating about this subject for the last several months in the context of its report on research involving persons with mental disorders that may affect decisionmaking capacity. In my written testimony and my oral testimony, I indicated some of the additional protections that the Commission is now considering, including not only supplementing IRBs with those individuals who have special knowledge of this population, but also familiarity with the individuals themselves, either family members or members of advocacy groups.

Our recommendation, our proposed recommendation that the common rule may be amended, is still up for discussion. The Commission has not decided exactly on the way it wishes to go because it has a number of potential recommendations relating to State and other Federal activities. In Dr. Ellis' chart, you'll notice that the yellow box indicates the components of the common rule. One of the issues that has been discussed is whether an additional subpart might be added so that special protections for that population would be available in law.

Mr. TOWNS. You know, I really have a great difficulty here with the whole thing about reform. We have so many problems here, we have to destroy this one and start over. Can you explain to us the ethical problems associated with using children in research that

presents more than a minimal risk of harm and does not provide any direct benefits to the subjects involved?

Yes, Dr. Meslin.

Mr. MESLIN. The Commission is not currently addressing research on children as vulnerable subjects. The focus of its two reports now are on persons with mental disorders that may affect decisionmaking capacity, and human biological materials. It is possible in its comprehensive report, that I mentioned in my testimony, that it will address broader questions of structure and function with respect to the system that may include questions about children. But at this point, they have not been addressed directly.

Mr. TOWNS. I'm concerned about situations where you give gifts, give toys to children. This to me is a problem. And the other part I think that I need to comment on, Mr. Chairman, is that I see here that in some of the research that's going on that the doctor is so involved in the research, and in trying to move forward that you need an outside person to sort of oversee. And we don't have IRBs that are certified. We have all these things, "I'm involved in my research and I'm so involved in it that there's other things that I should see, other signs I should see in terms of this patient's overall health at the time based on what we're doing, and, of course, I am so involved that I don't even think about that." So I think that this patient also needs an independent physician to look at the overall health of the patient rather than to just have a person that's in charge of research and that's all. And I think that when we talk about reform, I think we have to tear it down to be able to put these kind of things in place.

Mr. MESLIN. If I might add, in our report that I just described, which is available on our website as a staff draft and has been up since our last meeting, the website is bioethics.gov, you will note that there are a number of protections of the kind that you have just described, Congressman Towns, including independent consent monitors and other individuals not associated with the research. There are at least three or four in the staff's proposals to the Commission and we expect to get public commentary on those very soon.

Mr. TOWNS. Let me, Mr. Chairman, just have a few more seconds. Do you think there's a problem with IRBs recommending that children be given toys? How could that affect the subject's voluntariness? Yes?

Mr. ELLIS. Well, I'll respond if no one else wishes to.

Mr. TOWNS. And I'm looking at the chart that—go ahead, go ahead.

Mr. ELLIS. Do you want me to explain what the chart shows? I can't see it from here.

Mr. TOWNS. Yes. That's the form that the kids sign.

Mr. ELLIS. This is a Child's Assent Form.

Mr. TOWNS. Yes.

Mr. ELLIS. And it says, among other things, "I don't have to do anything I don't want to. Everything will be explained to me." And I think the sentence that you're focusing on is, "My family will get paid and I will also receive a gift." The Federal regulations require that informed consent for adults, be sought only under circumstances that minimize the possibility of coercion or undue influ-

ence, and remuneration for time spent in a research study is acceptable. The IRB has the authority to decide what level of remuneration is acceptable. This should not be thought of as a fee for submitting to risks in any way. I'm using the word "remuneration" for time spent. It would not be acceptable to scale the remuneration to a higher level when the risk is greater. That's not the point of the payment here. It's for time spent. It would be acceptable to scale the remuneration higher if more time is going to be involved.

Now, for children this becomes an even more sensitive issue. Money, as this indicates, a gift, may be involved. And I'm not making any comments, I must say, on the particulars of this study. I do not know, frankly, where this Child's Assent Form came from. I don't want to compromise any future thoughts that my office may express about this particular study. But the provision of remuneration to adults or children is a very sensitive issue. We see excesses here. Sometimes if we don't like what we see, we call attention to it.

Mr. TOWNS. Let me go to another one. Do you think there's an ethical problem with using law enforcement or probation office personnel to interview participants, especially where the study does not involve issues of crime or law enforcement?

Mr. ELLIS. I'm going to decline to answer that because this is so close to a case that we are investigating. I prefer not to express an opinion on that.

Mr. TOWNS. You know, Mr. Chairman, does anybody want to answer this question? Does anybody? Maybe we can go to the audience or somewhere. This is ridiculous. We're here with a hearing trying to get information to deal with a problem and everybody—I don't understand.

Mr. Chairman, were they aware of what this hearing was on? They were? OK, well, then I would like to say for the record that my questions are not being answered and I regret that because I think that we have a very serious problem and it's an opportunity to try to correct it or do something about it. And for some reason or another we're not getting the kind of information that we're requesting. So the questions are not being answered, Mr. Chairman, and I regret that.

Mr. SHAYS. Well, we'll have the second panelists and we'll also allow them to answer those questions. Dr. Ellis, let me just ask you, how many professionals do you have on your staff?

Mr. ELLIS. Our office is about 30 people total, professional support staff. We oversee protection of human subjects and animal subjects in research. I think you're probably most interested in professionals relating to human subjects.

Mr. SHAYS. Yes, don't even wonder, yes. So how many dealing with human beings?

Mr. ELLIS. We have probably 13 to 16 professionals. I don't have the chart in front me. We have support staff and professionals.

Mr. SHAYS. So about half?

Mr. ELLIS. A little more than half dedicated to human subject protection.

Mr. SHAYS. And half deal with animals?

Mr. ELLIS. That's right.

Mr. SHAYS. How many investigators do you have dealing with human subjects?

Mr. ELLIS. We have one full-time professional and portions of two or three other professionals.

Mr. SHAYS. When you say that I have a certain feeling when I hear it, do you have a certain feeling when you say it about the absurdity of it?

Mr. ELLIS. Absurdity is your word. Meager might be another word, meager resources given the effort.

Mr. SHAYS. Maybe pathetic. We've conducted 13 hearings on Gulf war illnesses and almost 700,000 of our soldiers were given an experimental drug, pyridostigmine bromide, PB. I would like you, Mr. Grob, if you would tell me what would the process have been for 700,000 of our soldiers to be given, ordered, commanded to take an experimental drug? What would be the process that should be followed before that happens?

Mr. GROB. It would not have been acceptable for them to be ordered or commanded to take an experimental drug. That would violate the code of informed consent, and voluntary consent to participate in experimental——

Mr. SHAYS. I want you to pull that mic over. I want you to say it loud and clear. Pull that mic up, speak right into that mic.

Mr. GROB. It would be contradictory to the principles of research for someone to be ordered to take an experimental drug, a basic principle is that it should be voluntary and that there should be informed consent.

Mr. SHAYS. Dr. Yessian.

Mr. YESSIAN. I agree. Absolutely.

Mr. SHAYS. Dr. Meslin.

Mr. MESLIN. I would agree as well.

Mr. SHAYS. Dr. Ellis.

Mr. ELLIS. Individuals must volunteer, not be compelled to be research subjects.

Mr. SHAYS. This wasn't the private sector. This was the Department of Defense. Was there a local IRB for the Defense Department? Mr. Grob.

Mr. GROB. I don't believe there would be a local IRB for the Defense Department.

Mr. SHAYS. Would there be any IRB?

Mr. GROB. There's not.

Mr. SHAYS. Dr. Yessian.

Mr. YESSIAN. I don't know what the situation—how that was reviewed. I just don't know.

Mr. SHAYS. Dr. Meslin.

Mr. MESLIN. We did not study that case so I can't comment on the specifics. We are, as I mentioned, looking at all Federal agencies to determine whether they are in compliance——

Mr. SHAYS. Dr. Ellis.

Mr. MESLIN [continuing]. With Federal rules.

Mr. SHAYS. I'm sorry.

Mr. ELLIS. That would be a question for the Department of Defense, Mr. Chairman.

Mr. SHAYS. Does it raise a question in your mind? You were talking, Dr. Ellis, about IRBs and you were talking about protecting

human beings and you were emphatic about the system isn't in jeopardy, emphatic. And we've had 13 hearings where we've had veterans all lined up and they were told they were ordered to take this experimental drug. We were told they were not told about its consequences. We were told they could be court-martialed if they did not take these drugs. Does that trouble you, Dr. Ellis?

Mr. ELLIS. First, my emphasis on the system not being in jeopardy was merely to parrot the Inspector General's final conclusion, which did not include the word "jeopardy" and she pointedly turned away from it.

To get to your larger question, my office is troubled any time that there is the possibility of coercion of an individual to be a research subject.

Mr. SHAYS. Dr. Yessian.

Mr. YESSIAN. Yes, Mr. Chairman, I'd like to add some perspective on that issue if I could. And I hear Congressman Towns' frustration too. We changed the title of our report. We did not change our central finding. We have one major finding. The finding is that the effectiveness of IRBs is in jeopardy. That's there loud and clear in that final report. When we say it's a time for reform, we're saying the current status quo is inadequate. We're not talking about tweaking changes at the edges. We're saying major change needs to be made. And our litany of findings reinforce that sense of how the effectiveness of the system is in jeopardy. We try to be balanced here and not be overly alarmist but at the same time we're offering a very loud warning signal. There are problems here and they warrant near term, immediate attention.

Mr. SHAYS. Thank you. Would someone on the panel tell me what pyridostigmine bromide is and what it's used for? Dr. Meslin.

Mr. MESLIN. I'm sorry, I can't. That's not in my area of specialty.

Mr. SHAYS. Dr. Ellis.

Mr. ELLIS. It's not my area of expertise, I'm sorry.

Mr. SHAYS. Dr. Yessian.

Mr. YESSIAN. I'm sorry, what was it used for?

Mr. SHAYS. What is PB used for in its general use?

Mr. YESSIAN. Oh, I don't know.

Mr. GROB. This is not a case that we studied.

Mr. SHAYS. How does the OPRR review the use of advanced directives to address the difficult issue of participating in challenge studies of mentally ill patients who must discontinue medication before entering the study?

Mr. ELLIS. The Department's regulations require legally effective informed consent. In some States, such advanced directives—I'll call them advanced research directives—may be legal under State law and that's something that the local IRB would be required to know. It's not something that the Federal Government would necessarily know. So, to answer your question, OPRR generally would not be in a position to be reviewing the use of an advanced directive for research.

Mr. SHAYS. Before calling on the other Members, I just want to understand why I shouldn't be concerned that we don't know how many IRBs are out there and how many patients are involved in the thousands and thousands of studies that are supposedly being overseen by these IRBs that range, give or take, 3,000 to 5,000.

Mr. GROB. Mr. Shays, you should be concerned about all of that. We have not changed a single finding in our report. We haven't changed a speck of the evidence. We did not turn away from anything that we had in the draft report. I will tell you that it was my recommendation to change the title because I thought——

Mr. SHAYS. I'm not into the title anymore.

Mr. GROB. OK.

Mr. SHAYS. This system is in jeopardy.

Mr. GROB. It is in jeopardy and it's a serious problem and we have to address it. We were just hoping that no one was challenging the need for reform and that a word change might help focus people's attention on what to do about it. But if I have to emphasize it, let me say right now, this system is in jeopardy and it needs major overhaul.

Mr. SHAYS. Thank you. Dr. Yessian, do we need to know the number of IRBs there are?

Mr. YESSIAN. I think we do. It's one point. But I think that it would help to have them registered. Certainly.

Mr. SHAYS. Dr. Meslin, would you answer that question?

Mr. MESLIN. The knowledge of IRBs is extremely important if we're going to be ensuring that we understand how well the system functions. The IRB part of the system is the linchpin that has been said by many. So without knowledge of where they are and what they're doing, it would be difficult to fully understand how well the system is working.

Mr. SHAYS. Dr. Ellis.

Mr. ELLIS. OPRR knows the names and addresses and the membership of every institutional review board under its formal Federal regulatory authority. Period. I think, Mr. Chairman, what you should be concerned about are the human subjects, the activities going on in areas outside of formal Federal regulatory authority. These are the most vulnerable human subjects.

Mr. SHAYS. With regards to the non-scientific member on the board, why should I feel comfortable that there is only one non-scientific member and feel that that's adequate? Yes, I'm going to ask each of you. We're just going to go right down the line.

Mr. GROB. You should not feel comfortable about that.

Mr. SHAYS. Dr. Yessian.

Mr. YESSIAN. Absolutely not. And there are other countries that have half of their IRB members who are lay members.

Mr. SHAYS. Dr. Meslin.

Mr. MESLIN. In our report, we're recommending additional members that are knowledgeable about the research that need not be scientists.

Mr. SHAYS. Dr. Ellis.

Mr. ELLIS. OPRR strongly recommends more than minimal compliance with the IRB membership requirements, not just in terms of the non-scientists——

Mr. SHAYS. I want you to address the non-scientists.

Mr. ELLIS. We strongly recommend more than minimal compliance, which is one.

Mr. SHAYS. Could I start an IRB if I wanted to?

Mr. ELLIS. The answer is yes if you are interested in receiving funds from any of 17 departments and agencies, or if you're going

to be investigating a drug, device, or biologic and seeking FDA approval, you'll have to comply with Federal regulations. If not, you can do whatever you want and involve human subjects in this country in research.

Mr. SHAYS. Dr. Meslin. I would have the ability, I don't have to be certified, Dr. Ellis.

Mr. ELLIS. No.

Mr. SHAYS. Dr. Meslin, I could start an IRB?

Mr. MESLIN. You could start an IRB.

Mr. SHAYS. Would I have to be certified?

Mr. MESLIN. Not to my knowledge.

Mr. SHAYS. Dr. Yessian.

Mr. YESSIAN. There's no real certification anyway. There are the assurances for the projects that are funded by the Government, but no certification requirement.

Mr. SHAYS. Mr. Grob.

Mr. GROB. Not at all.

Mr. SHAYS. Thank you. Mr. Barrett.

Mr. BARRETT. Thank you, Mr. Chairman. Dr. Ellis, maybe you can help me with just—bring me up to speed up here. The purpose of your organization is to oversee the IRBs, is that correct?

Mr. ELLIS. Our main purpose is to provide education to Institutional Review Boards, their staffs, their researchers. We implement the Department of Health and Human Services regulations for protection of human subjects, and those describe the function, activities, membership of IRBs within the arena of research conducted or supported by the Department of Health and Human Services.

Mr. BARRETT. OK, what is——

Mr. SHAYS. Dr. Ellis, you're Office of Extramural Research, my understanding is that's NIH studies done outside NIH and so there's an intermural research person, your equal, who oversees anything NIH does within house.

Mr. ELLIS. Actually, our office has the same formal oversight over the Nation's largest biomedical research program, the National Institutes of Health intramural program. We relate to that large program in the very same way we do to Johns Hopkins——

Mr. SHAYS. I'm not saying you don't relate but do you have——

Mr. ELLIS. We have the formal regulatory oversight authority.

Mr. SHAYS. You have one inside and you have one outside and you look at the outside research done funded by NIH, is that correct?

Mr. ELLIS. Yes, and we also look at the intramural program. We have formal regulatory authority over the intramural program.

Mr. SHAYS. OK. Is there another body that also does intramural as well?

Mr. ELLIS. There is an education office within the intramural program, NIH's Office of Human Subjects Research, but they do not—we hold the regulatory authority over the NIH intramural program despite being located in the Office of Extramural Research.

Mr. SHAYS. OK. That's real simple. [Laughter.]

Mr. BARRETT. Thank you for clarifying that for me, Mr. Chairman. [Laughter.]

Mr. SHAYS. I try.

Mr. BARRETT. From your earlier comments, I inferred that you are the person, or your organization is the one that is examining this New York situation that Mr. Towns has——

Mr. ELLIS. That's correct. We have a formal investigation.

Mr. BARRETT. Again, to help me understand this. What type of enforcement procedures are at your disposal?

Mr. ELLIS. Well, we don't have any reach-back sanctions. We don't have any punishment for past misdeeds available to us. Our authority, let's say, is forward-looking and so without making any prejudgment of the particulars of this case, in general, our office approves a formal written agreement, we call it an "assurance," with the research institution. And if, in our judgment, the trust that that agreement is based on has been violated, we can restrict that assurance. In the extreme, we can suspend the assurance.

Mr. BARRETT. When you say "suspend assurance," are you talking about an action taken against the review board or against——

Mr. ELLIS. Well, it would be against the institution. We hold the institution responsible for all the activities that occur there. In the case of a suspension of an assurance, Federal human subjects research dollars cannot flow to that institution.

Mr. BARRETT. So there are no sanctions then whatsoever that are available to the review board?

Mr. ELLIS. In the sense that you're asking, which I think is a punishment, extracting a fine, something like that, no.

Mr. BARRETT. Is that your understanding from the IG's office?

Mr. GROB. Correct.

Mr. BARRETT. So if you have an IRB board, is it IRB, that is completely screwed up, nothing happens?

Mr. GROB. There are no sanctions.

Mr. ELLIS. Well, we might make a determination that that institution cannot continue to be assured, and I must say that is viewed by the institutions as a death penalty. It's extremely serious. The Federal research dollars stop flowing if we make that judgment.

Mr. BARRETT. And I understand that but it seems that your organization is far less likely to give a death penalty. I just don't see you doing it.

Mr. ELLIS. The last time that our office suspended an assurance for human subjects research, I believe, was in 1991.

Mr. BARRETT. Let's turn to the particulars of this New York case, and I realize you can't comment on a lot of this so maybe some of the others can help me with this. A couple of things that Mr. Towns' has made reference to that jump out and maybe Dr. Meslin, since you're a bioethicist. Why would you have a study that excludes white people, white kids?

Mr. MESLIN. Well, from my perspective, as a bioethicist, not speaking on behalf of the Commission, there would have to be a pretty good justification for excluding any population from a study.

Mr. BARRETT. Dr. Yessian.

Mr. YESSIAN. I would certainly say the burden of proof would be on the ones proposing it. There should certainly be a bias against that.

Mr. BARRETT. Mr. Grob.

Mr. GROB. The subjects are supposed to be representative. It's not consistent with the principles.

Mr. BARRETT. I looked at it and I think as probably Mr. Towns and others did, I thought well, what's going on here, why would they write down that they're excluding white kids? And I'm maybe as baffled as Mr. Towns. Can you think of any reason to?

OK. Well, let me go on then because it wasn't just the exclusion of the white kids, then you had a memorandum that was written by the IRB, dated March 2, 1994, and point No. 5 is "Inclusion and Exclusion:

A. Reformat the listing of the inclusion criteria so that item number 4 for the fenfluramine procedure is the last item. Make explicit that youngsters are recruited from the main study." It seems to me that the concerns of the person writing this memorandum were more how this form looked than what the procedure was. In other words, it seemed it was a sort of totally bureaucratic, let's make sure that people don't know that this is what we're doing, as opposed to let's clean up the study. And I think that that's underscored by the fact that these comments, as I understand it, came several weeks after the subjects were chosen. So you were sort of working backward and the subjects were already chosen so you basically drop the ethnicity issue because you already had all the kids that you need. And I think that as we look at this, if you're looking at some sort of sanctions, there has to be some sort of sanctions for the IRBs. And that was more of a comment than anything else.

Again, Dr. Meslin, for you, the question I have and I think that Mr. Towns raised a very good question. If I'm a parent and I have a child that has been adjudicated in the juvenile courts system and my probation or parole agent for the child is in there and starts asking me about another sibling, I'm probably going to assume that this probation or parole agent has some sort of power over me. And I'd like you to comment on the ethical nature of having the probation or parole agent be the one that's making the inquiry here.

Mr. MESLIN. As you know, the Commission is not addressing this particular study——

Mr. BARRETT. I understand that.

Mr. MESLIN [continuing]. Directly. But speaking from my own personal perspective, any time you're in a situation where there's the potential for coercion or the potential to reduce the possibility of voluntariness, you're in a situation where that research can be judged to be ethically suspect.

Mr. BARRETT. Dr. Ellis, let me ask you this. What is the mechanism for ensuring that that does not occur?

Mr. ELLIS. Again, I'd prefer not to comment on——

Mr. BARRETT. On this case, I realize that. I'm not asking you to comment on this case but in general what is the mechanism to make sure that you don't have undue pressure placed on potential participants in the study?

Mr. ELLIS. Well, the IRB has several tools available to it. Under current regulations, it can mandate a consent monitor, a third party being present to monitor the consent process. That's the sort of additional protection that we look for IRBs to invoke when one can anticipate that there will be sensitive situations.

Mr. BARRETT. Yes, Dr.——

Mr. YESSIAN. Congressman Barrett, I think our larger inquiry really reinforces in general terms a couple of the points you're mak-

ing specifically in this case. One is had there been more lay members on this IRB, they would probably be asking the very same kind of questions that members of this subcommittee are. And pressing the point more vigorously. It doesn't take scientists to ask these questions.

A second point—and you were asking about informed consent forms, and that's the one for the children but they had a larger one for the family, I believe—IRBs pay great attention to informed consent forms, to the language of them. And many of them go on 10, 15 pages and are often more about protecting the liability protections for the institution than they are about anything that would help us assure that the human subject actually understands what he or she is getting into. The IRBs have very little basis and do very little actually from what we've seen to be able to say that human subjects understand what their signing up for and to understand how the process works at the point that a consent is being obtained. That's a whole other thing.

Mr. BARRETT. If I could followup on that because we have the Assent Form here. I think if you showed any 7- or 8-year-old in the world a form that said that you're going to give a gift and ask them to sign it, assuming they could sign their name, they would sign their name. What legal validity do you see that form having in light of that?

Mr. YESSIAN. I'm not a lawyer but it wouldn't seem to be much to me.

Mr. BARRETT. Dr. Meslin.

Mr. MESLIN. Well, I think the only thing to add is that there is a primary concern when you propose to conduct research on individuals who may not have the legal capacity to consent, leaving aside whether they may have the mental capacity to consent, as to what constitutes an unfair inducement or what constitutes a disclosure of information that might otherwise make them do something they wouldn't want to do. And compensation has been one of the major issues in the history of research ethics for the last 20 years as to be one of those potential inducements. It's not limited to children.

Mr. BARRETT. I agree. And, again, this forum also points out that the chart says, "I will get the child some new video games." Now, you could probably get kids 10 or 11 to sign this form as well. But I think that this underscores the need to have some sort of oversight. I can tell you in my own community one I had trouble with was actually a cocaine study that used regular cocaine users and told them that they were going to get paid. I think that we have to have a better mechanism for looking at the ethics for some of these issues.

I think my time has expired so I yield back the remainder of my time, Mr. Chairman.

Mr. SHAYS. Before I yield to Mr. Kucinich, quickly I just wanted to ask one question. When I was here before, I asked Dr. Ellis about, and I think you mentioned that there was a file or files on people that had either objected or been concerned about the treatment they got in these tests. Is that file or are those files available to the Congress?

Mr. ELLIS. One minor correction. They're arranged by institution, that's our unit of governance. But any closed investigation is available under the Freedom of Information Act.

Mr. SHAYS. Well, I think that Congress might like to take a look at some of those files to see how pervasive this problem is. Mr. Kucinich.

Mr. KUCINICH. Thank you, Mr. Chairman, for a few brief questions before we go and vote. There are ethical factors and there are common sense factors too. I mean, think about this. You're studying a population which you presume to have certain mental deficiencies and then you give him an opportunity to participate in the study group promising them gifts. This type of a scenario is not simply a matter of being unethical, it's anti-democratic because there has to be a symmetry between ethics and democratic principles. And what's happening here, this system is out of control because democratic principles are not being institutionalized into the structure of the system, which is the reason, Mr. Chairman, for this oversight. It's imperative that there be oversight here because what we need to study is not necessarily the behavior of the patients, but the behavior of the Institutional Review Boards.

I have a pointed question here. Dr. Ellis described corrective actions mandated by the OPRR to correct IRB deficiencies at the institution which conducted a problematic study of schizophrenia. Now, I don't believe you mention in this highly publicized case that the OPRR investigation was prompted by the suicide of a study participant. Now, on what basis do you conclude that the IRB system works well when the only real data you get comes in the form of complaints and reports of catastrophic events, like the death of a study participant.

Mr. ELLIS. The investigation you're referring to was actually prompted by two complaints, one of which you've described. And I don't think anyone would conclude that the Institutional Review Board in that case had discharged its responsibility properly. We faulted the institution very seriously. The institution was put under very close scrutiny for some number of years and that was not a case that anyone at the institution, or anyone anywhere was pleased about. It's not something that anyone would take lightly. And we invested much effort in helping that institution to today become, and this is some 4 years after our investigation was completed, what I would describe as a benchmark institution. That's not unknown that institutions that feel pain end up responding with great gain. And that institution now has some of the most sophisticated additional protections for subjects with questionable capacity to consent. That institution can describe better for itself, but just to summarize: third party monitoring of the consent process, a waiting period where there needs to be some hours, maybe a day passes before consent is taken when there's questionable ability to consent. So that institution now is a thought leader in this area.

Mr. SHAYS. Mr. Kucinich.

Mr. KUCINICH. Well, we probably have to go vote.

Mr. SHAYS. We have about 5 minutes left. Would you like for them to remain so you can continue questions?

Mr. KUCINICH. I would. I'd like to continue.

Mr. SHAYS. OK. We'll be back in about 20 minutes so have a cup of coffee and we'll be back. We'll stand in the recess at the fall of the gavel.

[Recess.]

Mr. SNOWBARGER. We're going to call the meeting back to order. I would like to indicate to those of you that have been here all morning and wonder where the chairman is, he asked me to give you his apologies. He is headed home to attend his daughter's high school graduation. So I'll be chairing the rest of the meeting.

As I understand it, Mr. Kucinich, you had some questions left?

Mr. KUCINICH. Thank you very much, Mr. Chairman. This is in regard to Dr. Meslin's testimony regarding the Commission conducting a study of research subjects with impaired decisionmaking capacity and an interim report due within 3 weeks. Now, I understand in this report a key issue is challenge studies in which schizophrenics are deliberately made worse. And many studies conducted on mentally ill patients are designed to make them worse in order to evaluate the causes and the course of their diseases. There have been concerns raised within the psychiatric community about the ethics and limited therapeutic utility of these studies for understanding or treating this devastating disease.

