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OFFICE OF INSPECTOR GENERAL

Institutional Review Boards:

A Time for Reform

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EXECUTIVE SUMMARY

PURPOSE

To summarize the challenges facing institutional review boards and to make recommendations for Federal oversight.

BACKGROUND

Role of Institutional Review Boards

Institutional review boards (IRBs) play vital roles in protecting human research subjects. They review initial research plans to make certain that the plans provide subjects with adequate opportunity to provide informed consent and do not expose subjects to unreasonable risks. They also conduct continuing review of approved research to ensure that human-subject protections remain in force. They carry out their initial and continuing review functions in accord with Federal regulations first established in the 1970s and applicable to all research funded by the U.S. Department of Health and Human Services or carried out on products regulated by the Food and Drug Administration.

This Summary Report

This is a synthesis report. It draws on our broad inquiry of IRBs and on findings we presented in three parallel reports. Its overarching conclusion is that the long-established system for protecting human research subjects has vulnerabilities that threaten its effectiveness. In the report we highlight the major elements leading to this conclusion and offer recommendations for improvement. The recommendations are especially important in view of current Federal plans to increase significantly the numbers of human subjects participating in clinical trials, and proposals to give IRBs increased responsibility in the areas of genetics and confidentiality.

With this report, we offer a warning signal and a framework for a concerted response to it. We do not document, nor do we suggest that widespread harm is being done to human subjects. We recognize the strengths of the current system and seek to build on them to enhance human-subject protections.

Methodology

Given our focus on the overall system of protections, we did not carry out audits of IRBs or investigations of particular cases. To help us understand the big picture, we conducted an extensive review of Federal records and pertinent literature; held interviews and group discussions with many Federal officials and with representatives of about 75 IRBs; visited IRBs at 6 academic health centers where extensive clinical research is taking place; attended IRB meetings; and accompanied FDA inspectors on IRB site visits.

FINDINGS

The Effectiveness of IRBs Is in Jeopardy.

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

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

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

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

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

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

RECOMMENDATIONS

With the above findings, we do not claim that there are widespread abuses of human research subjects. The current system of protections is supported by many conscientious research investigators committed to protecting human subjects and by many dedicated IRB members and staff doing their best under trying circumstances. A reviewer of this system can not help but be impressed by the contributions of these individuals, and the important function that IRBs have fulfilled over the past quarter of a century.

But our findings present an important warning signal. The capacity of IRBs to accomplish all that is expected of them is strained. In the years ahead, this difficult situation could become even worse in view of Federal plans to increase significantly the numbers of subjects in clinical trials and various proposals to give IRBs added responsibility in the areas of genetics and confidentiality. It is time, we believe, for reform.

Our recommendations offer a framework for such a response. We direct them jointly to the two HHS agencies responsible for IRB oversight: the Office of Protection from Research Risks (OPRR), which is located within the National Institutes of Health (NIH), and the Food and Drug Administration (FDA). These agencies oversee IRBs with different jurisdictions and operational approaches. It is essential, therefore, for them to collaborate closely if HHS as a whole is to respond effectively to the serious concerns that emerge from our inquiry. Below we present our general recommendations for the two agencies. In the text, we offer more explicit elaborations directed, as appropriate, to the particular agencies.

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

- Eliminate or lessen some of the procedural requirements directed to IRBs.

- Require that IRBs undergo regular performance-focused evaluations.

Strengthen Continuing Protections for Human Subjects Participating in Research.

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

- Provide IRBs with feedback on developments concerning multi-site trials.
- Routinely provide IRBs with feedback about FDA actions against investigators.
- Require sponsors and investigators to notify IRBs of prior reviews of research plans.
- Call for increased IRB awareness of on-site research practices.

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

- Require that research institutions have a program for educating its investigators on human-subject protections.
- Require that investigators provide a written attestation of their familiarity with and commitment to human-subject protections.
- Require that IRBs have an educational program for board members.

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

- Require more representation on IRBs of nonscientific and noninstitutional members.
- Reinforce to IRB institutions the importance of IRBs having sufficient independence.
- Prohibit IRB equity owners from participating in the IRB review process.

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

- Require that IRBs have access to adequate resources.

Reengineer the Federal Oversight Process.

- Revamp the NIH/OPRR assurance process.
- Revamp the FDA on-site inspection process.
- Require the registration of IRBs.

COMMENTS ON THE DRAFT REPORTS

Within the Department of Health and Human Services (HHS), we received comments on our four draft reports from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and jointly from the Assistant Secretary for Planning and Evaluation (ASPE) and the Assistant Secretary for Health (ASH). We also solicited and received comments from the following external organizations: the Applied Research Ethics National Association (ARENA), the American Association of Medical Colleges (AAMC), the Consortium of Independent Review Boards (CIRB), and Public Citizen's Health Research Group. We include the detailed text of their comments and our responses to them in appendix D. Below we summarize the major thrust of both their comments and our responses. We made a number of changes in the final reports. Most were technical in nature. Their comments sought to clarify certain findings and a few involved clarifications and elaborations concerning the recommendations.

NIH, FDA, and ASPE/ASH Comments

The HHS parties viewed the reports as raising important issues and recommendations warranting widespread discussion. They suggested various ways this could be accomplished. The NIH expressed particular support for our recommendation calling for the assurance process to be revamped so that it rests essentially on an institutional attestation to conform to IRB requirements and thereby enables OPRR to focus more on performance assessment and education. The FDA expressed reservations about refocusing its compliance-oriented inspection process, which it regards as having "great value," to one that is more performance-oriented. The FDA also raised concerns about the resource implications of some of our recommendations.

We will support efforts to engage broadly-based dialogue on our findings and recommendations. At the same time, we underscore the importance of practical near-term actions that can be taken to address the vulnerabilities we point out. We particularly urge that FDA and NIH incorporate into their oversight specific lines of inquiry to determine how well IRBs are actually protecting human subjects. This would call for examining such matters as how the processes of recruiting, selecting, and gaining informed consent from human subjects actually work. It would also call for addressing verification efforts to make sure that protocols are in fact submitted for review and that approved protocols do not stray off course. On the matter of resources, we agree that this is an important issue warranting serious attention in the research and policy communities, particularly in view of added responsibilities IRBs may well face in the years ahead.

External Organizations' Comments

While the external parties supported many of our findings and recommendations, they also raised some strong concerns. Basically, these involved differences of substance and objections to the use of certain terms and language. In regard to the former, Public

Citizen, in expressing considerable alarm over our findings, felt that we should have gone further with our investigations and recommendations. On the other hand, ARENA and AAMC had reservations about our call for performance-focused evaluations and for more outside representation on IRBs. They were also concerned that a more active IRB role in conducting continuing review could undermine the trust that has existed between IRBs and the research community. With respect to the language we used, ARENA, AAMC, and CIRB called for a more precise use of a number of terms. The ARENA indicated that our use of the term "IRB oversight" was particularly misleading. The ARENA and AAMC both indicated that some of our wording was unduly alarmist and more encompassing than our methodology warranted.

To facilitate a serious examination of the matters of substance we raise, we changed some of the language we used in the draft reports. Most notably, instead of referring to "IRB oversight," we focused on IRB responsibilities and authorities to conduct "continuing review," as specified in Federal regulations. But, this and various other such textual modifications we made in no way lessen our assessment that the effectiveness of the IRB system is in jeopardy. Our wide ranging and in-depth inquiry offers us ample basis to sound that warning. With respect to concerns raised that focus more strictly on matters of substance, we must underscore that if IRBs are to meet the significant challenges they face in the years ahead, they must become more fully accountable to the public. Trust in the investigators performing research is vitally important, but in itself is insufficient. The IRBs and Federal oversight agencies must find more effective and open ways of verifying that the consumer protection mission of IRBs is in fact being accomplished. This is especially important as the research environment in which IRBs function becomes increasingly commercialized.

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PURPOSE

To summarize the challenges facing institutional review boards and to make recommendations for Federal oversight.

BACKGROUND

On page three we offer a primer on IRBs: why they were established, what roles they perform, how they are organized, where they are located, and how they are overseen by the Department of Health and Human Services.

Prior Inquiries

For about a quarter of a century, IRBs have been playing an important role in protecting human subjects enrolled in research projects. Almost from the start, however, prominent studies have drawn attention to some of their limitations. A 1983 Presidential commission report raised concerns about the adequacy of the review procedures of some IRBs, about how well some of the members of these boards understood their roles, and about the commitment of some of the institutions to their IRBs.[1] Twelve years later, in 1995, a Presidential advisory committee raised even stronger concerns about the adequacy of the IRB review process, especially for research involving greater than minimal risks, and about the effectiveness of Federal oversight strategies.[2] In the following year, the General Accounting Office issued a report reinforcing these points and identifying numerous factors inhibiting IRB performance.[3]

In a recent inquiry of our own, we raised concerns about the continuing review effort of IRBs. In examining clinical trials involving four investigational medical devices, we discovered inadequacies related to IRB oversight in each case. These inadequacies 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.[4]

The concerns about human-subject protections become even more significant in view of current developments. These include current Federal plans to raise the level of funding for the National Institutes of Health (NIH), which would significantly increase the number of human subjects participating in clinical trials, and proposals to give IRBs increased responsibility in the areas of genetic testing and confidentiality.[5]

This Inquiry and Report

This inquiry builds on the prior reviews and, we hope, will contribute to the deliberations of the currently active Presidential advisory body examining the protections available to human subjects.[6] This report is one of four that has resulted from our total inquiry. It is a summary report that draws on our overall review and on findings presented in the three companion reports. It presents a picture of IRBs under considerable stress. It houses our recommendations for improving the current system of human-subject protections.

A second report, *Institutional Review Boards: Their Role in Reviewing Approved Research,* finds that continuing review of approved research is of vital importance but that IRBs are devoting little attention to this part of their mission. It also identifies key obstacles to effective continuing review. A third report, *Institutional Review Boards: Promising Approaches*, presents innovative strategies that IRBs have developed in six key areas of responsibility. These include promising approaches to managing the expanding workload and providing education to investigators and members. A fourth report, *Institutional Review Boards: The Emergence of Independent Boards,* finds that independent IRBs are becoming a significant force and addresses the advantages and disadvantages they present.

The inquiry that supports each of these reports draws on a rich variety of sources. These included analyses of Federal records; reviews of government documents and national commission reports produced over the past 25 years; articles and books addressing human-subject protections; site visits to IRBs in 6 academic health centers [7]; additional IRB site visits accompanying FDA inspectors; attendance at IRB meetings; 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 of varying sizes and auspices.[8] At the academic health centers, which are among the most heavily funded biomedical research centers in the country,[9] we interviewed not only IRB administrators and members, but also many others in the parent institutions who had a bearing on IRB performance. These included medical school deans; hospital vice presidents; heads of pertinent academic, administrative, and clinical committees or departments; attorneys; ethicists; and many others.

The thrust of our information gathering for this and the other reports was to gain a better understanding of the big picture involving IRBs. We focused on the IRB system as a whole and on the environment in which they function. We did not conduct an audit of their operations, nor did we carry out an investigation of specific IRBs or of specific research plans reviewed by IRBs.

We conducted this inspection in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

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 that 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, that advertisements are not misleading, and that the selection of subjects is equitable and justified. IRBs focus much attention on the informed consent document because 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 for its IRB and human-subject protections. Institutions consistently conducting multiple HHS-supported studies are eligible 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). A more detailed explanation of the agencies' oversight processes can be found in appendix C.

FINDINGS

The Effectiveness of IRBs Is in Jeopardy.

As they have for about 25 years, IRBs continue to provide vital protections for human subjects. But our inquiry leads us to the troubling central conclusion that the system of protections, that has been so carefully developed over the years, is in jeopardy. A recent review, published in *The Journal of the American Medical Association*, offered a similar conclusion: "Never before has such a pressure-cooker atmosphere prevailed within the IRB system, leading government officials, university administrators, research sponsors, and IRB members to wonder whether the IRB system will crack or reform."[10]

This vulnerability becomes especially significant in view of emerging budgetary developments that could add significantly to the number of human subjects taking part in clinical trials and proposals to give IRBs increased responsibility in the areas of genetic testing and confidentiality. It is crucial, therefore, to understand the major factors that jeopardize IRB effectiveness and then to take strong corrective actions. In our three other reports we identify and explain a number of such factors. Below, we highlight six that are particularly compelling and that buttress the case for reform at a national level.

IRBs Face Major Changes in the Research Environment.

Federal IRB regulations were formulated during the 1970s and early 1980s at a time when most research involving human subjects took place under government funding in a university teaching hospital with established research-related controls.[11] Clinical trials typically involved a small cohort of subjects and were generally conducted by a single investigator at a single institution.[12] In the wake of the Tuskegee experiments and other research abuses of human subjects, there was considerable awareness of the risks that research could pose for human subjects.[13] IRB workloads were, for the most part, limited enough to allow IRBs ample opportunity to deliberate about the research proposals before them.[14]

The environment in which IRBs operate has changed significantly in the past two decades. The chart on the next page identifies six major developments contributing to this change and outlines some of the key implications for IRBs.

One of the more visible reflections of this new environment is the widespread advertising that sponsors and investigators often rely upon to recruit human subjects. Such advertisements are prominently displayed in buses and subways, newspapers, university bulletin boards, and other places. Typically, they stress the personal benefits (including cash payments) that one may receive by signing up as a research subject and make no mention of attendant risks (see appendix A).

A CHANGING ENVIRONMENT FOR IRBs		
CHANGE	EXPLANATION	KEY IMPLICATIONS FOR IRBs
Expansion of Managed Care	Emphasis on cost control and competition. Squeeze on research support for academic health centers.	•Pressures to accommodate research sponsors who can provide research-related revenues for the parent institution. •Increased difficulty in obtaining staff and other resources. •More pressure on staff physicians to generate income, with less time available for voluntary commitments to IRBs.
Increased Commercialization of Research	Heightened industry role in sponsoring research. Sponsor emphasis on rapid product development.	•Institutional and sponsor pressures for quick reviews. •Sponsor shopping for customer-focused IRBs. •Added complexity on issues involving liability, academic freedom, and patient disclosure.
Proliferation of Multi-Center Trials	Proliferation of trials spread across hundreds of sites, even across the world.	•Diminished influence of "local" review. •Flood of adverse-event reports to review. •Lack of access to significant information concerning the status of ongoing research.
New Types of Research	Advances in biomedical research in the areas of gene testing and gene therapy; increased research on mental health issues.	•Need for new, highly specialized areas of expertise. •Emergence of thorny ethical issues involving informed consent and appropriate research. •Increased importance of having noninstitutional board members.
Increased Number of Proposals	Intensified efforts to obtain government funding and to develop new products.	•Significant increase in workloads. •Without sufficient increases in staff and/or efficiency, less time is available to review initial protocols and to conduct continuing reviews of approved research.
Rise of Patient Consumerism	Increased consumer demand for access to research.	•Presents major challenges in: Ensuring equitable recruitment of subjects. Ascertaining local attitudes and values. Maintaining distinctions between therapy and research.

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

IRBs across the country are inundated with protocols. Our study sites reported average increases of 42 percent in initial reviews during the past 5 years, with the result that some of them are now reviewing more than 2,000 protocols. At the same time, these IRBs are being deluged with adverse-event reports from the multi-center trials they oversee. One IRB we visited had received several boxes of adverse-event reports within the past few weeks. Another indicated that it was receiving an average of 200 such reports a month. Although the large academic health centers are hit hardest by mounting workloads, small IRBs are suffering as well. 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.

Despite the increase in workload, staffing levels and budgets have remained the same at many IRBs. At the same time, managed care cost pressures have constrained the time that IRB members have to devote to reviewing protocols. In an effort to cope, many rely on pre-assigned reviewers to examine and summarize research plans for the entire IRB. In some IRBs, unless one of the assigned reviewers raises a question or concern about the research, the IRB engages in little or no discussion at its meeting.[15] While some IRBs have been able to increase the length of their meetings, others squeeze more reviews into a fixed block of time. With limited personnel and few resources, IRBs are hard pressed to give each review sufficient attention. A 1996 GAO report stated that some IRBs may spend only one to two minutes of review per study.[16]

IRBs Under Pressure

The agendas of the IRB review meetings at academic health centers where most of the HHS-sponsored research occurs are packed, leaving busy reviewers little time to reflect on and debate issues raised by research protocols. As an illustration, at the sites we visited, their most recent meetings typically lasted about 2 ½ hours and included an average of 18 initial reviews, 9 expedited reviews, 43 protocol amendments, and 21 adverse-event reports.

Many IRBs find that they lack sufficient scientific expertise on their boards or staffs to adequately assess protocols. For example, protocols involving advanced biomedical techniques--such as gene testing--raise scientific issues, as well as moral and ethical questions, that might 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.

IRBs Conduct Minimal Continuing Review of Approved Research.

Continuing review has become a low priority at many IRBs, often relegated to the last few minutes of a meeting. For example, at one IRB meeting we observed, several annual reviews and amendments were approved within the last 15 minutes of the 2 ½ hour meeting. At another site, several members were visibly hurried to end the almost 6 hour meeting and the board relied mainly on the assessment of the primary reviewer for the annual re-reviews. 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 a paper-based activity at many IRBs. At the six academic medical centers we visited, officials reported that during the past year they seldom visited the research site. Five of the 11 independent boards we interviewed reported that they have no routine policy for visiting the research sites under their purview. Although many IRBs would like to, very few oversee the consent process or solicit feedback from subjects. According to one IRB chair, the lack of resources has forced IRBs to rely on the willingness of investigators to provide timely, accurate reports to the IRB. Many

members are uncomfortable with this degree of reliance on self-reported data and would like to devote more attention to 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 established by 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.[17] And, when a sponsor or investigator submits a research plan to the IRB, it may not inform the IRB of any prior review of that plan by another IRB.[18]

In an effort to improve continuing review, the OPRR and FDA have issued interpretations of Federal requirements in the forms of Dear Colleague letters and Information Sheets.[19] Many of these are outlined in appendix B. From the perspective of the IRBs, some of these have served to reduce IRB flexibility and add to their burdens. Of particular note is the OPRR issuance reinforcing the Federal intent that IRBs conduct substantive and meaningful annual reviews of active protocols. This issuance, some conclude, has had a particularly disruptive and demoralizing effect on many IRBs.[20]

IRBs Face Conflicts that Threaten Their Independence.

Clinical research is an important revenue source for most academic health centers. For example, at one of our sites, about 25 percent of the operating budget (nearly $200 million) derives from research activities. For decades, under the fee-for-service system, research expenditures were subsidized by patient-care revenues; under managed care, however, traditional financial support for research activities has been diminishing. In the process, commercial sponsorship has become increasingly important. At the academic health centers we visited, commercial sponsorship accounted for as much as 50 percent of the research funding.

Commercial sponsorship of research has heightened the potential for conflicts of interest. We found several examples of hospital IRBs that are housed in offices of grants and contracts or in clinical research programs, the very offices geared to bringing in research dollars. Such organizational placements, while not necessarily representing a conflict, certainly can accentuate pressures on IRBs to accommodate institutional financial interests. Independent IRBs, which primarily review commercially sponsored research, are subject to similar pressures. This may be particularly so for those independent IRBs that are owned by contract research organizations,[21] and those that allow equity owners to participate in the review process. The NIH policy for HHS-funded research reviews by for-profit IRBs is to prohibit IRB equity owners from participating in the review process, but there is no such policy for industry-sponsored studies submitted to FDA.

The phenomenon of IRB shopping, in which research sponsors seek out the IRB they choose to work with, places considerable pressure on IRBs and their institutions.

Commercial sponsors seek quick turnaround reviews for their protocols and can be tough negotiators on publication rights, liability issues, and other matters. Many academic health centers are struggling to respond to this new environment. They find it especially difficult to be as timely in their reviews as the independent, typically for-profit IRBs that are a growing presence. While they rarely can conduct initial reviews within a month, the independent IRBs often do so in little more than a week.[22]

Federal regulations calling for at least one IRB member whose concerns are primarily in nonscientific areas and one member who is not otherwise affiliated with the institution aim to provide a counterbalance to the kind of pressures noted above. But, we found few such "outside" members on the boards. Few IRBs seem to seek or to be able, on a consistent basis, to recruit and maintain lay and/or nonaffiliated members who play an active, effective role in helping the IRBs stay focused on their mission of protecting human subjects. It is not unusual for an IRB of 15 to 20 or more members to include only one or two noninstitutional members.

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

The IRB officials that we spoke with fully recognize the significance of educational outreach to research investigators and board members. Many have been active in holding seminars and/or providing individualized assistance to help investigators become more informed about and sensitized to human-subject protections. But nationally, in the context of the numbers of investigators and the complexity of the issues, such efforts are minimal. Further, they face significant obstacles which include not only insufficient resources, but the reluctance of many investigators, especially experienced ones, to participate.

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. A 1995 survey of 172 university-based IRBs found that one-quarter offered no training at all to their members. At the vast majority of institutions, training was limited to less than four hours.[23] This limitation is especially detrimental to the "outside" members who tend to need grounding not only in the basics of the regulations but also, in many cases, in the basic concepts, approaches, and terms associated with scientific research. The lack of such training further impedes their ability to serve as an effective counterbalance to institutional and scientific interests.

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

As we conducted our inquiry, we became increasingly aware of a striking reality: IRBs have little basis for knowing how well they are accomplishing their mission of protecting human subjects. The IRB and institutional officials we spoke with typically felt that their IRBs were quite successful. But when we asked them their bases for that judgment, they almost invariably pointed to the lack of serious problems or complaints that have come to their attention. Such factors are, of course, relevant to assessing effectiveness, but in themselves provide a weak foundation. Seldom, we found, do the IRBs seek out

feedback from human subjects or their families, examine the few complaints that they do receive to determine if they reflect broader, systemic problems, or initiate probing inquiries--for example, to determine how the informed consent process is actually working. Even more seldom, it appears, do independent, outside parties conduct such evaluations.

Federal oversight does not compensate for these deficiencies as it, too, is not geared to evaluating effectiveness (see appendix C). The OPRR's oversight is limited almost entirely to upfront assurances aimed at obtaining an institution's commitment to adhere to Federal requirements.[24] The majority of IRB staff we spoke with viewed the assurance as a paperwork process having no impact on IRB functioning. Only in instances of alleged breakdowns in IRB protections has the OPRR conducted site visits. Some of these reviews represent the most probing and results-focused inquiries 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 only one such visit was carried out.

The FDA oversight involves a more frequent on-site presence. In 1997, they conducted a little under 200 site visits (see appendix C). These visits are carried out by FDA inspectors who often are also responsible for inspections focusing on food products, research sponsors, and clinical investigators. They focus almost entirely on IRB compliance with the procedural requirements set forth in Federal regulations--concerning matters 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 offer FDA little direct feedback on the actual effectiveness of IRBs. For instance, in an information letter to IRBs, FDA calls for them 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. For example, the FDA inspectors do not review the adequacy of the IRBs' own bases for determining subject understanding.

RECOMMENDATIONS

The stress that so many IRBs now face compromises the protections that IRBs seek to provide to human research subjects. Federal leadership can be instrumental in addressing this vulnerability and in shoring up the system of protections that is vital to the continued progress of biomedical and behavioral research. It is toward this end that we present our recommendations. We call for some strong and inevitably controversial actions. But, the recommendations also seek to minimize unnecessary Federal regulation. They reflect a respect for the largely collegial manner in which IRBs operate and aim to nourish the volunteer contributions that have provided the underpinning of IRB reviews. They also take into account the increasingly important role being played by independent IRBs.

We direct most of our recommendations jointly to the Office of Protection from Research Risks (OPRR) which is located within the National Institutes of Health (NIH),[25] and to the Food and Drug Administration (FDA), since they are the two focal points for IRB oversight in the Department of Health and Human Services (HHS). In those instances where we direct a recommendation to one of the agencies, we specify the agency.

In presenting our recommendations jointly to NIH/OPRR and FDA, we fully recognize that they have different jurisdictions, mandates, and operational approaches. Yet they are bound by a common intent to protect human subjects and by what is, for the most part, a common set of regulations. If they are to respond effectively to the very serious warning signal that our findings present, then it is essential that they collaborate closely among themselves and with other pertinent HHS components. In that context, they might also address how the Department's responsibilities for overseeing IRBs could be organized in a manner that is most effective and allows for the clearest possible Federal leadership.

In their deliberations on how to enhance human-subject protections, we also urge NIH/OPRR and FDA to take the lead in finding ways to involve other non-HHS parties. This should include representatives of the research community, the institutions in which IRBs are located, and most of all IRBs themselves. Many of these individuals bring valuable front-line perspectives on how best to protect human subjects and can offer valuable insights into how the Federal government can provide effective leadership.

Finally, we must emphasize that emerging developments add a sense of urgency to the reforms we propose. Most notably, these include Federal plans to increase substantially the Federal investment in cancer and other biomedical research. This expanded research holds forth great potential benefit to society and perhaps even to subjects participating in clinical trials, but at the same time it will add to the review burden of IRBs. So too, if enacted, could recent proposals to expand IRB responsibilities in overseeing genetic testing and in ensuring patient confidentiality. In considering these developments, it is particularly vital that sufficient financial provisions be made to buttress IRB and Federal efforts that aim to provide essential protections for research subjects.

1. Recast Federal IRB Requirements so that They Grant IRBs Greater Flexibility and Hold Them More Accountable for Results.

Such a redirection is an essential starting point. We have found that IRB members and staff tend to be strongly committed to human-subject protections and have many ideas about how to improve performance. Our report on promising approaches reveals many of the innovative efforts they are undertaking, even under current restraints.[26] The NIH/OPRR and FDA could help unleash further innovation by giving IRBs more flexibility in how they carry out their responsibilities. But, in doing so, a necessary quid pro quo, we believe, would be a greater accountability for results.

What we call for here is in accordance with what is occurring generally in the field of health care quality assurance. For instance, in recently announcing major reforms in Federal conditions for hospitals' participation in Medicare, HHS Secretary Shalala noted: "We are doing away with old requirements that focused on process rather than results, and instead we're telling hospitals that they must monitor the quality of care they provide, improve that quality, and document that improvement."[27]

1 a. Eliminate or Lessen Some of the Procedural Requirements that Federal Regulations Impose on IRBs.

The aim here should be to enable IRBs to be more strategic in how they use their limited time and resources and, in that context, to concentrate their attention on those research practices posing the greatest risks to human subjects. Too much of their attention now focuses on perfunctory review responsibilities yielding little protective value.

The NIH/OPRR and FDA should work with IRBs and others in identifying the specific Federal requirements to be eliminated or modified. One especially strong candidate is the requirement that IRBs conduct full, annual reviews of approved protocols. On the basis of our review, this mandate generates substantial burdens on IRBs and does not have the intended effect. It compels IRBs to devote too much effort to routine, paperwork reviews at a time when the quantity of that paperwork is mounting. It impedes them from taking a more strategic approach--one that would enable them to concentrate on research involving substantial risks to human subjects, to conduct periodic reviews, and to visit research sites to determine how the informed consent process is actually working.

Another candidate for consideration would be what some call the "unfunded mandate," whereby IRBs must conduct complete reviews of Federal funding applications prior to the funding decisions. Other candidates would be those Federal requirements that limit what IRBs can accomplish in conducting protocol reviews outside of convened board meetings.[28]

1 b. Require that All IRBs Under the Purview of NIH/OPRR and FDA Undergo Regular Performance-Focused Evaluations that are Carried Out in Accord with Federal Guidelines.

This is the direction called for by the Advisory Committee on Human Radiation Experiments. In its 1995 report, it concluded (as we have) that the Federal system for overseeing IRBs is inadequate. An adequate system, it indicated, would require "that the system be subjected to regular, periodic evaluations that are based on an examination of outcomes and performance and that include the perspective and experiences of research as well as the research community."[29]

Federal guidelines for IRB evaluations should call for the evaluation results to be available to the public (to foster accountability). The guidelines should be minimal and should stress assessments of IRB effectiveness. In this regard, they should be attuned to the Institute of Medicine's recent recommendation that IRB systems be examined to determine how well they are functioning. Among the basic questions posed by the IOM that we believe warrant particular attention are the following: "1) Are IRBs successfully representing the interests of human subjects in research and not merely those of the sponsoring institution? and 2) Do IRBs generally fulfill their goals?"[30] We suggest that NIH/OPRR and FDA convene symposia with IRBs to discuss the type of performance measures and evaluations that would foster a system of accountability based more fully on results.[31]

The federally mandated evaluations could be self-evaluations or, better yet, ones conducted by independent, outside parties. Their frequency should depend on the quantity of protocols being reviewed by an IRB, but probably no less than every 5 years. To reinforce their importance, NIH/OPRR could include an evaluation requirement as a component of the assurances it obtains from research institutions.

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

In a prior study focusing on investigational medical devices, we found significant deviations from IRB-approved protocols and raised concerns about the adequacy of IRB oversight of such protocols.[32] In this study, which was more broadly based, we found little basis for easing those concerns; in fact, they have been intensified.

It is essential, we believe, for NIH/OPRR and FDA to ensure more rigorous and accountable oversight of research approved by IRBs. As we have noted, the current regulatory infrastructure was established at a time when research was typically conducted by a principal investigator, working at one institution, with a local cohort of subjects.[33] Now, a significant portion of IRB approved research is part of multi-site trials involving many investigators and subjects at sites across the nation and even the world.[34] The Federal regulations should be updated to account more fully for these changed circumstances.

2 a. Require Data Safety Monitoring Boards for Multi-Site Trials that are Under NIH/OPRR and FDA Purview and that Meet Specified Conditions Warranting Such a Safeguard.

Data Safety Monitoring Boards (DSMBs) are independent review bodies that review ongoing research to assess the efficacy of the data, the adherence of the research to the approved protocols, and the continued safety of the subjects. These boards include medical, scientific, and other expertise that typically is not available on IRBs. The NIH institutes do require DSMBs for many of the cooperative group projects they fund. But, there are no Federal regulations calling for the routine establishment of DSMBs.[35] The NIH/OPRR and FDA should take the lead in seeing that DSMBs become more firmly established as oversight mechanisms and be made more clearly accountable in that regard. Among their designated responsibilities should be those of assessing, summarizing, and determining when and how to follow up on adverse-event reports submitted by sponsors/investigators.

The NIH/OPRR and FDA should define the types of trials for which DSMBs would be required. These could include trials that involve many subjects, that include control groups not having access to the research interventions, and/or that involve new drugs, devices or procedures that present significant risks to human subjects. In addition, the NIH/OPRR and FDA should set forth requirements for the composition of DSMBs.

2 b. Provide IRBs with Regular Feedback on Developments Concerning Multi-Site Trials.

As we have noted, a substantial portion of the research that many IRBs now oversee involves local research investigators and local subjects participating in national or international multi-site trials bound by a common research protocol. To provide adequate continuing review in these situations, IRBs must be informed about key developments concerning the trial as a whole. For instance, if an IRB receives a report about an unexpected adverse outcome experienced by a local subject, it will be hard pressed to assess the significance of that information unless it knows how many such outcomes have occurred for the overall trial. During the course of our inquiry, we identified two key sources of information of this kind that should regularly be shared with IRBs.

First, and probably most important, is information from DSMBs. Instead of receiving large quantities of individual adverse-event reports submitted by sponsors and investigators, IRBs should receive compilations and assessments of those reports prepared by DSMBs. At present, most IRBs receive little if any feedback from DSMBs.[36] Routine, substantive feedback from DSMBs would allow the IRB to concentrate its time and resources on reviewing that which it knows best--the continued suitability of the local environment to the research project in question. Regular feedback from the DSMB will serve to increase the effectiveness and thoroughness of IRB reviews, as well as its efficiency.

A second important, external source of information is that which federally funded cooperative research groups obtain from their monitoring visits to research sites that are part of a single protocol.[37] This is valuable information collected and analyzed by individuals expert in the research being conducted. The reports incorporating this information are sent to the research investigators, but rarely are shared with the IRBs.[38] The IRBs should receive these reports routinely and thus have the opportunity to draw upon them as a complement to their own reviews.

2 c. Routinely Provide IRBs with Feedback on FDA Actions Taken Against Investigators Under their Jurisdiction.

The FDA inspections of research investigators can result in a variety of actions, from warning letters to a disqualification from participating in pre-market research. Officials at FDA indicate that legal restrictions under the Privacy Act preclude FDA from disclosing all investigator-related correspondence to IRBs and sponsors on a routine basis. Certain information, however, is available to the public on an FDA web site or through the Freedom of Information Act. But many IRBs do not have the time to regularly scan the FDA website and might not know when to request information from the FDA about one of their investigators. The FDA is in the process of seeking approval to modify the relevant Privacy Act systems notice so that the sharing of this information with IRBs and sponsors will be made easier. We think this is important as the lack of information sharing puts IRBs in an untenable position if they are to be held accountable for protecting the interests of human subjects.

2 d. Require Sponsors and Investigators to Notify IRBs of any Prior IRB Review of a Research Plan.

We heard of a few situations where sponsors and/or research investigators who were unhappy with one IRB's reviews switched to another without the new IRB being aware of the other's prior involvement. This kind of IRB shopping deprives the new IRB of information that it should have and that can be important in protecting human subjects. The ground rules should be changed so that the sponsors and investigators have the clear obligation to inform an IRB of any prior reviews.[39] The obligation should be applied to all those conducting research funded by HHS or carried out on FDA-regulated products. It will have particular importance for those sponsors and investigators working with independent IRBs.

2 e. Call for Increased IRB Awareness of On-Site Research Practices Involving Human Subjects.