Could you tell us how do the Inspector General, the OPRR, and the NBAC view the ethical and scientific utility of studies which deliberately make mentally ill patients worse?

Mr. MESLIN. I can certainly speak on behalf of the Commission in the deliberations that it has had so far. We've heard testimony from patients, from their families, from investigators, from regulators, and others on a variety of subjects. Most recently, at our meeting in Cleveland last month, we heard testimony from investigators describing the scientific justification for symptom-provoking or challenge studies. In the staff draft, which is available, as I've said, on our website, we have tried to make clear our concerns with respect to providing adequate justification for selecting these kinds of studies. We have been concerned both by the testimony that we've received and have tried to indicate in our ongoing work that studies where there is an attempt to cause harm, raise serious moral concerns. And we are now developing recommendations, as I've described in my testimony, for requiring of investigators that they provide a justification that is scientifically accurate and ethically acceptable for those studies.

Mr. KUCINICH. Are you aware of any IRBs who did research with children in the area of Prozac?

Mr. MESLIN. No, I am not.

Mr. KUCINICH. Dr. Meslin or anyone else on the panel can answer this question. Both the GAO and HHS Inspector General have called for registration of 3,000 to 6,000 IRBs in the United States. As we've discussed, the exact number is unknown since the IRBs do not have to notify the FDA of their activities if they're not overseeing clinical trials in support of a drug, or device, or biologic application. Now, NIH does not need to be notified. The NBAC, in its 1997 annual report, called for the twin protections of IRB review and the informed consent of all human subjects of research. Now it appears that the Government requires better accounting of rodents in clinical trials than people. Now what prevents the OPRR

and the FDA from instituting a registry of IRBs to facilitate oversight and inspection?

Mr. ELLIS. Let me answer for OPRR. We do currently have the name and address of every IRB that's under our authority. I can't speak for the Food and Drug Administration, but I do note in the FDA's response to the Inspector General report that the FDA seems quite interested in moving forward with some type of registration. Again, that's for them to address but it's in the documentation in front of us.

Mr. KUCINICH. Now, so you're saying that constitutes a registry, keeping the name and address, is that—I mean what other information?

Mr. ELLIS. Our office has the name and address of every Institutional Review Board under our jurisdiction. We want to have that. We need to have that because we want to communicate with them. We send out lots of information in an educational mode to them. The Food and Drug Administration, I don't believe has what's called a mailing list of every IRB under its jurisdiction but in their response, their formal response to the Inspector General, there's language there that seems to express interest by the FDA in pursuing such a registration.

Mr. KUCINICH. Well, just as a followup, how does OPRR view the use of advanced directives to the difficult issue of participation in challenge studies and especially when we're talking about mentally ill people who must discontinue medication?

Mr. ELLIS. Our regulation——

Mr. KUCINICH. Before entering the study?

Mr. ELLIS. Our regulation, the HHS regulations, require legally effective informed consent. That can take several forms. Obviously, the consent of the competent research subject. In some States, the State law describes other ways to obtain consent through legally authorized representatives, or, perhaps, through an advanced research directive. The Federal Government does not dictate to the States the particulars of how consent might be obtained other than to say that it must be legally effective and that's a reference to prevailing State or local law on consent.

Mr. KUCINICH. Thank you, Mr. Chairman.

Mr. SNOWBARGER. Just a real quick question here. In my reading on this, it sounded like there are times where the treatment that is being overseen by an IRB is—well, I used the wrong word already and that was "treatment"—that the research that's being done is non-therapeutic in nature. In other words, it is basic science to try to determine how a particular treatment might affect a human subject. And, again, my understanding is that when a person is desperately ill, they're going to try anything that they can leading them to think, whether it's correct or not, that what they're going through is therapeutic treatment. How can an IRB ensure that patients with life-threatening illnesses understand that these clinical trials that are conducted to approve a new drug or to advance a practice of medicine are not necessarily intended to directly benefit the participating patients?

Mr. ELLIS. I think that patients with life-threatening illnesses are among the most vulnerable potential research subjects. One scholar at Boston University, George Annas, has proposed that

these patients never be used in research. That's an extreme view. Shy of that, this is a potential subject population where we would like for IRBs to redouble their efforts in providing additional protections and anything that can be conveyed to the potential subject that helps the person understand that the person is being asked to participate or accept an intervention that is not known to work. It's not a treatment. If it was known to work it would be unethical to proceed and not deliver it. So this is the so-called "therapeutic misconception." A potential research subject does not always know or understand, although they should, that this is an intervention that is not known to work. It's being done for the purpose first of obtaining generalizable knowledge, and if incidentally it benefits the subject, well that's all the better. So this is a very vulnerable patient population.

Mr. SNOWBARGER. I feel like what you just said was that I asked a valid question. I didn't hear an answer.

Mr. ELLIS. We look for IRBs to redouble their efforts to provide additional protections when a research study proposes to involve patients with terminal illness.

Mr. SNOWBARGER. Do we have any ideas what those extra steps might be?

Mr. ELLIS. Well, the regulations provide for, for instance, a consent monitor, a third party to be present to monitor the interchange of information. IRBs can employ that right now. Some of them do.

Mr. SNOWBARGER. Some of them do but not all. Well my other question is if it was inherent in the way it was asked. We talk about patients with life-threatening illness, and somehow that affects the judgment that they can make on that treatment as well. Any other of the panel members care to comment on the question?

Mr. YESSIAN. We gave a good bit of emphasis in our report to how little continuing review is done to identify the very kinds of situations you pose. That's not done often. And there are things that could be done to better understand how the consent process works at the point at which it's happening. Dr. Ellis mentioned an observer, but there—of course, these things involve resources. But there is authority to play a more active role, particularly, in riskier situations to observe how the process actually works. I might also add to look at the kind of advertisements that are used sometimes that are what is the basis—that interests the subjects for coming into the research in the first place. Some of those ads say little about risks and really emphasize the benefits.

Mr. SNOWBARGER. Thank you. Does any of the panel members care to make a parting comment? We're going to wrap up with panel one here and go to panel two. Do any of you care to say something that's come to mind in the meantime? Dr. Meslin.

Mr. MESLIN. Just very briefly, Mr. Chairman, I wanted to note that NBAC takes the substance of this hearing extremely seriously and we recognize that these are issues that are of great of importance. We are working, I think, very effectively to date and we'll be meeting next month in Portland, OR, where I can assure you that we will be raising many of the issues we've heard today. And I can certainly offer our staffs' assistance to advise and brief any

of the members of this subcommittee or their staff on our activities as we move forward.

Mr. SNOWBARGER. Mr. Grob.

Mr. GROB. Yes. Thank you, Mr. Snowbarger. I am concerned—I know Chairman Shays said he wasn't concerned—about the affects of the title change that happened between the draft report and the final report but I think I'm concerned about it now because of the gist of some of the comments that have been made here. And I would like to in parting emphasize that we stand by everything that we said in those draft reports. We offered up some language that we felt would be more conducive to getting to discussing these results. But since I won't be around when the next panel meets, I don't want anyone to forget these final words that the change to that language was not a steering away in any way from the conclusions of our study, of the findings of our study, about the inadequacy of the system that we have, or the jeopardy of that system. We stand by that. The findings are in there. And I just want to really make that very clear so that the discussions about it won't be off the mark.

Mr. SNOWBARGER. Dr. Ellis.

Mr. ELLIS. I think that we stand poised at this time to finish the job that we started 30 years ago in protecting human subjects formally and which has been evolving ever since. And it is time to establish a prevailing ethic across the land that irrespective of funding sources for the research, you don't do something to or with someone for the purpose of obtaining generalizable knowledge without asking their consent and without making sure that a group of unbiased observers—an IRB—reviews it ahead of time.

Mr. YESSIAN. I would just offer the simple point that the IRB system has done many good things over the years and is based fundamentally on system of trust. There's much that's very good about that. A good part of our critique is that along with the trust must go some verification. So how do we have a system that has appropriate degrees of verification, along with a system of trust that's there. I think the seriousness of the issues warrants that.

Mr. SNOWBARGER. Thank you, gentlemen, very much. We appreciate your input into this hearing and with that I think we're ready to go on to panel two. So we'll have a little brief interlude here while we get panels shifted around.

Before the members of panel two get too settled, we're going to have you rise again and take an oath so you might want to just remain standing for a minute.

In this second panel, we're going to have Dr. Angela Bowen from the Western Institutional Review Board; Dr. Timothy Walsh, Institutional Review Board of the New York Psychiatric Institute; and he's accompanied by Dr. John Oldham, who is the director of the New York Psychiatric Institute; Dr. Bert Spilker, who is senior vice president, Scientific and Regulatory Affairs for the Pharmaceutical Research and Manufacturers of America; Dr. Robert Levine, professor of medicine at Yale University School of Medicine, and he's speaking on behalf of the American Association of Medical Colleges; then Dr. Moreno, who's professor of biomedical ethics, the director for the Center of Biomedical Ethics, University of Virginia; finally, Dr. Paul Appelbaum, the American Psychiatric Association.

[Witnesses sworn.]

Mr. SNOWBARGER. Note for the record that all the witnesses responded in the affirmative.

And with that, Dr. Bowen.

**STATEMENTS OF ANGELA BOWEN, M.D., PRESIDENT, WESTERN INSTITUTIONAL REVIEW BOARD, OLYMPIA, WA; B. TIMOTHY WALSH, M.D., CO-CHAIR, INSTITUTIONAL REVIEW BOARD, NEW YORK PSYCHIATRIC INSTITUTE, ACCOMPANIED BY JOHN OLDHAM, M.D., DIRECTOR, NEW YORK PSYCHIATRIC INSTITUTE; BERT SPILKER, PH.D., M.D., SENIOR VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA; ROBERT J. LEVINE, M.D., PROFESSOR OF MEDICINE, YALE UNIVERSITY SCHOOL OF MEDICINE, ON BEHALF OF THE AMERICAN ASSOCIATION OF MEDICAL COLLEGES; JONATHAN D. MORENO, PH.D., PROFESSOR OF BIOMEDICAL ETHICS, DIRECTOR OF THE CENTER FOR BIOMEDICAL ETHICS, UNIVERSITY OF VIRGINIA; AND PAUL S. APPELBAUM, M.D., AMERICAN PSYCHIATRIC ASSOCIATION**

Dr. BOWEN. Thank you, Mr. Chairman. The Western Institutional Review Board commends the committee for its interest in human subject protection, and as president of Western, I am pleased to present our views concerning the oversight of Institutional Review Boards and the Inspector General's proposals.

Western was privileged to participate in the OIG's study and to review the draft report. Western was established in 1968 and is the oldest and the largest of the independent boards. This 30 years of experience has afforded us the opportunity to know the present oversight process intimately, and especially in the FDA arena.

Since the IRB regulations were implemented 20 years ago, biomedical research has changed dramatically. The expansion of technology and regulatory focus on multi-site studies for product approvals has caused the number of clinical trials to increase dramatically. This has necessitated increased staff, board expertise, and technical support to meet these needs. We have worked diligently to adapt to these changes.

While we believe that the present IRB regulations continue to be effective in providing human subject protection, it is appropriate that we should pause and re-evaluate the process at this time because even the perception of problems in the system will undermine public confidence.

The OIG has made several recommendations that we support. The recommendation to require IRBs to register with FDA and/or OPRR would improve protection of human subjects by allowing these agencies to manage their oversight efforts more effectively. It would also aid IRBs in communicating with each other and sharing information. Therefore, Western strongly supports IRB registration.

While the overwhelming majority of sponsors and investigators have demonstrated high integrity during the IRB review process, we believe it is important that these parties be obligated to inform the IRB of any prior disapprovals. Further, so that an IRB can effectively monitor the progress of research studies, it should be provided copies of all FDA and OPRR inspection reports. Finally, be-

cause clinical investigations are already subject to auditing and monitoring by other parties, information sharing between these parties and IRBs could be extremely helpful.

Concerns have been raised about the ability of IRBs to act independent of sponsors or the institution to which they are affiliated. This issue of independence applies equally to institutional IRBs and to independent IRBs.

We believe it is best to minimize these potential conflicts of interest through appropriate corporate or institutional structure that eliminates financial interest as part of the ethical review process. For example, through separation of administrative and review functions. We also support the OIG's recommendation that IRBs should include more non-scientific and non-institutional members and that all members should be adequately trained. We highly value the important role that these non-scientific members play in protecting human subjects. This composition, however, does require a very structured board member education program. We agree with the OIG that similar oversight policies between FDA and OPRR would strengthen the protection of human subjects. A common policy would result in a more efficient regulatory scheme that would improve the ability of IRBs to comply with Federal regulations.

America continues to be the international leader in both protection of human subjects and in biomedical research and development. And although congressional efforts in the 1970's established an excellent system of oversight, your review is needed to address changes in the research process and to provide consistent continuing oversight.

The central issue for IRBs is to ensure the protection of human research subjects, using efficient and consistent review processes.

We thank you for the opportunity to present our views and we look forward to continuing to work with you to protect the rights of human research subjects.

[The prepared statement of Dr. Bowen follows:]

*Statement of Dr. Angela J. Bowen*
*President, Western Institutional Review Board*

*Before the Subcommittee on Human Resources*
*of the Committee on Government Reform and Oversight*
*of the United States House of Representatives*

*Hearing On*

*"Institutional Review Boards: A System in Jeopardy?"*

*June 11, 1998*

Western Institutional Review Board® ("WIRB®") commends the Committee for its interest in human subject protection and, as President of Western Institutional Review Board, I am pleased to present our views concerning the present system of oversight covering institutional review boards ("IRBs") and our proposals to address future human subject protections. WIRB is the oldest and largest of the independent boards. It was established in 1968 and has operated continuously since that time. Our work is primarily Food and Drug Administration ("FDA")-regulated research, and the majority of our clients are small hospitals and clinical investigators who do research in private settings. We also serve as part of the University of Rochester's IRB system.

## I. PRESENTATION OVERVIEW

The Office of the Inspector General ("OIG") of the Department of Health and Human Services ("HHS") has conducted an extensive study of IRBs over the past year. This study involved the voluntary participation of a number of IRBs, both institutional and independent, and has resulted in the drafting of four reports. WIRB was one of the IRBs interviewed by OIG and was privileged to review the draft reports.

### *A. The History and Function of the IRB System*

The OIG's draft report entitled "Institutional Review Boards: A System in Jeopardy" contains an excellent history of IRBs in the scientific review process. While separate regulations govern federally-funded research and FDA-regulated research (i.e., research conducted to support FDA approval of new drugs, medical devices, and new food substances), the IRB responsibilities are the same. First, IRBs are responsible for an

initial review of the research plan presented by the clinical investigator. Without IRB approval, the investigator cannot commence clinical trials. The initial review encompasses the research protocol, the informed consent document to be signed by subjects, any advertisements to be used in recruiting subjects, and any other relevant documents. IRBs are responsible for ensuring that the research meets specific regulatory and ethical requirements. The risks to human subjects must be reasonable in relationship to the anticipated benefits, and the risks must be minimized. The selection of subjects must be equitable and justified. In addition, IRBs must ensure that the informed consent document clearly provides the information necessary for the potential subject to make a decision about whether or not to participate in the research, ensure that advertisements to recruit human subjects are not misleading, and ensure that there are adequate protections for the subjects, especially vulnerable subjects. After the IRB approves the research study, it is then responsible for providing continuing review of the research. The continuing review includes review of all study amendments and reports of unexpected adverse experiences to ensure that the risk-benefit ratio remains acceptable. The FDA and NIH/OPRR regulations require at least yearly review.

The FDA has oversight jurisdiction concerning research conducted as part of its product approval process, while the Office of Protection from Research Risks ("OPRR"), which is located within the National Institutes of Health ("NIH"), has oversight jurisdiction concerning federally-funded research. However, the two federal agencies approach oversight very differently. The FDA relies on an inspection process. FDA inspects IRBs, research sponsors, and research investigators. In its inspection of IRBs, FDA reviews IRB records, examines written procedures, and audits the research protocols and informed consent documents approved by the IRB.

The NIH/OPRR relies primarily on assurances as its oversight mechanism. An "assurance" is a document in which the institution commits to compliance with Federal regulations for human-subject protections. To ensure compliance with an assurance once it is filed, OPRR can limit, suspend, or withdraw an institution's assurance or require special reporting. While OPRR has the authority to conduct investigations, these are usually conducted only in response to subject complaints, or as a result of other information indicating protection breakdowns.

*B. Recent Changes in the U.S. Research System*

Biomedical research has changed significantly since the IRB regulations were first implemented. At that time, most clinical trials involving human subjects were federally-funded and conducted within a single institution, by a single investigator. However, due to a number of factors, including an increase in regulatory requirements for premarket clinical testing, the number of research studies funded both by public and private sources has increased dramatically. These factors have encouraged medical

clinics and physicians in private practice to participate in clinical research. Moreover, primarily because of federal clinical testing requirements for new products, clinical trials, especially industry-funded ones, now focus on multi-site studies involving thousands of human subjects. Without doubt, this increase in research conducted at multiple sites has allowed a greater understanding of the benefits and risks of a drug or device before marketing. Now more than ever, IRBs must have sufficient staff, expertise, and technical support to meet the demands of the changing research environment.

## II. RECOMMENDATIONS FOR IMPROVING THE CURRENT SYSTEM

WIRB believes that the present IRB regulations can be effective in providing human subject protection, but because of the dramatic change in the research environment, it is appropriate to pause and reevaluate the process at this time. As the OIG draft report noted, there is no indication that the current regulatory system has resulted in harm to research subjects. However, we believe that even the perception of problems in the system will undermine public confidence and could adversely affect the advances in medical research. Therefore, the recommendations made by the OIG would be helpful in maintaining our country's leadership in the protection of the rights of research subjects.

### *A. IRB Registration*

WIRB supports the concept of IRB registration. At present, NIH/OPRR and FDA lack basic information on the existence, location, and make-up of IRBs, and they must rely on IRB information that is either provided by sponsors or investigators in their applications to FDA or provided by institutions in assurance documents with NIH/OPRR. WIRB believes that requiring such basic information would help to improve protection of human subjects by allowing the agencies to manage their oversight efforts more effectively and to fully communicate with IRBs.

### *B. Information Sharing*

WIRB also strongly supports the OIG's recommendation concerning "information sharing." There have been situations where certain sponsors or investigators were displeased with an IRB's review and switched to a new IRB without informing the new IRB about the previous review. While the majority of sponsors and investigators have demonstrated integrity during the IRB review process, WIRB believes that it is important that these parties be obligated to disclose any prior disapprovals of the research. Further, so that an IRB can effectively monitor the progress of research studies, copies of all FDA and OPRR inspection reports concerning clinical studies which the IRB has approved should be provided to the reviewing IRB. Finally, because clinical investigations are

already subject to government and sponsor auditing and monitoring, we believe that extending the required "information sharing" between the parties would be helpful to the IRB's oversight of research without adding more oversight to an already overworked clinical investigator.

*C. Ethical Considerations: Structure of Board*

Concerns have been raised about the ability of IRBs to act independently of the sponsors or the institution to which they are affiliated. The issue of independence applies equally to institutional IRBs as well as independent IRBs. We strongly support formal studies that analyze actual conflicts of interests in all IRBs. Without knowing whether conflicts of interest bias IRB decisions, it would be difficult to implement meaningful regulatory change.

It appears that the best way to control conflicts of interest is through organizational structures that eliminate the financial interest of the board members in their decision making. WIRB already practices this through separation of its administrative and review functions.

Moreover, WIRB strongly supports the OIG's recommendation that IRBs should include more non-scientific and non-institutional members. WIRB highly values the important role that these members play in protecting human subjects and understands the OIG's view that present regulations requiring merely one non-scientific member and one non-institutional member may not be adequate.

WIRB also strongly supports the OIG's recommendations for increased board member training. IRB members need initial and continuing education to understand and stay current with the complex scientific, regulatory, and ethical issues in today's research environment. WIRB also supports an increase in investigator training, both inside and outside of institutions. There are few educational resources available for investigators. and this contributes to the problem of investigator non-compliance with regulations.

*D. Common Policy Shared by FDA and NIH/OPRR*

We strongly support the concept of a "shared" policy between FDA and NIH/OPRR in oversight of IRBs. As discussed previously, regulatory mechanisms employed by FDA and NIH/OPRR vary. FDA oversight of IRBs is included in the process of evaluating the safety and efficacy of drugs, devices, and biologics. Its approach is more compliance-based, focusing on inspection of IRB research sites. In contrast, NIH/OPRR oversight of IRBs focuses on assurances.

Each of these systems incorporates valid oversight tools. However, we agree with the OIG that similar oversight policies and close collaboration would strengthen the

protections to human subjects. Moreover, a common policy would result in a more efficient regulatory scheme that would be advantageous to both the federal government and to IRBs. We believe that a shared policy between FDA and NIH/OPRR will improve the ability of IRBs to comply with federal policies, regardless of whether the research protocol is regulated by NIH/OPRR or by FDA. We also support the OIG's recommendation that NIH/OPRR and FDA involve other departments in the Department of Health and Human Services, as well as non-federal parties such as IRBs, sponsors, and clinical investigators, in development of a shared policy.

## III. CONCLUSION

Congressional efforts in the 1970s established an excellent system of oversight. The United States continues to be an international leader in both oversight of human subjects participating in clinical trials and biomedical research and development. However, WIRB supports a review that seeks to address changes in the research environment and to provide consistency in oversight of clinical trials, whether funded by the federal government or the private sector. The central issue is to ensure human subject protection through the use of an efficient and consistent oversight policy.

Independent IRBs have responded to the legitimate needs of the medical research community by providing an independently based assurance of human subject protection. As independent IRBs, we play a critical role in protecting rights of research subjects as well as facilitating the development of new medical therapies.

We thank you for the opportunity to present our views and we look forward to continuing to work with Congress, HHS and FDA to protect the rights of human subjects who choose to participate in clinical research.

Mr. SNOWBARGER. Thank you, Dr. Bowen.

Next is Dr. Timothy Walsh from the Institutional Review Board for the New York Psychiatric Institute. Dr. Walsh, welcome to the committee.

Dr. WALSH. Mr. Chairman, and distinguished members of the committee, I'm here with Dr. John Oldham, who is chairman of our Institute. We very much appreciate the opportunity to testify about the critical issue of protection of human subjects in research.

In my remarks, I'd like to highlight a few important issues about the study that have already been raised in the remarks this morning. The research study that we've been asked to discuss was focused on violence and anti-social behavior among youth. The recent deadly shootings at schools across our country and the rising tide of youth suicide are tragic reminders that we must do more to understand and to prevent violence among young people. The purpose of the study conducted at Psychiatric Institute was to learn more about the origins of such problems. The broad goal of the project was to identify psychological, environmental, and biological factors which increase a child's risk of developing anti-social behavior. The hope was that, if successful, this research would lead to targeted interventions to help prevent these difficulties from developing in youngsters at risk.

In its review of this proposal, our IRB carefully considered both the scientific merits of the study and the potential risks and benefits to the subjects, and concluded that approval of the study was consistent with Federal and State regulations, as well as with accepted ethical principles. The study was carried out and to the best of our knowledge, it was concluded without any harm to any participant.

The fenfluramine study was one part of a larger project which involved 126 boys with an older brother who had been adjudicated a juvenile delinquent. Because the research involved numerous meetings with families over several years, the investigators sought potential participants living in proximity to our Institute, which is at the northern end of Manhattan adjacent to the Bronx, and so they obtained information on eligible families from the family courts of those two boroughs. The overwhelming majority of individuals in this system, and, therefore, the overwhelming majority of participants in these studies were from minority ethnic groups.

The investigators recognized that such work should be more broadly based and this study was planned as the first phase of a larger research program. Consistent with this plan, the investigators later submitted to the IRB and to NIH a proposal to conduct similar research in a larger and more geographically and ethnically diverse sample.

One major concern which has been raised about this study is its use of fenfluramine. There is strong evidence that the brain chemical, serotonin, plays an important role in the regulation of violent behavior. And by giving participants a single oral dose of fenfluramine, a pill, on one occasion, and then measuring changes in hormone levels in the blood, investigators could obtain an indirect measure of brain serotonin function. The procedure is very analogous to the widely used glucose-tolerance test.

At the time the study was proposed, fenfluramine had been on the market as Pondimin for approximately 20 years for obesity, and was commonly used in research to assess brain serotonin function. The IRB thoroughly reviewed the potential risks, and concluded they were minor at most. Fenfluramine studies were carried out in 36 youngsters and to the best of our knowledge, none experienced significant problems.

Concern about the use of fenfluramine subsequently developed because of the association between its use as Redux and heart valve abnormalities. These concerns first emerged in 1997, well after the conclusion of the Psychiatric Institute study in 1995. The concerns about valve damage are about obese individuals who took fenfluramine for months, almost always in combination with another medication, phentermine, the Fen-Phen combination. Fen-Phen was not used in the studies at Psychiatric Institute, only a small single dose with a pill of fenfluramine. There is no indication that this use of fenfluramine is associated with any risk of cardiac damage.

In closing, we would emphasize our belief that research on the development and the prevention of violent behavior among young people is critical for our country. Studies in this sensitive area, as in all research, must be carried out with the strictest attention to safeguards for all the participants. We welcome the opportunity to provide information to the committee, and we'll be happy to answer your questions.