To some readers, this recommendation might represent a violation of the long established ethic of trust that has guided IRBs' relationships with the research community. It might be interpreted as "surveillance" and "policing" that could compromise the research enterprise. But given the scope and type of research now under the purview of IRBs, the risks that much of this research presents to human subjects, the widespread blurring of

research and therapy, and, the kinds of violations we identified in our previous OIG report, trust alone does not provide sufficient continuing protection. The credibility of the IRB process in protecting human subjects requires more. While trust must remain an important part of the system, it should be accompanied by a greater readiness to verify that IRBs are accomplishing their consumer protection mission. Such verification is allowable under current Federal regulations and, in fact, consistent with the intent of the National Commission that laid the groundwork for those regulations.[40]

Increased awareness of actual practice is consistent with our earlier call for a greater focus on results and can be carried out, we believe, in a manner that does not shatter the foundation of trust. For projects that are particulary sensitive and/or risky, the increased awareness we call for can involve observers, intermediaries, or counselors who are available to make sure that the informed consent process functions in the interests of the human subjects. It can involve periodic, announced or unannounced, random visits by IRB representatives, both to review pertinent records and to observe the informed consent process. It can involve surveys of and/or focus groups with human subjects. As illustrated in our report on promising approaches, several IRBs have begun implementing these techniques.[41] However it is done, the aim should be to provide IRBs with greater assurance that stated intentions involving human subjects are, in fact, being fulfilled.

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

In the final analysis, the most important continuing protection for human subjects is the presence of well-trained and sensitized investigators. Such investigators can also serve to minimize the need for regulatory intervention, be it by the Federal government or by IRBs themselves. Accordingly, our recommendation calls for strong Federal action concerning education. It is in accord with the President's May 1997 statement of apology for the ethical transgressions of the Tuskegee syphilis study. In that statement, the President announced a commitment "to strengthen researchers' training in bioethics" as a means of ensuring that human subjects' "rights and dignity will be respected as new drugs, treatments, and therapies are tested and used."[42]

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 can help convey to researchers that along with the considerable independence that they enjoy in the research process there exists a significant responsibility to ensure that human subjects are protected in accord with established principles and Federal law. It can assist IRBs and their institutions by developing generic educational materials and model curricula. The NIH may want to consider working with the FDA, and with groups such as PRIM&R and ARENA, to develop these materials.

3 a. Require that Institutions Receiving Funding Under the Public Health Service Act for Research Involving Human Subjects Have a Program for Educating its Investigators on Human-Subject Protections.

This is similar to and an extension of a current NIH requirement calling for institutional recipients of research training grants to have acceptable plans for instructing trainees in the responsible conduct of research.[43] It parallels a recommendation offered in 1995 by the Commission on Research Integrity[44] and is the kind of recommendation that NIH/OPRR sometimes directs to an institution after it has investigated a lapse in the institution's system of human-subject protections. Such a requirement is currently in place for research involving animals.

The education we call for could be provided through various modalities such as seminars, individual instruction, videos, or on-line tutorials. A number of the IRBs we interviewed have, of their own accord, developed innovative educational programs along the lines we call for. The NIH/OPRR could promote these efforts and our recommendation generally by calling for an educational assurance as part of its multiple project assurance (MPA) with health care institutions. This assurance would more clearly commit the institutions to seeing that its investigators have appropriate training in human-subject protections. Further, since institutions with MPAs typically apply the IRB requirements to all research conducted by affiliated researchers whether or not they are funded by NIH, such an educational assurance could help to reach a larger universe of investigators than just those funded under Public Health Service Act programs.

3 b. Require that Investigators Receiving Funding Under the Public Health Service Act for Research Involving Human Subjects Provide a Written Attestation that They Are Familiar With and Will Uphold Federal Policies Concerning Human-Subject Protections.

This recommendation, which again parallels one that the Commission on Research Integrity set forth with respect to the "the responsible conduct of research," asks that the investigators acknowledge their awareness of the pertinent policies and procedures. It aims to heighten their awareness of their responsibilities as investigators and their interest in participating in educational programs addressing human-subject protections. The FDA, it is important to note, already requires a similar attestation for investigators submitting an investigational new drug application or investigational device exemption to the agency.[45] Further, some of the institutions we contacted already require that investigators sign statements assuring the IRB that they are familiar with and will adhere to the human-subject protection requirements.

Even with such an attestation, we recognize that its effectiveness is likely to depend heavily on high-quality educational offerings being readily available to investigators. The prior recommendation calling for institutions to provide educational offerings responds to this need. The NIH/OPRR and FDA could also help meet it by conducting more educational outreach of their own. This could involve the convening of conferences, as they have periodically, as well as preparing and disseminating self-study materials.[46]

3 c. Require that Each IRB Under the Purview of NIH/OPRR or FDA Have an Orientation Program for New IRB Members and a Continuing Education Program for All Members.

The core content of these education programs should cover not only the basic requirements spelled out in Federal law, but also a broader review of ethical principles governing human-subject protections and of ways in which IRBs can address those principles. For noninstitutional and nonscientific board members, the educational programs should also serve as a primer on scientific and research issues, with the intent of helping the members gain a better appreciation of key concepts, terms, and context. Here, again, a prescription that NIH/OPRR sometimes offers as a corrective action in response to an adverse event involving human subjects should be incorporated on the front end as a required preventive measure and could be included as part of multiple project assurances.

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

Two long-time analysts of IRBs have described IRB regulations as "a permeable shield, with no strong framework to ensure that the subjects' interests take precedence over institutional ones." They added that in balancing risks and benefits, an IRB "that consistently makes the calculus in favor of research will hardly ever be identified."[47] While many Federal and IRB officials are likely to object to this assessment, the minimal information they have on the effectiveness of IRBs makes it difficult for them to rebut it. Even more troubling, in an environment where IRBs are expected to be responsive to the financial pressures facing their parent institutions and/or the sponsors, some IRBs are finding it difficult to maintain sufficient focus on their core mission; thus the above recommendation.

Our point is not that IRBs can or should be completely independent entities impervious to developments in an increasingly market-based health care system. Rather, it is that they and the Federal government must be alert to pressures that might lead some IRBs to become overly accommodating to the significant financial pressures that surround them. One of the most important roles that NIH/OPRR and FDA can play is to help prevent such accommodations.

4 a. Require More Extensive Representation on IRBs of Nonscientific and Noninstitutional Members.

This is a vital matter that responds to a commitment that the President made in his May 1997 Tuskegee statement.[48] Individuals not associated with the institution or with the research enterprise can provide a valuable counterbalance to pressures that threaten IRB independence. But to do so, it is important not only that they be well-trained, but also that there be enough of them on a board so that their voices are more likely to be heard and their sense of belonging more likely to be enhanced. The current requirement that there be one noninstitutional and one nonscientific member on a board (this requirement

can be satisfied by the selection of a single individual) is clearly inadequate in this regard. In its 1978 report the National Commission recommended that at least one third but no more than two thirds of IRB members be scientists as a way "assure the IRB's access to [scientific] expertise, yet guard against self-interest influencing or appearing to influence IRB determination."[49] The case remains strong both for increasing the number of noninstitutional and nonscientific members and for requiring that at least one noninstitutional member be present at any board meeting where research plans are reviewed. It may well be desirable, we would note, to include scientists among the noninstitutional members considered for IRBs.

4 b. Reinforce to IRBs and Their Parent Institutions the Importance of IRBs Maintaining Sufficient Independence in Their Mission to Protect Human Subjects.

We suggest that an IRB with sufficient independence is one that is not under any institutional or ownership pressure whatsoever to approve protocols and related documents; bases it reviews on the merits of a proposal and the attendant risk/benefit ratio, without regard for business concerns; does not report directly to the part of the institution responsible for bringing in research funds; is not compensated based on the outcome of a review; and has recourse, should it feel subject to any pressure.

Through "Dear Colleague" and informational letters, NIH/OPRR and FDA could draw greater attention to the danger signs that inhibit IRBs from operating with sufficient independence and to the kind of preventive measures that they and parent institutions might take to ensure a proper focus on their core mission. The FDA, in its compliance site visits, could give special attention to the emergence of any of these signs and could bring them to the attention of the IRB and its parent institution. The NIH/OPRR could reinforce the issue by including in its multiple project assurances a clause that institutions will afford their IRBs sufficient independence in their mission of protecting human subjects. Although the immediate, practical effect of such a commitment is uncertain, it could serve to generate additional consideration to this important matter.

4 c. Prohibit IRB equity owners from participating in the IRB review process.

Such participation, in itself, does not necessarily inhibit the independence of the review process, but it creates a situation that can be conducive to ownership influence in that process and, certainly, it undermines a perception of impartiality. The OPRR practice of prohibiting such participation should be formalized. The FDA should follow suit and prohibit ownership participation in IRB reviews for industry-sponsored research on products to be submitted to FDA for approval.

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

Federal actions along the lines we have called for in our previous recommendations would help reduce IRB workload pressures. IRBs would be freed of a number of procedural requirements that are of questionable value and of the torrent of adverse-event reports they now receive. Further, if greater educational outreach led to investigators becoming better informed about the purpose and particulars of regulations to protect human subjects, IRBs quite likely would find that research applications submitted by these investigators would require fewer changes (thus saving IRBs' time).

Yet, even with such changes, the adequacy of the resources available to IRBs would remain a significant issue of concern. If the external pressures we have described in this report continue (as seems likely) and if IRBs do more continuing reviews and evaluation (as we call for), IRBs could still be struggling to maintain a sufficient level of human and other resources (such as computer equipment and office space).

5 a. Require That IRBs Have Access to Sufficient Resources to Enable Them to Carry out Their Responsibilities as Intended in Federal Law.

The resources we refer to are, above all, the human resources represented by staff and board members, but also space, computers, and other elements essential to an efficient and effective IRB. We recognize that the term "sufficient" is a general one, not easily measured.[50] Yet, the centrality of the resource issue and the clear shortages that many IRBs now face, call for enhanced Federal attention to it. One direction that NIH/OPRR and FDA could take toward that end could be the development of indicators of minimally adequate resource levels, below which IRBs are likely to find themselves in a danger zone. For instance, these could involve measures of numbers of staff and board members to the number of active protocols, or the number of protocols reviewed per meeting. As a starting point, the NIH/OPRR and FDA could survey IRBs about their current resource levels.

The NIH/OPRR Multiple Project Assurance currently requires institutions to provide meeting space and sufficient staff. When negotiating an MPA, the NIH/OPRR could reinforce the importance of resource adequacy by bringing the same scrutiny to it when negotiating those assurances as it does when conducting an investigation of an IRB's lapse in protecting human subjects.[51] Similarly, the FDA could modify its site visit protocol to identify signs of inadequate resource levels to use that information to present recommendations, or if serious enough, warning letters to the IRBs involved.

6. Reengineer the Federal Oversight Process.

As it now functions, the Federal oversight of IRBs is not equipped to respond effectively to the warning signal we present in this report. The FDA conducts just under 200 IRB site inspections a year, but its procedural, compliance-focused reviews reveal little about IRB effectiveness in protecting human subjects. The NIH/OPRR, on the rare occasions

when it visits IRBs, gets closer to assessing IRB performance but its emphasis on upfront assurances is of questionable value. Further, while there is some sharing of information between the two agencies, they operate in very different domains, rooted in separate statutory bases and organizational cultures.

It is time, we believe, for a fundamental reexamination and reengineering of the HHS oversight process, viewed as a whole. The principal aims of this ambitious effort should be twofold: (1) to develop more streamlined, coordinated, and probing means of assessing IRB performance and (2) to enhance the Federal capacity to identify and respond to emerging problems before they result in serious transgressions.

6 a. Revamp the NIH/OPRR Assurance Process

We suggest reorienting the assurance process so that it rests essentially on an institutional attestation to conform to the IRB requirements set forth in Federal regulations.[52] This attestation could be provided in a brief statement referencing the pertinent regulations. As a result, the scarce NIH/OPRR resources that are now devoted to reviewing and negotiating assurances could be freed up to conduct periodic performance-based reviews along the lines we have been noting and to provide education to help investigators and IRB members become knowledgeable about and sensitized to human-subject protections.

Along this line, we also suggest that NIH/OPRR consider providing some incentive for smaller IRBs to tie in with larger ones (both hospital-based and independent) that can bring more experience to the job. This is important in view of the increased complexity, sensitivity, and scale of so much of the research taking place. It is also important because it could help concentrate Federal oversight resources more effectively, moving in the directions we call for in the prior recommendations.

6 b. Revamp the FDA On-site Inspection Process.

This is especially important under current conditions whereby FDA is the only HHS agency conducting IRB site visits with any degree of regularity. We recognize that there is some value to the compliance checks that are the core of FDA inspections. But we suggest that FDA search for ways of revamping its inspections so that they focus less on narrow compliance matters and more on performance issues. Such reviews would probe deeper and wider and would pay particular attention to how individuals are actually being approached about participating as human subjects and to how IRBs are making continuing assessments of risk-benefit trade-offs.

We suggest further that FDA and NIH/OPRR collaborate on ways in which they could focus more directly on "front-line" practices that have particular bearing on human subjects. For instance, they might probe on how often potential subjects actually turn down requests to participate in research or on how much time they are given to deliberate about participation. They might also examine the marketing approaches being used to

entice the participation of subjects, paying particular attention to whether too much emphasis is given to potential personal benefits and not enough to risks.

Both 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.[53] The Federal agencies could include such a peer review element as part of some of its own reviews and/or offer some kind of incentive for IRBs to include it as part of a continuous quality improvement effort. In either case, it would represent a way of incorporating greater outside expertise into site reviews focusing on performance.

6 c. Require That All IRBs Register with the Federal Government and on a Regular Basis Report Minimal Descriptive Information.

Uncertainty as to the number of IRBs subject to regulatory oversight by FDA and NIH/OPRR is a major hindrance to effective oversight by these agencies. We recognize the concerns about Federal intrusions that could add unnecessary burdens to the research process. We suggest that a requirement that all IRBs register with the Federal government need not be much of an intrusion. It could involve a simple registration process in which IRBs regularly update the Federal government on minimal descriptive information. This information, for example, could include their location, contact information, and the number of protocols and human subjects under their jurisdiction. Such a requirement would help NIH/OPRR and FDA to target their oversight, to communicate more effectively and fully with IRBs, and, in the final analysis, offer improved protections to human subjects.

COMMENTS ON THE DRAFT REPORTS

Within the Department of Health and Human Services (HHS), we received comments on our four draft reports from the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and, jointly, from the Assistant Secretary for Planning and Evaluation (ASPE) and the Assistant Secretary for Health (ASH), who is also the Surgeon General. We also solicited and received comments from the following external organizations: the Applied Research Ethics National Association (ARENA), the American Association of Medical Colleges (AAMC), the Consortium of Independent Review Boards (CIRB), and Public Citizen's Health Research Group. We include the complete text of the detailed comments in appendix D. Below we summarize the major comments and, in italics, offer our responses.

NIH, FDA, and ASPE/ASH Comments

The HHS parties responded in generally positive terms. They viewed the reports as raising important issues and recommendations warranting serious and widespread attention. The NIH urged that the final reports be sent to all 16 Federal agencies adhering to the common Federal regulations on human-subject protections; indicated that it will take our recommendations to the National Science and Technology Council, which is responsible for uniform implementation of the common Federal regulations; and suggested that our recommendations will be addressed at the FDA's March 1999 National Forum on Human Subject Protections. The FDA expressed its intention to place some of the issues posed in the report on the agenda of the Forum. And ASPE/ASH suggested that all the reports be placed on the HHS website.

Both NIH and FDA also offered comments on our specific recommendations calling for a revamping of NIH and FDA practices of overseeing IRBs. The NIH responded that our call for reorienting the assurance process so that it rests essentially on an institutional attestation to conform to IRB requirements was "well-taken." It added that the OPRR has been seriously considering "a redirection of its intensive assurance effort toward performance-based reviews of IRBs." The FDA, which has a long-established system of conducting compliance-oriented inspections of IRBs, responded with some caution to our call that the inspections focus less on narrow compliance matters and more on performance issues. The FDA indicated that it regarded the current inspection program as having "great value," and that developing performance measures would be "a major challenge."

Finally, the FDA, as well as some of the subsequent commenters, pointed out that some of our recommendations, if enacted, could be "resource intensive" for IRBs and as a result could add to the stress on the IRB system. Such impact, it suggested, must be carefully considered.

We appreciate the interest in using our reports to stimulate widespread discussion on how the IRB system can be reformed to further human-subject protections. We will cooperate fully in such efforts. At the same time, we urge immediate attention to the specific recommendations, such as those concerning information sharing, education, and training, which can have important near-term effects in improving protections. We ought not allow the need for discussion to obscure the importance of practical actions that can be taken immediately to address the vulnerabilities we present in our reports.