[The prepared statement of Dr. Walsh follows:]

*UNITED STATES HOUSE OF REPRESENTATIVES*
*COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT*
*SUBCOMMITTEE ON HUMAN RESOURCES*
*JUNE 11, 1998 HEARING*
*"INSTITUTIONAL REVIEW BOARDS: A SYSTEM IN JEOPARDY?"*

Written Testimony of

B. Timothy Walsh, M.D.
Co-Chair, New York Psychiatric Institute Institutional Review Board, 1990-1997
Psychiatrist, New York Psychiatric Institute
Professor of Psychiatry, College of Physicians & Surgeons, Columbia University

John M. Oldham, M.D.
Director, New York Psychiatric Institute
Professor of Clinical Psychiatry, College of Physicians & Surgeons, Columbia University

Overview of the Research and the IRB Review

The research study which we have been asked to discuss was focused on violence and antisocial behavior among youth. The recent deadly shootings at schools across our country and the rising tide of youth suicide are tragic reminders that we must do more to understand and to prevent violence among young people. The purpose of the study conducted at New York Psychiatric Institute (NYPI) was to learn more about the origins of troubled behavior among young people, in particular, the development of antisocial behavior. At present, no effective treatment exists for such behavior, and the broad goal of the project was to identify factors–psychological, environmental, and biological–which increase a child's risk of developing such problems. The hope was that, if successful, this research would lead to targeted interventions to help prevent these difficulties from developing in youngsters at risk.

After receiving the investigators' initial application, the NYPI Institutional Review Board (IRB) requested additional materials to evaluate both the scientific merits of the study and the potential risks and benefits to subjects. These issues were carefully considered, as was the

process of seeking consent from and providing information to the participants and their families. During its review, the IRB applied the governing federal regulations as well as the underlying ethical principles. Time does not permit a comprehensive discussion of all the issues involved, but we have previously provided the Subcommittee with extensive documentation which was submitted to the Department of Health and Human Services' Office for Protection from Research Risks.

Who Participated

The fenfluramine study was one component of a larger, foundation-funded project which involved 126 boys with an older brother who had been adjudicated a juvenile delinquent. The investigators provided the IRB with strong scientific evidence that such younger brothers were at significant risk for the development of antisocial behaviors. The study of risk factors is important in many fields of medicine. For example, individuals in families at high risk for heart disease may be studied to determine how factors such as elevated cholesterol contribute to the later development of the heart disease. The investigators believed that a study of youngsters at risk for developing antisocial behavior would increase understanding of the factors that contribute to this problem, and thereby provide leads toward interventions to prevent it. The IRB was convinced that the proposed study had scientific merit

Because the research involved numerous meetings with these families over several years, the investigators sought potential participants living in proximity to NYPI. Officials of the Family Courts of Manhattan and the Bronx provided information on eligible families from the court records, in accordance with New York law. The overwhelming majority of individuals in this court system and, therefore, the overwhelming majority of participants in these studies were from minority ethnic groups, primarily African-American and Hispanic. The investigators

recognized that such work should be broadly based, and this study was the first phase of a larger research plan. Consistent with this plan, the investigators subsequently submitted to the IRB a proposal to conduct similar research in a larger and more geographically and ethnically diverse sample. This proposal was also approved by the IRB, and was submitted to and reviewed by NIH, but not funded, with no criticism whatsoever of the human subjects safeguards.

Benefits to Participants

It was hoped that this study would result in new knowledge about identifying youngsters at highest risk for developing antisocial behavior and about ways to prevent the development of this behavior. Although the study was not primarily designed to provide direct benefit to the participants, it was anticipated that each child would receive a number of indirect benefits, including comprehensive medical and neuropsychological evaluations designed to detect learning, emotional or medical problems. When problems were detected, families were assisted in obtaining appropriate services. For example, a serious heart problem was discovered in one child, and the family of another sought help from the research staff for a child who was dealing with his father's suicide.

The Consent Process

Recruitment into the larger study was initiated by a letter mailed by the investigators to the families. If the parents and child were interested, the study was explained in detail and consent was obtained. Only families who had participated in the larger study were considered for the fenfluramine study, on which we are focusing today. Families were told that a related study was underway, and asked if they might be interested. If they were, they were referred to the lead investigator who explained the study in detail. The consent process occurred over several visits,

and children participated only if both parents and children fully agreed to the procedure at all times. If a parent expressed interest but a child did not, the child did not undergo the procedure. For example, those children who objected to having their blood drawn did not participate. As is customary in research studies of this type, participants were compensated for their time (6 to 8 hours, including transportation) and effort; parents were given $100, and children were given a $25 gift certificate.

The Use of Fenfluramine

A large body of scientific evidence suggests that the brain chemical serotonin plays an important role in the regulation of violent behavior, both outwardly directed, such as aggression, and inwardly directed, such as suicide. The investigators were interested in obtaining a measure of brain serotonin function in these youngsters, and, since brain serotonin cannot be measured directly, proposed to give subjects a single oral dose of the medication fenfluramine. By measuring changes in the level of hormones in the blood after fenfluramine, the investigators could obtain an indirect measure of brain serotonin function. An analogy might be the glucose tolerance test: a dose of glucose is given to individuals at risk for diabetes, and blood sugar levels are measured as an indication of the body's release of insulin.

At the time this study was proposed, fenfluramine had been marketed as Pondimin for over twenty years for the treatment of obesity. The NYPI IRB, which included a pediatric neurologist, carefully reviewed the potential risks of fenfluramine known at that time, and obtained information from other investigators who were familiar with its use in children. After a thorough and lengthy review, the IRB concluded that the use of fenfluramine in this study entailed "no more than a minor increase over minimal risk" and therefore could be conducted under the applicable federal regulations governing research with children. Fenfluramine studies

were carried out in 36 youngsters, and, to the best of our knowledge, none experienced significant problems.

Concern about the use of fenfluramine has subsequently developed because of the association between the use of fenfluramine, marketed as Redux, and the development of heart valve abnormalities. It may therefore be useful to review some additional information about fenfluramine. First, concerns about valvular damage emerged in 1997, well after the IRB's review and the conclusion of the NYPI study in 1995. Second, the data which have emerged suggest that valve damage occurs in a fraction of obese individuals who took fenfluramine for months, often in combination with another medication, phentermine. There are no data of which we are aware suggesting that a single, low dose of fenfluramine alone, as used in this study, is associated with any risk of cardiac damage. In fact, even after fenfluramine was withdrawn from the market for the treatment of obesity, the FDA has continued to permit the use of a single dose of fenfluramine in research studies. Finally, researchers outside of NYPI have described experience with more than 1,000 research subjects, including over 200 children and adolescents, who have participated in fenfluramine studies. All of these studies were presumably approved by the relevant IRB's, and many or most were conducted with support from NIH, which carries out a separate ethics review. The widespread use of fenfluramine in these research studies supports the view, taken by the NYPI IRB, that this procedure was of low risk.

The Research Findings

This study provided important information for developing prevention and treatment strategies for children with anti-social behavior. First, it demonstrated that the relationship between behavior and brain chemistry may change during development. While nerve cells

which use serotonin appear to be underactive in certain adult psychiatric illnesses, the opposite (overactivity) may occur in certain child psychiatric disorders. Second, the researchers found that this difference may relate to the rearing environment. Children who were reared in nurturing environments generally had serotonin levels associated with lower levels of aggressive behavior.

These findings emphasize the potential importance of early interventions to prevent the development of problems in young people. For example, the results of the study suggest that some forms of treatment might not only help behavioral problems, but also prevent changes in the chemistry of the brain which may make later treatment more difficult. Moreover, by describing the link between nurturing behavior and serotonin, the study may ultimately allow us to understand those aspects of the parent-child relationship that are most protective against the development of antisocial behavior.

The importance of the published results of this fenfluramine research was recognized in an editorial in a leading medical journal and by the American Academy of Child and Adolescent Psychiatry.

In closing, we would emphasize our belief that research on the development and prevention of violent behavior among young people is critical for our country. Studies on this sensitive topic must be carried out with the strictest attention to safeguards for the research participants. In the study under consideration today, the NYPI IRB carefully applied the federal regulations governing research and the ethical principles on which they are based.

Mr. SNOWBARGER. Thank you. Next, Dr. Bert Spilker from Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers. Dr. Spilker.

Dr. SPILKER. Mr. Chairman and members of the subcommittee, I am Bert Spilker, senior vice president of Scientific and Regulatory Affairs of the Pharmaceutical Research and Manufacturers of America. PhRMA represents the Nation's leading research-based pharmaceutical and biotechnology companies.

I am pleased to be here today to present PhRMA's views on the way in which IRBs are exercising their oversight of pharmaceutical company-sponsored clinical trials.

PhRMA believes that the IRB system is sound and is working well for pharmaceutical company-sponsored clinical trials. Patients are being informed of their rights in accordance with the basic elements required in the informed consent document that they must read and sign. Their safety is being fully considered and drugs are being appropriately researched.

Modest reforms can be made without new legislative authority to improve the efficiency of the IRB process, and reduce duplication of efforts, allow IRBs to spend more time on ethical and safety considerations, and make new cures and treatments available sooner to patients.

IRBs are a critical safeguard to ensure that the rights and safety of patients, who enter clinical trials, are fully considered. This is absolutely essential and this is occurring in clinical trials sponsored by pharmaceutical companies. With any clinical trial, as with any drug, there are always risks. The potential risks to patients of any trial must be balanced against the potential benefits to be gained from the development and approval of the drug being tested. It is the job of IRBs to determine that the potential benefits to patients exceed the potential risks before they allow a clinical trial to proceed.

PhRMA agrees with the March 1998 draft report of the Inspector General on IRBs that changes are needed to streamline the IRB process. Improvements, such as the four I will mention, can be made by FDA and the OPRR on their own without new legislative authority.

First, a procedure should be established for regional and/or national IRBs to function more broadly and to meet more frequently than local IRBs do now. This would help facilitate the initiation of multi-centered clinical research and also reduce the growing workload of local IRBs. Duplication of effort would be reduced, local IRBs would be able to spend more time on ethical and safety considerations relating to their own single-site trials and new medicines would be made available sooner to patients.

Two, IRBs should be encouraged to hold regional and/or national meetings where they would discuss best practices and help each other improve their efficiency.

Three, IRBs should be urged to provide all patients with a copy of their informed consent form.

Four, FDA and OPRR should increase the flexibility of IRBs in whatever ways they deem appropriate. For example, they could encourage IRB chairs to appoint one or two members who would have

the authority in the absence of the Chair to approve protocol amendments, and some do this now.

The IRB system is a vital link in the drug development process. It is crucial that patients be protected and that the process function as efficiently as possible. The system has served us well for many years. We have a chance now to make it better but we must proceed carefully and deliberately so that we do not make it more burdensome. We are, after all, dealing with the safety of patients in clinical trials, as well as the health of patients who are waiting for new cures and treatments.

Mr. Chairman, that concludes my statement.

[The prepared statement of Dr. Spilker follows:]

# Statement PhRMA

BERT SPILKER, PH.D., M.D.
SENIOR VICE PRESIDENT
SCIENTIFIC AND REGULATORY AFFAIRS

PHARMACEUTICAL RESEARCH AND
MANUFACTURERS OF AMERICA

BEFORE THE

GOVERNMENT REFORM AND OVERSIGHT
SUBCOMMITTEE ON HUMAN RESOURCES

UNITED STATES HOUSE OF REPRESENTATIVES

JUNE 11, 1998

Mr. Chairman and Members of the Subcommittee, I am Bert Spilker, Ph.D., M.D., Senior Vice President of Scientific and Regulatory Affairs of the Pharmaceutical Research and Manufacturers of America. PhRMA represents the nation's leading research-based pharmaceutical and biotechnology companies, which discover and develop most of the new medicines used in the United States and around the world.

I am pleased to present PhRMA's views on the way in which Institutional Review Boards (IRBs) are exercising their oversight of pharmaceutical company sponsored clinical trials.

The IRB process has been firmly established in the United States for many years. IRBs are located primarily in institutions where clinical research is conducted. They review and approve a research plan before the research is conducted and exercise continuing oversight of the research. Federal regulations require that the boards have at least five members with varying backgrounds. At least one member must have primarily scientific interests, one must have primarily nonscientific interests, and one must be unaffiliated with the institution in which the IRB is located.

PhRMA believes that the IRB system is sound and is working well for pharmaceutical company sponsored clinical trials. Patients are being informed of their rights in accordance with the basic elements required in the informed-consent document they must read and sign (21 CFR 50.25), their safety is being fully considered, and drugs are being appropriately researched.

Modest reforms can be made without new legislative authority to improve the efficiency of the IRB process and reduce duplication of efforts, allow IRBs to spend more time on ethical and safety considerations, and make new cures and treatments available sooner to patients.

IRBs are a critical safeguard to ensure that the rights and safety of patients entering clinical trials are fully considered. This is absolutely essential – and this is occurring in clinical trials sponsored by pharmaceutical companies.

In addition to safety considerations, we must make sure that the IRB system functions as efficiently as possible – so that important new medicines for such diseases as cancer, Alzheimer's, and AIDS can be made available to waiting patients as expeditiously as possible.

With any clinical trial, as with any drug, there are always risks. The potential risks to patients of any trial must be balanced against the potential benefits to be gained from the development and approval of the drug being tested. It is the job of IRBs to determine that the potential benefits to patients exceed the potential risks before they allow a clinical trial to proceed.

PhRMA agrees with the March 1998 draft report of the Inspector General of the Department of Health and Human Services on Institutional Review Boards that changes are needed to streamline the IRB process. Improvements, such as those suggested below, can be made by the Food and Drug Administration (FDA) and the Office of Protection from Research Risks (OPRR) on their own without new legislative authority:

1. A procedure should be established for regional and/or national IRBs to function more broadly and meet more frequently than local IRBs do now. This would help to facilitate the initiation of multi-center clinical research and reduce the growing workload of local IRBs. Duplication of effort would be reduced, local IRBs

would be able to spend more time on ethical and safety considerations relating to their own single-site trials, and new medicines would be made available sooner to patients.

2. IRBs should be encouraged to hold regional and/or national meetings to exchange ideas, discuss best practices, and help each other improve their efficiency. IRB members may want to consider establishing their own professional society.

3. IRBs should be urged to provide all patients with a copy of their informed-consent form.

4. FDA and OPRR should increase the flexibility of IRBs in whatever ways they deem appropriate. For example, they could encourage IRB Chairs to appoint one or two members who would have the authority in the absence of the Chair to approve protocol amendments.

Amount of Research Increasing

During the past two decades, the amount of clinical research has been increasing and the nature of the research has become more complex. This applies to clinical trials conducted by academicians as well as non-academicians, and to research sponsored by pharmaceutical companies and conducted by clinicians in many different settings.

The result has been a major increase in the workload of most IRBs. While IRBs were initially located primarily in hospitals and academic institutions, the increased number of trials has led some contract-research organizations (CROs), site-management organizations (SMOs), community-based physicians, and pharmaceutical companies to form IRBs. Even professional for-profit IRBs have been established.

IRBs have dealt with their increased workload in many ways. They have, for example, met more often; formed subcommittees to review protocols and make recommendations to the entire IRB; hired additional administrative staff; charged sponsors a fee to process their protocols, and increased the number of protocol amendments reviewed by the Chair alone and not the full IRB.

Multi-Center Trials

The rise in multi-center trials has been a major factor in the increased workload of IRBs.

One of the major issues faced by government, industry, academic, and other sponsors who want to conduct multi-center trials is that the protocol must be approved by the IRB at every site. Before each site can begin the trial, its own IRB must approve the protocol and informed-consent form. Thus, for a three-center trial, for example, three separate IRBs require essentially the same applications and paperwork. Each of the IRBs may have different comments, suggestions, and requirements for changes in the protocol, informed-consent form, and/or data-collection forms they review.

The premise of a multi-center trial is that every site uses the same protocol. Changes required by one IRB must be sent to all of the others for their review and approval. While minor changes may be approved in some cases through expedited procedures, the Chair may desire that an entire IRB consider any changes required by another IRB. Because IRBs generally meet monthly and sometimes every six weeks, the review-and-approval process can take a take a considerable amount of time.

The difficulties can be compounded when more sites are involved. It is not unusual for more than 100 sites to participate in a clinical trial. This is almost always the case for treatment INDs, a procedure sometimes used for drugs of special value that are administered only to a few patients at many different sites while an NDA is being prepared or reviewed.

With treatment INDs, one or more regional and/or national IRBs often are formed, and they review the protocol. When the protocol is approved, local IRBs can also review it, but most do not choose to do so. Thus, the use of a regional or national IRB serves to cut the Gordian knot of great expense, paperwork, and time required for multiple IRB reviews, while protecting the rights and safety of patients.

The concept of a regional or national IRB could be utilized for multi-center trials of more than a specified number of sites (e.g., five or 10). This would lead to a substantial decline in the number of protocols that local IRBs have to review and would result in a more rapid evaluation of the most complex protocols by national IRBs. The ultimate result: new life-saving, cost-effective medicines would reach patients more quickly.

A national IRB protocol review could be conducted while a sponsor is finalizing its contracts with the individual institutions and/or investigators. This would save a great deal of time because many IRBs now refuse to review a protocol until the institution's lawyers have completed their negotiations with the sponsor. Because of the heavy workload in major academic institutions, it may take a few additional months before a protocol is reviewed – even though it has not been changed for a long time.

Contract discussions are extremely important to both a sponsor and an institution, but they rarely lead to any changes in the protocol itself or even in the informed-consent form. The investigator and not the sponsor is responsible for creating the informed-consent form, which must conform to federal regulations (21CFR 50).

The Inspector General's Findings

Turning to the Inspector General's report, it is indicated that IRBs should take a much more active role in monitoring ongoing clinical research within their institutions or at the sites in the community where the trials are being conducted.

PhRMA does not believe that this is necessary or even appropriate for clinical trials sponsored by pharmaceutical companies. These trials already are being monitored and audited by the companies themselves, the CROs they hire, or by SMOs. Moreover, the pivotal clinical trials in a New Drug Application (NDA) submitted to FDA are monitored and audited by the agency. FDA has the right to monitor any clinical trial conducted under an Investigational New Drug application (IND) or NDA.

Specific findings in the Inspector General's report are quoted and discussed below:

- "IRBs have too little information about how the informed consent process is working and about how well the interests of subjects are being protected."

PhRMA believes that the informed-consent process is working well in pharmaceutical company sponsored clinical trials. An IRB has the right to request information from an investigator directly and/or indirectly from other sites in a trial by requesting such data from the investigator.

Nevertheless, IRBs should focus on those few clinical trials with the greatest potential risk to patients.

- IRBs "face conflicts that threaten their independence."

This finding describes a problem that is more theoretical than real. Rarely, if ever, are requests made for additional "outside" representation on IRBs – but, nevertheless, they currently have the authority to include as many outside members as they desire.

- IRBs "provide little training for investigators and Board members."

This finding may be true, but there should not be much need for a significant amount of training. A short handbook should be available for distribution to all new members of an IRB. Some IRBs already distribute such a handbook.

The training should concentrate on the requirements of the Department of Health and Human Services and FDA for clinical trials and on Good Clinical Practices. IRBs also could hold meetings periodically, as described above, to discuss best practices and ways to improve efficiency.

The Inspector General's Recommendations

The Inspector General's recommendations generally urge that IRBs be given more flexibility to achieve their goals. We agree with this view and emphasize that this can be achieved through regulations or guidelines without new legislative authority. Specific recommendations of the Inspector General are quoted and discussed below:

- "Require Data Safety Monitoring Boards for some multi-site trials."

IRBs should always consider appointing such boards rather than requiring them for "some" trials. How will "some" be defined? There are bound to be exceptions (i.e., where such a board is not appropriate) and these would create issues or problems for a trial's sponsor (if any) and for the clinical investigators. Moreover, FDA already has strict safety guidelines for conducting clinical trials, and therefore data safety monitoring boards should not be "required."

- "Require sponsors and investigators to notify IRBs of prior reviews of research plans."

This could be accomplished by adding a question to this effect on the form for submitting a protocol to an IRB. Sponsors rarely contact IRBs directly, but provide information to investigators who do have such contact.

- "Require that research institutions have a program for educating its investigators on known-subject protections."

A prepared booklet, in addition to video and other materials, could be used to achieve this objective.

- "Require that IRBs have an educational program for board members."

See immediately preceding comment.

- "Require more representation on IRBs of nonscientific and noninstitutional members."

PhRMA does not believe that this recommendation would improve the ways in which IRBs function, and could cause tangential issues to be raised and discussions to bog down. The objective can be achieved under current conditions because, as previously noted, there is no limit to the size of an IRB. Those who advocate such a view should provide data and evidence to support it and convince the IRB community to add more nonscientific and noninstitutional members.

- "Require that IRBs have access to adequate resources."

PhRMA agrees with this statement, but the recommendation requires substantial discussion of the possible sources of such resources and how they will be used.

- "Revamp the FDA on-site inspection process."

The FDA inspection process should be simplified, with the aim of ensuring that only essential procedures are followed. It would be valuable if the Inspector General were also to evaluate the positive aspects of IRBs and how well they are functioning. We are unaware of data evaluating the outcomes of a large number of IRBs. There is a journal that publishes and shares information on IRBs. This is one way to disseminate information on "Good IRB Practices."

Conclusion

The IRB system is a vital link in the drug-development process. It is crucial that patients be protected and that the process function as efficiently as possible.

The system has served us well for many years. We have a chance to make it better, but we must proceed carefully and deliberately so that we do not make it more burdensome. We are, after all, dealing with the safety of patients in clinical trials as well as the health of patients waiting for new cures and treatments.

Mr. Chairman, that concludes my prepared statement. I will be pleased to respond to questions.

APPENDIX

Bert Spilker, Ph.D. M.D., FCP, FFPM, is the Senior Vice President of Scientific and Regulatory Affairs for PhRMA (Pharmaceutical Research and Manufacturers of America) based in Washington, D.C. He was President and cofounder (in 1983) of Orphan Medical, Inc., a public pharmaceutical company that develops and markets important medical products for patients with uncommon diseases. He is Clinical Professor of Pharmacy Practice at the University of Minnesota and Adjunct Professor of Medicine and Pharmacy at the University of North Carolina in Chapel Hill. He is well known as the author of 15 books on clinical trial methods and the processes of drug discovery and development. These books are considered by many as the standard reference on clinical trials and drug development. He has worked at four major pharmaceutical companies for over 20 years (Pfizer, Philips-Duphar, Sterling-Winthrop, and Burroughs Wellcome) in medicine discovery, development, and management. He serves on three Boards of Directors and is on the Steering Committee for the International Conference on Harmonization, or ICH. He has received numerous honors, including FDA Commissioner's Special Citation for work in the orphan medicine area. His medical training in pharmacology and internal medicine was at Cornell Medical College, State University of New York (Downstate Medical Center), University of California at San Francisco, University of Miami Medical School (Ph.D. to M.D. Program), and Brown University Medical School.

The testimony presented today is on behalf of the association, not any individual member company or group of member companies. PhRMA makes no representation with regard to any federal grants or contracts, if any, received by any PhRMA member company.

BOOKS BY BERT SPILKER

Guide to Clinical Studies and Developing Protocols
Raven Press, 1984

Guide to Clinical Interpretation of Data
Raven Press, 1986

Guide to Planning and Managing Multiple Clinical Studies
Raven Press, 1987

Multinational Drug Companies: Issues in Drug Discovery and Development
Raven Press, 1989

Inside the Drug Industry
With Pedro Cuatrecasas, Prous Science Publishers, 1990

Quality of Life Assessments in Clinical Trials
Editor, Raven Press, 1990

Presentation of Clinical Data
With John Schoenfelder, Raven Press, 1990

Patient Compliance in Medical Practice and Clinical Trials
Edited with Joyce Cramer, Raven Press, 1991

Guide to Clinical Trials
Raven Press, 1991

Data Collection Forms in Clinical Trials
With John Schoenfelder, Raven Press, 1991

Patient Recruitment in Clinical Trials
With Joyce Cramer, Raven Press, 1992

Multinational Pharmaceutical Companies: Principles and Practices
Raven Press, 1994

Medical Dictionary in Six Languages
Raven Press, 1995

Quality of Life and Pharmacoeconomics in Clinical Trials
Lippincott-Raven, 1996

Introduction to Quality of Life and Pharmacoeconomics
With Joyce Cramer, Lippincott-Raven, 1997

Mr. SNOWBARGER. Thank you, Dr. Spilker. I guess I can go to the name tag if nothing else helps. Dr. Levine, who's the professor of medicine, Yale University School of Medicine, and speaking on behalf of the American Association of Medical Colleges. Welcome, Dr. Levine.

Dr. LEVINE. Mr. Chairman, thank you very much. I'm very pleased to have this opportunity to come here to comment on the IRB system. Although I come from Yale University, I am here to represent the Association of American Medical Colleges. This topic is of importance to AAMC because their member institutions conduct the majority of clinical research in the United States.

I want to preface my remarks by saying that I wish Mr. Shays were here because I would welcome the opportunity to respond to some of the questions that he asked of the first panel. I would also welcome the opportunity to respond to Mr. Towns' questions, and to Mr. Snowbarger's questions, particularly the questions about the conduct of non-therapeutic procedures on vulnerable populations.

The cornerstone of the current system of protections is the IRB, and thus the sound functioning of these bodies is of the utmost concern. I have been attentively involved with IRBs on a national level for over 25 years. And, as my written statement outlines, I intend to bring both historical and nationwide perspectives to bear on the issues before this subcommittee.

The Inspector General's report has created much alarm about the ability of IRBs to fulfill their responsibilities in protecting human research subjects. I believe that the report mischaracterizes the role of the IRB, and that its tone conflicts with its substance. Although the report's title, "A System in Jeopardy," has recently been modified, as we heard in the first panel, there is no retreat from the substance of its narrative, which seems to portray a system in crisis. It would be easy to infer from this that there is a systematic threat to patients. Yet, quite to the contrary, the report which I have reviewed in draft form, acknowledges that the study yielded no evidence of harm, no evidence of abuse to patients. Based on my extensive interactions with IRBs on all levels, I concur with this finding.

I agree with the report's assertion that the system is "supported by many conscientious investigators committed to protecting human subjects and by many dedicated IRB members and staff who are doing their best." In that vein, the report does offer constructive examples of how IRBs have been innovative in dealing with an array of issues ranging from education to informed consent to ongoing oversight of protocols. This is the aspect of the report that should be emphasized.

As for improving the system, the Inspector General's proposal to alleviate the perfunctory oversight responsibilities and otherwise to lighten the workload of IRBs is laudable. So much of the energy of the IRB is dissipated and tending to bureaucratic trivialities. For example, IRBs, over the last few years, have been deluged with reports of all adverse drug experiences that occur during studies of investigational new drugs, and the adverse experiences that occur anywhere in the world. Most of these adverse experiences are already very well known to the IRB. The system could be made very much more efficient by limiting the reporting requirement to ad-

verse events that are unlike anything described in the protocol or consent form or events that are of a much more serious nature than was originally anticipated. All of these thousands of adverse experience reports now come with no advice whatever except for a legalistic statement that the mere reporting of this adverse event cannot be used to imply that we acknowledge that their could be a cause/effect relationship. In the past, we used to get some estimate from the drug company as to whether or not they thought there was a possibility of relationship.

There are a number of other welcome suggestions and I believe these are adequately covered in my written statement. But now I want to mention some of the obstacles to implementing some of the report's recommendations.

The report proposes the development of indicators of minimally adequate resources. It would be most difficult, if not impossible, to develop workable criteria or normative standards. But even more importantly, the IRB of 1988 or 1998 is not interested in meeting minimal standards. You have heard repeatedly that there's a requirement that there be five members, one of whom has a non-scientific background. At Yale, and I don't think we're extraordinary, we have 28 members, of which only 15 have scientific backgrounds. I'll elaborate on that if you wish.

The report recommends that IRBs must have greater representation of non-institutional and non-scientific members. Participation on an IRB is a demanding, time-consuming task, undertaken on a voluntary basis. Getting public members to serve is not easy. Getting faculty to serve is an increasing challenge. It used to be easy to recruit the so-called "best and the brightest" from within the institutions when they felt they were doing something important, and they felt that it was appreciated. But now it is not.

There are several factors that undermine faculty motivation, that diminish the sense of satisfaction with serving on an IRB. A lot of this has to do with the dilution of its efforts into trivial pursuits and the frequent attacks on the integrity of IRBs and IRB members that appear in the press, press reports of the sort that were occasioned, unfortunately, by the report of the Inspector General.

Finally, one aspect of the report that merits consideration is the perception that IRBs are conflicted in carrying out their duties. This implies that IRBs regularly have institutional interests at heart at the expense of research subjects. This presumes that the subject's interests are in conflict with those of the institutions. And the IRB somehow must choose between the two. Nothing could be more in the interest of the institution than protecting the subjects of research. Apart from the firm commitment that all medical schools have to the ethical principles of the Belmont report, violations of these principles put institutions at extreme risk, not only of adverse publicity, which none of us want, but also of the increasing litigation in the field.

The predominant pressure that IRBs feel from the parent institutions is to be rigorous in their review. In this regard, nothing can replace a highly motivated faculty participation in the IRB, particularly having members of the IRB who are well-respected within the institution. If we were to attempt to replace their functions with large batteries of consent auditors, monitors, and others who

would conduct on the scene oversight, projecting the attitude that researchers are not to be trusted, we're going to lose that respect. And that would be a tragedy.

Mr. Chairman, that concludes my statement. I would be very pleased, as I mentioned earlier, to respond to your questions.

[The prepared statement of Dr. Levine follows:]

Good morning. I am Dr. Robert Levine, Professor of Medicine and Lecturer in Pharmacology at Yale University School of Medicine. I also chair the Institutional Review Board (IRB) at Yale-New Haven Medical Center. I am speaking today on behalf of the Association of American Medical Colleges[1]. 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 a significant concern of this organization.

The cornerstone of the current system of protections for human subjects in research is the IRB, and thus the sound functioning of these bodies is of the utmost importance. I have been intensively involved with IRBs on a national level for much of my career over 25 years and, therefore, am intimately familiar with the concerns that led to their establishment. I was, in fact, a special consultant for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose reports included the "Belmont Report," which summarized fundamental ethical principles and articulated the distinctions between research, investigational practices, and standard therapy. The Commission also issued a report on Institutional Review Boards, which contained recommendations that became the mainstream of

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[1] For fiscal years 1995-97, the AAMC received $1,956,359 in Federal funding from the Agency for Health Care Policy and Research ($809,314), National Institutes of Health ($641,063) and the Health Resources and Services Administration ($505,982). Dr. Levine has received the following grant and contract support from the federal government during the past 3 years: Since August 1997, through a grant to Yale University to support its Center for Interdisciplinary Research in AIDS, he receives $3,125 each month as part of his University salary. For service on various committees and for various consultations with various federal agencies -- including, but not limited to NIH, CDC, FDA, DOE, DOD, NASA -- he has received an average of $1,500 per year.

federal regulations for the protection of human subjects, the so-called "common rule" (-- CFR 46). In addition, the Commission reports on the fetus, prisoners, and children form the basis for current Department of Health and Human Services regulations in these categories.

I also am on the board of Public Responsibility in Research and Medicine (PRIM&R), an organization which for over 20 years has brought the IRB community together to address emerging issues and current problems. In addition, I am currently preparing the third edition of my book, *Ethics and Regulation of Clinical Research*. Also, since its inception 20 years ago, I have been Editor of *IRB: A Review of Human Subjects Research*, an important journal for this community. Thus, in my testimony today, I will bring both historical and national perspectives to bear on the issues before the subcommittee.

I will begin by noting that IRBs are not policing bodies, watchdogs, or auditing agents. They were established to weigh the risks the proposed research may pose to the research subjects against the benefits the research may offer to the patient and society. IRBs are thus constituted in a way that enables examination of these *ethical* considerations in the context of the guiding principles set out by the Belmont Report -- beneficence, justice, and respect for persons. IRBs were established to work *collaboratively* with investigators, the vast majority of whom are altruistically motivated and intend to do the right thing. IRBs aid investigators in their work by ensuring that subjects are fully informed, and that any risks are reasonable in relation to anticipated benefits.

Part of the impetus for this hearing is a recent draft report of the Department of Health and Human Services (HHS) Inspector General, titled "A System in Jeopardy." This report has created much alarm about the ability of IRBs to fulfill their responsibilities in protecting patients. I would next like to address this very important matter since it has drawn so much public attention. I worry that the title of the report and much of the narrative portrays a system in crisis. It would be easy to infer from this document that there is a systemic threat to patients. Yet, quite to the contrary, the report acknowledges that the study yielded no evidence of harm or abuse to patients. Based on my extensive interactions with IRBs on all levels, I would concur with this last finding, and also agree with the report's assertion that the system is "supported by many conscientious research investigators committed to protecting human subjects and by many dedicated IRB members and staff doing their best...."

The report purports to describe the current state of the IRB system, even though it is based on a literature review, interviews with a limited sampling of IRB representatives, and visits to only six institutions. While certain observations are certainly true anecdotally in single instances or for individual institutions, an impression is given that they apply to all, or even a majority, of IRBs, which may not be the case. I believe that the tone of the report conflicts with its substance, which is misleading and unfortunate.

The report does have some positive aspects that I would like to touch on. Many of the recommendations in the draft report (as opposed to its various observations) are in fact quite reasonable. These were detailed in an AAMC letter of comment that has been attached to my

testimony for the record. The report also includes one volume titled "Promising Approaches" which offers constructive examples of how IRBs have been innovative in dealing with an array of issues from education to informed consent to ongoing oversight of protocols. This section of the report is highly useful and offers IRBs the kind of constructive information that should be the emphasis of the report. The report does make some observations that in fact are quite valid. For example, IRBs do indeed face tremendous workloads, and there is no question that they could benefit from greater resources.

Again, focusing on the positive, I will turn to some of the recommendations of the report that I find sound. I think the IG's proposal to alleviate the perfunctory oversight responsibilities and otherwise to lighten the workloads of IRBs is laudable. For example, in recent years IRBs have been deluged with reports of all "adverse drug experiences" that occur anywhere in the world in connection with studies on investigational new drugs. The vast majority of these reports are often of incidents that are either completely unrelated to the drug or, if related, are already well-known and have already been anticipated in the protocols and consent forms. In the past, IRBs would receive these reports along with some advice from the sponsor regarding the possibility of a causal connection between the drug and the event. Now IRBs almost invariably review formal disclaimers that state that the report itself does not constitute an acknowledgment on the part of the sponsor that there in any causal connection. This system could be made much more efficient. I suggest that the reporting requirement be limited to adverse events that are both serious and not anticipated, meaning that one of the following two criteria is satisfied: 1) the event is unlike anything described in the protocol or consent form, or 2) the event may be like

something anticipated in the protocol and consent forms, but is of a much more serious nature than originally anticipated.

Another workload issue involves the vast number of protocols that are reviewed by IRBs but never funded, since federal agencies require IRB review as a condition of their accepting applications for support. Changing the system to require IRB review only after funding decisions have been made would greatly reduce the workload while still ensuring that any research performed with human subjects has had IRB review.

Another activity that is absolutely key is education and training for both investigators and IRB members, something the report emphasizes, and something that the IRBs themselves welcome. Many institutions have made impressive efforts at providing outreach to patient groups, developing mechanisms for educating patients about research protocols, and developing formalized orientation programs for new IRB members. PRIM&R, the group I mentioned earlier, is also conducting these activities at a national level. Through its conferences, some of which have been done in collaboration with the AAMC, IRB administrators and members become educated about the many thorny ethical matters confronting IRBs and engage in workshops to discuss their experiences and solutions to the problems they face. The faculty for these conferences include personnel from the National Institutes of Health's Office for Protection from Research Risks (OPRR), as well as the Food and Drug Administration (FDA) and other federal agencies. PRIM&R will also be sponsoring an "IRB Training Institute" which will take a curriculum for new IRB members and administrators "on the road," if you will, making this kind

of training -- which will be led by nationally recognized experts -- accessible to institutions all around the country. The OPRR, too, conducts education and training.

Finally, I would concur that better communication between the FDA and IRBs is highly desirable, and that the role of Data Safety Monitoring Boards must be formalized for multi-site trials, which present particular communication and coordination challenges for IRBs.

There are nonetheless a number of obstacles to implementing some of the recommendations. For example, the report cites the existing federal requirements for the provision of adequate resources by the awardee institution. However, it is difficult if not impossible to develop workable criteria or normative standards for determining the types and levels of resources that would be adequate for the very diverse set of IRBs that are now in existence in highly heterogeneous research institutions. In addition, bureaucratic accretion coupled with institutional cost sharing is making the identification of institutional resources for cost sharing on federal grants increasingly difficult. Institutions do their best to provide IRBs with the materials they need, but could benefit greatly from the development of a specially designated source of federal support for IRB activities, either through a mechanism that would be funded in proportion to NIH-funded human subjects research, or through a more generalized flexible funding mechanism, such as the "Research Innovation Opportunity" program, which the AAMC has proposed as a substitute for the now defunct Biomedical Research Support Grant (BRSG) program.

One significant focus of the report is on ongoing review of protocols. It is important to note that not all protocols entail the same level of risk and complexity, and thus, the need for ongoing review must be assessed according to these criteria. It may conceivably be possible to develop criteria that would stratify protocols according to the level of ongoing review that they would merit, including none. The IG report suggests a "performance" focus for evaluating ongoing review, which *may* be useful, depending on how the criteria for assessment were defined. The report also notes how some institutions have involved patient advocates as a means of looking after the patient's interests during conduct of the protocol, which can be a workable, though expensive, means of handling some aspects of this issue.

The report also recommends that IRBs have greater representation of non-institutional and non-scientific members. It is important to realize that participating on an IRB is generally a demanding and time-consuming task that people undertake on a *voluntary* basis. Thus, getting the participation of public members is not easy. Second, once appointed, these individuals often do not become significant contributors to IRB deliberations until they have served for a long enough period of time to develop a relevant ethical and scientific knowledge base. At that point, they generally bring the same concerns and perspectives to the table as their other colleagues on the board. Adding additional non-scientific and non-institutional members is thus likely to put a strain on IRBs while these individuals are recruited and "brought up to speed," which will not be outweighed by the ongoing contributions of such participants. In the end, what benefits the IRB process and patients the most is the *quality* of outside members and the contributions they make, not simply the number of them on the committee.

I might add that there is a false impression that only individuals who have no connection with the institution can provide an "outsider" perspective. Medical students can be extremely effective members of IRBs. Because they understand the language and the risks, there is little that escapes their attention.

The challenge of getting people to serve on IRBs also is quite germane to faculty. It used to be easy to recruit the "best and the brightest" faculty when they felt that they were doing something important and that it was appreciated. But now it is not. There are several factors that undermine faculty motivation and a sense of satisfaction for serving on an IRB, ranging from the increased workload and the amount of time and energy that must be expended to address and document in detail even relatively minor issues to the negative publicity surrounding IRBs.

It must be re-emphasized that this is a voluntary system. It requires a significant amount of time that is uncompensated from people who tend to be very busy with clinical and academic responsibilities. There is a widely held misconception that we could increase the motivation of academics to serve on IRBs by formally recognizing the contributions they make in terms of time and commitment. Certainly, they should get compensated in salary and release time. But this alone will not accomplish the desired ends. People choose academic careers because they want to do research and they want to teach. The true coins of the academic realm lie in recognition by peers of their academic accomplishments. Academics routinely accept lower salaries to find "protected" time to do their research. In a certain vitally important sense nothing can compensate them for the time and energy devoted to committee work. They should at least have a sense that

they are doing something important and that they are appreciated for doing it.

One aspect of the report that merits correction is the perception given that IRBs are conflicted in conducting their duties. This observation implies that IRBs regularly have the institutional interest at heart at the expense of those of research subjects. This sets up a false logic whereby the subjects' interests are presumed to be in conflict with those of the institution, and the IRB somehow must choose between the two. The fact of the matter is that nothing could be more in the institutional interest than protecting the subjects of research. Apart from the firm commitment that all medical schools have to the ethical principles underlying the Belmont Report, violations of those principles put institutions at extreme risk. Thus, the predominant pressure that IRBs feel from their parent institutions is to be rigorous in their review.

With those observations made, I will be happy to take any questions.

Robert J. Levine is Professor of Medicine and Lecturer in Pharmacology at Yale University School of Medicine and Chairperson of the Institutional Review Board at Yale-New Haven Medical Center. He is a fellow of the Hastings Center, the American College of Physicians and the American Association for the Advancement of Science; a member of the American Society for Clinical Investigation and American Society for Pharmacology and Experimental Therapeutics; Past-President of the American Society of Law, Medicine & Ethics; and Past-Chairman of the Connecticut Humanities Council. Dr. Levine, former editor of Clinical Research, is the current editor of IRB: A Review of Human Subjects Research, and has served as consultant to several federal and international agencies involved in the development of policy for the protection of human subjects.* He is the author of numerous publications and is currently preparing the third edition of his book, Ethics and Regulation of Clinical Research.

* Recent activities include:

Member of the AIDS Program Advisory Committee, National Institutes of Health, and Chairman of its Subcommittee, the National Human Subject Protections Review Panel.

Member of the Ethics Subcommittee of the Director's Advisory Committee, Centers for Disease Control and Prevention.

Joint United Nations Programme on HIV/AIDS (UNAIDS), Project on ethics in HIV vaccine trials, chairperson of the project to develop a "Guidance Document" for trials of preventive HIV vaccines.

World Association of Medical Editors: Chairperson: Ethics Committee.

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Jordan J. Cohen, M.D., President

May 4, 1998

June Gibbs Brown
Inspector General
Department of Health and Human Services
Fifth Floor
330 Independence Avenue, N.W.
Washington, D.C. 20201

Dear Ms. Brown:

On behalf of the Association of American Medical Colleges (AAMC), I would like to thank you for sharing with us your March 1998 draft report on institutional review boards. The AAMC's membership -- all 125 accredited U.S. medical schools, over 400 teaching hospitals, and 89 scientific and academic societies -- conducts the majority of clinical research in this country, and ensuring the safety of those who volunteer to participate as subjects is a significant concern of this Association. The keystone of the current system of protections is the institutional review board (IRB), and thus the sound functioning of these bodies is of the utmost importance.

The study your office conducted was reported in four volumes, but they include many recurrent themes and observations. Thus, for the sake of simplicity and brevity, this letter will focus on the most salient issues and recommendations, rather than comment on each report separately. First, a few very general observations are in order.

Taken together, the reports do not adequately acknowledge the proper role of IRBs in assuring the protection of human subjects in research. IRBs were established as a consequence of the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Belmont Report), which identified the basic principles of beneficence, justice, and respect for persons that have become the cornerstones of ethical clinical research. Guided by these principles, the role of the IRB is to weigh the risks posed by the research against the benefits that the research may offer to the patient and society. IRBs are thus constituted in a way that enables examination of these *ethical* considerations. They were established to work *collaboratively* with investigators, the vast majority of whom are altruistically motivated and intend to do the right thing. IRBs aid investigators in their work by ensuring that subjects are fully informed, and that any risks are reasonable in relation to anticipated benefits.

In contrast to these objectives, the report seems to presume instead a policing or auditing role that, in fact, is inconsistent with the mission articulated for IRBs in the Belmont Report. For

example, the summary report observes, "the IRB process is rooted in trust," and asserts that this characteristic is in conflict with the oversight role of these boards. This observation seems to serve as a premise for much of the report and reflects a fundamental misunderstanding about how IRBs were intended to function. It is the trust that exists between the IRB and investigator that permits this system to work effectively because it encourages openness, responsiveness, and collaboration.

Nonetheless, as the report amply notes, IRBs indeed face tremendous stresses at this time. They unquestionably bear enormous workloads and could undeniably benefit from additional resources. The AAMC is sympathetic to many of the observations cited in the report along these lines, but finds that the title of the report and some of the introductory text are disproportionately alarming. The system is neither in crisis, nor on the verge of collapse, as some might infer. As your cover letter appropriately states, the system is "supported by many conscientious research investigators committed to protecting human subjects and by many dedicated IRB members and staff doing their best..." This fact is beautifully illustrated by the volume of your report on *Promising Approaches*, which provides in a very constructive and positive way useful examples of how particular IRBs have been especially innovative in overcoming obstacles and in enhancing their effectiveness. As a consequence of this dedication and resourcefulness, the system has worked remarkably well in the face of many challenges.

The report is also prone to generalizations and very sweeping conclusions, even though it is based on a literature review, interviews with a limited sampling of IRB representatives, and visits to only six institutions. While certain observations are certainly true anecdotally, an impression is given that they apply to all, or even a majority, of IRBs, which may not be the case. Statements in the report concerning continuing review are a particularly salient example of this type of writing.

On the topic of resources, the report notes the extent to which IRBs need to have adequate material support to enable them to carry out their responsibilities. The AAMC concurs with this statement, but notes that the greatest challenge is finding the necessary funds to develop and to make available such resources as office space, computers, and administrative support. Institutions face both increasing cost sharing on federally supported research (through the cap on reimbursement of administrative costs, for example) coupled with an accretion of compliance and other regulatory requirements, and thus funds for these sorts of resources are increasingly scarce. One solution may be to develop a specially designated source of federal support for IRB activities, either through a mechanism that would be funded in proportion to NIH-funded human subjects research, or through a more generalized flexible funding mechanism, such as the "Research Innovation Opportunity" program, which the AAMC has proposed as a substitute for the now defunct BRSG program.

Recommendations

While many of the recommendations in the report are reasonable, some are problematic or in need of refinement. Detailed comments are provided below:

**Recommendation 1: Recast Federal IRB Requirements so that They Grant IRBs Greater Flexibility and Hold Them More Accountable for Results** -- The Association agrees that IRBs spend too much of their attention on perfunctory review responsibilities, and that lessening some of these requirements would be a useful step, particularly review of protocols that ultimately never get funded. Performance-focused evaluations can be desirable for certain activities, but may be problematic for IRBs. The key will be to discern the appropriate performance-based criteria to use for evaluation of IRB performance, which is very qualitative in nature. The report recommends making IRB evaluations available to the public, but it is not clear what types of information would be provided and how lay people could assess it meaningfully. Until this is better defined, the AAMC would discourage routine public dissemination of such reports.

**Recommendation 2: Strengthen Continuing Protections for Human Subjects Participating in Research** -- Multi-site trials do indeed pose special challenges for oversight, and it would be reasonable to require that Data Safety Monitoring Boards play a significant role in assessing, summarizing, and determining when and how to follow up on adverse-event reports. The AAMC also agrees that IRBs should be informed about the progress of multi-site trials as a whole, even though an individual board's review may be limited to the work being conducted at a particular institution. Indeed, IRBs need to be aware of adverse events occurring elsewhere, such that the risks of the protocol can be reassessed for the local study population. More systematic communication from the FDA to IRBs about actions taken against investigators is also a laudable objective, as underscored in the report.

Finally, while appreciating the intent of recommendation 2e -- increased IRB awareness of on-site research practices -- it should not be conducted in a manner that threatens the collaborative relationship between the IRB and investigator. As stated earlier, IRBs are not watchdogs, and neither have the resources nor mission to be expected to conduct surprise visits on investigators.

**Recommendation 3: Enact Federal Requirements that Help Ensure that Investigators and IRB Members are Adequately Educated About and Sensitized to Human-Subject Protections** -- This is perhaps one of the most important recommendations in this report. Problems, when they occur, are most often attributable to inadequate training and sensitization on the part of investigators. Individual institutions, as well as national organizations, such as Public Responsibility in Medicine and Research (PRIM&R), are developing educational programs, some targeted at investigators and others focused on IRB members. NIH-supported mechanisms

should be developed to support these kinds of outreach and clinical research training activities that require significant resources to function effectively.

**Recommendation 4: Help Insulate IRBs from Conflicts that Can Compromise Their Mission in Protecting Human Subjects** -- This recommendation is improperly framed and problematic in practice. The observations made at the outset of this recommendation imply that IRBs regularly have the institutional interest in heart at the expense of those of research subjects. This sets up a false logic whereby the subjects' interests are presumed to be in conflict with those of the institution, and that the IRB somehow must choose between the two. The fact of the matter is that nothing could be more in the institutional interest than protecting the subjects of research. Apart from the firm commitment that all medical schools have to the ethical principles underlying the Belmont Report, violations of those principles put institutions at extreme risk. Thus, the predominant pressure that IRBs feel from their parent institutions is to be rigorous in their review.

At the very least, any amplification of the current requirement for representation of non-scientific and non-institutional members should be at the discretion of the IRB. First, participation on an IRB is done voluntarily and demands significant amount of time. Finding members of the public who are willing to give of themselves to this degree can be exceedingly difficult. Second, once appointed, these individuals often do not become significant contributors to IRB deliberations until they have served for a long enough period of time to develop a relevant ethical and scientific knowledge base. At that point, they generally bring the same concerns and perspectives to the table as their other colleagues on the board. Adding additional non-scientific and non-institutional members is thus likely to put a strain on IRBs while these individuals are recruited and "brought up to speed" that will not be outweighed by the ongoing contributions of such participants. In the end, what benefits the IRB process and patients the most is the quality of outside members and the contributions they make, not simply the number of them on the committee.

**Recommendation 5: Recognize the Seriousness of the Workload Pressures that Many IRBs Face and Take Actions that Aim to Moderate Them** -- The need that IRBs have for ample resources cannot be overstated, yet merely to require adequate resources is insufficient. As stated earlier, bureaucratic accretion coupled with institutional cost sharing is making the provision of resources increasingly difficult at a time when IRBs face unprecedented burdens. Institutions do their best to provide IRBs with the materials they need, but a special NIH support mechanism as previously described should be developed. In addition, the provision of adequate resources should be a priority, but is not implementable as a *formal* requirement. It would be difficult if not impossible to develop workable criteria for determining the types and levels of resources that would be adequate for the very diverse set of IRBs that are now in existence. Their workloads and local circumstances are very different, as are consequently their resource needs.

**Recommendation 6: Reengineer the Federal Oversight Process** -- The report repeatedly cites the inadequacies of IRB oversight of ongoing protocols. It is important to note that the need for oversight varies widely, depending on the complexity and risks posed by each protocol. Thus, any performance-based assessments should take this into account. With this in mind, the AAMC particularly supports the proposals to emphasize institutional assurances of conformance with federal IRB requirements, and education to help investigators and IRB members become as attuned as possible to human subjects concerns. Similarly, the shift in emphasis proposed for FDA review -- from narrow compliance checks to more performance-based criteria -- may be workable, but should take into account the caveat expressed earlier about the need to develop sound performance based criteria first. We particularly applaud the proposed involvement of experienced IRB members in reviewing IRB performance as a form of "peer review." The registration of all IRBs with the government seems reasonable, as well.

**Special Issues: Advertising to Recruit Human Subjects** -- All advertising for the purposes of patient recruitment is considered part of the research protocol, and thus must be reviewed and approved by an IRB. IRBs thus examine the text of these advertisements with an eye on ensuring that they are not overly coercive with regard to financial inducements, nor misleading with regard to the stated benefits of participation in research. Nonetheless, patient recruitment can be a challenge, since volunteers must give of their time and often must be inconvenienced to participate in a protocol. Thus some modest level of compensation is generally reasonable.

The specific advertisements provided in the report are highly anecdotal and do not enhance the reader's understanding of the predominant way in which such advertising occurs. Nor does this approach recognize the extent to which subjects become informed of clinical research through their physicians, voluntary health societies, or patient advocacy groups, which have historically acted quite responsibly and often with the benefit of IRB input, either directly or indirectly.

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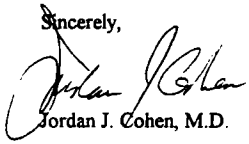
In conclusion, it is important to emphasize that, overall, this is a system that has worked remarkably well, and one that is not on the verge of collapse. Thus the alarmist tone in some sections of the report, particularly the overview, should be lessened to make the level of concern expressed more proportional to the magnitude of the problems identified in the report. We also strongly suggest that the title of the report be changed to be less sensational and more constructive in tone. In addition, the traditional and proper role of IRBs in ensuring the application of the Belmont Report principles to human subjects research must be emphasized, and text implying an auditing or policing role should be eliminated.

On the other hand, the AAMC finds the OIG's report to raise many valid and important observations. The most salient include those that relate to the extent to which IRBs face

tremendous workloads and could benefit from additional resources. The report also provides much useful and constructive information on how specific institutions have been innovative in enhancing IRB effectiveness. This material, found largely in the volume on *Promising Approaches*, should be amplified and become a central focus of the report.