On the matter of revamping NIH/OPRR and FDA oversight practices, we strongly urge that both agencies give a priority to identifying specific ways of conducting more extensive and effective performance assessments as part of their on-site reviews. We recognize that for FDA this will involve a major departure from a well-established compliance approach that does help assure conformance with processes called for in Federal regulations. But given the scope and significance of IRB responsibilities, it is imperative, as the Institute of Medicine has indicated, to gain a better understanding of how well IRBs are fulfilling their goals to represent the interests of human subjects. Over time, this performance assessment could involve developing specific quantitative measures that could be helpful in comparing the performance of different IRBs and of individual IRBs over time. But the move to performance assessment should not await such measures. Many practical steps can be taken in the near-term to help assess or verify that IRBs are having their intended impact.

We would be happy to work further with FDA and/or NIH to examine specific ways in which their on-site reviews might focus more closely and effectively on results. Among the key questions that should be addressed in any such effort would be the following: How do we know that the informed consent process is carried out in a manner that minimizes the possibility of coercion or undue influence? How do we know that the process of recruiting and selecting human subjects is being carried out in an equitable manner? How do we know if protocols that should be submitted for review are not submitted? Or if approved protocols stray in ways that are not identified in paperwork submitted to the IRB? These vital questions call for some kind of verification by Federal parties as well as IRBs themselves. We ought not allow the quest to develop quantitative performance measures delay practical steps that can be taken immediately.

Finally, FDA's point about the resource implications of our recommendations is a very important one, warranting further deliberation. We suggest that some of our recommendations, such as those that relieve IRBs of some Federal procedural requirements and of some of the burden of adverse action reviews, would help free up resources. But we recognize that the "trust but verify" thrust we call for is likely to add to resource needs as are other forces now being exerted. Most especially, these forces include a potentially significant increase in Federal funding for research on cancer and other serious diseases. They also include policy proposals to enhance IRB responsibilities to protect individuals participating in genetic tests and to ensure confidentially of information obtained on human subjects. The jeopardy that we suggest exists now could well be exacerbated if IRBs are not provided with sufficient resources to

carry out the vital functions being entrusted to them. This matter, we believe, warrants serious attention in both the research and policy communities.

External Organizations' Comments

To varying degrees, the external parties supported many of our findings and recommendations. But, overall, they reflected a number of strong concerns. Generally, these concerns involved differences of substance and objections to our use of certain language.

Overall, the substantive differences were wide ranging. Public Citizen found many of our findings to be alarming and expressed concern that we failed to go far enough with our investigations or recommendations. Among other things, it called for more funding of IRBs, greater representation on IRBs of disinterested parties (including scientists) from outside the institution, and FDA regulation of advertising seeking human subjects for clinical trials. On the other hand, the ARENA and AAMC both expressed reservations about our call for performance-focused evaluations and for more outside representation on IRBs. Both also noted concern that a more active IRB role in conducting continuing review could undermine the trust and collegiality that is key to the success of an IRB. The AAMC added that our intent to insulate IRBs from conflicts with their parent institutions "was improperly framed" because "nothing could be more in the institutional interest than protecting the subjects of research."

The concerns about our use of certain terms and language, expressed by ARENA, AAMC, and CIRB, were almost as strong as the ones about substance. The ARENA, in particular, found our use of the term "IRB oversight" to be misleading because it suggested IRB responsibilities greater than those the IRBs are mandated to carry out. Further, both ARENA and AAMC raised concerns that some of our wording was inappropriately alarmist and more encompassing than our methodology warranted.

In response to these concerns, we changed some of the terms and language we used in the draft reports. Most notably, instead of referring to IRB "oversight," we referred to IRB responsibilities and authorities to conduct "continuing review." We also modified some statements in ways that we hope more clearly and precisely express our findings and concerns. We made these changes because we seek to focus attention and dialogue on the important substantive matters revealed by our inquiry and on the need for reform (for which we believe there is widespread support). Our modifications in no way lessen our very real concern that the effectiveness of the IRB system, which has performed a valuable protective function for many years, is now in jeopardy. Our wide-ranging data gathering involving in-depth discussions and reviews in many different settings provides us with a sound basis to present this warning.

On the substantive matters, we must underscore that if IRBs are to meet the significant challenges facing them in the years ahead, they must become more fully accountable to

the public. For the system to be effective, trust in those conducting research must remain an important part of the system. But, it must be accompanied by a greater readiness to verify that IRBs are accomplishing their consumer protection mission. Such verification is allowable under current Federal regulations and, in fact, consistent with the intent of the national commission in the 1970s that laid the groundwork for those regulations. We must also emphasize that in an increasingly commercialized research environment that is much different than that which existed when the regulations were first established, guarding against conflicts that in subtle ways could compromise the IRBs' role in protecting human subjects is a matter of increasing urgency.

APPENDIX A

Advertising to Recruit Human Subjects

When Federal human-subject protections were established in the 1970s, a key principle was that there should be clear distinctions between research and therapy. Subjects should participate in research out of a desire to contribute to generalizable knowledge and they should understand that any personal benefits were secondary. Central to their participation was an assurance that they understood the risks inherently involved in research; their signature on the informed consent document was meant to convey this understanding.

Over the past two decades this distinction has increasingly blurred due to changes in subjects' and the investigators' perceptions. Many potential subjects have begun to view access to research as their best hope for effective therapy and do not want regulators inhibiting such access out of a desire to protect them. At the same time, the growth of multi-site trials increased the importance of recruiting large numbers of research subjects. This, in turn, created increased attention to marketing approaches to attract these potential subjects as researchers and their sponsors began to emphasize the personal benefits that human subjects could gain from participation in research. An effect of these changes has been that the line between research and therapy has become increasingly blurred. As the Advisory Committee on Human Radiation Experiments noted: "there is reason to worry that participants in research may have unrealistic expectations both about the possibility that they will personally benefit from participation and about the discomfort, pain, and suffering that sometimes accompany some research." The committee further stated that "it is important that in the informed consent process, it is clearly communicated to the potential subject . . .that the primary intent of 'research' is to advance medical knowledge and not to advance the welfare of particular subjects."[1]

During the course of our inquiry, we identified and collected many advertisements seeking individuals to participate as human research subjects. These advertisements are readily accessible to potential subjects, being found in newspapers and on public transportation. In a few of these advertisements, even though the study's experimental nature is mentioned, the accompanying language strongly implies that the procedure is treatment.[2] Even when this is not the case, the mention of research is either placed at the end of a long list of benefits or is embedded in language so enticing that the inevitable

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[1] Advisory Committee on Human Radiation Experiments, *Final Report,* Washington DC: U.S. Government Printing Office, Chapter 18, Section 2 (1995).

[2] It is important to note that research advertisements are not substitutes for the informed consent process. Participants must still sign an informed consent document after they contact the researchers and agree to participate.

risks of research are easily overlooked. The advertisements cite an overwhelming array of these benefits (see accompanying box and photos at the end of this appendix). In only one study did the advertisers stress the voluntary nature and not personal gain. Much more commonly, the advertisements supported the view that participation in research was an opportunity for the subject.

The danger of these advertisements is that subjects may come to a research study with misconceptions. For example, a person may enter into research believing it will treat his or her depression, panic disorder, diabetes, etc. The allure of freedom from such an ailment is likely to be highly motivating. Persons may also become attracted to research participation by the promise of alleviation from financial as well as physical distress. They may be motivated by the promise of free treatment, free screening, or extra money. It is essential, therefore, that both the informed consent document and the individual involved in the recruitment of subjects are vigilant in making sure the risks involved in research are clear. But as we have noted in this report, IRBs devote little attention to how the consent process works, focusing all too often solely on the document's language.

Examples of Marketing Efforts Aimed at Recruiting Human Subjects

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DO YOU HAVE ASTHMA?

If you qualify for any of our asthma studies, you can:
- Learn to care for your asthma!
- Receive free medications!
- Receive up to $1,730!

Women: Receive $2710!

Healthy, non-smoking/drug-free women (20-40) needed for USDA research study. Live-in 24 hrs/day for 78 days

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Speed or Cocaine?

Need help getting clean?
Free Treatment & Medication.
Repeat Callers Welcome!!! Get Paid $$$

Women With PMS

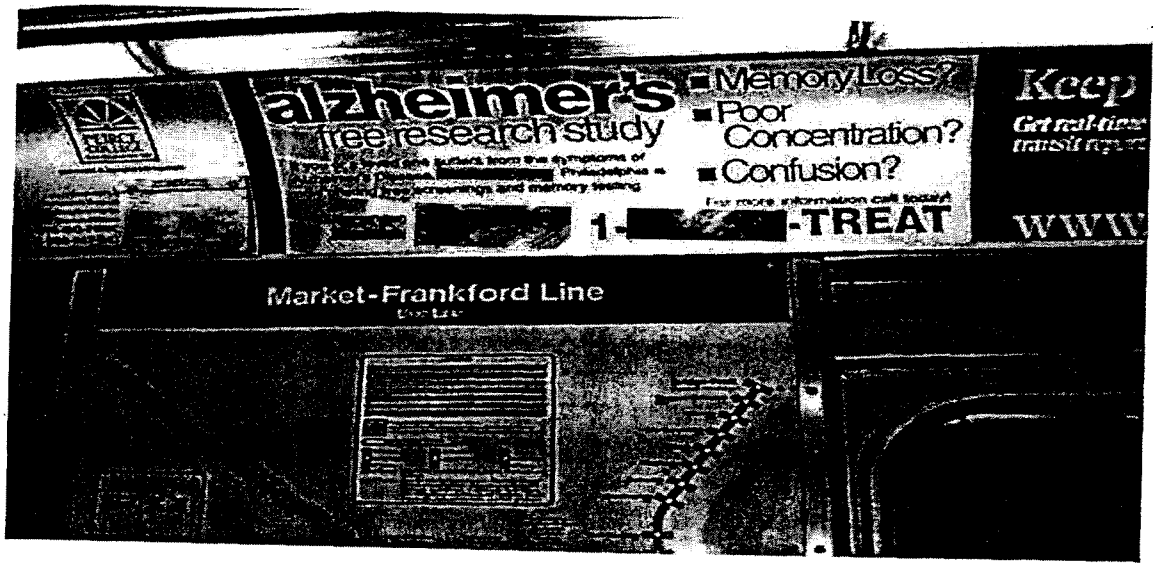
If you are between the ages of 18 and 40 and suffer from PMS (Premenstrual Syndrome), you may qualify to participate in a research study using an investigational drug for the treatment of PMS.

If you qualify to participate you will receive:

Free Medical Exams	Free Pap Smears
Free Labwork	Study Medications

Up to $455 for Time and Travel

The following two photos were taken on a Philadelphia subway car in January 1998.



Photos courtesy of the OIG Office of Evaluation and Inspections, Philadelphia Regional Office

Federal Requirements on IRB Continuing Review

Institutional review boards' role in protecting human subjects does not end after the completion of an initial review. An IRB is responsible for reviewing, and has the authority to monitor, a research protocol from the time of approval onward--until the close of the study. The Department of Health and Human Services, through the auspices of both OPRR and FDA, has specific requirements concerning how this review should be conducted.[1] These are specified in the regulations and elaborated on in various agency issuances such as OPRR's "Dear Colleague" letters and FDA's information sheets. The regulations are intended to be used as minimum requirements and IRBs are encouraged to impose greater protections as they see fit.

The continuing review process is multifaceted and involves both an annual review by the IRB and the ongoing review of amendments, modifications, and adverse event reports as they are received. What follows is a brief description of the elements of this process.

Continuing Review

A continuing review must be completed at "intervals appropriate to the degree of risk, but not less than once per year."[2] This interval has been interpreted as no less than 12 months from the date of initial review.[3] The review must be completed by a convened board unless the protocol qualifies for an expedited review process. The review should include an assessment of the protocol and any amendments/modifications. A status report from the investigator containing such information as the number of subjects accrued, descriptions of any adverse events or withdrawals of subjects, new information pertaining to the study and the current informed consent document should also be reviewed.[4] In particular, attention should be focused on determining whether the risk-benefit ratio remains adequate based on the new information and/or risks that were discovered.

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[1] 45 C.F.R., sec. 46 (HHS/OPRR) and 21 C.F.R., sec. 56 (FDA)
Currently, 16 other Federal departments and agencies abide by these regulations through the Common Rule for the protection of human subjects in research, effective August 19, 1991.

[2] *Ibid.*

[3] OPRR "Dear Colleague Letter", 10 January 1995, Continuing Review--Institutional and Institutional Review Board Responsibilities.

[4] *Ibid,* FDA Information Sheets, 1995.

Modifications and Adverse Event Reports

Periodically, the IRB may receive amendments/modifications for active protocols. They may include a change in address of a sponsor or something more significant such as a change in the actual design of a protocol or eligibility requirements. The ongoing review of adverse-event reports is another integral and ongoing task for IRBs. An adverse event is generally defined by the FDA as a serious experience by a subject that was not previously anticipated in nature or severity. "Serious" events include anything fatal, life-threatening, permanently disabling, or requiring in-patient hospitalization. The requirements can be found in 21 C.F.R., section 312 (for drug research) and 21 C.F.R., section 812 (for device research). They must be reviewed by the IRB or its representatives who can then require changes to the protocol. The required changes most often result in updating the informed consent document to more accurately explain risks to subjects.

Monitoring

An IRB has the authority to directly observe (or require a third-party to observe) both the consent process or the actual research.[5] IRBs must also follow written procedures for determining which studies require verification from a source other than the investigator that no changes have occurred and for ensuring that any changes are not initiated without IRB review and approval.[6]

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[5] 45 C.F.R., sec. 46 (HHS/OPRR)
21 C.F.R., sec. 56 (FDA)

[6] Changes may be initiated before IRB approval if they are necessary to eliminate immediate hazards to subjects. See *Ibid.*

Federal Oversight of IRBs

An estimated 3,000-5,000 IRBs can be found across the country. Two agencies within HHS responsible for the oversight of IRBs: OPRR and FDA. Each agency has its own set of regulations which have many similarities. However, their processes for oversight are markedly different.

The exact number of IRBs is unknown in part because of each agency's relationships with IRBs. The OPRR becomes aware of IRBs after an assurance is submitted naming the IRB as its source of review. Under a single project assurance (see below), the IRB has already reviewed the protocol and only NIH funding is needed. The FDA's contact with IRBs comes only at the time of an Investigational New Drug or Investigational Device Exemption application. By this time, the IRB has already reviewed and approved the protocol and the research is being conducted. Because the exact number is uncertain, the FDA acknowledges that it is more difficult to exercise their regulatory oversight.

Office for Protection from Research Risks (OPRR)

Assurances

The OPRR's oversight of IRBs focuses on an upfront assurance. The assurance is a document specifying an institution's commitment to the human-subject protections specified in Federal regulations. It outlines the organization and purview of the IRB in addition to its processes for reviewing protocols and other procedural issues. Research funded by HHS can only be conducted at a facility holding an assurance with OPRR. There are three types of assurances:

Multiple Project Assurances (MPAs): The MPA allows institutions to conduct any number of HHS-funded research projects for an initial period of three years after which it can be renewed for 5 year intervals. Regulations require the MPA only for HHS-funded efforts, but most of the nearly 450 MPA institutions have extended the protections to all research being conducted at their institutions. Though a minority of IRBs hold MPAs, these institutions account for nearly 75 percent of NIH-funded research.

Single Project Assurances (SPAs): For those institutions that do not have the high volume of protocols necessary to support the use of an MPA, a single project assurance is used. For each project an institution wishes to conduct, it must apply for an SPA. This presents extra work for the institution as well as OPRR, who must not only review the institutional commitments to the IRB and human-subject protections, but also must review the research protocol and informed consent documents for each project assurance. Currently, there are approximately 3,000 active SPAs.

Cooperative Project Assurances (CPAs): The HHS funds approximately 25 cooperative groups which conduct thousands of clinical trials across the country. An institution wishing to conduct any of the groups' protocols that does not have an MPA can apply for a cooperative project assurance. The CPA can then be used for any number of cooperative projects. Currently, there are approximately 1,500 CPAs.

The assurance application process is conducted entirely through document transmittals and phone communication. An institution wishing to apply for an assurance can receive a template from OPRR. After the institution tailors the template to its specific setting, it is submitted to OPRR. There, assurance branch officers will review the document.[7] Any problems or suggestions are worked out through the institutional official(s) and the assurance officer before an approval decision is made.

To ensure compliance, OPRR has the authority to limit, suspend, or withdraw an institution's assurance or require special reporting.

Investigations

Compliance investigations are another component of OPRR's oversight. The OPRR conducts investigations primarily on the basis of subject complaints, after becoming aware of incidents that appear to have resulted from protection breakdowns or from referrals within the department found as a result of audits.[8] The OPRR reports that the focus of the investigations has shifted in the past five years from micro-level to systemic solutions. There is no set investigational protocol as the corrective actions are prescribed according to the violation and the needs of the IRB. Since 1990, there have been 438 investigations of which 360 are considered complete. However, the great majority of investigations occur through paper and phone communication. Only rarely does OPRR go on site. Between 1990 and April 1996, OPRR went on site to investigate compliance only 18 times. In fact, OPRR conducted only one such visit between April 1997 and May 1998 because of staffing problems.[9]

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[7]For an SPA, the protocol and informed consent document must be reviewed as well as the assurance template. The OPRR reports that it spends much more time on SPAs even though more research projects and more subjects are involved under MPAs.