The AAMC thanks you once again for this opportunity to comment and invites you to contact the Association again if we can be of service.

Sincerely,



Jordan J. Cohen, M.D.

Mr. SNOWBARGER. Thank you, Dr. Levine.

Next, would be Dr. Jonathan Moreno, who's professor of biomedical ethics, director of the Center for Biomedical Ethics at the University of Virginia. Dr. Moreno.

Mr. MORENO. Thank you, Mr. Chairman. I should say for the record that I'm in transition from the State of New York Health Science Center at Brooklyn to the University of Virginia.

Some months ago, I was honored to participate in your hearings on federally sponsored medical research involving human subjects from underdeveloped communities at home and abroad. I'm pleased that you've decided to take the next step and engage in an examination of our local review system of human subjects research.

In my view, the current system has worked reasonably well, though not perfectly. Some important improvements should be made, some in the short term. It's worth noting that most protocols are reviewed by a minority of IRBs and they may be the ones that need the most assistance in the short term. And I'm going to suggest some ways in which institutions could have incentives to improve support for IRBs locally.

As to the future, while the system is by no means in danger of imminent collapse, in my view, there are reasons for concern about the IRB system in general. My perspective is that of one who has been the faculty of several medical schools, as a member of an IRB, as one who has submitted protocols for IRB review, and as a staff member of two Presidential commissions.

I won't repeat all the details of my written testimony that I've submitted, Mr. Chairman, but I do want to emphasize the responsibilities of local review centers, local institutions in the support of their IRBs. That support is not, for the most part, very generous. There are some happy exceptions to that generalization but for the most part institutions can be doing more with the funds that they are taking in from research to support IRBs which are a critical part of our research system.

In our current system, the key element is local review. Even a regionalized or national system, and I don't think we want to necessarily advocate more Government in this area, would not be able to replace the virtues of the local review. Rather, ways must be found to encourage institutions to provide more support for IRBs. There are, as Dr. Levine just mentioned, few, if any, rewards for IRB service. People do it out of a sense of altruism because they think they're helping their colleagues, because they feel some loyalty to the institution, or out of scientific curiosity. But it can be very difficult to recruit new members who will be devoted to the review process, particularly in an era in which practicing physicians are under increasing pressure to spend time in their practices, bringing in practice dollars rather than sitting on what can be a very time-consuming activity. And IRB staffs are often very good people but they are stretched very thin. A good staff person, helping a good IRB administrator, can go very far in making the IRB's work more effective and sensitive to the kinds of issues that we're talking about today.

Most importantly, IRB review is mostly a paper compliance process. IRBs rarely monitor the actual conduct of research, as you know, including informed consent processes, though they do have

the authority to do so. But it's one thing to talk about IRBs doing more concrete monitoring. It's another thing for them actually to have the resources to do it. Without the IRBs being provided far greater resources by the institutions than they currently command, it is sheer fantasy to think that monitoring will take place much more frequently in the future.

Now, what are some of the consequences of the limitations on the resources of IRBs? Well, consent processes could be improved with more independent scrutiny. Consent forms could be made more readable and intelligible. In some cases, the design of studies could be enhanced and unnecessary risks reduced. The need for reform will be still greater if human subjects research grows at the rate projected. The director of the National Cancer Institute has called for five times as many participants in cancer studies, a goal that may be realized as the NIH budget is increased by as much as 50 percent in the next 5 years as is being discussed. With so many more vulnerable subjects in phase one studies, which are not designed, Mr. Chairman, necessarily to help them, they are toxicity studies and many of these people are very seriously ill. These are arguably among the most ethically troublesome studies. And the subsequent increase in privately funded research for marketable products as spin-offs off of basic research will also produce more pressure for IRBs and many other IRBs, many more than is the case now, will be in danger.

Now, I believe the Federal Government can meet its public obligations without exercising a heavy hand over local institutions. Rather than substantive mandates directed at research centers, the Government can and should affect certain procedural reforms that can create incentives for institutional change. These reforms are neither radical nor expensive but they are basic to any quality assurance mechanism. They entail three stages: registration, which has been discussed, audit, and disclosure. First, in my view, all institutions receiving Federal funds, and those that are not currently receiving Federal funds, as we've heard already, should somehow be put under the Federal rubric. Now, I'm not a lawyer, only a simple country philosopher but it seems to me that a way must be found to affect this kind of change.

I recognize that the registration that I have in mind, which includes obtaining various kinds of information from the IRB on an annual basis, could conflict with the Paperwork Reduction Act. But, again, I believe that the justification is sound. In order for the Federal Government to profile the evolving IRB system and communicate with all IRBs, these kinds of reforms should be in place.

Second, the OPRR or the FDA should have the authority to conduct audits of IRB records and procedures without cause. This would be similar to current arrangements, as I understand them, for animal care and use committees which have succeeded in prompting local facilities to maintain standards.

Third, information gained by the OPRR about the IRBs should be published by OPRR annually. All OPRR and FDA actions with respect to IRB compliance and conduct should also be published annually. Even apart from these requirements, research centers should be encouraged to publish any policies governing particular categories of research.

Mr. Chairman, openness can do the work otherwise required of substantive regulations, regulations that may take years to create. And the conduct of institutions benefiting from Federal funds, as well as those that enjoy the other benefits associated with being part of American society should be open to public scrutiny.

Thank you.

[The prepared statement of Mr. Moreno follows:]

Testimony to the Committee on Government Reform and Oversight

Jonathan D. Moreno, Ph.D.
Emily Davie and Joseph S. Kornfeld Professor and Director
Center for Biomedical Ethics
University of Virginia
11 June 1998

Mr. Chairman, Honorable Members of this Subcommittee;

Some months ago I was honored to participate in your hearings on federally sponsored medical research involving human subjects from underdeveloped communities at home and abroad. I am pleased that you have decided to take the next step, and engage in an examination of our local review system of human subjects research.

In my view, the current system has worked reasonably well, though some important improvements should be made. As to the future, while the system is by no means in danger of imminent collapse, there are reasons for concern. My perspective is derived from my role as a teacher of medical ethics in several medical schools, as a member of an institutional review board, as one has submitted protocols for IRB review, and as a staff member of two presidential commissions.

Discussions of the ethics of human experiments tend to focus on informed consent. Although informed consent or appropriate surrogate permission is a necessary condition for ethical research, it is not sufficient. Especially under the kinds of stresses that accompany serious illness, even reasonably well informed people may be willing to take risks for remote or only imagined benefits. And no one, whether healthy or well, should be asked to participate in research that is poorly conceived, no matter how small the risk.

Ethical research demands community input, because both morality and science are social institutions. The prior review of a scientific proposal properly involves both scientists and

laypeople. It should reflect local concerns and interests, and also be subject to scrutiny by the wider community, through our system of government. This is the essence of our IRB system, with OPRR and FDA oversight.

But the current system was designed when most research was conducted by a single investigator at a single institution with a handful of subjects, and when public sponsorship was predominant. Today, each of these elements has changed, and at the busiest research centers the burdens on IR'Bs have greatly increased. Yet there are few rewards, if any, for IRB service. As a result, it can be difficult to recruit new members who will be devoted to the review process, and institutional investment in IRBs, which is normally modest at best, is often stretched thin.

Most importantly, IRB review is a paper compliance process. IRB's rarely monitor the actual conduct of research, such as informed consent processes, though they have the authority to do so. Without far greater resources than IRB's currently command, it is sheer fantasy to think that research monitoring will take place much more frequently in the future.

What are some of the consequences of these limitations? Consent processes could be improved with more independent scrutiny. Consent forms could be made more readable and intelligible. In some cases, the design of studies could be enhanced.

The need for reform will be still greater if human subjects research grows at the rate projected. The director of the National Cancer Institute has called for five times as many participants in cancer studies, a goal that may be realized at the NIH budget is increased by as much as 50% in the next five years. With so many more subjects in Phase 1 studies, which are

arguably the most ethically troublesome, and the subsequent increase in privately funded research for marketable products, many IRBs will cease to function effectively.

The federal government can meet its public obligations without excercising a heavy hand over local institutions. Rather than substantive mandates directed at research centers, government can and should effect certain procedural reforms that can create incentives for institutional change. These reforms are neither radical nor expensive. Rather they are basic to any quality assurance mechanism. They entail three stages: registration, audit, and disclosure.

1. All institutions receiving federal funds (whether they have a current project assurance or not) should be required to register annually with Office for Protection from Research Risks and provide the following information, at a minimum:1. Are they currently conducting human subjects research? 2. If the answer to 1 is no, have they done so within the last 3 years and do they anticipate doing so within the next 3 years? 3. If they have an IRB currently, who are the chair and the responsible administrator? 4. How many protocols have they reviewed, on average, within the last three years? 5. Roughly how many subjects have been included in these protocols each year? This registration requirement would facilitate OPRR's ability to track and profile the evolving IRB system and communicate with all IRBs.

2. The OPRR or the FDA should have the authority to conduct audits of IRB records and procedures without cause. This wold be similar to current arangements for animal care and use committees, which haved succeeded in prompting local facilities to maintain standards.

3. Information gathered annually by the OPRR about the IRB's should be published by OPRR annually. All OPRR and FDA actions with respect to IRB compliance and conduct

should also be published annually. Even apart from these requirements, research centers should be encouraged to publish any policies governing particular categories of research. Openness can do the work otherwise required of substantive regulations, and the conduct of institutions benefitting from federal funding should be open to public scrutiny.

Mr. Chairman, fifty years ago this year, seven Nazi physicians and bureaucrats were executed for murders committed in concentration camps under the auspices of medical research in the service of the Third Reich. The famous Nuremberg Code governing the ethics of human experiments that was part of the judges' decision is today celebrated as one of the lessons of that terrible period of human history.

But the Nuremberg Code did not directly influence the conduct of medical research in the United States. The Nazi crimes were considered too extreme to be relevant to normal medical science. Instead, our regulatory system, with its twin pillars of informed consent and group review, emerged from legal pressures, scientific traditions, government reforms, and especially, publicity about the Public Health Service Syphillis Study in Tuskegee.

It is important to keep in mind that our current system that protects the rights of human subjects while permitting science to progress was not the product of a single dramatic experience like the trials of the Nazi doctors, but was the result of many individual efforts and historical factors over decades. Your efforts today are part of that undramatic but critically important process.

Thank you.

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Mr. SNOWBARGER. Thank you, Dr. Moreno.

Our final panelist on panel two is Dr. Paul Appelbaum, American Psychiatric Association. Dr. Appelbaum.

Dr. APPELBAUM. Thank you, Mr. Chairman. I am testifying on behalf of the American Psychiatric Association, which represents more than 42,000 psychiatric physicians nationwide. I serve the APA as its secretary and chair of its Ethics Appeals Board, and I'm also professor and chair of the Department of Psychiatry at the University of Massachusetts Medical School.

My research over the last two decades has focused on informed consent, including consent to medical research, for which I have been a strong advocate. I've also consulted with or made presentations to a wide variety of organizations, including the National Bioethics Advisory Commission and Public Responsibility in Medicine and Research. I and the APA welcome the subcommittee's interest in the critically important issue of insuring that individuals who participate in clinical trials are thoroughly protected.

If we are to master the diseases that affect the brain, we must have the assistance of persons who, unfortunately, suffer from mental disorders. We want to be clear, however, about our values here. The interests of the participants in research come first. If research cannot be performed without violating the rights of participants, it should not take place. Coercive techniques to obtain consent are unacceptable, as are inadequate or deceptive disclosures of information to potential subjects. We reject the claim that knowledge must be advanced at any price. And we welcome many of the suggestions made by the Inspector General's report and others for improvements in the system.

The American Psychiatric Association endorses as its starting point two key principles that should guide the work of IRBs in this area. First, minimizing risks to those persons who volunteer to participate in research studies; and, second, maximizing participants' knowledge of what their involvement will entail.

How can these principles be implemented? We have three general suggestions: First we must recognize that some populations evoke greater concern and may require greater efforts at protection than others. Given the concerns we've already heard here today regarding resources available for patient protections, it makes most sense to focus those resources on those subjects in research studies who are at greatest risk.

Second, we believe that additional safeguards for subjects should be tailored to the needs of particular participant populations rather than being applied on a blanket basis. This is consistent with the conclusions of the recent NIH panel report on research involving individuals with questionable capacity to consent, which I commend to you as having taken quite a level-headed approach toward these issues.

What might IRBs require of investigators in appropriate cases? We know that the presence of some degree of cognitive impairment, for example, is likely to call for special efforts at education to ensure that patients who are entering research studies understand the implications of research participation. Psychiatric researchers have already begun to employ some of these techniques for protecting participants' interests but we would like to see them applied on

a much broader scale. These approaches include: screening suspect populations for decisionmaking impairment prior to attempting to recruit them for research studies; testing potential participants after information disclosure to ensure that they have understood what is involved in research participation; and utilizing waiting periods between information disclosure and entry into the study to minimize the possibility of situational coercion. These are all measures that can be taken now under existing regulations and with the powers that IRBs currently have in hand. It is crucial, though, for each research project to be considered on its own with a determination made as to the cost and benefits of added protections in each particular case.

Third, mechanisms with appropriate safeguards are required for permitting persons who lack decisionmaking capacities because of age or illness to participate in research projects. Failure to provide such mechanisms, mechanisms such as those that Congressman Kucinich referred to earlier, advanced directives, would mean that no clinical research could take place on a variety of disorders, including dementia in the elderly and leukemia in children.

With regard to the HHS Inspector General's report itself, I believe that the observations in the draft report ring true and that the general thrust of the recommendations would, in fact, strengthen the IRB system on which the protection of research participants depends.

And in the discussion period, I would be delighted to amplify on particular changes that might, in fact, be widely adopted and useful for protecting research participants.

In conclusion, the American Psychiatric Association believes, and we hope that the members of this committee will agree, that the pursuit of answers to important questions about illness and the protection of the interests of research participants are not and should not be seen as mutually incompatible goals. We view this hearing as the beginning of a process and we look forward to continuing working on these issues in greater detail with you and with your staff.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Appelbaum follows:]

Mr. Chairman, I am Paul Appelbaum, MD, testifying on behalf of the American Psychiatric Association (APA). The APA is America's oldest medical specialty society, representing more than 42,000 psychiatric physicians nationwide. I serve the APA as its Secretary and Chair of its Ethics Appeals Board, and I am also Professor and Chair of the Department of Psychiatry at the University of Massachusetts Medical School.

My research over the last two decades has focused on legal and ethical aspects of medical practice, including informed consent to medical research. I welcome the subcommittee's interest in the critically important issue of insuring that individuals who participate in clinical trials are thoroughly protected.

If we are to master the diseases that affect the brain, we must have the assistance of persons who unfortunately suffer from mental disorders. We want to be clear, however, about our values here: the interests of the participants in the research project come first. If research cannot be performed without violating the rights of participants, it should not take place. Coercive techniques to obtain consent are unacceptable, as are inadequate or deceptive disclosures of information to potential subjects. We reject the claim that knowledge must be advanced at any price. Careful attention to the interests of research subjects is especially critical for persons whose illnesses may impair their cognitive or emotional functioning, thus reducing their capacities to protect themselves. Of course, protections must be carefully crafted so as not to unnecessarily impinge on the pursuit of new knowledge about these terrible disorders.

Scope and Importance of Research on Conditions that May Impair Cognitive Capacities

This Committee is undoubtedly well aware of the suffering associated with disorders that may impair cognition, including psychiatric, neurological, and other medical disorders. A recent World Health Organization report noted that of the ten leading causes of disability in the world, five were psychiatric conditions: unipolar depression, alcohol use, bipolar affective disorder, schizophrenia, and obsessive-compulsive disorder. The direct and indirect costs of mental illness and substance abuse in the United States totaled more than $313 billion in 1990. More than 2 million people in the United States are estimated to suffer from schizophrenia and bipolar disorder, and more than 4 million from Alzheimer's disease, the leading cause of dementia in the elderly. With the number of persons over 65 years of age expected to double by the year 2030, the prevalence of dementia and its costs for families and society will grow accordingly.

Effective research is the key to more effective treatment of these disorders and to reduction of the suffering they cause. The introduction of the first effective treatments for schizophrenia and other psychotic disorders in the 1950s permitted, for the first time in history, the long-term treatment of persons with these disorders in the community, rather than in institutions. More recently, the development of a newer generation of antipsychotic medications, with greater efficacy and fewer side-effects, has been estimated to have yielded savings of $1.4 billion per year since 1990. Lithium treatment for bipolar disorder, introduced in this country in the 1960s, has restored tens of thousands of patients to functional membership in society, at an estimated cost savings of $145 billion. None of these advances would have

been possible without the assistance of persons suffering from these disorders, who volunteered and with informed consent agreed to participate in trials of the effectiveness of these new medications.

Kathleen, who suffers from schizophrenia, is just one example of the millions of individuals who have benefited from psychiatric research. She explains: "Today I am happy to be alive. Taking a new anti-psychotic drug [olanzapine] has changed my life and my attitude." Kathleen says "the fifteen years before I found this medication were not easy." At age 31, Kathleen started to have schizophrenic episodes. "My husband divorced me...my children became ashamed of me," Kathleen explains, I lost my family, my home and nearly my life." In 1993, Kathleen started taking a new drug called olanzapine. She no longer suffers from symptoms of schizophrenia. Her family is together again and proud of her recovery. "I am ever so thankful for my success in overcoming my mental illness with this drug."

The future for research on disorders affecting the brain is also a bright one. New imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), promise advances in our ability to identify regions of the brain associated with cognitive and affective disorders. Precise characterization of the shape of neurotransmitter receptors in the brain is permitting the design of drug molecules targeted specifically at disordered brain systems.

Inevitably because the brains of human beings are unique in nature, human volunteers drawn from patients afflicted with these illnesses are essential for progress to be made. Moreover, unless research is to be restricted to the mildest forms of the disorders--which may limit our abilities to treat those people whose suffering is greatest--persons whose cognitive capacities are impaired will need to be involved. Thus, the urgency of the questions with which this Committee and other groups, such as the National Bioethics Advisory Commission, are dealing.

Protecting Persons in Research Projects on Conditions that May Impair Cognitive Capacities

The American Psychiatric Association endorses as its starting point in addressing the complexities of this area the dual importance of two key principles: 1) minimizing risk to those persons who volunteer to participate in research studies; and 2) maximizing participants' knowledge of what their involvement will entail, so that they can provide meaningful informed consent to participation. Were it not for the willingness of persons suffering from psychiatric, neurologic, and other disorders to join research projects, as I noted previously--often with the critical support of their families--no progress would be possible in the treatment of these disorders. Unless potential participants can be assured that their interests are being taken fully into account, the basis of trust on which the process depends will crumble.

How can these principles be implemented? First, we must recognize that some populations evoke greater concern, and may require greater efforts at protection, than others. This is not to suggest that attention should not be paid to protecting the interests of all persons recruited into research projects. Inadequate information about what a project entails, or confusion about how research participation may affect one's own care can impair the ability of even the most capable person to guard his or her own interests. Thus,

continuous improvement in the consent process and ongoing monitoring of its effectiveness is required for all medical research.

There is no question, however, that some potential participants in research will have a harder time than others in grasping what is involved. Defining this group is no simple matter. Reflection quickly reveals that potential problems are not limited to persons with psychiatric and neurological disorders. Other medical conditions--such as infection, lack of oxygen in the bloodstream, and metabolic imbalances--can impair thinking and compromise decision making abilities. Even something as ubiquitous in medical settings as physical pain can distract a person from attending to and assimilating information necessary for a knowledgeable consent.

Thus, if we are to fulfill our duty toward those participants most in need of protection, we cannot limit the scope of our attention only to persons with psychiatric or neurological disorders. Nor is the presence of a psychiatric or neurologic diagnosis alone sufficient to place a person in a high-risk group for difficulties in the consent process. Research has shown that the decision making abilities of many persons with mental disorders are no different from those of comparison groups free of such disorders. To classify all persons with mental disorders as cognitively or emotionally impaired would revive the stereotypes against which we have been struggling for so long. Rather, if resources are not to be wasted, effort diffused, and stigma promoted, individualized judgments must be made about the likelihood of decision making impairment in any population identified for inclusion in a research project. In our current regulatory system, those judgments are the responsibility of the Institutional Review Board (IRB). When the presence of such impairment is likely, additional safeguards would appear to be required.

The second focus for implementation of the principles that we suggest are central to protecting persons in research is that additional safeguards for subjects should be tailored to the needs of particular populations, rather than being applied on a blanket basis. This is consistent with the conclusions of the recent National Institutes of Health Panel Report on Research Involving Individuals with Questionable Capacity to Consent. Specifically, as the likelihood of cognitive impairment increases in a given population, and as the potential risks associated with research participation rise, greater attention should be given to additional protections for research participants. To do otherwise is to inappropriately burden medical research with the costs of putative protections that are unlikely to benefit the very people which they are intended to assist.

What is key, we believe, is to recognize that the presence of some degree of cognitive or emotional impairment does not in and of itself mean that potential participants cannot give an adequate informed consent to research. They may, however, require special efforts at education, with particular emphasis on ascertaining that they understand and appreciate the implications of research participation. Psychiatric researchers have already begun to employ some of these techniques for protecting patients' interests, but we would like to see them applied on a much broader scale. These approaches include screening suspect populations for decision making impairment; testing subjects after information disclosure to insure that they have understood what is involved in research participation; utilizing waiting periods between information disclosure and entry into the study to minimize the possibility of situational coercion, and

to allow potential participants to reflect on their desires and to discuss options with family members and other advisers; and providing extended educational sessions, including family members and persons who already have participated in the study in question, to maximize potential participants' grasp of what it means to enter this research project. By no means is this an exhaustive list of possibilities. It is crucial, though, for each research project to be considered on its own, with a determination made as to the costs and benefits of added protections in each particular case.

Third, mechanisms with appropriate safeguards are required for permitting persons who lack decision making capacities--either because of age or illness--to be entered into research projects. Failure to provide such mechanisms would mean no clinical research could take place on any disorders affecting children--from leukemia to depression. Such failure would also compromise research on dementia and other degenerative disorders. The National Institutes of Health have developed an innovative mechanism that allows persons who retain decision making capacity to designate someone else to make decisions for them when they are no longer able to choose whether or not to enter research projects. These and other approaches to utilizing advance directives in this area have the greatest promise for protecting the autonomy and fulfilling the wishes of research subjects.

Children, however, present a different set of problems. They are, by definition, unable to make decisions for themselves or to designate someone to do so on their behalf. Current regulations limit the degree of risk to which children can be exposed without prospect of therapeutic gain--and appropriately so. They also encourage respect for the desires of children to participate or not participate in research projects, despite their lack of legal competence. Of course, additional protections might be needed in high-risk studies.

HHS Inspector General Report

I believe the HHS' Inspector General's draft recommendations on improving the functioning of IRB's will help move our discussions forward. And I would like to remind everyone that the draft report does not claim that "widespread abuses" of the IRB process exists. I also would encourage the Committee to proceed carefully and methodically on these important and sensitive issues.

While the system is not in jeopardy, it is my view that we must recognize that because of the changing nature of medical research the IRB system that was established over 20 years ago could be improved and updated. In my view the most valuable recommendations that are worth further consideration in the report involve additional procedures relating to the expansion of large multi-site trials, additional training and sensitization of investigators, peer review and registration of IRBs, and greater evaluation of their work.

Conclusion

APA believes, and we hope the members of this Committee will agree, that the pursuit of answers to important questions about illness and the protection of the interests of research participants are not--and should not be seen as--mutually incompatible goals. As stated in the beginning: If we are to master the diseases that affect the brain, we must have the assistance of persons who unfortunately suffer from mental disorders. We view this hearing as the beginning of a process and we look forward to continue working on these issues in greater detail with the Committee.

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Mr. SNOWBARGER. Thank you, Dr. Appelbaum, and all the participants. For our questioning, I'm going to first turn to the chairman of the full committee, Mr. Burton.

Mr. BURTON. First of all, I want to thank all of you for participating and I hope that the impression has not been left on anyone that we think that research is not absolutely essential in our society. I think everybody understands that in order to come up with new methods to cure people of cancer and all other kinds of maladies that you have to conduct these clinical studies. And so we're not here to try to say that we shouldn't do them. What we're here to do is to try to find out how we can make this system better because, evidently there have been some real problems.

Mr. Spilker says in his testimony that he believes, that

> PhRMA believes that the IRB system is sound and is working well for pharmaceutical company-sponsored clinical trials. Patients are being informed of their rights in accordance with the basic elements required in the informed consent document they must read and sign, 21 CFR 50.25. Their safety is being fully considered and drugs are being appropriately researched.

When you read the report, the report says these letters, there were 69 letters, 69 of the 84 letters describing deficiencies that the FDA issued to drug researchers between April 1980 and 1995, says,

> These letters cited instances of serious misconduct, including failure to obtain informed consent; forgery of subject signatures on informed consent forms; failure to inform patients that a drug was experimental; fabrication of data to make subjects eligible for the study; submission of false electrocardiograms, x-rays, and lab tests results to the company underwriting the research; failure to report subjects' adverse reactions to drugs under study, including a subject's death; failure to obtain informed consent and an IRB approval in a study touting a human growth hormone as a cure for Alzheimer's disease; proceeding with a cancer study after FDA had suspended it for protocol deficiencies; and failure to inform patients that a drug sold to them was experimental and contained a steroid.

This is a GAO report, incidentally.

We had a fellow before our full committee not long ago, Mr. Joe Foster, and he had hypertension, very severe hypertension, and Mr. Foster decided to go into a study that he read about. He called and he went into this IRB study and they gave him a placebo. And the man had a heart attack and a stroke in just 6 days after he started the study. The man was here in a wheelchair and his life has been ruined because they gave him a placebo. Now that's a mistake that should not have been made.

And so there are deficiencies and for PhRMA to say that the system is sound and working well and there's no problems, at least that was the implication of that statement. It just isn't so. There are problems and they need to be corrected.

And the wash-outs that Mr. Foster talked about when he was before us concerns me a great deal. Where somebody is in the study and they're considered a wash-out and so they're not included in the statistical of the study. So you take people that may have a problem during the study, that may have an impact on the study, they're washed out and so they're not included. And so the study is biased and not complete, at least that's the appearance to me. And, of course, I'm a laymen. I'm not a scientist or a doctor. But when this stuff comes before us, it does concern us because we're here representing the American people.