[8]Less frequently, investigations are conducted as a result of suggestions from Congress or the media.

[9] "Technical-assistance" site visits are also conducted. These visits are intended to be an educational opportunity for IRBs and do not signal noncompliance. Between 1990 and April 1996, 13 such visits were completed.

Food and Drug Administration (FDA)

Inspections

The FDA's oversight of IRBs is one of many activities conducted in the process of evaluating the safety and effectiveness of the drugs, biologics, and devices it regulates. The goal of the monitoring process is to routinely inspect an IRB once every 5 years.[10] However, inspections can also be conducted as a part of the product-approval process or because of possible noncompliance. There are three centers within FDA that are responsible for conducting inspections: Center for Drug Evaluation and Research (CDER), Center for Device and Radiologic Health (CDRH), and the Center for Biologics Evaluation and Research (CBER). An inspection can be generated by any of the centers, but the inspections are carried out by the same group of FDA inspectors in regional offices across the country. The following table illustrates FY 1997 data for each of the three centers including the number of inspections and the number of official and voluntary actions indicated.[11]

FY 1997 Inspection Data

Center	# Inspections	# OAI	# VAI	# Informed Consent Deficiencies	# Continuing Review Deficiencies
CBER	9	3	4	n/a	n/a
CDER	149	5	124	68	31
CDRH	36	0	19	6	11
Totals	194	8	147	74	42

The inspection guidelines focus on ensuring compliance through the review of IRB records and examination of written procedures. Another component of the inspection is the file review of at least three actual research studies approved by the IRB. The files are examined to determine such things as a timely continuing review, current consent documents were used, adverse-event reports were submitted and reviewed, and whether a

[10] This is difficult to achieve because of workload constraints; IRBs found previously to be significantly deficient are re-inspected more often.

[11] Actions taken are classified according to the strengthen of the action needed to correct the deficiencies noted. "Official action indicated" (OAI) is the most serious and warrants FDA action. "Voluntary action indicated" (VAI) signifies that the institution will correct the deficiencies and often report their progress to FDA at regular intervals. "No action indicated" (NAI) is used for inspections which do not reveal any significant deficiencies.

quorum was present during the voting procedures. Based on the results of the inspection, FDA has the authority to issue a 'warning letter' signifying serious deficiencies or enact administrative sanctions.

Research investigators can also be inspected by FDA. Generally speaking, the inspections are designed to ensure data integrity and ensure human-subject protections to the extent of whether or not the informed consent document was signed and dated in a timely manner.

DETAILED COMMENTS ON THE DRAFT REPORTS AND OIG RESPONSE TO THE COMMENTS

In this appendix we present the full comments of all parties that responded to our four draft reports and our response to each set of comments. In order, the comments that we present in this appendix are from the following parties:

- The National Institutes of Health, U.S. Department of Health and Human Services
- The Food and Drug Administration, U.S. Department of Health and Human Services
- Assistant Secretary for Planning and Evaluation and the Assistant Secretary for Health/ Surgeon General, U.S. Department of Health and Human Services
- Public Citizen's Health Research Group
- Applied Research Ethics National Association
- American Association of Medical Colleges
- Consortium of Independent Review Boards

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

Ms. June Gibbs Brown
Inspector General
U.S. Department of Health and Human Services
Wilbur J. Cohen Building, Room 5250
330 Independence Avenue, S.W.
Washington, DC 20201

Dear Ms. Brown:

I am writing in response to your March 26, 1998 memorandum that provides four draft reports on Institutional Review Boards (IRBs)[1] for review and comment by the National Institutes of Health (NIH).

The requirements for IRB membership, function, operations, review of research, and record keeping are described by the core regulations for Protection of Human Subjects of the Department of Health and Human Services (DHHS) at Subpart A of Title 45 Code of Federal Regulations 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 sixteen other agencies.[2] 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 ask that you convey the final versions of the four reports to your counterpart at each respective department and agency.

Also to further the broad appreciation of your recommendations, NIH will take your final overview and recommendations to the Subcommittee on Human Subjects Research, Committee on Science, National Science and Technology Council. The Subcommittee will have great interest in your 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 common regulations. This committee is chaired and staffed by the Office for Protection from Research Risks (OPRR), in the NIH. Because of OPRR's authority in negotiating and approving assurances of regulatory compliance for Federal-wide use, policy changes by OPRR of the sort

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[1] Institutional Review Boards: Their Role in Overseeing Approved Research (OEI-01-97-00190); Institutional Review Boards: Promising Approaches (OEI-01-97-00191); Institutional Review Boards: The Emergence of Independent Boards (OEI-01-97-00192); Institutional Review Boards: A System in Jeopardy (OEI-01-97-00193).

[2] 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.

contemplated in your reports are best not imposed unilaterally. Rather, such policy changes need to be shaped by the departments and agencies that will be affected.

Your report makes many valuable suggestions about the role of increased education for scientists and IRB members as well as the need for institutions to manage the process of IRB review with an eye to the growing number and complexity of projects for their review. It would appear that there could be streamlining in the processes from the Federal side and from the institutional side as well. One area that may need further elaboration is the special challenges posed by multi-site clinical trials. Many of the steps that you would recommend the IRBs take are already within their authority to take; therefore, we expect that your report will prove useful to them as they seek to strengthen their processes.

NIH has already taken some steps to bring improved understanding to one area - informed consent. Last year we awarded 13 research grants to scientists who are studying informed consent. In regard to the needs for education and training, we have issued two solicitations for training initiatives in bioethics. One will provide post-doctoral 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.

OPRR has increasingly made information that is useful to IRBs available on its website. OPRR is committed to vigorous consultation with IRBs and institutional officials. This level of consultation, for example, is instrumental in the development of meaningful performance measures for IRBs--as called for in your reports. OPRR and the Food and Drug Administration (FDA) are scheduled to meet with numerous IRB members and staff in regional conferences in seven different U.S. cities. Furthermore, NIH will participate in the FDA's March 1999 National Forum on Human Subject Protection, at which the recommendations from your reports - as well as other reviews of IRB functioning -- will be a focus of discussion. We look forward to that meeting as an opportunity to discuss with the IRB community some "best practices" in areas of education, orientation, management and assessment of IRBs. Your report recommends additional requirements to be placed on IRBs, but we hope to focus on the attainment of the improvements rather than increased Federal regulations.

Your suggestion that the assurance process be reoriented so that it rests essentially on an institutional attestation to conform to the IRB requirements set forth in DHHS regulations is well-taken. OPRR has been seriously considering a redirection of its intensive assurance effort toward 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 a next-generation, competency-based mechanism for assuring compliance.

Twenty-four years after the initial promulgation of our Department's rules for protection of human subjects, your summary of the challenges today facing IRBs, and your recommendations for DHHS oversight, form important additions to the evolving body of analysis of our system of

protecting human subjects in research. NIH appreciates both the opportunity to comment on your evaluation, and your contribution to the ethical conduct of NIH-sponsored research.

We would be willing to meet with your staff and discuss these comments.

Sincerely,

Anthony L. Itteilag
Deputy Director for Management

OIG RESPONSE TO NIH COMMENTS

We welcome NIH's positive response to our reports and its readiness to use them to stimulate widespread discussion of our findings and recommendations. Given that several Federal departments and agencies share a common Federal policy on IRB protections, we agree that it would be particularly important and useful to involve them in considerations of our reports. We will send our final reports to each of the departments and agencies.

At the same time, we must note that some of our recommendations have particular relevance to NIH and involve matters that we believe warrant near-term action. These include our recommendations that Data Safety Monitoring Boards be required for multi-site trials that meet specified conditions and that these boards regularly provide to IRBs feedback on developments concerning these trials. They also include our recommendations concerning education and training of both investigators and IRB board members. In these areas, we believe it is important to move quickly to spur developments that can provide valuable support to IRBs as they review more and more research proposals for NIH funding.

We recognize and support NIH's interest in streamlining its review processes and in reducing any unnecessary regulatory burden on IRBs and researchers generally. This is in accord with encouragement offered in a House of Representatives committee report for the 1998 NIH appropriations bill. It is also in accord with our recommendations to eliminate or loosen some of the procedural requirements directed to IRBs and to revamp the NIH institutional assurance process so that it rests essentially on an institutional attestation to conform to the IRB requirements set forth in Federal regulations.

The NIH adds that it will not "abandon its current preemptive oversight procedures. . . before putting in place a next-generation, competency-based mechanism for assuring compliance." We support this commitment and agree that a transition to a different system of oversight must be carefully orchestrated. In this redirection, a major challenge facing NIH and the IRBs themselves is to devote more continuing inquiry to developing mechanisms that will help assure that the intended human-subject protections sought by the IRB regulations are, in fact, being achieved. It was striking to us, during our own review, how little inquiry of that kind now occurs. The NIH is well-positioned to provide leadership and guidance in this important transition.

Finally, we note that the freed NIH resources that would result from the streamlining process would offer an important opportunity for OPRR to become more proactive in educating investigators and IRB members to become more knowledgeable about and sensitized to human-subject protections. Such outreach could be of great value to IRBs and could help in conveying a broader appreciation for the importance of ascertaining just how well IRBs are achieving their mission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: May 11, 1998

To: Inspector General

From: Lead Deputy Commissioner

Subject: Comments on the March 1998 Draft Office of the Inspector General Reports on Institutional Review Boards

We appreciate the opportunity to comment on the March 1998 draft reports on Institutional Review Boards (IRBs). We believe that these reports represent a thoughtful and detailed examination of the IRB system as well as the roles of the Federal and private sector parties involved in that system. We will carefully consider the findings, recommendations, and supporting information contained in these reports, which provide valuable information that will need to be considered by FDA in collaboration with NIH, other federal agencies, and the research community.

While we agree with the reports' conclusion that the IRB system is stressed, we are pleased that the reports described how many IRBs have found successful and creative measures to deal with this stress. The reports should be particularly helpful to that portion of the IRB community still struggling with some of the problems described in the reports.

We note that some of the recommendations which could increase the protections provided to research subjects also could be very resource intensive for IRBs, clinical investigators, and federal agencies and could, if implemented as requirements, increase the amount of stress on the IRB system. We believe that it is, therefore, very important to consider the impact of each recommendation not only in terms of its impact on the protection of research subjects but also in terms of burden on the system.

In commenting on our compliance activities as they relate to IRB inspections, the reports recommend shifting to an approach of measuring effectiveness. We consider the current FDA inspection program to have great value, and think that establishment of effectiveness measures would be a major challenge. This is a very complex issue, and we see the need for a thorough exploration of the possibilities in advance of any decisions.

We recognize that there are significant challenges facing the IRB system. Your reports highlight and add support to a number of areas where we believe change may be needed (e.g., a registration requirement for IRBs would, among other things, enhance our abilities to provide educational materials to all IRBs). We look forward to receiving the final reports and to working with our federal and private sector colleagues in further improving the efficiency and effectiveness of the IRB system. We anticipate intense discussion of a number of the recommendations by the research community at IRB and clinical investigator meetings and we

intend to place some of these issues on the agenda for our annual national conference on human subject protection to be held March 5, 1999.

I have attached a number of specific comments that we hope you will consider before publishing your reports. Again, thank you for providing us the opportunity to comment on these draft reports.

Michael A. Friedman, M.D.

Attachment: Specific comments

Attachment

FDA's Specific Comments on OIG Draft Reports on IRBs

Institutional Review Boards: Their Role in Overseeing Approved Research

(pg ii) Heightened Workload Pressures

Inclusion of numbers to support statements about workload would highlight the magnitude of the problem.

Limited feedback on FDA Actions Against Investigators

Last line: Insert "routinely" after "from" to read "precluded from routinely"

(pg iii) FDA Oversight Focuses on Inspections...

"The FDA conducted just over 200 site visits in 1997."

Follow this statement with the number of IRBs (3,000-5,000). FDA conducts inspections of IRBs, while OPRR conducts site visits.

(pg 3) Where Are They Located?

"An estimated 3,000-5,000 IRBs can be found across the country."

It should be noted that the uncertainty in the number of IRBs subject to the regulatory oversight by Federal agencies is part of the problem in exercising that oversight.

(pg 4) The Limits of Informed Consent

"They may not realize that the primary mission of the research is to advance medical knowledge rather than the welfare of the subjects."

This could be misinterpreted to mean that the research is being conducted in violation of the Declaration of Helsinki [21 CFR 312.120(c)(4)]. It may be clearer to state: "They may not realize they are being asked to participate in an experiment rather than being offered an approved medical treatment of known safety and efficacy." This point is made in the section immediately following, titled "The Blurring of Research and Treatment".

(pg 9) Limited Feedback on FDA Actions Taken Against Investigators

Line beginning "purged": Change to read "purged of trade secret and confidential commercial information, and ..."

Next sentence: Change "inspectors" to "inspections"

Last line: Insert "with IRBs and sponsors" after " information"

Institutional Review Boards: Promising Approaches

(pg 8) Promising Approaches

The meaning of the last sentence of the first paragraph could be improved if "however, as" were changed to "because each"

(pg 15) Federal Reference Points

The last sentence should clearly state that "FDA information sheets" is a set of documents. The proper citation for these sheets is "FDA Information Sheets for IRBs and Clinical Investigators"

Institutional Review Boards: The Emergence of Independent Boards

(pg ii) Independent IRBs Offer Advantages That Institutional IRBs Find Hard to Match

Third paragraph may be strengthened by a description of what is meant by "single source of review." While it is true that the IRB would be the only review board for all sites it is also true that the board would have to review the protocol for each individual site that wants to conduct the study. For each submission the IRB would want to discuss the needs of the individual community (ethnic groups in the community, research subjects available in each community, ensure that the protocol can be conducted in each community, etc.) before approving the protocol for that community.

(pg iii) Conclusion

Last sentence in the second paragraph. Change "At the same, . . . " to "At the same time, . . ."

(Pg 4) While There are Relatively Few of Them, Their Number has been Growing

Although the report recognizes the growth of independent IRBs, the report does not provide a reason for their formation. We suggest that the reason for more independent IRBs stems from a change in FDA's regulations in 1981. Prior to 1981, FDA required IRB review of studies involving institutionalized subjects or studies conducted in an institution accepting responsibility for the study (e.g., what would now be considered an institution with a multiple project assurance of compliance with HHS). In 1981, FDA expanded the scope of its IRB regulations to include a requirement for IRB review of studies conducted outside of an institution (e.g., by private practitioners). In making this change, FDA explained its rationale: human subjects, whether institutionalized or not, are entitled to the protections that these regulations offer. The agency recognized that in some instances such physicians may not be affiliated with an institution or have direct access to an IRB. In the preamble to the regulations, the agency described three options available to these physicians: request review of a study from an existing IRB, request review from an IRB created under the auspices of a local or State government, institution, society, foundation, or organization, or use an IRB created by the sponsor. Independent IRBs were created to fill this void and fulfill the 1981 requirement for IRB review of all studies involving FDA regulated products.

Institutional Review Boards: A System in Jeopardy

(pg 13) Recommendation 2.a

The report should note that there is one regulation which requires the establishment of an independent data monitoring committee. The FDA regulation that provides for an exception from the informed consent requirements in certain emergency research (21 CFR 50.24) requires that a study conducted under the exception have established an independent data safety monitoring board to review data during the study in order to exercise oversight of the study.

OIG RESPONSE TO FDA COMMENTS

We appreciate FDA's commitment to carefully consider the findings, recommendations, and supporting information presented in our reports and to place some of the issues we raise on the agenda of the annual national conference on human-subject protections to be held in March 1999. Such deliberations can be of great importance in fostering the follow-through that we hope will occur as a result of our inquiry.

As we suggested in our response to NIH, however, we believe it is important to link this longer term deliberation with some near-term actions that can begin to address vulnerabilities we point out in our report. With respect to FDA, we particularly urge near-term action in ensuring that it routinely provide IRBs with feedback on any actions it takes against investigators under the jurisdiction of IRBs. If IRBs are to carry out their protective role adequately, it is essential, we believe, for them to be fully informed on such matters. Further, we urge FDA to begin examining how it can incorporate a more results-oriented focus into its on-site inspection process.

In making this recommendation to FDA, we do not intend to discredit the compliance-oriented inspection process that it has established. We recognize the contributions that process has made and that it helps to ensure that IRB processes conform to the letter of the law. Yet, we strongly suggest that the increasingly results-oriented approach that has come to characterize health care quality assurance/improvement efforts also has applicability for both IRBs and Federal bodies overseeing their performance. It is especially important that FDA take initiative in refocusing Federal oversight because, at least at the present time, it has more on-site IRB presence than any other HHS entity.