The other thing that concerned me, of course, is the Fen-Phen study, to which you alluded, Dr. Walsh. You said that the kids only had one pill and obviously there could be no damage. I hope that was the case but the study appeared to be discriminatory on Hispanic youths and black youths and didn't include other ethnic people, and that was a concern of mine, and perhaps my colleague will expand on that a little bit further.

But I believe that the pharmaceutical industry and the universities that are involved in these studies and the scientific community needs to, along with the FDA and HHS and the others involved in this, needs to make absolutely sure that they close every single loophole to make sure that people like Joe Foster and their lives aren't ruined because of a mistake or because of miscalculation or because somebody didn't fill out the form or didn't inform the patient properly. That's just tragic.

And that Fen-Phen study on those kids—not the Fen-Phen, but the fenfluramine study on the kids in New York, they should be fully informed too. And I'm not sure that a lot of the parents were aware of the possible problems that could occur when they signed that consent form. They were concerned about the money, many of them, who were from lower income groups more than they were concerned about other issues.

With that, Mr. Chairman, I'll yield back my time.

Mr. SNOWBARGER. Thank you.

Mr. BURTON. If anyone cares to comment, I'll be glad to hear your comments.

Mr. SNOWBARGER. They're dumbfounded with your statement, Mr. Chairman. Thank you. Well, Dr. Levine.

Dr. LEVINE. I wish we had the time for me to react to everything you said. Let me just take up the issue of Mr. Foster. I'm not familiar with the case. It sounds very odd. First, the people who are included in most trials, placebo controlled trials of new anti-hypertension drugs, almost always are people who are in the category that we call "mild hypertension." It would help me so much if I knew what his diastolic pressure was.

Second, the probability of stroke or heart attack during a 1-week wash-out period is something that I actually calculated and published quite some time ago. I wish I knew that we were going to discuss this this morning but I can, if you'd like, tell you where you can find my calculated probability. But it's very, very tiny.

Third, the implication or the explication that people who get into trouble during the wash-out period are not incorporated into the final report is generally incorrect. It may be correct for that study but most typically the statistical design of these studies is what we call an intent to treat model where everybody is included whether or not they ever end up getting either the placebo or the drug.

But the major point I want to make is that when statements of this sort are made, stripped of their context, as they must necessarily be on this occasion, and then they are picked up in the press, it creates devastating effects. When the press picks up that children in New York were given a drug that was known to produce damage to the heart valves, that's incorrect. And it creates a terrible impression with the reading public.

First, the thing that was shown to produce damage to the heart valves was not fenfluramine, it was a combination of two drugs. And this effect was not seen until a year after that study was completed. Second, in order to get any problem of any sort it requires consistent exposure over a period of time, not an isolated single dose of one of the two drugs. But these stories then are picked up and presented without context and create the sorts of disincentives for people to serve on IRBs that I tried to call attention to in my prepared testimony.

Thank you.

Mr. BURTON. Mr. Chairman, may I briefly respond? Mr. Foster had extremely high hypertension. He should not have been in that study. He was inappropriately enrolled in the study. He was not reported as an adverse occurrence. He did not sign an informed consent form. And so this may be an aberration. It may be an aberration. It may be an IRB study where you had some people conducting it who weren't doing their job properly. But the fact is that should not occur.

And although you take issue with some of the statements we've made, and I understand that, it's evident to the IG who did the inspection—or the GAO study, that there's been problems. And there's been problems from people we had testify before the committee like Mr. Foster.

And we're not trying to stop people from being on IRBs. We understand that scientific research does have to take place and we want it to take place. But we want it to be as safe as possible and make sure that the people who are in the studies are fully informed and that it's controlled. And we have cases that have come before us where that was not the case.

Dr. LEVINE. I can't disagree with that. I just wanted to tell you that I just listed some of the bits of information that I would need to fully evaluate the report on Mr. Foster. And thank you, you've given me some of it.

Mr. BURTON. I'll be happy to give you all of that at the conclusion of the meeting.

Dr. LEVINE. Thank you.

Mr. SNOWBARGER. Dr. Oldham, you had a comment?

Dr. OLDHAM. Congressman Burton, I just wanted to make a quick comment in response to your remarks. First of all, just to appreciate the overall importance of what you're saying as the need to review this IRB process, while at the same time protecting the importance of continuing research. And I couldn't agree more. I think it's extremely important. We hope that we can continue to improve every aspect of our own institutional IRB functioning and we've been also participants in larger discussions in New York State, looking at specific ways to improve the system, some of which have been suggested here.

Regarding the specific study, I know Congressman Towns has raised some questions as well and Dr. Walsh may also be able to provide some more information that we hope can at least correct what I think has been some misunderstanding about this particular study. Our hope always and our belief is that we, in fact, carried out this study with correct and appropriate approvals in a safe and ethical way. And we believe that, in fact, this particular study

is one that did not produce any significant harm to any of the subjects. We can't prove that at this point and we try to remain as concerned as we can be and as involved as we can be. But there have been, I think, a series of misstated and misunderstood aspects of this situation that we would hope we can try to at least clarify.

Mr. SNOWBARGER. Thank you. Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. Let me begin by saying that in the New York study, the researchers reported that only a few children reported side effects. Having at least one study involving adults and fenfluramine, 90 percent had side effects. Some had side effects that were so severe that they were unable to perform their normal activities 1 day after receiving only a single dose. Several press reports have referred to children who have complained of physical and behavioral problems since participating in this trial. My question is what have you done to locate and provide examinations or treatment for these children, Dr. Walsh and Dr. Oldham?

Dr. WALSH. Yes, sir. Let me see what information I can provide for you. The information that you mentioned first about the study of adults, in which 90 percent were reported to have severe side effects. I'm familiar with that study. That study was actually published after the conclusion of the fenfluramine study that we're discussing here today. And I have some methodological concerns about it, which I'm not sure are worth going into. I would point out that the most frequent side effect was fatigue, affecting about 80 percent of the patients, and the next most frequent was headaches. So they were not in any way dangerous. But I'm also concerned that this study is inconsistent with a very large amount of information about the fenfluramine challenge procedure which has been used in research in both general medicine—Alzheimer's disease, substance abuse, irritable bowel syndrome, chronic fatigue syndrome—as well as in a variety of psychiatric illnesses, in, I think some thousands of individuals over the last 5 or 10 years. And there is consensus that this type of study is of low risk.

Finally, I think what reassures me the most is that the IRB was concerned. The concerns about the side effects of fenfluramine were present in the IRB's mind when these protocols were considered. We actually asked the investigators to report back to the IRB, after the first few subjects were done, to let us know if our initial judgment that this was a low risk study was correct because we wanted to be sure. After the first few subjects, the investigator assured us that he had both visited them frequently during the day. He actually had them fill out a "feeling thermometer" so they could rate how uncomfortable and unhappy they were. And all of the unpleasant ratings were low. We also asked the investigator to call the families the week after the study was done and to report back to the IRB whether families had serious concerns, or any concerns, and how the kid had done in the days and week following the test. And, again, uniformly, the report back to the IRB was that there were no significant problems. There were a couple of headaches and one episode of mild diarrhea but none of the families was concerned about these side effects.

So I don't know why, sir, the first study you mentioned—the Muldoon study—is an outlier. It does not seem to be typical of the

very large experience with this test and with the experience of Psychiatric Institute. But I am very, very comfortable in assuring you that I don't think any of these children experienced significant discomfort or distress certainly during this procedure.

Mr. TOWNS. But even with adults, fatigue was so severe they couldn't go to work the next day.

Dr. WALSH. Yes, sir. Indeed, that is the way it was described. The methodological issue, sir, is that there was no control group. We don't know how they would have felt if they hadn't gotten the pill. And it would be useful to know if the environment in which they were in, they were asked to fast for some long period of time at the time of the study, whether they were really reporting fatigue that was a result of other aspects of the study and not related to the use of fenfluramine. It's an unknown.

Mr. TOWNS. OK.

Dr. WALSH. But that question was not addressed by that study and I do think the study is an outlier. It isn't consistent with a lot of other information.

Mr. TOWNS. I'm not going to push the issue. I'm going to move on.

Mr. BURTON. Would the gentleman yield real briefly?

Mr. TOWNS. I'd be glad to yield.

Mr. BURTON. Why wasn't a placebo used so you could tell?

Dr. WALSH. You'd have to ask the investigators. I would concur.

Mr. TOWNS. Let me move very quickly because the yellow light is on. In today's New York Post, an assistant director at the New York State Psychiatric Institute said, "Researchers decided to target black and Hispanic children because they were the majority of the children in the family court's system." I have previous statements by the New York State Psychiatric Institute saying the children in the study were black and Hispanics because they reflected the make-up of the Washington Heights area in which the building is located. These are totally different explanations of the same situation. Mr. Chairman, I would like the witnesses, under oath, to tell us which is the truth, all the truth?

Dr. WALSH. I'd be pleased to, sir. There has been a lot of confusion about this. Let me see if I can tell you what I understand the facts to be. If I might, let me start with the protocol page that was presented earlier this morning that does, in fact, mention an inclusion criterion of being African-American or Hispanic and an exclusion criterion of being white. This was submitted to us when the protocol first arrived. I believe the circles around those ethnic descriptions are circles from the IRB because the IRB questioned this as soon as it arrived. And the investigators provided an explanation that, in fact, this was the make-up of the population that they expected to be included in the study. I'll get back to that.

They thought for scientific reasons it would be useful to exclude a small sub-group of individuals, namely the Caucasians. The IRB understood there was some scientific rationale behind it but felt it was not appropriate. And, therefore, asked the investigators—and I should point out, this is the investigators of the originating study, the mother study from which the participants in fenfluramine study came.

So we requested very clearly that these exclusion criteria be deleted. They were. The final protocol, the final study that was approved and conducted, did not use those criteria. What it did do was select—and this is the direct answer to your question——

Mr. TOWNS. Yes.

Dr. WALSH. The method by which families were asked to participate was that from the family court system of the Bronx and Manhattan, which are the boroughs they were either in or right next to, the investigators received the names and addresses of families who had an older boy who had been adjudicated a juvenile delinquent. There was no contact between the court system or the probation system and the family about the study. The investigators got information on how to contact the families, sent them a letter, asked if they might be interested in hearing about a research project, and then followed up with a phone call, and obtained informed consent, and so on.

Mr. TOWNS. Got the information from where? Where did they get that information from?

Dr. WALSH. Which information, sir?

Mr. TOWNS. In terms of how to get in touch with the families?

Dr. WALSH. Oh, from the family court system?

Mr. TOWNS. They provided that?

Dr. WALSH. The family court system, in accordance with State law. We had it checked by the attorneys and what I believe to be the appropriate legal folks in the New York court system, the family court system, provided just that information to the investigators, name and address, and identifying information. And then the investigators took it from there, period.

Dr. OLDHAM. If I may interject just one thing. When the letter went out from the investigators to the families, the families were asked to respond if they had no interest in participating and that was the end of it as far as any family was concerned if they chose not to go forward.

Dr. WALSH. It turns out that the ethnic distribution of people in this court system tends to be largely minorities and that is how the population of this sample was obtained. There were a few Caucasians in the mother study, not many. But that is the explanation. That's my understanding of the explanation for how the study was done and the facts.

I would point out that——

Mr. TOWNS. I understand what you're saying but the plan indicated to exclude them. I'm having trouble with that part.

Dr. WALSH. Sure. The——

Mr. TOWNS. Help me with that.

Dr. WALSH. I'll do the best I can, sir. As I said, the IRB also had a question about it. The rationale from the investigators was that there would—from what they understood, they already had obtained information, I assume by preliminary contact with the court system, that most of the kids would be African-American or Hispanic. And they were concerned that if they had small subgroups of other ethnic groups that it might complicate their analysis. If somehow the characteristics of the subgroups, for example, if they had other, greater access to services, if they had less discrimination in housing, might affect some of the factors that they were looking

at. And, therefore, they were worried about how to analyze the results. Often in the early phase of a study, people try to get a very uniform population of subjects. That was the explanation that we were given. And, as I said, the IRB, while having some understanding of the scientific niceness of having a uniform sample, did not feel it was appropriate and it was not permitted.

Dr. OLDHAM. Could I just add a word about that, Congressman Towns? That's not an unusual scientific approach.

Mr. TOWNS. Why did you wait—I'm sorry, I don't want to cut you off. I want to hear you.

Dr. OLDHAM. Let me just finish the point. There was a report in the New York Times a few months ago about a genetic study where, in fact, exactly the same methodology was reported where it was stated that because there was a need to make the sample as homogenous as possible and to remove any non-essential variables, all non-Caucasian subjects were excluded from that study. It was the reverse proportion but nonetheless the same methodology. In any event, as Dr. Walsh said, this group and the IRB felt that that was not an appropriate or sufficient scientific justification to make that decision in spite of the methodological reason that the investigators presented.

If I could add two other things: this was, at the time, once it was perceived that the predominance of this population would be minority, phase one in a large plan, which was to begin with this population and then move to an additional stage of the study that would move to other geographic areas so that we would end up with a large and ethnically quite diverse population. And, in fact, a second phase of the study was written up in an application and a protocol and submitted and reviewed by the National Institute of Mental Health. They noted in their "pink sheets," they're called, in their review that the subject selection and methodology were perfectly appropriate and that this would be a broadening population and would include additional ethnic groups. So that was part of the original plan but the starting place was with the populations that we had——

Mr. TOWNS. And funded—go ahead, go ahead.

Dr. OLDHAM. It was not ultimately funded but it was reviewed by NIMH and their critique of the methodology involved no criticism of the subject selection or the population component.

Mr. TOWNS. Well, let me just, Mr. Chairman, could I just have another few seconds? In your statement—I'm going to leave that part alone—you refer to recent shootings involving young people. And those shootings have been in the national news. White adolescent male children have also been involved. Yet, according to the research plan we have here, none of the younger siblings of those children would have been eligible to participate in this study. Is that an accurate statement?

Dr. WALSH. I don't think so, sir.

Mr. TOWNS. Why? Tell me why exactly?

Dr. WALSH. As I said, I mean it's a hypothetical. You're asking if a tragedy like that occurred in Manhattan and it was by a Caucasian——

Mr. TOWNS. Right.

Dr. WALSH. And that person was adjudicated as a juvenile delinquent and therefore met the criteria for the study, would they have been eligible for this study? The answer is yes. As far as I know, they would have been absolutely eligible for this study.

Mr. TOWNS. No, not according to the plan because they were excluded according to the plan. And I don't think you deny that. That's in writing.

Dr. WALSH. What gets confusing about the paperwork and the paperwork is certainly a burden IRBs have to deal with and the confusion is very understandable. But I can assure you both from my memory and from the facts, and I've got it here if you would like to see it——

Mr. TOWNS. I don't think you should consider this as a wild statement because the record is all I have. And that's the record.

Dr. WALSH. All right. Let me be very clear, as clear as I can be about this one. The display is down now. The first proposal, with the protocol to make the white exclusion arrived in January 1992——

Mr. SNOWBARGER. Could I ask that we put the other one back up again?

Mr. WALSH. So this is the one you're referring to, I think the one you're particularly concerned about, sir. This was the first draft of this protocol and the IRB's review of this protocol in March 1992 was, "Please delete the inclusion/exclusion criteria with regard to ethnicity." And that is what was done and that's the way that study was carried out. Some of the confusions maybe relate to this. I am very clear about this fact.

Some of the confusion may result from there being two protocols. There was one mother study and, embedded in it, was a second study, which was the fenfluramine study. In order to get to the fenfluramine study, the subject had to be in the mother study. And the memo I just read you deals with the mother study. So we made it very clear to the investigators from the first time we reviewed it that ethnic exclusions were not acceptable. They complied. And that's the way the study was run. You may have noticed in the fenfluramine study protocol file that ethnic exclusions reappear. The IRB again said these are not appropriate. These were not approved. What we were told was an investigator had obtained an earlier copy of the protocol and used it in an IRB submission inappropriately. So it was a paperwork mistake. But there was no doubt about the IRB's intention about this, and as far as I know, sir, the IRB's request to eliminate these ethnic exclusions were honored. To the best of my knowledge, this is the way the study was done.

Mr. TOWNS. Two years later.

Dr. WALSH. No, sir. No, sir. No, no, no, no, no. This is the paperwork problem.

Mr. TOWNS. Yes.

Dr. WALSH. For the mother study that ended up with 126 kids, we said the only way the investigators could get these kids was with no inclusion/exclusion criteria for ethnicity. That's the way every kid was recruited into the mother study, and only kids who got into the mother study, got to the fenfluramine study. I think the concern is that 2 years later we've got another protocol that

says "ethnic exclusions." So we said, "What?" We thought this issue had been resolved and the investigators said, "We pulled the wrong protocol from the file. That was the original one. We didn't intend to that." The IRB again said, "You can't do it this way." But they said it occurred—and I believe them, I mean I honestly believe them because there was a change in personnel on the investigator team. Those ethnic exclusion criteria were eliminated when they were first seen by the IRB. They were not used by the investigators in the conduct of this study. I've spoken to the investigators and that's what I've been told. Everything that I know, sir, agrees with the story that I'm telling you.

Mr. TOWNS. Mr. Chairman, I must say this and then I'm going to shut down and then let you move on. I just think it's sad that we can't rely on the record. I think that's very sad. I think that proves that the IG was right in terms of the statement that you made. In concluding let me just say that you've been very gracious with the time and I really appreciate that. Thank you so much.

Mr. SNOWBARGER. All right, Mr. Towns. In fact, I'm going to go back to Mr. Burton for a few questions.

Mr. BURTON. Yes, I have some brief questions. The Physician's Desk Reference says, "Caution should be exercised in prescribing fenfluramine for patients with a history of mental depression. Further, depression of mood may become evident while the patient is on fenfluramine or following withdrawal of fenfluramine." And it goes on. It also says, "Regarding pediatric use, safety and effectiveness in children below the age of 12 years has not been established. Fenfluramine hydrochloride is a controlled substance in schedule four. Fenfluramine is related chemically to the amphetamines, although it differs somewhat pharmacologically. The amphetamines and related stimulant drugs have been extensively abused and can produce tolerance and severe psychological dependence."

So I just have a couple of questions here. Is there any research data that would indicate it's safe for use in children under 12?

Dr. WALSH. Let me step back and then come to address that question directly.

Mr. BURTON. All right. Well, just keep that in mind because I want to give you two or three questions and answer them all at the same time.

Dr. WALSH. All right. Fine, fine. Very good.

Mr. BURTON. According to the Physician's Desk Reference, the safety and effectiveness on children below the age of 12 has not been established so I really would like to see if there is any research data on that.

Was the fenfluramine dosage adjusted for weight? Or did they all receive the same size pill? And what was the dose?

And then let me give you two more quick questions and then I'll let you answer all of them and I'll be finished.

Did anyone on the IRB object to using children in a non-therapeutic experiment that put them unnecessarily at risk, or possibly unnecessarily at risk? And since the fenfluramine challenge and experimental procedures were not reasonably commensurate with these children's actual or expected medical, dental, psychological, social, or educational situations, and were not likely to yield generalizable knowledge about the subjects' disorder or condition, as re-

quired under Federal regulations 45 CFR 46.406, by what ethical standard—by what ethical standard—was the experiment approved? If you'd just answer those questions, I'd appreciate it?

Dr. WALSH. Yes, sir. There are a number. Let me take the ones that you raised in the end of your question about the risk for kids commensurate with experience and generalizable knowledge.

Mr. BURTON. And ethical standards.

Dr. WALSH. And the ethical standards, yes, which are part of the ethical standards. In terms of risks for kids, yes, it's quite correct that fenfluramine was not approved, I don't think ever, for use in kids. Two things: approved refers to therapeutic use and it turns out that in our system, most of the drugs used in kids for treatment are not approved for use in kids. There is very, very limited testing of drugs that are routinely given by pediatricians to kids for treatment of illness. So that while this was of concern to the IRB, I mean the IRB recognized it hadn't been approved for use in kids, that fact didn't indicate that there was danger or a high-risk.

What the IRB did, and it did it on several occasions, was try to speak with people who were knowledgeable about fenfluramine used in the way it was proposed to be used in this study. It was adjusted per weight. The average dose was, I think, 34 milligrams. The top dose in the PDR was 120. So it was a low dose study. We tried to speak with other investigators who had used it in kids and to refer to the literature and to consult with other investigators who had used it in adults in this way. The consistent message that we got was this was regarded, used in this way, as a low-risk procedure. That, honestly, wasn't quite sufficient for us. We remained concerned about it. And as I tried to make clear earlier, we were sufficiently concerned to ask the investigators to report back to us on their initial experience with the first few kids to make sure that what we had been given to believe by these sorts of contacts and looking at the literature was, in fact, true. And I think we were reassured about it.

In terms of the ethical issues that you raise, which are part of the current Federal regulations for research with kids which is not directly intended to benefit them. Commensurate with their expected experience, the IRB did worry about this and consider it. After some thought, it was our judgment that the study was similar to a visit to a doctor in which they would get a blood test and it was sufficiently commensurate with that, that the risks of, and the distress of the study were commensurate with that procedure—similar enough to that procedure so that it could be approved under that rubric. It met the criterion that is specified that you described.

In terms of the generalizable knowledge, this, too, we worried about. The issue here was prediction of, or understanding of, the development of troubled behavior among youth. These kids were thought to be at risk for developing troubled behavior down the road under the timeframe of this study, so that increasing symptoms would likely emerge. And it was thought that it was a critically important issue to understand better, to understand the whatever biological component there may be to that development and see how it relates to the rearing environment. That was really the purpose of this study was to see if some of the biology, mostly

from studies of adults, seems to be somehow tied to violence, whether that sort of biology was alterable, was altered by the rearing environment. So it was felt to be of substantial importance to an important topic. The results of this study have actually been cited in the literature as being of importance, independently cited, as being of importance. So I think that the IRB's judgment was a reasonable one. Certainly other people might have come to different judgments, but it seemed like a reasonable judgment.

Dr. OLDHAM. Could I just follow with two points: One is that, in fact, just along the point Dr. Walsh was just making, there was a followup application to the National Institute of Mental Health to do a prevention study with these families to try to help these at-risk children and help the families cope with what had been a series of difficulties and high-stress situations in the families, and that was funded by NIMH and is currently underway as a prevention study to help these families directly as a second-step beyond this first study.

The other point, I just wanted to add a word about to underscore was the point you were asking about relating to the PDR and the approval of the medication. In fact, it is a problem. It is a problem that researchers are struggling with in many ways. There really are in this country very few FDA-approved drugs that are specifically approved for use with children. And that's extremely important because, in fact, certain uses of drugs that work well in adults may not have the same mechanism or the same degree of safety in children. We don't think that in this case that was a factor because, again, we were giving only the single low-dose and it was not even related to what the PDR talks about which is approval or not for therapeutic use over time at higher doses.

The problem is still a generic one and a large one that the NIMH has noticed. In fact, one of the directives that NIMH has sent out recently is that researchers must not only consider carefully in their research design the inclusion of all ethnic groups, but they must also consider the inclusion of children; so that there's a mandate from the Federal agency to focus on children because we don't have enough research in this area. How to balance that with all of these safety and ethical concerns is part of the reason why I think this entire oversight is critically important because these are particularly vulnerable populations and I think we need to figure out a way to do it but to do it ethically and safely.

Mr. SNOWBARGER. Dr. Spilker, would you care to followup on the pediatric research on pharmaceuticals and the new mandate that he just mentioned, from a pharmaceutical perspective?

Dr. SPILKER. Thank you. Pharmaceutical companies must approach pediatric trials very carefully and very conservatively. It requires a great deal of care on their part. They have to decide at what point during a drug's development it's appropriate to look to the pediatric population, that is, should they do that before the drug is on the market for adults, or should they wait until after it's on the market for adults? And usually it makes a lot more sense to gain more experience clinically in adults, and after the drug is on the market, to study it at that time.

Very often special formulations of the drug are needed for the pediatric population, a smaller size pill, a different dosage form, et

cetera. This takes research time and companies have to do that as well before they can initiate the trials. We realize there are special considerations in children and one of those is the question of age. For example, when I was at Burroughs-Wellcome, there were studies that were done on Actifed in different patient populations of 12 to 18, 5 to 12, 2 to 5, above 6 months. So you cannot just generalize and say, "pediatrics," you have to decide which are the different groups to study and you do this with the FDA. And this is worked out in collaboration with them so that the companies can decide how many separate populations have to be studied.

But, as you are probably aware, I'm sure you are, through FDAMA rules that were approved, which have a strong incentive for additional pediatric studies and the FDA's recent publication of a list of drugs where pediatric trials are being requested, there is going to be and is already ongoing a much larger number of clinical trials in pediatric populations than heretofore was the case, and I know that this will continue in the future.

Mr. SNOWBARGER. Thank you. I'm going to try to broaden this discussion out a little bit and get to an issue that, very frankly, I've got a little more experience with and that's the issue of informed consent. When I was in private life, I was an attorney and one of my clients was a relatively small hospital and so we dealt on a fairly consistent basis with consent forms; and there's only one thing worse than a doctor's explanation of what the consequences might be and that's the attorney for the doctor explaining what the consequences might be. [Laughter.]

And so I'm a little bit more familiar with the problems of trying to get a truly informed consent, both in terms giving the appropriate information but also having that information received in a meaningful way.

And not to pick on the New York Psychiatric Institute, but just to use it by way of example, it's my understanding in following up on the informed consent process, something like 1 out of every 10—only 1 out of every 10 persons seem to realize after the fact what they'd actually agreed to or what the study was all about, what it was supposed to show. And, again, they aren't researchers. They're not medical scientists. And so I suppose when we go in to ask them for informed consent, we are presuming an awful lot of what they can absorb in terms of the information.

But, again, to make it broader, I'd like to know what those of you who deal with this on a day-to-day basis are doing to assure that when someone says, "Yes, you can do this," or "Yes, you can do this with my child," how do we know that they indeed have given not only informed consent but that it isn't somehow pressured by the condition that they may find themselves in, that kind of thing. Dr. Moreno.

Mr. MORENO. Congressman, there's very little data in this field but it happens that the President's Advisory Committee on Human Radiation Experiments did conduct, in 1995, an extensive survey of people in medical oncology, radiation oncology, and cardiology studies, all around the country in about 1,900 individuals, and some of the findings may be interesting to you. And I'm going to try to do this from memory. We found that approximately 92 percent of the individuals who were in studies knew that they were in studies.

Raised the interesting question, what about the other 8 percent? How significant was the fact that they didn't seem to know they were in studies?

Mr. SNOWBARGER. Did it go one step further and they knew what the study was about?

Mr. MORENO. We also asked them in focus groups what their understanding was of the study. Many of them said, and the focus groups were not translatable into numbers, these were qualitative studies at this point, but many of the people said that they didn't really understand very much about the study when they signed the form. And that what they tended to do, in fact, some of them when they were being interviewed actually pulled the forms out of their briefcases or purses, they carried them around with them, much the way that I might carry around my insurance form if I didn't understand it and had a question about it. I might show it to a friend who understood how to read these things better than I did, or a relative, so that—this result actually gave me some comfort as somebody who had been in IRB editing consent forms, we often were worried that people didn't really read them before they signed them.

But it turns out that at least some people do read them. They use them as a source of information when they have a question. It also turned out—you may find this interesting, Mr. Chairman—that about a third of the people who said they were in studies, were not. And that may be because they were asked to be in a study and they signed a form and were never enrolled. Or it may be that they confused a regular therapeutic consent form with a research consent form. So the short answer to your question is we found, through the Radiation Advisory Committee, that most people knew they were in studies. The 8 percent who didn't know were in only minor increment over minimal risk studies. They were not in high-risk studies. Now that's not a perfect result.

We also found—and I think this is quite interesting—when we asked people in these focus groups why they stayed in research and some of them were very sick, why they got in and why they stayed in. They said, "I'm in research. I got into it because I hoped it would help me." "Well, didn't you know, weren't you told that this probably wouldn't help you? "Yeah, but I hoped. That was the only thing I had." But now some of them said, "As I'm getting sicker, I realize it's not going to help me and now I'm staying in because maybe it will help somebody else." So the altruism that is supposed to motivate the system in principle does kick in, but it doesn't always kick in right away.

Mr. SNOWBARGER. Dr. Levine.

Dr. LEVINE. Thank you. I want to comment on two of the questions that have come up. First, on informed consent. With very few exceptions, all studies on informed consent are not studies on informed consent, they're studies on memory. What do you remember about something somebody said to you some time ago? We have ample documentation that most patients and most research subjects do place as a high priority on informed consent as we do. There was one study where they videotaped informed consent to open heart surgery, and came back post-operatively and two out of three of the patients said, "No, there had never been a discussion

of informed consent." even though there they were on videotape. It's very hard to evaluate the process itself.

Second, I've heard all through the morning a common misunderstanding that informed consent is the consent form. It's not. Informed consent is a process involving a minimum of two people, the professional and the patient or subject. We emphasize that at Yale and I do know that many other IRBs do similar things. We have what we call the standard second paragraph which says in order to give consent to the study, you must understand various things. This will take place in a discussion. Do not read this form until you have decided that you want to consent, and then what we have is a document. And what the document does is serve as a reminder, as John Moreno says. They can carry it around. They can show it to their family and friends, "What do you think of this?" So there's two things about informed consent I wanted to say.

I also wanted to say something about the minority issue that came up earlier. In the 1970's, there was widespread perception that members of minority groups were being exploited in research. In response to that, many IRBs took pains to protect minorities and other presumably vulnerable populations from the burdens of participation in research. In the mid-to late 1980's, it became clear that we were committing a grave era by protecting minorities, by protecting women, by protecting children. We were depriving them, as a class of persons, of the benefits of knowledge that's developed about them and we've attempted to correct that. The Federal Government, through the National Institutes of Health and through the Food and Drug Administration, issued directives in the early 1990's saying from NIH, "We will not approve your application for funds unless you can demonstrate that you have reached out to include adequate numbers of minorities, adequate numbers of women." And more recently, as you heard, "adequate numbers of children in your protocols." And FDA has joined in this and said, "We don't approve or disapprove research protocols but if you don't have them in your research when you apply for a marketing permit, we're going to deny your marketing permit unless you've shown that you've recruited minorities, women, children." Now we have here a protocol which seems to stand the whole thing on its head. All they recruited were minorities. I just wanted to say that the messages that are coming——

Mr. TOWNS. I'm missing the point. The issue here is that they were all minorities. So I'm missing your point?

Dr. LEVINE. My point is that this is a very great departure from the current discussion of whether or not minorities should be included at all. The general trend has been to portray research, specifically since 1986, as more beneficial to groups of people than it is harmful, and that you have to reach out and make sure you include all groups. I am not trying to say that it is justified to include entirely one group or another. And I've had it explained to me by Dr. Walsh, that although it appears in this thing that there would be an exclusion of white people, his IRB said, just as my IRB would say, "No, you may not exclude white people."

Mr. TOWNS. Doctor, what happened here is that originally the IRB found that this test posed more than minimal risk and provided no direct benefit to the children and all of sudden they went

out and got all these minority kids and started the research. So the question in my mind was what change took place to allow for the experiment to move forward? That's the question. So I understand what you're saying but you're not really giving me the answer to that question in this specific situation.

Dr. LEVINE. Mr. Towns, I can't answer that question.

Mr. TOWNS. OK. Thank you.

Dr. LEVINE. What I am trying to say is that much has been made in the press of having recruited minority people and I just wanted to create a context. The national conversation on this issue has been oriented toward encouraging the recruitment of minority, as well as other populations previously considered vulnerable, because we recognized that our earlier behavior deprived these people. It was recognized as a class injustice, that they were being deprived of the benefits of developing new knowledge about them.

It's the very same phenomenon that creates what we call "the orphaning clause" on the package label for fenfluramine. Because if you didn't have data on children, it comes out saying, "We cannot give advice about the safe and effective use of fenfluramine in children under 12 years old." That we have recognized is a systematic deprivation of children as a class of the benefits of developing new knowledge about drug use.

Thank you.

Mr. SNOWBARGER. Dr. Appelbaum, back on informed consent, I think.

Dr. APPELBAUM. Yes, I wanted to respond to your question as to what can be done to ensure that subjects entering research in fact understand what the projects are about and appreciate what they're getting into. I think as an example of a question that can be addressed with relatively simple approaches that are within the current regulatory power of IRBs to require, and which some people are not employing but which are not routinely required. And let me tell you what I mean. If we, in studies that presented substantial risks in which we worried that participants might undergo harm, required that investigators demonstrate participants understanding of the information that was disclosed, prior to accepting them into the study which could be done by asking a relatively simple series of questions, probing their understanding. We would have documentation on all of the research subjects in those studies and how well they understood. And for those subjects who did not understand sufficient amounts of the information about what the study was about, we could then require that they undergo special additional educational procedures, watching videotapes, talking with people who had participated in those same studies previously, having special educational sessions one-on-one with people whose job it is to educate subjects about what research involves. All of those become possible and it begins with the relatively simple approach of asking a few questions to, in fact, ascertain that subjects understand what they're getting into.

Mr. SNOWBARGER. Any other comments on informed consent and where we go with that? Mr. Towns, do you want some more time?

Mr. TOWNS. No, I just——

Mr. SNOWBARGER. No, but you're going to talk anyway? Go right ahead, go right ahead. [Laughter.]

Mr. TOWNS. No, I really don't need more time. I just want to say the risks—it's one thing when you're going to benefit from something but then with a situation where you're being used as a guinea pig, that's another thing. And I think that's the thing that I'm sort of struggling with here. And I agree with you that there has been an effort to begin to reach out to include others and get a good cross-section but we're talking about something that took place where this was not the case. And we're talking about that specific situation. And, of course, that's the reason why I'm having some problems, Dr. Levine, in terms of following everything you're saying because here's a situation we're talking about that did—this happened. And we're not talking about 1980, what did you say when we started reaching out?

Dr. LEVINE. 1986 is the——

Mr. TOWNS. This happened after that.

Dr. LEVINE [continuing]. Sort of the windfall or the watershed year.

Mr. TOWNS. Yes, yes.

Dr. LEVINE. It was during the placebo-controlled trial of AZT in patients with AIDS. Let me say that I'm very sympathetic about the problem of doing research that has no components that could benefit the participants. I must say, however, that it's a necessary prelude to doing any research that is designed to develop a product or information that will benefit the participants. It's a painful thing. We take great pains when there is no objective of benefiting the subjects, participants, or patients and make it very clear in our standard boiler plate language in consent forms. We expect this also to be reflected in the discussions I talked about. The passage under the subtitle, "Benefits," the standard first sentence is, "This study is not designed to bring any direct benefit to you." We state it as starkly as we can. I know, however, that in phase one oncology studies, where we're giving very toxic drugs to people with near terminal cancer, for the first time they're ever put into humans, we make very stark statements about "not designed to benefit you." And then we go back the next day and ask these people, "Why are you in this study?" And they'll say, "It's the only chance I have." I don't know what we can do about that. We have even had studies where the funding dried up and patients in phase one studies have asked to pay for phase one studies out of their own pockets. I can't remake human nature and human hopes. I can tell you that we try very hard though.

Mr. TOWNS. Thank you very much, Mr. Chairman.

Mr. SNOWBARGER. Let me followup just on the last comment there because that was one of the questions I was getting at with trying to get a truly informed consent. Again, when you have someone that is that desperate. Let me just ask this question generally. Are these research subjects always, sometimes, never, compensated for participating in the studies?

Dr. LEVINE. Thank you for that question. First, if the Inspector General's office came out and looked at our IRB, they would find no IRB-appointed monitors of the consent process. We have different approaches to try to meet the needs in specific situations. In phase one oncology cancer chemotherapy studies, we put in the consent form and expect this to be reflected in the conversation,

"Don't sign up for this until you take not only the consent form, but the protocol and show it to your own doctor and ask for his or her advice as to whether it's a good idea for you to get involved in this." That doesn't show in the bureaucratic balance sheet. But I think—I would venture to say that offers more protection than any proposal I've heard for auditors, monitors. There are many, many examples of this.

What about compensation, to finally get to your question. I was quoted correctly in our local newspapers about 10 years ago that when you walk around the campus and you see advertisements that offer money for participation in research, the higher the number, the lower the risk. If there's no risk or minimal risks, we just let customary market factors determine the payment. But when we see that there's any serious risk in it, then we start hard-nosed negotiations. We do not want undue inducements to people in exchange for their bearing risks. And so if you see a low number, watch out.

Mr. SNOWBARGER. I'll tell my college-aged son. [Laughter.]

Dr. LEVINE. The other thing I heard this morning is that it's an undue inducement to offer kids a gift. In the 1970's, when we began thinking about who were we going to offer what, we decided as an institutional policy that we would offer parents a bit of compensation for their time and energy but that we would also offer something to the children. And some of the more suspicious, skeptical members of our committee said, "Well, if you give them money, the parents will probably take it away from them." So we gave them gift certificates. And we thought we were trying to accomplish a good thing to make sure the kids get this. We never said it was a quid pro quo. We never said up front, "We're going to give you this thing." But after the fact, we would say, "We're so glad you did this. We want to give you a present to show our appreciation." So you can look at any of these things through so many different perspectives.

Thank you, sir.

Mr. SNOWBARGER. Does anybody else care to comment on that? I want to make a couple of observations and then anybody that cares to respond, please do.

The report that really was the impetus for this hearing, a number of you have commented that it sounds bit too much like panic and high criticism, maybe a crisis situation. I'll tell you I did not take it that way. The title may sound that way but the report doesn't sound that way. But what I've heard from this panel is sort of the same thing but just from a different perspective and that is the system is great but it could use some help. Rather than it can use some help but it's great. So I'm not sure that you're really saying anything differently, it's just that, perhaps, you're a little more protective about the status quo and want to move slowly on future changes.

I just find this a little bit curious that, on the testimony of Dr. Bowen and Dr. Levine, one from a non-institutional public IRB and then one from an institutional one, it just seemed to me that Dr. Bowen was saying we need to have more public involvement, that we need to have training of our board members. And I almost got the impression that in the university setting it's preferable from

your perspective to have a more closed system. And I understand you may have gone outside the medical faculty to start pulling in people for the board. But if you don't get completely outside the institution, in my mind, it raises some question about how accurate the study is because the institution does have some interest, in the outcome of a study.

Dr. LEVINE. I apologize if I created that impression. What I meant to say is that we do not merely meet minimal requirements. The regulations say we need five members, one a non-scientist. We have 28 members, of which a large minority are non-scientists. Of our 28 members, 16 are scientists. So we're not messing around with the margins. We're trying to do the right thing.

Mr. SNOWBARGER. Dr. Bowen, do you want to comment about the membership training that you do?

Dr. BOWEN. Yes, I'll be happy to do that. The membership on our board, we have a total of 43 standing members and alternates, and of those, about one-third are non-scientific members. Usually we have attendance at a board meeting of seven or eight, either standing members or alternates.

And then the second part of your question?

Mr. SNOWBARGER. The training?

Dr. BOWEN. Training. When new people are recruited into the board, they are assigned a mentor and that mentor carries them through about 6 weeks of board meetings and the member decides when they are willing to assume the responsibility of the board. In addition to that, we provide quarterly training for all of the members, that's regulatory training as well as ethical, consciousness-raising, if you will. We have provided for 14 years an open meeting to all IRB members, a training seminar that includes both regulatory aspects as well as ethical, enlightenment training, if you will.

Mr. SNOWBARGER. Well, I want to just close this out by thanking all the panel members for your attendance here today. We really do appreciate the information that you've given to us. I would like to say for the record that we will probably be sending some follow-up questions and would appreciate your response to those questions. And with that, the hearing is adjourned.

[Whereupon, at 2 p.m., the subcommittee adjourned subject to the call of the Chair.]

[Additional information submitted for the hearing record follows:]

**Statement**

**of the**

**Health Industry Manufacturers Association (HIMA)**

**to**

**The House Government and Oversight Committee**
**Human Resources Subcommittee Hearing**

**on**

***"Institutional Review Boards (IRBs):***
***A System in Jeopardy"***

**Thursday, June 11, 1998**

The Office of the Inspector General's (OIG's) four recent reports on the Institutional Review Board (IRB) system describe the many challenges that face IRBs in today's dynamic health care environment. In particular, OIG expresses concern that the dramatic growth in clinical studies and biomedical research, combined with other factors, has placed the IRB system in jeopardy.

Yet - reports in the general media notwithstanding - OIG does not claim that widespread abuses exist. Instead, OIG's conclusion is that, overall, the current IRB system works well. HIMA concurs with this conclusion.

HIMA is a trade association representing more than 800 manufacturers of medical devices, diagnostic products and health information systems. HIMA members sponsor clinical investigations to establish the safety and effectiveness of medical devices. This Statement reflects HIMA's views on the IRB process applicable to clinical investigations of medical devices.

HIMA supports the role of the IRB process in the testing and clinical development of new medical devices. In the case of medical devices, the efforts of IRBs and industry, in conjunction with the Food and Drug Administration's (FDA's) oversight function, have combined to accelerate growth in the development and introduction of safe and effective medical devices. The healthy expansion of the medical device industry with its new technologies is, in part, directly attributable to the success of the IRB system.

Nonetheless, HIMA supports OIG recommendations that will help IRBs retain their capacity to operate in an efficient and effective manner. HIMA endorses OIG proposals to eliminate or lessen procedural requirements that promote a system of ministerial, rather than substantive, evaluation of research projects. Moreover, IRBs should be relieved of their responsibility for functions that are duplicative of those for which industry or government agencies are responsible. For example, FDA receives and reviews adverse event reports. FDA also has the expertise to analyze those reports. It is unreasonable to expect that IRBs can, or should, duplicate this task. The other activities described in OIG's report Institutional Review Boards: Promising Approaches that promote innovation in the management of IRBs' existing responsibilities should be encouraged.

HIMA also sees a role for industry in assisting IRBs accomplish their goals. For example, industry sponsors and their trade associations, like HIMA, could work with FDA and IRBs to develop training materials to educate IRB members on the scientific, technical and ethical issues associated with the testing of new technologies. In addition, industry, government agencies and patient advocacy organizations might cooperate to explore new technologies for promoting subjects' understanding of clinical research. Interactive software, videotapes and other teaching aids might be developed to complement the individualized dialogue with study participants.

FDA, with input from industry, could develop guidance documents that would help IRBs to most productively use their resources and expertise in a way that builds their unique capabilities. For example, these documents could describe the appropriate use of Data Safety Monitoring Boards, how to determine when the IRB should request information on prior IRB reviews, or how to evaluate the qualifications of proposed investigators. These guidelines would serve to protect human subjects by helping IRBs evaluate research protocols and research results, while still providing individual IRBs the flexibility to assess the merit of particular studies on a case-by-case basis.

HIMA does not support OIG's proposals to expand the role of IRBs to include responsibility for directly overseeing the operations of research sites or to conduct substantive performance evaluations. Given the growth in clinical studies, expansion of IRB responsibilities is inappropriate. IRBs do not have the time and resources to conduct the extensive oversight and research site-specific evaluation functions suggested by OIG. An IRB's time and energy should more appropriately be directed to its essential purpose: conducting thoughtful and meaningful reviews of proposed research projects, including the associated informed consent and ethical issues.

HIMA agrees that additional oversight at research sites might be helpful in certain narrowly defined circumstances. However, the direct oversight of approved research sites rests more appropriately with study sponsors and FDA. These parties are in the best position to establish strategies for ensuring the continued protection of human subjects participating in

ongoing clinical research. FDA, for example, extensively regulates clinical trials, and device companies regularly monitor the individual sites at which studies are conducted.

HIMA supports OIG's proposal for the development of performance evaluations to determine how well the informed consent process is actually working. Device companies currently strive to ensure that informed consent forms are meaningful, and that informed consent is properly obtained. However, HIMA rejects the implication that IRBs alone should be held accountable for ensuring success of the informed consent process. An IRB is a critical component of the informed consent process, but it cannot control the manner in which clinical investigators actually obtain the consent of research subjects. Nevertheless, performance evaluations of the actual informed consent process may provide constructive feedback useful to IRBs, investigators, sponsors and research facilities.

HIMA supports OIG's proposal that the National Institute of Health's Office of Protection From Research Risks (OPRR) and FDA convene symposia to develop performance measures and evaluation strategies based more fully on results. However, HIMA recommends that the symposia involve not only members of IRBs, but clinical investigators, industry sponsors, communication experts, patient advocates, the public and others. In this way, valid performance measures that reflect the entire environment in which the informed consent process takes place can be identified. Developing meaningful performance measures will require input from throughout the research community.

In conclusion, HIMA welcomes OIG's efforts to explore the issues facing IRBs. HIMA supports OIG's proposals to improve and facilitate the operation of IRBs. HIMA supports changes to the IRB system that promote efficiency to encourage the timely development of life-saving products without compromising the protection of human subjects. IRBs are integral to the protection of human subjects. Their role in ensuring that proposed research projects include adequate protections for the study subjects is well established. Efforts to reshape IRB operations should be designed to help them perform that function well. Responsibility for other activities, including direct oversight of clinical trial sites and performance evaluations of the informed consent process, rests more appropriately with study sponsors and the government.

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June 10, 1998

The Honorable Christopher Shays
House of Representatives
1502 Longworth House Office Building
Washington, DC 20515

Dear Chairman Shays:

The Biotechnology Industry Organization (BIO) is pleased to respond to your request that we comment on the report from the Office of Inspector General (OIG) which examines the state of Institutional Review Boards (IRBs). Unfortunately, we have not had sufficient time to review and work with our member companies to formulate policy positions on all the issues identified by the OIG's draft report. Since this will be an ongoing issue which deserves great attention, BIO is eager to work with you and your staff on this issue as we analyze the impact of these recommendations on the current IRB system.

As you know, BIO represents 770 biotechnology companies, academic institutions, state biotechnology centers and other organizations. Our members work with hundreds of IRBs annually to ensure that people who participate in research are not placed in danger and that there are no breaches to the confidentiality of the information that is used to research and develop life-saving medical technologies. In pursuing the development of new drugs and biologics, our members work with the Food and Drug Administration (FDA) to ensure that information from clinical research is obtained in compliance with federal regulations that protect human subjects in research.

It is extremely important to our members to establish protections for people who participate in biomedical research. Therefore, we urge you to continue consulting our industry as a resource on appropriate guidelines for IRBs. In fact, we were quite disappointed that the office of the OIG did not consider the involvement of the biotechnology industry nor seek its input during the year the agency spent preparing this report and recommendations. To the agency's credit we were only contacted for comment once this hearing was announced, however the notice was not timely enough for us to do substantive review of the recommendations. Changes to the current IRB system or any additional requirements for oversight of IRBs will have a

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direct impact on our members. The biotechnology industry has a great deal at stake in ensuring that IRBs and the system of protection research subjects is strong enough to continue to instill public confidence in the medical research system.

Contrary to the title of the draft OIG report, we do not believe that the IRB system is truly in "jeopardy." We agree that the system is under stress. However, we see no evidence that the system is in danger of collapsing. Due to the pressures on the current system, BIO urges both the legislative or administrative branches to avoid burdening IRBs with additional, tangential responsibilities. The biotech industry, academic medical centers, patient advocates, and representatives of IRBs need to assess the opportunities for reform and foster change and growth with a sensitivity to its impact on these vital institutions.

Although BIO is open to evaluating specific recommendations for reform, we would like to state for the record that we strongly support the basic structure of the current IRB system. There are numerous advantages to the current system. The parochial nature of IRBs and the mix of expert scientists and lay participants help promote sound review and decision-making regarding research protocols. IRBs ensure that there is local community input into decisions on safety in ongoing biomedical research and that local community perspective on protocols are considered.

We also are supportive of measures that would enhance the effectiveness of IRBs. Improving IRB performance in a way that will not impose additional burdens and requirements is necessary. We applaud the OIG's recommendation to improve the education and knowledge of IRB members. This will foster greater expertise in mission and substance and will only improve the quality of IRBs as they protect human subjects. This is particularly important if the number of lay participants is increased. We also agree that it is vital that IRBs to maintain their independence in evaluating protocols. We believe this can be achieved by firm statements and support from the FDA or the National Institutes of Health (NIH). IRB independence is imperative to avoid potential conflicts of interest that could compromise the protection of research subjects.

Although we agree with many of the OIG's recommendations, this report contains a number of suggestions for solutions to problems which BIO is not yet convinced exist. We are examining several of these issues. However, in our preliminary analysis, we do not feel that it is necessary at this time to revamp the current

assurance process at NIH, enlarge the FDA inspection processes, nor increase IRB on-sight research practices. We are concerned that these recommendations will only serve to detract from the IRBs' effectiveness and efficiency, rather than enhance their performance and mission.

The issue of improving the IRB system deserves thoughtful attention. As your subcommittee begins to examine possible methods of improving the IRB system, BIO hopes that you will continue to seek the advice of our organization and others that are currently involved in using IRBs. The National Bioethics Advisory Commission was charged with evaluating current federal protections for human subjects in research to ensure their rights and welfare; it is currently poised to examine the issue of IRBs. We encourage members of Congress to work with them and other experts as well as the biotech industry on this issue.

Thank you for this opportunity to begin our conversation on this important issue. BIO's Bioethics Committee was formed several years ago to examine ethical issues involved in research, particularly biomedical research on people who volunteer to test experimental therapies. We are currently reviewing the issues raised in the OIG document. As we formulate a position on this issue, we will be happy to share our findings with you. We look forward to working with you and your staff on these critical issues in the near future.

Sincerely,

Carl B. Feldbaum
President

B O S T O N U N I V E R S I T Y M E D I C A L C E N T E R
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June 3, 1998

for the Record

The Honorable Christopher Shays
Chairman
Subcommittee on Human Resources
Committee on Government Reform and Oversight
United States House of Representatives
B 372 Rayburn HOB
Washington, DC 20515

Dear Congressman Shays,

On April 24, 1998 I sent a letter to Clifford C. Sharke who heads the Assurance Office in the Office of Protection from Research Risks regarding their investigation of studies in which fenfluramine was administered to children in research that could not directly benefit the child-subjects. I am enclosing that letter to you and request that it be included in the record of the hearings that you have scheduled for June 11, 1998.

While my letter directly addresses the fenfluramine studies under investigation, I think it is important to note that these studies raise generic questions concerning the appropriate use of children as research subjects and the effectiveness of the regulations found at 45 CFR 46.401 *et seq.* in adequately protecting children as research subjects. Those regulations were promulgated in 1983 and it is time to evaluate them.

I am also enclosing a copy of a book co-edited by me and Dr. Michael A. Grodin entitled Children as Research Subjects: Science, Ethics and Law. I hope you will find this to be a useful reference during the course of your work on this topic.

I would be happy to provide you with further assistance in the future.

Sincerely,

Leonard H. Glantz, JD
Professor of Health Law

April 24, 1998

Clifford C. Scharke, D.M.D., M.P.H
Chief, Assurance Office
Division of Human Subjects Protections
Office of Protection from Research Risks
6100 Executive Blvd., Suite 3B-01
Rockville, MD 20892-7507

Dear Dr. Scharke,

I am writing to support the request of attorneys Ruth Lowenkron and Cliff Zucker for your office to investigate certain research activities conducted on children that was made in a letter to you dated December 23, 1997. I also support the concerns that were expressed in a letter that was sent to you on February 16, 1998 by professors Elizabeth Iglesias and Francisco Valdes and numerous other concerned academics and child advocates. These letters concern three published research studies that purport to investigate the relationship between serotonin and aggression in prepubertal children. The studies in question that I wish to comment on are, Pine et al, Neuroendocrine Response to Fenfluramine Challenge in Boys, 54 Arch Gen Psych 839 (1997) and Halperin et al, Serotonin, Aggression, and Parental Psychopathology in Children with Attention Deficit Disorder, 36 J Am Acad Child Adolescent Psychiatry 1391 (1997). Recent newspaper reports indicate that the concern of the press, at least, is focused on the administration of fenfluramine to children. While this presents a serious problem I believe that your review of these studies should look at several other issues as well.