To focus more on how well IRBs are actually protecting human subjects, it would be helpful to develop specific measures of IRB performance. This, we recognize, is a complex undertaking that should involve other Federal agencies and the IRB community. But progress in developing more performance-based reviews should not be dependent on just such measures. There is much that FDA can and should do in the near-term to help it assess more fully how well IRBs are protecting human subjects.

We would be happy to work with FDA to identify ways in which they might focus their oversight more closely and effectively on results. Among the key questions that could guide this process are the following: How do we know that the informed consent process is carried out in a manner that minimizes the possibility of coercion or undue influence? How do we know that the process of recruiting and selecting human subjects is being carried out in an equitable manner? How do we know if protocols that should be subjected to review are not being submitted for review? How do we know if protocols stray from the directions set forth in the paperwork reviewed by an IRB? The FDA can begin to obtain better answers to such questions through selected reviews at actual research sites, through interviews with human subjects themselves, through different lines of inquiry with IRB staff and board members, and through other methods.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

TO: June Gibbs Brown
Inspector General

FROM: Assistant Secretary for Planning and Evaluation
Assistant Secretary for Health and Surgeon General

SUBJECT: Comments on the Four Draft Reports on Institutional Review Boards

Thank you very much for the opportunity to review and provide comments on the four draft OIG reports on institutional review boards (IRBs). We appreciate the amount of work and effort that your staff has devoted to preparing these reports. It shows not only in their understanding of the organization and functions of institutional review boards but also in the nature of the recommendations that have been proposed.

Your principal finding that the IRB system is experiencing significant vulnerabilities is an issue that we do take seriously. Inasmuch as this system is responsible for protecting human subjects involved in research funded or conducted by the Federal Government, we rely on it to safeguard the rights and interests of all those who participate as subjects of such research. We appreciate your recognition of the hundreds of diligent and conscientious IRB members, staff and principal investigators who are strongly committed to the protection of human subjects and who labor towards this end in less than ideal circumstances.

Your observations regarding the current stresses on the system are well taken; and it is certain that, absent strengthening and corrective measures, such pressures will increase as a result of a likely growth in the number and complexity of clinical trials, including trials to evaluate and validate genetic tests and trials of xenotranplantation therapies.

We also recognize that institutions at which IRBs reside are our partners in this system to protect human subjects. Thus we have a responsibility to share with them the findings that your office has made and to engage them further in strengthening the IRB system. To this end, we hope you will make the final reports available on the DHHS website.

Margaret A. Hamburg, M.D.

David Satcher, M.D., Ph.D.

OIG RESPONSE TO ASPE/ASH COMMENTS

The ASPE and ASH stress the role of IRBs as safeguards and agree that they face vulnerabilities that must be taken seriously. We applaud their further comment that without "strengthening and corrective measures" the pressures on IRBs are likely to intensify. Our recommendations are offered to mitigate those pressures and shore up IRBs for the vital roles they will continue to play.

We particularly welcome the interest of ASPE and ASH in these issues because their broad, department-wide focus on the functioning of IRBs can be enormously important in moving forward with the kind of reforms we urge. As we note in this overview report, the primary HHS agencies responsible for oversight of IRBs, NIH and FDA, have very different jurisdictions, mandates, and operating approaches. If they are to respond effectively to the warning we present, they will have to collaborate. It would appear that ASPE and ASH could play an important role in ensuring that such collaboration goes beyond surface-level efforts to substantive interactions that address the seriousness of the current situation.

Comments by Sidney M. Wolfe, MD and Peter Lurie, MD, MPH
Public Citizen's Health Research Group
Concerning the HHS Inspector General Reports on Institutional Review Boards
(©EI-01-97-00191-93)

Since these reports find that "the System," referring to Institutional Review Boards (IRBs), is "in jeopardy," it is clear to us that the health and safety of thousands of human experimental subjects are also in jeopardy since the protection of people in these experiments is the most important function of the IRB system. Although these reports conclude that there are not "widespread abuses of human research subjects," the increasingly large number of violations found by FDA investigators in IRB-approved informed consent documents, the dangerous lack of on-site inspections for HHS-funded research by NIH's Office of Protection from Research Risks (OPRR), the rise of for-profit IRBs--much of whose work is to monitor research done by for-profit clinical trials companies--and many other problems documented in these reports belie the conclusion of "no widespread abuse." This conclusion seems particularly inappropriate as no systematic search for abuses was conducted nor were known abuses examined.

<u>The most alarming findings of the Inspector General's Reports are:</u>

1. Unsafe workload of IRBs: According to the Inspector General's Report, "at the sites we visited, the [IRB] meetings typically lasted about 2 ½ hours and included an average of 18 initial [research proposal] reviews, 9 expedited reviews, 43 protocol amendments, and 21 adverse event reports." The report cites other studies finding that the average academic medical center IRB was reviewing 297 proposals a year. It is clear that adequate time is not being devoted to this difficult task. Worse, there is "minimal" attention spent by the IRBs on monitoring the research after it has begun to see if the study's conduct is consistent with the approved protocols.

2. Massive number of informed consent violations: According to the report, the FDA annually does site visits to only about 200 of the 1,500 to 1,700 IRBs involved in overseeing research which includes FDA-regulated products. These investigations are mainly not done for cause and therefore it can be assumed that the sites inspected in a given year are representative of the larger universe of IRBs. In FY1997, there were a total of 74 informed consent deficiencies found at the 210 IRBs visited. Since 210 is 210/1,500 or only 14% of all of the IRBs, it is reasonable to project that in 1997 there were a total of 528 informed consent deficiencies (74/14%). Of the inspection findings deemed by FDA to be "most serious", there were 8 in FY 97 among the 210 IRBs inspected which projects to a total of 56 for the whole country in that one year alone.

3. Misleading advertisements to recruit patients to join experiments: 60 newspaper or public transportation advertisements were examined to estimate the extent to which the line between treatment and research was being blurred. People are

lured into experiments by emphasizing treatment instead of research: "the mention of research is either placed at the end of a long list of benefits or is embedded in language so enticing that the inevitable risks of research are easily overlooked....The danger of these advertisements is that subjects may come to a research study with misconceptions....They may be motivated by the promise of free treatment, free screening or extra money." One ad illustrating this stated: "Do you have asthma? If you qualify for any of our asthma studies, you can: learn to care for your asthma, receive free medication, receive up to $1,730!"

4. New conflict of interest problems with "Independent" (For-profit) IRBs: Because a progressively larger fraction of research undertaken in order to get drugs and medical devices approved is done by for-profit drug and device testing companies which are not part of university medical centers, there has been a proliferation of "independent" IRBs to service them. Although they are "independent" of an academic research institution, as for-profit entities they are quite dependent on pleasing their customers (the for-profit research companies) and their owners. The Inspector General study found that "some IRB officials are concerned that an independent, for-profit IRB might compromise its review process to advance the financial well-being of the firm. Such concerns are heightened to the extent that corporate-equity owners or employees serve on the IRB review boards and are sustained to some extent by the fact that reviewers are paid for their services." An additional problem involves the fact that most of these are nationwide and therefore do not have local representation and input from the localities where the trials are being conducted.

5. Inadequate oversight of IRBs by FDA or OPRR: As mentioned above, only 210 out of 1,500 to 1,700 IRBS which review studies involving FDA-regulated products are inspected by the FDA in a given year. Thus, it may be five or more years between inspections, during which hundreds or more studies will have been approved by the IRB with no on-site oversight. OPRR does even fewer on-site inspections of IRB monitoring functions, mainly employing phone and paper investigations. "Only rarely does OPRR go on-site. Between 1990 and April 1996, OPRR conducted only 18 compliance visits...[there were] no on-site visits between April 1997 and February 1998 because of staffing problems." Thus, with thousands of NIH-funded human experiments being monitored by IRBs, there is dangerously little oversight by the OPRR which is, in another example of conflict of interest, part of NIH.

6. Little evaluation of real effectiveness of IRBs: According to the Inspector General's Report, "officials [of IRBs] reported that during the past year they seldom visited the research site. Although many would like to, none oversees the informed consent process or solicits feedback from subjects." One IRB member said "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."

Inadequacies of Inspector General Investigations

There is an enormous amount of important information and recommendations in these reports but there are two areas of investigation which would have been useful to include:

1. Failure to interview subjects of human experiments: Since IRBs themselves do not find out if informed consent was really obtained (see #6 above), relying on a review of the document content instead of finding out if patients actually understand the nature of the experiment in which they agreed to participate, it would have been useful to interview a representative sample of patients in trials, particularly those who had finished trials.

2. Failure to assess differences between boards based on review of a standardized protocol or to collect data on differences between IRBs in rejection rates or rates of requiring serious modifications in protocols: In the United Kingdom, studies have shown that ethical review committees, the equivalent of IRBs, differ greatly in the way they approach and criticize a standardized protocol. Rather than collecting such systematic data, the Inspector General reports depend primarily on site visits and qualitative information. Such data would be very instructive in better training and education of IRB members. Data examining the extent to which the rate of rejection or serious modification of studies reviewed by IRBs differed from one IRB to the next might focus on conflicts of interest or other problems with the training and education of IRB members. It would also set standards by which IRBs could be objectively compared.

Recommendations beyond those made by the Inspector General

1. Funding for more adequate review by IRBs: This should be done as an automatic predetermined portion of academic overhead for clinical trials. In other words, since academic centers are getting funded to do the trials, a sufficient portion of this overhead should go to assuring that a much more rigorous review of the research, initially and while the trial is underway, is done.

2. Change in composition of IRBs including much more attention to conflicts of interest, especially at for-profit IRBs: Despite recommendations dating back 25 years that scientists from outside the institution and non-health professional lay persons should be included in IRBs,[1] this need, especially the outside scientist element, is not being adequately addressed. Given the strong institutional bias to say yes to the

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[1] Barber B, Lally JA, Makarushka JL, Sullivan D. Research on Human Subjects. Russell Sage Foundation, New York. 1973.

possible flow of money, it is particularly important to temper the institutional enthusiasm with these more disinterested parties.

The idea of a for-profit IRB is appalling. It is one thing for a loyal academic to say yes to a research proposal which will benefit his or her institution but another for the IRB member, possibly an executive or a major stockholder in the IRB, to personally gain from approving research proposals. The policy for HHS-funded research reviews by for-profit IRBs is to exclude IRB equity owners from participating in the review process, but there is no such policy for industry-sponsored studies which are to be submitted to the FDA. If it is not possible to abolish for-profit IRBs, at least this extreme conflict of interest for the approval of studies of drugs, devices and other FDA-regulated products should be ended. This conflict of interest also facilitates the phenomenon of IRB-shopping, in which sponsors take a protocol rejected at one IRB (perhaps a University IRB as in a recent case mentioned in congressional testimony [2]) and take it instead to a for-profit IRB which has every incentive to approve the protocol lest it gain a reputation as "too strict" and therefore lose business.

3. Regulation by the FDA of advertising done by clinical trials units: As discussed under finding #3 above, patients can easily be lured into participating in human experiments by the misleading advertising discussed in the Inspector General's Report. The FDA should expand its regulation of IRBs to include the recruiting materials such as advertisements and these materials should also be part of the materials received by the IRBs. Combined with misleading information in the informed consent forms, the result may be for patients to participate in an experiment without adequate informed consent.

4. Requirements for a central registry of all trials and that the results of all trials be made public within one year of completion. In a recent article entitled, *Are Research Ethics Committees Behaving Unethically? Some Suggestions for Improving Performance and Accountability,* British researchers concluded that the committees were behaving unethically "by endorsing new research which is unnecessary and by acquiescing in biased underreporting of research which they have approved." [3] They concluded that research ethics committees should:

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[2] Wilfond B. Testimony before the House Subcommittee on Human Resources, Committee on Government Reform and Oversight, U.S. House of Representatives, May 8, 1997.

[3] Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *British Med J* 1996; 313:1390-3.

a/ Require systematic reviews of existing research before approving research;
b/ Require that a summary of relevant systematic reviews be made available to potential participants;

c/ Require registration of clinical trials at inception as a condition of approval [national registry];

d/ Require a commitment by investigators to make the results publicly accessible as a condition of approval; and

e/ Audit the reporting of results of research previously approved by them. (IRB monitoring of publication is critical to avoid publication bias or debacles such as Knoll Pharmaceutical's suppression of the levothyroxine equivalency study.[4])

5. Analysis of close votes at IRBs to see if and why those protocols got approved.

6. Retrospective analyses of IRB meetings which approved trials now considered unethical.

7. Remove OPRR from NIH because of conflict of interest: As long as OPRR is part of the institutional block diagram and under the control of the NIH, over whose research it is supposed to exert independent control, it is highly unlikely that it will be able to fulfill its important mission. It should be moved outside of the NIH but still within HHS.

8. Implementing as mandatory for IRBs some of the strategies discussed in *Institutional Review Boards: Promising Approaches (OEI-01097-00190)* : With the growing number of research applications, it seems reasonable at the present time to put a limit on the number of applications a given IRB can review per year. IRBs should also be required to provide some educational outreach to faculty and students, at a minimum including a lecture series on ethics, including lectures on recent controversies and new directions in ethics. We were particularly impressed with the computer-assisted monitoring of research activity at the University of California, San Diego which determined that fully 10% of recent publications by faculty members had not received IRB approval; this monitoring function, which is rapid and inexpensive, should also be made mandatory. Periodic informed consent audits by third parties, as conducted at the University of Texas Health Sciences Center, should also be required, as should the presence of a bioethicist on the IRB.

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[4] Rennie D. Thyroid storm. *JAMA* 1997; 277:1238-43.

OIG RESPONSE TO PUBLIC CITIZEN COMMENTS

Public Citizen incorrectly states that we concluded that there are no widespread abuses of human subjects. Our concluding assessment on this point was that "we do not claim there are widespread abuses" of such subjects. We made that point to place our main finding about the jeopardy that exists in context and to try to avoid overly alarmist reactions to it. As Public Citizen correctly indicates, in this study we did not conduct a systematic search for abuses, nor did we investigate known abuses. Rather, our focus was on the big picture. We sought to bring greater clarity and understanding to the overall system of protections that exist in a varied and rapidly changing environment.

Concerned about the seriousness of our findings, Public Citizen regrets that we did not go further with our review. In particular, it suggests that it would have been useful to have interviewed human subjects themselves and to have used a standardized protocol as a way to assess differences among IRBs. We agree that both of these techniques could have value. However, we were unable to incorporate them as part of our review. We amended our report to indicate that such techniques should be considered as part of the regular performance-focused evaluations of IRBs that we recommend.

Public Citizen also offers a number of recommendations beyond those that we presented in the report. They are thoughtful recommendations that warrant careful consideration by the policy and research communities. In two cases, our own consideration of them led us to make some changes in the text. In our recommendation calling for more noninstitutional members on IRBs, we clarified that such members could well include scientists from outside the institution. In our findings and recommendations concerning conflict of interest, we clarified that while equity owners are precluded from participating in the review process for studies under NIH purview, they are not precluded from doing so for those just under FDA's jurisdiction. We added a recommendation specifying that such participation should be disallowed in all cases involving NIH or FDA jurisdiction. At the very least, the involvement of equity owners of IRBs in reviewing research protocols undermines the public credibility of what should be an independent review.

Public Citizen's comments about the importance of proper funding parallel those of FDA and other parties. They are well-taken. We reinforce this concern in the introduction to our recommendations when we note that "sufficient financial provisions" must be made to buttress IRB and Federal efforts to protect human subjects."

Finally, we also take note of Public Citizen's call for FDA regulation of advertising done by clinical trials units. While we are not ready at this point to make such a recommendation, we do have considerable concern, as we indicate in the reports, that such advertising is currently being used in ways that give potential subjects an unbalanced perspective of the risks and benefits of participating in research and that both IRB continuing review processes and Federal oversight processes fail to give sufficient attention to this matter.

May 12, 1998

June Gibbs Brown, Inspector General
Department of Health & Human Services
Office of the Inspector General/Office of Evaluations and Inspections
Room 5458 Kohen Bldg.
Washington, D.C. 20201

Dear Dr. Brown:

Thank you for giving the Applied Research Ethics National Association (ARENA) the opportunity to comment on the four draft inspection reports (OEI-01-97-00190, 00191, 00192, 00193) on the Institutional Review Board (IRB) system. ARENA is a subsidiary of the Public Responsibility in Medicine and Research (PRIM&R), which is a nonprofit organization dedicated to promoting the ethical conduct of research. ARENA is a professional association with over 800 members who are administrators or members of Institutional Review Boards and Institutional Animal Care and Use Committees throughout the United States. ARENA's membership is in part dedicated to the protection of human research subjects and compliance with federal regulations governing IRB operations and informed consent.

ARENA applauds your efforts to address the complex research culture in which IRBs currently function. The inspection report entitled "Institutional Review Boards: Promising Approaches" provides excellent examples of innovative IRB strategies for enhancing effectiveness and efficiency in protecting human subjects. This report illustrates that many IRBs have developed creative and effective approaches to managing the challenges presented by the changing research environment.