**Subject Selection**

The letter by Professors Iglesias and Valdes and others focuses primarily on the vastly disproportionate use of minority children as subjects in these studies. Since these studies clearly offer no benefit to the children while having the capacity to stigmatize this population of children, this raises a most serious question under 45 CFR 46.111(a)(3) which requires the "equitable" selection of subjects. This section further requires IRBs to be particularly scrupulous in this regard when the research involves "vulnerable" populations or "economically or educationally disadvantaged persons." Again, it is obvious from the published research papers that all the subjects fell into this vulnerable category.

Recent newspaper reports indicate that a spokesperson for one of the institutions has argued that the vastly disproportionate African American and Hispanic make-up of the research subjects reflected the make-up of the population in its "catchment area." Even if this is true, it is entirely nonresponsive to the concern. The institution, in performing research, is not restricted to its catchment area for recruiting subjects. It could have recruited subjects that better represented the population if it chose to make the effort. By restricting its recruitment to its geographic location the researchers made it easier and somewhat less expensive for them to conduct the research. But convenience to the researchers in no way responds to the requirement that subject selection be "equitable."

**Risks**

The regulations require that an IRB find that the "risks to the subjects are reasonable in relation to anticipated benefits . . ." It is tempting to only review the risks of the administration of fenfluramine to children, particularly since the drug has apparently not been approved for use in children and was not administered with the intent to benefit the children but rather to induce a biological response. It is also important to review the risks to the children in terms of the psychiatric diagnoses or labels that were made purely for the purposes of the study. In the Pines study for example, it appears that children entered the study with no psychiatric diagnoses but left with diagnoses of oppositional defiant disorder, conduct disorder and attention-deficit hyperactivity disorder. Because labeling can have a negative impact on the way children are perceived and treated, and because these diagnoses were not made for the purposes of supplying treatment, this must be viewed as one of the significant risks these children incurred.

**Benefits**

It is without a doubt that these children-subjects were not intended to receive any benefit from participating in this research. As a result the question remains whether there was some other foreseeable benefit sufficient to justify the study under 45 CFR 46.111(2). In order to approve a research proposal, the IRB must determine the "importance of the knowledge that may reasonably be expected to result" from the research. The Pine study discusses the limits of the knowledge that could be gained from its results on page 844 of the published article. The authors note that they did not compare the children in this study with children who did not have a family history of delinquency, that there were no placebo challenges performed on a control arm, and that two dynamic constructs (rearing environment and serotonergic activity) were measured at single points in time. One could add to this that only children from minority groups were studied and so the relevance of the results to the general population cannot be known. Given these serious limitations in research design, all of which would be known at the time of IRB review, it is difficult to see how the IRB could determine that the "importance of the knowledge" could justify the approval of this research.

In this instance, since this research is governed by 45 CFR 46.406 (discussed further below), the research study must produce "generalizable knowledge... of vital importance." No project with the admitted methodological limitations this project had could meet this standard.

**Assent**

The children in the Pine study were from 6 to 12 years old and the publication says that "36 of the 56 eligible boys agreed to participate." (page 840) Similarly, Halperin notes that "consent was obtained from the parent and assent was obtained from the child (page 1393). The question that needs to be examined is how this was accomplished with children (as young as 6) who supposedly suffer from disorders that make them "oppositional," antisocial or unable to concentrate and listen closely. Indeed, one of the criterion for oppositional Defiant Disorder is, "often actively defies or refuses adult requests." (DSM-III-R diagnostic criteria for 313.81 Oppositional Defiant Disorder A.(3) ). The related issue is how any efforts of the children to withdraw from the studies were handled. Since many of the children were diagnosed with conditions that supposedly affect their ability to comply with adult commands, to concentrate or even to sit still ("often fidgets," "has difficulty remaining seated when required to do so," "is easily distracted" - DSM-III-R criteria for 314.01 attention-deficit Hyperactivity Disorder) one would expect that at least some of the children would have tried to exercise their right to "discontinue their participation at any time." (45 CFR 46.116(a)(8) ) Indeed, one would expect that many children when confronted with a needle that would remain in their arms for five hours would make an effort to refuse to participate, and that others would make an effort to terminate participation during the five hours that the fenfluramine challenge took. As part of your investigation you should determine how this provision was interpreted and applied by the investigators.

**Payment**

Given the nature of these studies, one wonders why a parent would agree to their child's participation. One newspaper reported that the parents were paid $125 for their child's participation in one of the studies. Given the impoverished nature of the subject population, it is important for OPRR to determine if there was any undue influence in this regard. Further, it is important to determine how and when the money would be paid. Were the parents paid the full amount for enrolling their child or only when the child completed all the studies? If the latter, this could affect the child's ability to withdraw from the study as discussed above.

**Washout period**

The Halperin study, in which the subjects were all diagnosed with ADHD, included a "1-month washout period for subjects who were taking medication." (page 1393) The Pine study says that the children had to be "free of medications for at least 1 month," but does not say that the children were taken off medication for the purposes of the study.

Assuming that the children in the Halperin study were seriously enough affected by ADHD so that medication was appropriately prescribed to treat the condition, the withdrawal of therapy from these children solely for the purposes of research places them at high risk for adverse consequences. There is no indication that the therapeutic drugs were withdrawn because they were not effective or caused undesirable side effects. Rather, therapeutic drugs were withdrawn solely for the purpose of preparing children to become subjects for the administration of a non-therapeutic drug. If the drugs to treat ADHD were withdrawn during the school year, then these children would have been deprived of a therapy that is intended to enable them to perform at school for at least 10% of the school year.

I would suggest OPRR investigate the methods the researchers used to ensure that the children suffered no adverse consequences from the withdrawal of therapy. For example, were they in contact with the children's teachers to determine if there was any deterioration of the child's behavior and performance at school.

**The application of 45 CFR 46.406 to these studies**

Since it is absolutely clear that these studies presented "no prospect of direct benefit to the individual subjects" the studies are governed by the provisions of 45 CFR 46.406. This section requires the IRB to find;

(a) "the risk represents a minor increase over minimal risk."

The term "minimal risk" means the magnitude and probability of harm or discomfort are not greater than those encountered in "daily life" or during the performance of "routine" physical and psychological examinations or tests. Certainly the withdrawal of an effective medication that is not producing intolerable side effects is a risk that is not found in daily life or in routine medical care. Nor are young children routinely subjected to five hour catheterizations and the ingestion of nonbeneficial drugs. It is also hard to imagine how the removal of a therapy that is designed to provide children a better chance of school success can be deemed a "minor increase" over minimal risk. Similarly, when one looks at the entire research process in the Pine study, which includes psychiatric testing and labeling only for research purposes, a 5 hour catheterization and the ingestion of a drug with no indication for use in children, it is hard to imagine how this all amounts to a "minor increase" over minimal risk.

(b) "the intervention or procedure presents experiences to subjects that are reasonably commensurate with these inherent in their actual or expected medical, dental, psychological, social or educational situations."

Prior to their enrollment in the research at issue, these children did not have any need for any type of care other than that expected by typical children. Certainly, the five hour drug challenge and intensive psychiatric testing would not be part of their "actual or expected" care absent enrollment in the study. Clearly, the withdrawal of an effective therapy that is not causing serious adverse effects is not "inherent" in any actual medical situation.

(c) "the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition."

This section of the regulation limits non-beneficial research to subjects who have a "disorder" or "condition" to enable the discovery of something of "vital importance" about the disorder or condition. In the Pine study the children had no diagnosed disorder or condition until they entered the study. The diagnosis of their "disorders" or "conditions" were only made by the investigators to determine the children's suitability to enter the study. Even then, not all the children in the study were diagnosed with such disorders or conditions. Of the 34 subjects, 10 were diagnosed with oppositional defiant or conduct disorders and 14 with ADHD, meaning that 10 other subjects had no condition or disorder. The 10 without a disorder or condition could not possibly be eligible to be in a study governed by 46.406, which makes having a "condition" or "disorder" a prerequisite to being a subject.

More importantly, the purpose of these studies was not to learn anything about these disorders or condition, but rather to attempt to only learn something about the relationship between aggression and serotonin levels. The children in the Pine study were not chosen as subjects because they had oppositional defiant or conduct disorder or ADHD, they were chosen as subjects because they had brothers who had been adjudicated delinquent. Their "conditions" or "disorders" were only determined after they were chosen as subjects. The psychiatric diagnoses were made in an attempt to determine which children-subjects were likely to become aggressive, the purpose of the study. The comment section of the Pine study discusses "serotonin and aggression" and "serotonin and rearing factors."(Pages 843-844) There is not any discussion of what was learned about any of the conditions with which the children were diagnosed.

Similarly, in the Halperin study, the results do not indicate that anything was learned about ADHD. (Pages 1396-7) Rather the results concern the relationship of aggression, prolactin response and parental history of aggressive behavior.

Whatever value the Pine and Halperin studies may have, they in no way provide any information that is of "vital importance to the understanding or amelioration of the subjects' disorder or condition." This is because the studies were not designed to study any disorder or condition. Rather the investigators used the subjects' disorders or conditions as a way of

determining eligibility for a study of aggression and serotonin. As a result of this, it appears that studies do not comport with the requirements of 45 CFR 46.406.

Your review of these studies provides an important opportunity to determine the appropriate use of children in non-beneficial research studies. Your conclusions will not only determine the appropriateness of the use of the children in these particular studies, but will provide important guidance to IRBs and investigators in the future. I would be happy to provide any additional information that you might find helpful.

Sincerely,

Leonard H. Glantz, JD
Professor of Health Law

Testimony before the House Government Reform and Oversight Committee

Subcommittee on Human Resources.

Representative Christopher Shays, Chairman.

Washington, DC

June 11, 1998

My name is Robert Helms. I am a house painter, an activist, and a writer living in Philadelphia. For the past three years I have been regularly supplementing my income by serving as a healthy test subject in scientific experiments. I have done this 25 or 30 times, mostly in Phase One clinical trials for Investigational New Drugs.

Since 1996 I have been publishing a small periodical called *Guinea Pig Zero*, which attempts to foster self-respect among research volunteers and also to advocate for our rights and welfare. By sharing information in our own interest and developing a culture independently of our learned employers, we are less likely to be exploited, maltreated or abused.

Among the regular features of this periodical are site evaluations that I call "Research Unit Report Cards." I collect information on clinical research facilities both from my own experiences and from the testimonies of other volunteers. I evaluate the units by comparing them with each other, not by holding them to a standard that I have established in the abstract. Some of the criteria I use are the level of professional staff skills, the attitudes of clinical staff (whether respectful or not), the quality of the food and accommodations, and the compensation rates. Obviously some of these items are more important than others.

My testimony today pertains to the way in which the informed consent documents are handled by recruiting staff at the clinical research units where I have volunteered in recent months. All of the units I know provide each volunteer with his or her own hard copy of the informed consent document. The

problem is that some research teams hand it over only after the volunteer has checked into the research unit for the in-patient phase of the clinical trial, or even hold it until the time of the person's discharge from the unit. Most units do it the right way, i.e. they give the volunteer a copy of the document at the time when the s/he first reads it and signs it.

Failing to provide a healthy volunteer with the consent document at the earliest possible time is wrong in a several ways. Here I will narrate one recent example of each of these methods and then explain why I feel that every volunteer should receive and possess the document as early as possible in every clinical trial. Both of the establishments that I will presently describe are staffed by competent and respectful staffs, and I wish to stress that while the first of these establishments handled the informed consent documents in a way I consider problematic, the staff there was forthcoming on the matter and they made it clear that the IRB had instructed them to handle the documents as they did.

The following is an example of the problematic pattern:

On January 4, 1998, I reported for a pre-study screening appointment at ICCR (now called Phoenix Neptune) at 105 Neptune Blvd. in Neptune, New Jersey. On that day the nursing staff took a urine sample, several tubes of blood, and an electrocardiogram to ascertain that I was free of drugs of abuse and that I was eligible for the study. I was shown a draft copy of the informed consent document for Protocol Number CV131-123, WIRB 980045. It was a study for two hypertension drugs that had already been approved by the FDA, to be used in combination. I saw no problem in the study, I read and signed the document, and the staff interviewed me in the usual way to be sure that I knew what I was doing. When the screening was over I confirmed my time and date for admission to the study, of course on the assumption that my blood and urine would pass muster. However, as I was leaving I asked for a copy of the consent document. The recruiter said that she could not provide me with one because the copy I had signed was a draft, and not the final, approved copy of the document. On the previous occasions when I

had done studies at ICCR, I was always given a copy when I screened, whether it was a draft or not. This is why I was puzzled by the change. I went ahead with the study anyway, because I needed the money.

At 7:30 AM on January 11, 1998 I reported again to ICCR in Neptune NJ for admission to the study. On that particular occasion the admission took all day because there were quite a few people being admitted to the unit. It included a repeat of all the tests that had been done at the screening appointment and a physical exam by a physician. At about 1:15 PM all of the volunteers for the study in which I was to participate were called together so that the informed consent document could be explained in detail, then read and signed by the volunteers. When this process was finished I again asked to be given my own copy of the document. The head nurse, Ms. Patricia Haws, explained that she would provide a copy of the document at the end of the study, when all the volunteers were discharged, which meant three days later. Afterwards I approached Ms. Haws and asked why this delay in handing over the volunteer's copy was necessary. She very patiently explained to me that there were two reasons: first, there had been a misunderstanding between a volunteer and the staff in an earlier study because of a change in the number of blood draws after a draft copy of the consent form had been given out. The volunteer had called the Western Institutional Review Board (WIRB) in Olympia, Washington and complained that he should be getting a larger stipend, but he had based this assumption on the draft copy. The second reason was that she did not like to see the documents casually left around the unit by volunteers, as had happened many times in the past. She said that she took informed consent very seriously, so it was annoying to find one of the documents in the rest room or on top of the television.

Next I will narrate an example of how the documents should be handled:

On March 17, 1998 I reported for a screening visit at the Covance Clinical research Unit at 309 West Washington Avenue in Madison, Wisconsin. I gave blood and urine samples, was examined by a doctor, and was shown two copies of the informed consent document for study number 8569-2, Revision A. There was an interview by which the staff nurse made sure I understood what I was doing, I signed

both copies and the nurse also signed both as a witness. She then kept one of them, and gave me the other copy to keep, without my having asked for it.

I reported for admission to the study at Covance a week later, on March 24. After repeating the blood samples and the usual routine, my group was called together and told that because of a wording change in the informed consent document, we had to go through the entire informed consent process again. The verb "causes" had been changed to "may cause." That was the only change, and it had moved the document from Revision A to Revision B. Again I was handed two identical forms and kept one for myself. The study was performed, medical science moved forward, and I received $1,300.

Now I will explain why the practice of giving over the hard copy of the consent document at the earliest opportunity is the only right way, and why waiting until any later time is always the wrong way. In my opinion the most critical and profound piece of business that takes place during the testing of a new drug or medical procedure is the process by which informed consent is obtained from the human subject. As everyone here today knows, the collective conscience of good scientists throughout the world agrees with me. When I seek casual employment by volunteering my flesh for clinical trials, there will almost always be a time lapse of 1-2 weeks between the screening and the beginning of the study itself. During that time I like to read over the consent document, call friends in health care professions with questions, and when I do this I name or describe the drugs, and give the dosage levels. Then I listen for an assurance that the study I've agreed to doesn't sound strange or more likely to cause harm than I thought it would. When I make these calls I must have the information contained in the informed consent form, and for me to possess that information I must have it on paper. In other words, informed consent is made of information. Neither I nor any other research subject is able to memorize a six-page document by reading it once.

If I must wait until the admission date before I possess the information I've consented to, I will be less able to back out of the study then because I will have redrawn my monthly schedule to accommodate the study, and I may have earmarked the money I was to earn there to pay off specific debts. If I have the

document from the time of the screening visit, I can change my mind the next day without creating any problems for myself.

Let me explain it in business terms: The informed consent document is a contract between the researcher and the experimental subject. It can involve a transfer of anywhere from $100 to $10,000. Anyone who signs a contract without receiving a copy thereof is either a fool or a person who has been negotiating from a position of extreme disadvantage. If I were to buy merchandise for any amount in this range, I would want a receipt, and if one were not forthcoming I would question the motives of the seller. When I don't get a consent form from a research unit until the information in it describes past events, I come to believe that the firm's legal team has bent the laws in their own favor, in precisely the moment when every possible choice should be decided in favor of giving more and better information to the subject. Let's remember that in almost every case, the volunteer does not have a lawyer. Even without one, I can figure out that I will not be harmed in any way because my fellow subject has left his paperwork in the bathroom or because another has argued with an IRB member after misreading the draft copy of his consent form.

I should note that the unit in Neptune is not the only place where the consent form was copied to me later than it should have been. The same problem arose in a Philadelphia research site and at another in New Brunswick, New Jersey, both during 1996. I mention Neptune only because the case is more recent. I am confident that no statistics exist that include a mention of this phenomenon and that it is the practice at many research units throughout the United States.

Ladies and gentlemen, this is not an etiquette problem. If there is any argument supporting or allowing for the delayed delivery of informed consent documents, it must by necessity come from the researchers' point of view. For this reason the practice should be brought to an end.

THANK YOU.

# AMERICAN HOME PRODUCTS CORPORATION

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June 10, 1998

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
Committee on Government Reform & Oversight
U.S. House of Representatives
B-372 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Shays:

Wyeth-Ayerst Laboratories, the pharmaceutical division of American Home Products Corporation, was the manufacturer of fenfluramine (brand name Pondimin). As such, we received an inquiry from Congressman Towns' staff as to our knowledge of a study using this product that was conducted in New York commencing in 1994. Wyeth-Ayerst has searched files in multiple internal departments and has found no record of being contacted by any investigator involved in this study. Our knowledge of the study is limited to information provided in press accounts.

If you have any further questions, please feel free to contact me.

Sincerely,

Leo C. Jardot

Leo C. Jardot

cc: Honorable Ed Towns

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6 June 1998

The Honorable Christopher Shays
Chairman, Subcommittee on Human Resources
Committee on Government Reform and Oversight
House of Representatives
Washington, D.C.

Dear Congressman Shays,

As your committee reviews the workings of the Institutional Review Board system I ask that you give a portion of your attention to the nonaffiliate member, that person who serves to bring "sensitivity to such issues as community attitudes" as well as contributing to a thorough review.

It is important to acknowledge that the community, represented by the nonaffiliate member, has a unique perspective that deserves to be heard and should be recognized and encouraged. This, of course, means commitment to education and training of nonaffiliate members as well as to raising consciousness of the value of these members.

If your committee members can imagine yourselves as patients considering research participation you will appreciate the need for a strong voice which fearlessly seeks to protect, interpret, empathize, and understand you. We all understand this need, and we must pay special attention to developing and supporting nonaffiliate IRB members whose charge it is to strengthen this special voice, a voice that is essential for proper institutional review.

At the present time, some simple reforms could greatly improve the IRB system. In particular, I hope you will consider a reevaluation of Part 46, 46.108 of the regulations before you. Presently, nonaffiliates lack standing in the power structure sufficient to carry out their job, as is evidenced by the regulations which do not specify the requirement that the nonaffiliate community member be in attendance in order to conduct a meeting or a vote. As a result, the institution is not protected against challenges to research approved "in house." I also believe strongly that an expansion of the number serving to bring the ratio of community members to affiliated members closer to the 1:5 recommended in the proposed regulations is forward looking.

I have served for many years on institutional review boards. It is fascinating, rewarding, important work. As a voice of community interest, I want to see the nonaffiliate contribution become indispensable.

Sincerely,

Melinda Hurst

Melinda Hurst

Nonaffiliate Member
California State Committee for Protection of Human Subjects, Health and Welfare Agency
Los Angeles County/University of Southern California Medical Center, IRB

# FEDERALLY FUNDED
# RELAPSE PRODUCING EXPERIMENTS in PSYCHIATRY:
# DRUG WASHOUT AND CHEMICAL PROVOCATION

Statement
To

Sub-Committee on Human Resources
Committee on Government Reform and Oversight
United States Government
U.S. House of Representative

by

Vera Hassner Sharav, M.L.S.
Director, Co-founder

**Citizens For Responsible Care in Psychiatry and Research**

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June 11, 1998

**Fifty years after the Nuremberg Doctors Trial**

We have found published evidence that high risk, wholly nontherapeutic, speculative chemical "symptom-provocation" experiments (a.k.a. "challenge" "probe") are being conducted by American neuropsychiatric researchers on severely disabled patients and disadvantaged children. These experiments offer no possible benefit for the subjects– they are designed to exacerbate or induce severe psychotic symptoms in especially vulnerable patients:

> First, patients are subjected to abrupt withdrawal of their prescribed antipsychotic medications – thereby causing 40% to 67% to relapse;
>
> Then, rather than treating them, psychiatric researchers further exacerbate their patients' excruciating symptoms with psychosis-inducing chemical "probes" such as: amphetamine, L-dopa, methylphenidate and the PCP-derivative, ketamine, among others.

**Such experiments clearly undermine the welfare of severely disabled patients who seek treatment from doctors whom they perceive as "healers."**

The human subjects of these experiments are cognitively impaired, uncomprehending patients who are especially vulnerable, since their inability to function independently limits their free choice. Indeed, lacking the capacity to evaluate the risks and potential consequences involved, such individuals cannot volunteer to give or withhold informed consent for biochemical experiments – as is their human right since the Nuremberg Code. Researchers say "chemical challenge" experiments are a means of studying the underlying pathophysiology of severe mental illness, such as schizophrenia, ultimately leading to the development of improved treatments for future patients. **But, are experiments undermine the rights and welfare of involuntary human subjects morally acceptable?**

**The fenfluramine "challenge" experiments**, which we also discovered and brought to public attention, were conducted on 6 to 12 year old minority boys against their own best interest, with no intended benefit to them. These children were subjected to invasive, traumatic procedures and given a neurotoxic drug, thereby putting them unjustifiably at risk – to test the investigators' hypothesis of a biological predisposition to violence and delinquency by inducing and measuring the boys' serotonin levels. The inappropriate use of children in these stigmatizing experiments were approved and funded by the National Institute of Health (NIH) through the National Institute of Mental Health (NIMH) the National Center for Research Resources (NCRR):

The researchers acknowledge the federal grants awarded in their published report (See, Pine, et al, 1997; and Halperin, et al, 1997): MH-16432; MH-43878; MH-01391; MH-01039; 1 RO1 MH-46448; 5MO1 RR0071.

**Factors contributing to unethical experimental exploitation -- especially of vulnerable persons, including children, who are unable to refuse:**

(1) Federal regulations are silent about what is not permissible in human experimentation - particularly in experiments involving those whose condition renders them "decisionally impaired," persons incapable, therefore, of protecting themselves from unwanted experimentation.

(2) Federal regulations leave the entire human research enterprise in the hands of researchers and their colleagues on Institutional Review Boards (IRBs). This includes evaluation of the merit of the proposed research, the design of the protocol, the procedures, risks, selection of subjects and capacity assessment, determining what is disclosed in informed consent documents and the procedures for obtaining consent -- monitoring the subjects' well-being and reporting "adverse incidents" are also left to their discretion. This absolute power in the hands of researchers over helpless and disenfranchised persons gave rise to major conflicts of interest.

Indeed, three federal agencies, the General Accounting Office, the Office of Protection from Research Risks, and the Office of the Inspector General each concluded after their separate investigations, that IRBs often do not, in fact, examine even the high risk human studies they approve. IRB are almost exclusively composed of colleagues of the researchers whose own and the institution's interest in obtaining lucrative research contracts can easily override their sense of moral responsibility toward vulnerable human subjects.

(3) the absence of accountability for causing human subjects undue pain and torment -- even when ethical or clinical standards have been violated -- has led over zealous investigators who assumed no personal risks, to require their unprotected human subjects to assume ever greater risks and potential long-term harm "for the sake of scientific knowledge."

(4) a powerful consortium of "confluent" interests has set the practice standards for psychiatric research and given themselves permission to use uncomprehending, "decisionally impaired" patients as means to their end: the American College of Neuropsychopharmacologists (ACNP) and NIMH who are actively lobbying against regulatory reforms such as independent oversight.

**NIMH bears the major responsibility for current ethical violations in psychiatric research:** As the authorized federal agency approving federal mental health grant proposals involving mentally disabled human subjects and children, NIMH is also entrusted to ensure that "the rights and safety of participants of clinical research" are protected. However, NIMH is contradicting public policy by supporting, conducting and funding experiments in which human rights are violated, and the welfare of disabled subjects endangered.

The agency's failure to protect "the rights and safety" of disabled research subjects, as is its public responsibility, arises from a fundamental, though undisclosed conflict of interest: NIMH's leading researchers and administrators are members of ACNP, some actually serving on its governing Council, formulating lobbying strategies against federal regulatory safeguards. This conflict of interest is reflected in NIMH's January 30, 1998 response to our requests, under the Freedom of Information Act (FOIA), for Informed Consent documents involving symptom-provoking experiments conducted at, or funded by NIMH: "NIMH is not a repository for informed consent documents; grantee institutions are not routinely required to submit copies of these records in clinical research studies."

> **Who then, ensures that ethical and legal safeguards are followed and that Informed Consent forms fully disclose the risks involved to comprehending subjects?**

NIMH's failure to review Informed Consent documents demonstrates the agency's disregard for the rights and welfare of human subject and an absence of monitoring and accountability -- thereby validating the need for oversight by independent auditors. **Citizens for Responsible Care in Psychiatry & Research** consequently call for a thorough, independent examination of the nature and conduct of neuropsychiatric experiments so that meaningful protections are enacted. As the attached list of over 100 published symptom-provocation experiments shows, such experiments are funded by the federal government and conducted at premier academic medical research centers, Veterans Affairs hospitals and the National Institute of Mental Health.

> **Who is accountable for the conduct of biomedical research on vulnerable persons such as mentally disabled patients and children?**

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**RELAPSE PRODUCING EXPERIMENTS in PSYCHIATRY:**
**DRUG WASHOUT AND CHEMICAL PROVOCATION**

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