We support the recommendations delineated in the summary report (OEI-01-97-00193) but have general concerns about the four reports' findings. The general concerns and our specific comments on the recommendations are discussed below.

GENERAL CONCERNS

Use of the phrase "IRB oversight" is not appropriate and is misleading to readers who do not have IRB expertise. This phrase has been confused with the mandated charge of IRBs to conduct continuing review, review of unanticipated problems, and review of proposed changes in approved research. IRBs are not mandated to conduct data monitoring or daily quality assurance

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of research procedures carried out under approved protocols, as the phrase "oversight" clearly implies. The responsibility for oversight and safety monitoring rests with federal regulatory agencies, sponsors, and Data Safety Monitoring Boards. The phrase should not be used in the headings, subtitles, or the narrative of the four reports because it does not accurately refer to the IRB mandate for continuing review.

The "global" language used in the title, the introductory text and the subtitles found in the OEI-01-97-00193 and OEI-01-97-00190 is very problematic. The general public, congressional leaders, and anyone who does not read the report in detail may be left with a blanket condemnation of the IRB system. Based on our assessment of the methodology used in conducting the OIG inspection, global generalizations which appear alarmist need to be avoided. The OIG sample was small and the study used qualitative interviews, not quantitative measures to determine IRB effectiveness. Although the reports acknowledge the limitations in the methodology and appropriately point to strengths in the system, these limitations are lost amid global statements like "rarely does," "the little review that does occur...," and "few IRBs seem to be able..."

For example, in OEI-01-97-00193 the OIG refers to a prior study that focused on investigational medical devices in which significant deviations from IRB approved procedures were identified. The report goes on to state "in this study, which was more broadly based, we found little basis for easing those concerns; in fact, they have been intensified." A representative from one of the six academic health science centers site-visited, who also reviewed these draft reports, was troubled by this sweeping statement. That person pointed out that during the three day OIG site-visit the OIG did not review any specific protocol. It is therefore difficult to understand why the OIG would conclude that deviations from a specific IRB can be applied to a more broad based look at IRBs and ascertain there is a widespread problem.

Another general concern is that it is unclear in the report on continuing review and the summary report whether the findings and recommendations apply only to selected segments of the IRB community or whether they apply to the entire community of IRBs including independent boards. As currently written, it appears that OEI-01-97-00190 findings and recommendations only apply to institutional IRBs. There is no mention in the methodology section of the continuing review report that 11 independent IRBs were also interviewed. There is no discussion of the continuing review topic included in the report on independent boards. Also, in the methodology section of the summary report, there is no mention of interviews with independent board representatives. However, some of the findings appear to include independent boards; others do not.

SUMMARY REPORT RECOMMENDATIONS

As indicated above, in general ARENA supports the recommendations in the summary report. However, we do have some specific concerns, which are included in the following discussion.

Recommendation 1: Recast Federal IRB Requirements so That They Grant IRBs Greater Flexibility and Hold Them More Accountable for Results

ARENA agrees that IRB effectiveness would be greatly improved if the federal policies that focus upon "paper trail" aspects of IRB operations or perfunctory review processes were eliminated or recast. For example, in two of the reports it is stated that ongoing review of adverse event reports is an integral and ongoing task for IRBs. An argument can be made that monitoring for adverse events is actually a Food and Drug Administration (FDA) and sponsor function that has over time been delegated to the IRB through FDA policy and procedures rather than regulatory mandate. The Department of Health and Human Services (DHHS) and FDA IRB regulations do not specifically address adverse event monitoring responsibilities. ARENA acknowledges that IRBs have a role in reviewing adverse events, but the scope of that role is subject to debate. In accord with regulatory requirements, all adverse event reports are sent to the FDA. FDA, with trained scientific reviewers, is in the position to evaluate the reports and determine if risks for a test article have changed. The FDA could transmit this information to sponsors and IRBs if the recommendation to register IRBs is adopted.

In principle, ARENA supports the recommendations that IRBs undergo performance-focused evaluations. However, based upon past experience with the federal regulatory process, we are concerned that developing an evaluation system of this type could lead to increased bureaucratic workload, which would further drain limited IRB staff resources.

Developing an effective "performance-focused" evaluation program would be an exceedingly difficult task, which would require identification of appropriate performance-based criteria and considerable infusion of resources in both the development and implementation phases. Performance-based criteria should be developed by those heavily experienced in IRB processes. The criteria should be standardized and universal in its applicability. IRB review is a peer review process. Ethical decision-making does not lend itself to traditional procedures for assessing effectiveness. In part, that is the reason why the current inspection system tends to focus upon the "quantitative" measures (presence of a quorum, continuing review conducted within 365 days and so forth) rather than qualitative ones.

The report also recommends that the evaluations be made available to the public. We question how valuable that information would be to the lay public. The performance-based system should first be developed before the decision is made on whether the evaluations provide enough valuable information to warrant dissemination to the general public.

Recommendation 2: Strengthen Continuing Protections for Human Subjects Participating in Research

ARENA agrees that the role of Data Safety Monitoring Boards should be expanded and that providing IRBs with feedback on the developments in multi-site trials would strengthen human subjects' protections. Also, ARENA concurs that IRBs should be provided with feedback about FDA actions against investigators. Many IRBs have compensated for the lack of feedback from

auditing organizations by requiring the results of any inspection be reported to the IRB as part of the continuing review application.

In addition, ARENA members have expressed serious concerns about the potential in the current system for sponsors to seek out IRBs which do not raise substantive issues or request numerous modifications in the informed consent document. We support any recommendations which would discourage "IRB shopping" for ease of approval. We support the recommendation that sponsors and investigators notify independent boards of prior reviews of research plans. Implementing this recommendation may not be appropriate for institutional IRBs which review multi-site trials that have previously been reviewed by numerous other IRBs at other sites.

There are some safeguards currently in the system that deter "IRB shopping." The FDA form *FD1572* requires an investigator to report any change of IRB. Most independent IRBs ask about submission to other IRBs when they first receive a protocol for review. Many of the multi-site studies seen by independent IRBs are also reviewed by one or more institutionally-based boards. Also, it is commonplace for institutions to require investigators to use their internal IRBs. An investigator in an institution generally has no choice about which IRB to use. He or she must use the IRB covered by the Office for Protection from Research Risks (OPRR) Assurance for that institution.

In principle, we support the recommendation that IRBs should have increased awareness of on-site practices. However, ARENA has two concerns. First, our experience in the field suggests that the most effective IRBs are ones that have a collegial relationship with investigators. Violation of the long established "ethic of trust" would undermine IRB effectiveness. We agree with OIG assessment that one of the most significant challenges facing IRBs is how to achieve increased awareness of on-site practices without undermining the "ethic of trust." Our other concern is a practical one. The approaches for increasing awareness of on-site practices suggested in the report (e.g., random audits, observing the consent process) would require considerable staff and IRB resources to implement. This concern is addressed in more detail in the comments on Recommendation 5.

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

Philosophically, ARENA supports the recommendation for mandatory training of investigators and board members. However, institutions and IRBs do not have adequate resources to comply with mandated requirements for training programs. These efforts should be a shared responsibility and should not fall solely upon the IRB or the institution. The responsibility of conducting ethical and sound scientific research is a shared responsibility of the investigators. Training on the ethical conduct of research should become part of the medical or graduate school curriculum. Investigators should also be responsible for providing training to their entire research team.

Responsibility for providing training should also be shared with federal agencies. Both FDA and OPRR should be provided the resources to expand their training initiatives. Also, a number of national organizations such as ARENA and PRIM&R offer training and are in the process of developing new programs which focus on both investigators and board members. DHHS funding programs should be developed to support initiatives of this type. Also, expenses for providing ethical conduct of research training should be an allowable cost for all DHHS funding mechanisms. Efforts to cap indirect costs only serve to further drain dwindling institutional resources.

ARENA does not support the recommendation that investigators provide written attestation of their familiarity with and commitment to human subject protections. This procedure would not serve as an effective training tool. Our experience suggests that investigators submitting grant proposals have a number of demands upon their time. Signing the attestation statement will become just another bureaucratic hoop that investigators go through in submitting the grant application.

Recommendation 4: Help Insulate IRBs from Conflicts that can Compromise Their Mission in Protecting Human Subjects

Although ARENA would agree that IRBs should be insulated from conflicts, we are uncomfortable with this recommendation because it implies that the IRB mission is currently compromised. In fact, our experiences have not supported that conclusion. We acknowledge that at institutional IRBs there is increased pressure from both investigators and the administration to "do more faster." However, the focus has generally been on "improving efficiency" not upon diminishing protections for human subjects. Most institutions are committed to protecting human research subjects as are the IRB members and staff. ARENA also found this recommendation confusing because it did not include any reference to independent board conflicts. Not addressing this issue in the recommendations implies that conflicts are only problematic for institutional based IRBs; this conclusion conflicts with the observations regarding potential financial conflict of interest included in the OEI-01-97-00192 report.

Although ARENA agrees that nonscientific and noninstitutional members serve an important role in reviewing protocols, we do not support the recommendation that additional federal requirements for increased representation be enacted. We do not agree with the OIG conclusion that the current requirements are inadequate. Regulations and federal policy require that the membership include a nonscientist and a noninstitutional representative. Meeting these requirements by appointing a single individual is not a standard IRB practice. In addition, the requirements specify that a nonscientific member must be present to conduct a full review. The decision to "add" additional members should be left to the discretion of the IRB. From a practical standpoint, obtaining a quorum for "full review" is difficult and increasing the total number of members will only serve to exacerbate this problem. Based upon our experiences, we do not agree with the OIG statement that few "outside members" are on boards. Our experience suggests that this is simply not the case. IRBs always include at least one such member and many IRBs include additional noninstitutional members. Also, the statement "Few IRBs seem to

seek or be able, on a consistent basis, to recruit and maintain lay members..." may be true for some IRBs but in our experience is not true for the majority of IRBs.

Recommendation 5: Recognize the Seriousness of the Workload Pressures that Many IRBs Face and Take Actions that Aim to Moderate Them

ARENA applauds OIG's recommendation to require that IRBs have access to adequate resources but does not think that "requiring" is sufficient. One of ARENA's overriding concerns about the recommendations is that they have the potential to establish a number of "unfunded" mandates. Recommendations 1, 2, and 3 will require considerable additional resources to implement. The findings of the assessment as outlined in the continuing review and the summary reports clearly indicate that IRBs are currently lacking in adequate resources; yet, the implementation of the recommendations will only serve to increase costs and the need for additional staff and resources. Many institutions are committed to providing adequate resources but in fact do not have sufficient funds to do so. At the federal level, the problem is exacerbated by increased agency requirements for cost sharing and continual efforts to reduce indirect cost rates. DHHS needs to develop support mechanisms to assist in funding the new initiatives. The OIG should include acknowledgment that it is likely the proposed recommendations will not be effective unless additional resources are available.

Recommendation 6: Re-engineer the Federal Oversight Process

ARENA agrees with the recommendations to revamp the National Institute of Health/Office for Protection from Research Risks (NIH/OPRR) assurance mechanism and refocus the FDA on-site inspection process on performance based criteria. As pointed out in our comments on Recommendation 1, we support performance-based evaluations but are concerned about the difficulties in developing a system of that type. Efforts must be made to ensure that in re-engineering the Federal oversight process that the "old" bureaucratic hoops are not simply replaced with "new" bureaucratic hoops with only marginal relationship to quality and effectiveness of reviews. ARENA feels that it is important to periodically evaluate the IRB review system. It is equally important that this system be assessed fairly and appropriately.

ARENA also wants to stress the importance of FDA and NIH/OPRR continuing to coordinate federal policy development. If FDA and OPRR policies are as uniform as possible, given the legislative mandate for each agency, the bureaucratic burden on IRBs would be greatly reduced. Also, we strongly support the recommendation that experienced IRB members and staff should play an on-site role in reviewing IRB performance and the suggestion that Federal agencies include a peer review element or offer IRBs some type of incentive as part of a continuous quality improvement effort. We also support the recommendation that all IRBs be registered with the Federal Government, provided the mechanism is streamlined. Based upon our experiences in the field, ARENA is concerned that even though the registration process is proposed to be "simple" the procedures could, in fact, become "complicated," adding to the already unmanageable IRB administrative workload.

In conclusion, ARENA acknowledges the effort OIG made in reviewing IRB regulations and procedures. It is a difficult task to write reports that encompass the activities of IRBs from such a wide variety of facilities and institutions involved in the conduct of human subject research. ARENA also appreciates the inclusion of innovative procedures select IRBs have developed to cope with the ever burgeoning task of IRB review. It provides a balance for what will be perceived as a negative report on IRB processes. Many IRBs do conduct substantive reviews and simply do not get the recognition deserved for the ethical diligence.

The recommendations made by OIG, for the most part, are ones that could be implemented by many IRBs to improve the quality of their reviews. It is true that with additional resources many IRBs could become more sophisticated in their review processes. It is not clear from the report, however, from where these resources will originate. It is a long leap from "requiring" such resources to actually receiving them.

ARENA thanks you for the opportunity to comment on the reports. If any additional information is required, please do not hesitate to contact us.

Sincerely,

William Freeman, M.D.
ARENA President

Ada Sue Selwitz, M.A.
Chair, Public Policy Committee

pc: Drafting Committee:

Gary Chadwick	Erica Heath	Gwenn Oki
Norma Epley	Moira Keene	Joan Rachlin
Sharon Friend	Susan Kornetsky	Beth Ribbeck
Karen Hansen	Helen McGough	Pat Scannell

OIG RESPONSE TO ARENA COMMENTS

In our review, we gained great respect for the work and commitment of IRB administrators and members, often under very trying circumstances. We listened, sometimes at considerable length, to them articulate concerns about the developments that threaten the effectiveness of their boards. Sometimes we were able to supplement these conversations with a review of records and reports concerning their operations. In its response to our draft report, ARENA, whose members are IRB administrators and members, did not tend to reflect the same message we heard so consistently from the individual administrators and members during our year-long inquiry.

As the ARENA response itself suggests, perhaps to some degree this disconnect is attributable to some of the language we used in our draft reports. In an effort to improve communication and focus attention on the necessary reforms, for which we believe there is considerable support, we have changed some of the language we used. Thus, we have changed the title of this overview report from "A System in Jeopardy," to "A Time for Reform." We have made other such changes and elaborations to indicate, even to the casual reader, that our reports are not intended as a "blanket condemnation" of the work of IRBs. At the same time, we must stress that we still find that the effectiveness of the system is, indeed, in jeopardy. As an independent overseer, it is vital that we present such a warning when we find it applicable, and do so in a manner that is clearly communicated. Thus, within the report, the jeopardy warning remains as our central finding.

Another key linguistic change we made was in the use of the term "oversight." Given ARENA's concerns, we reserved that term for the monitoring of IRBs done by the Federal agencies (NIH and FDA). With respect to IRBs themselves, we now refer to their role in conducting "continuing review" of approved research rather than oversight. This is consistent with the language used in the Federal regulations concerning IRBs. We must note, however, that those regulations clearly give IRBs the authority "to observe or have a third party observe the consent process and the research"--something that, in fact, they rarely do. Further, an OPRR "Dear Colleague" letter to IRBs calls for continuing review to be "substantive and meaningful"--a characterization that many IRB officials say does not describe current practice. This limited attention to continuing review is unfortunate, because while to varying degrees other parties conduct continuing review of approved research, they, unlike IRBs, do not have a central mission of protecting human subjects.

Our focus on continuing review emerged because a prior OIG inspection concerning investigational medical devices found, in four case studies, considerable evidence of inadequate continuing review, and because of the findings of various other studies cited in the report. We state in this report that our inquiry has led us to become even more concerned about the inadequacy of continuing review. The ARENA questions the basis for that conclusion, citing the observation of a representative of one of the academic

health centers we visited. That person wondered how we could reach such a conclusion when during the 3 days we spent at that center we did not review any specific protocol. Our response is that, as we note in the report, we did not seek in this inquiry to conduct any audits of particular protocols or investigations of specific cases. It was our broader systemic analysis that led us to recognize the limits of the continuing review that IRBs do conduct. It was the substantial accumulating evidence associated with that awareness that led to the intensification of our concerns about the adequacy of continuing review.

In regard to ARENA's comments on our recommendations, we must stress what we perceive to be the importance of IRBs becoming more fully accountable to the public. It is toward this end that we strongly urge ARENA to recognize the overriding importance of performance-focused evaluation, not just in terms of the complex task of developing performance measures, but even more so in terms of concrete actions that IRBs can and should take to assess and verify the actual results of their efforts in protecting human subjects. (Our response to FDA elaborated on some of the questions that could be raised in this regard.) It is toward the same end of shoring up public accountability that we urge greater representation of outside interests on IRBs. As IRBs become more involved in conducting reviews involving genetics research, which raises vital issues involving the use and confidentiality of information, such broader representation will become even more important. The public credibility of the entire IRB review process could depend heavily on such representation. We know that many IRB officials agree with this assessment and that they have been frustrated by their lack of success in recruiting and maintaining a sufficient core of nonaffiliated members who provide an effective counterbalance to institutional interests.

With respect to our recommendation calling for investigators to provide a written attestation of their familiarity with and commitment to human-subject protections, we regret that ARENA viewed it as an unjustifiable demand on investigators' time. This recommendation parallels one carefully considered and presented by the Commission on Research Integrity. We submit that the signing of the attestation by investigators would take minimal time, but would represent an important formal commitment to take seriously their responsibilities in upholding human-subject protections as called for in Federal regulations. Many IRB officials themselves suggested that they had a difficult time getting investigators to devote sufficient attention to those regulations.

On the matter of insulating IRBs from conflicts, we agree with the comment that our draft report made it appear that the possibility of conflicts were greater for institutionally based IRBs than for independent ones. Accordingly, we have revised the text to more fully and clearly express our concern about how conflicts can compromise the mission of all types of IRBs. We also agree with the concerns raised about the adequacy of resources, as we have commented on in response to the FDA comments.

Finally, in response to ARENA's concern about the type of IRBs to which our findings and recommendations apply, we note that they are presented as applicable to the IRB

community as a whole. Obviously, some will be more relevant to some types of IRBs than others. Occasionally we point that out when we have reason to believe that to be the case. Overall, we have given more attention to IRBs in academic health centers, where, as we point out, a significant portion of research continues to be conducted. So our findings have particular applicability to them. But in the course of our inquiry we have interacted with representatives of IRBs in many other settings, including hospitals of various sizes, public agencies, and independent, free-standing bodies. We would not exclude them from the main thrust of our findings.

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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.

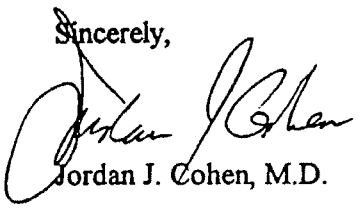
In conclusion, it is important to emphasize that, overall, this is a system that has worked remarkably well, and one that is not on the verge of collapse. Thus the alarmist tone in some sections of the report, particularly the overview, should be lessened to make the level of concern expressed more proportional 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.

OIG RESPONSE TO AAMC COMMENTS

We concur with AAMC that the IRBs are the keystones of the current system of protections and that "the sound functioning of these bodies is of the utmost significance." That is why we have given so much attention to just how they are functioning and how they might be improved. Obviously, we disagree with AAMC on a number of the particulars.

One of the most important of these particulars has to do with how we interpret the role of IRBs in carrying out their protective responsibilities. The AAMC stresses that from the beginning the essence of that role has been one based on trust, whereby IRBs work collaboratively with investigators to help them ensure that the necessary human-subject protections are in place. It points to the Belmont Report, produced in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, as establishing the basis for this collegial role. It suggests that we misunderstand this backdrop and assume "a policing or auditing role" for IRBs.

As we note in our reports, we recognize the fundamental importance of trust between IRBs and the research community. At the same time, we underscore that trust in itself is insufficient. This is particularly true today as IRBs face many possible conflicts in an increasingly commercialized research environment. But even in the 1970s, the National Commission noted above had more than trust and collegiality in mind when delineating the role of IRBs. The Belmont Report cited by AAMC is an important report setting forth ethical principles of research. But prior to it, the National Commission produced many other reports. One, as we elaborate on in Footnote 28 of our report on continuing review, focused specifically on IRBs. In that report, the Commission elaborated on the verification efforts that IRBs might undertake. These included interviews with human subjects, requirements that investigators give subjects a form through which they may report their research experiences to IRBs, and even, in certain cases, requirements that a neutral party be present to help a potential subject to consider the pros and cons of participating in a research effort.

We emphasize this matter here at the outset of our response because it is fundamental to the kind of reforms we (and many others) regard as necessary. If our calls for greater accountability through more results-focused assessments, broader representation on IRBs, and other measures, are routinely dismissed as violating the essential principles of IRBs, then little progress is likely. Thus, further discussion of this important matter in the research and policy communities would be highly desirable. Our intent is to maintain the foundation of trust, but to complement it with various types of verification that are essential for a review body having a vital role in protecting human beings.

The changes we have made in some of the language we use, as we noted in our response to ARENA, may help address some of the concerns AAMC expresses about our generalizations and conclusions. We do not conclude that the IRB system is necessarily

"on the verge of collapse," but we certainly do have reason to conclude that its effectiveness is in jeopardy. We have tried in these final reports to use language even more carefully to express our serious concern without conveying a greater degree of imminent danger than we have basis to suggest.

The AAMC, as other commenters, addressed the matter of resources and how they might best be tapped to support the IRBs' important role. It suggested that some specially designated source of Federal support might be developed. As we have noted in other responses in this appendix and in the introduction to our recommendations, we recognize that this is an important issue warranting further examination, especially as IRB responsibilities expand.

The AAMC supports our recommendation that IRBs be granted greater flexibility in carrying out their responsibilities, but is wary of performance-focused evaluations, especially if made available to the public. As we have noted in response to FDA and ARENA, there are many practical ways of incorporating a greater focus on results, both in the IRBs' own continuing review efforts and in outside assessments of IRBs. And we would add that these could be carried out and presented in ways that lay people would find quite possible to understand. Further, we stress that a greater accountability for results must be integrally associated with efforts to grant IRBs greater flexibility.

In regard to our recommendation urging that NIH and FDA help insulate IRBs from conflicts that can compromise their protective mission, AAMC indicates that "nothing could be more in the institutional interest than protecting the subjects of research." We agree with the principle expressed in that comment. But in settings where clinical research represents as much as a quarter or more of the operating income of IRBs' parent institutions, where IRBs are urged to expedite their review processes and make other adaptations to accommodate sponsors, where IRBs serve under the auspices of organizational units primarily responsible for bringing in research dollars, we submit that it is reasonable to be concerned about the kind of conflicts we point out. Many IRB officials themselves have emphasized this point to us, quite strongly.

Finally, on the matter of advertising to recruit human subjects, AAMC indicates that our warning is "highly anecdotal" and that we exaggerate the danger associated with these advertisements. Our response is that with little difficulty we accumulated 60 advertisements that were highly imbalanced in presenting risks (rarely mentioned) and benefits and that we could easily have collected many times that number. Notwithstanding the fact that many subjects are recruited through quite responsible means and that all must sign an informed consent form, we suggest that the advertisements do represent a danger that warrants careful attention. Just a mere glance at the inducements offered in many of these advertisements makes that quite obvious.

CONSORTIUM OF INDEPENDENT REVIEW BOARDS

May 4, 1998

June Gibbs Brown
Inspector General
Office of Inspector General
Department of Health and Human Service
330 Independence Avenue, S.W.
Washington, D.C. 20201

Re: Draft Reports Concerning Institutional Review Boards

Dear Ms. Brown:

On behalf of the Consortium of Independent Review Boards ("CIRB"), we congratulate the Department of Health and Human Services' ("HHS") Office of Inspector General ("OIG") on its four comprehensive reports on a difficult issue. In addition, CIRB thanks you for the opportunity to meet with you and comment on the OIG reports concerning the effectiveness of current Institutional Review Board ("IRB") regulations, policies, and practices. Provided below are our comments concerning the following documents: (1) *Institutional Review Boards: A System in Jeopardy (Draft)*; and (2) *Institutional Review Boards: The Emergence of Independent Boards (Draft)*. The CIRB membership hopes that these comments will be helpful to OIG as it finalizes the draft documents.

1. INSTITUTIONAL REVIEW BOARDS: A SYSTEM IN JEOPARDY (DRAFT)

As the document *Institutional Review Boards: A System in Jeopardy (Draft)* clearly reflects, the environment within which IRBs currently operate is very different from that which existed when the Federal IRB regulations were first implemented. Thus, CIRB agrees with the OIG's recommendation to recast these regulations so that the focus will be on IRB performance rather than merely IRB compliance. OIG's suggestions to modify or eliminate certain perfunctory Federal requirements that may not be necessary to protect human subjects, and to establish new Federal regulations or guidances that require, and set standards for, IRB Performance-Focused Evaluations will greatly assist in implementing this recommendation. The OIG report correctly observes that many IRBs operate under significant time and resource constraints. While a large proportion of the Federal regulations certainly support human subject protection, when IRBs must spend precious time complying with redundant or unnecessary

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Federal regulations, inadequate time and resources are left for ongoing activities. Elimination of such regulations would allow IRBs to focus their limited resources on strategies that would allow more effective initial review of research activities by providing time to carefully consider the research and the protocol.

In addition, CIRB strongly endorses the recommendation that NIH/OPRR and FDA convene symposia with IRBs to discuss performance measures and self-evaluation measures that will encourage IRB accountability to its stated purpose: the protection of human subjects. We believe that such symposia would result in fruitful dialogue between the agencies, the IRBs, and other interested parties or users of IRBs, such as investigators and sponsors, and would allow the agencies to develop effective oversight policies.

We also strongly support the OIG's recommendations concerning "information sharing." While the majority of sponsors and investigators have demonstrated integrity during the IRB review process, we believe it is important that these parties be obligated to inform a reviewing IRB about any prior reviews. Further, so that an IRB can function effectively, it should be provided copies of all FDA and OPRR regulatory inspectional reports and correspondence with investigators concerning clinical studies which the IRB has approved and for which it continues to provide oversight. Finally, because clinical investigations are already subject to government, contract research organization, and sponsor auditing and monitoring, we believe that extending the required "information-sharing" between the parties could be extremely helpful in providing "oversight" without adding the burdens of additional site visits to an already overworked clinical investigator.

We do have one concern, and that is the definition of the following terms: "continuing review," "monitoring," "oversight," "visits," and "inspections." Clearly, these terms can have different meanings to different people and it is not completely clear how these terms are being defined in this report.

2. INSTITUTIONAL REVIEW BOARDS: THE EMERGENCE OF INDEPENDENT BOARDS (DRAFT)

While we agree with much of what is reported in the document entitled *Institutional Review Boards: The Emergence of Independent Boards (Draft)*, we are concerned about the report's emphasis on the independent IRB's ability to consider local concerns and attitudes as it reviews research protocols. We note at the outset that the ready availability of information sharing tools, such as the Internet, has made it more feasible for independent IRBs to become knowledgeable about local attitudes and interests. Moreover, as the OIG's draft report, *Institutional Review Boards: A System in Jeopardy*, aptly reflects, the environment in which IRBs operate has changed significantly over the past twenty years in that, among other things, there has been a steady rise in national and multi-site studies. An advantage of an independent board reviewing a multi-center or national trial is that it can develop a better understanding of the safety profile of the product because it receives a broad spectrum of serious adverse event reports

from multiple sites. Such information may not be made available to single site boards. Thus, while it is important to maintain a review system that addresses local attitudes and concerns, in a national or multi-center study environment, the local community is best protected where IRBs have the ability to work with a number of sites.

Moreover, as the report notes, in the last twenty years there has been an incredible increase in the number of protocols requiring IRB review, while at the same time, the research community and pharmaceutical industry are demanding that protocols be reviewed more quickly and efficiently. As a result, the need to address local attitude must be assessed in light of the national trends that have developed since the early 1970s. We believe that this is a multi-faceted issue which is ripe for discussion in a symposium setting.

Again, we extend our congratulations on the report and thank you for the opportunity to comment on these draft documents. We hope that the OIG will feel free to contact CIRB if we can be of any assistance.

Sincerely,

John Isidor, J.D.
Chairman

AMB/amb

cc: Chesapeake Research Review, Inc.
Essex IRB
Ethical Review Committee
Independent Review Consulting
Quintiles, Inc.
New England IRB
Research Consultants' Review Committee
Schulman Associates IRB, Inc.
Western IRB

OIG RESPONSE TO CIRB COMMENTS

We appreciate CIRB's generally positive comments about the reports. With respect to its concerns about the definition of certain terms, we have, as noted in prior comments, sought to be more precise in our use of the terms "continuing review" and "oversight." We use the term "monitoring" infrequently and mainly in context of the work of bodies other than IRBs. We use the term "inspections" mainly in context of FDA's regular on-site inspections of IRB and the term "visits" to refer to visits to the IRB site, whatever the basis for the visit.

The CIRB also expresses concern about our "emphasis" on independent IRBs' "ability to consider local concerns and attitudes as it reviews research protocols." It elaborates on how these IRBs are able to take into account local issues and how in the case of multi-site trials the independent IRBs are able to tap into a broad spectrum of information from multiple sites.

We recognize the latter as one of the perceived advantages of independent IRBs and indicated that in our report on independent IRBs. At the same time, we felt compelled to note the lack of a local presence as one of the perceived disadvantages of independent IRBs. We did not emphasize the point. We simply cited it as one of the factors that many in the IRB community express concern about when assessing the role and contributions of independent IRBs. We reiterate here that our report on the independent IRBs is not an evaluation of their performance but rather a description of their growing role and of the major advantages and disadvantages attributed to them.

Endnotes

1. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Implementing Human Research Regulations: Second Biennial Report in the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subjects*, (Washington, DC: U.S. Government Printing Office, 1983).

2. For a fuller explanations of these concerns see Nancy E. Kass and Jeremy Sugarman, "Are Research Subjects Adequately Protected? A Review and Discussion of Studies Conducted by the Advisory Committee on Human Radiation Experiments," *Kennedy Institute of Ethics Journal,* Vol. 6, (1996), No. 3, pp. 271-82, and the Advisory Committee on Human Radiation Experiments, *Final Report,* (Washington DC: U.S. Government Printing Office, 1995).

3. U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996.

4. Department of Health and Human Services, Office of Inspector General, *Investigational Devices: Four Case Studies* (OEI-05-94-00100), April 1995.

5. According to the President's Budget for Fiscal Year 1999, the NIH, which is the flagship of the President's Research Fund for America, would be increased by nearly half over five years. For more discussion, see Robert Pear, "Medical Research To Get More Money From Government," *New York Times*, Saturday, 3 January 1998, pp. A1 and A8.

The Task Force on Genetic Testing calls for placing greater emphasis on the role of the IRB in evaluating genetic research protocols. (Eds. Neil A. Holtzman, and Michael S. Watson, *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing,* NIH-DOE Working Group on Ethical, Legal, and Social Implications of the Human Genome Research, September 1997.) In addition, a recent Senate bill would rely on the IRB to determine measures of confidentiality, such as whether subject identifiers should be retained (S.1921, 105th Congress, sponsored by Senators Jeffords and Dodd).

6. The body is the National Bioethics Advisory Commission. It was established by Presidential executive order on October 3, 1995. Its charter, issued in July 1996 by the Assistant to the President for Science and Technology, calls for it to focus its attention on: "A. Protection of the rights and welfare of human research subjects; and B. Issues in the management and use of genetics information including but not limited to human gene patenting." For some background on the Commission and its emergence, see Alexander Morgan Capron, "An Egg takes Flight: The Once and Future Life of the National Bioethics Advisory Commission," *Kennedy Institute of Ethics Journal*, Vol. 7, (March 1997) No. 1, pp. 63-80.

7. We use the term "academic health centers" in accord with the following definition offered by Blumenthal, et al: "One of 125 institutions in the United States that consist of at least a medical school and an owned or closely affiliated clinical facility in which faculty instruct physicians-in-

training. These centers classically conduct teaching, patient care and, in many cases, research." (David Blumenthal, Eric G. Campbell, Joel S. Weissman, "The Social Missions of Academic Health Centers," *New England Journal of Medicine*, Vol. 337, 20 November 1997, No. 21, pp. 1550-53.)

8. These IRBs are overseeing research at institutions receiving over 1.4 billion dollars of Public Health Service (PHS) awards. As of March 1998, these institutions received over 27 percent of the PHS dollars awarded extramurally for human-subject research.

9. These six institutions alone account for over half a billion dollars of Public Health Service (PHS) awards. As of March 1998, these institutions received over 11 percent of the total PHS dollars awarded extramurally for human-subject research.

10. Charles Marwick, "Institutional Review Boards Under Stress: Will they Explode or Change?" *Journal of the American Medical Association*, Vol. 276, (27 November, 1996), No. 20, pp. 1623-1626.

11. Charles MacKay, NIH Office of Policy for Extramural Research Administration, Letter to Reports Clearance Officer, PHS, Request for Office of Management and Budget (OMB) Review and Approval for the study "Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects", Concept Clearance 9025-0404, March 10, 1995. See also Harold Edgar and David J. Rothman, "The IRB and Beyond: Future Challenges to the Ethics of Human Experimentation," *The Milbank Quarterly,* Vol. 73 (1995) No.4, pp. 489-506.

12. This according to the comments of Dr. Jim Childress, meeting transcript of the National Bioethics Advisory Commission, 9 January 1997, (Eberlin Reporting Service: Silver Spring, MD), p. 20.

While this phenomenon was true for drug studies, the situation was reversed for medical device studies. The intraocular lenses studies involved thousands of subjects. Most of the studies were conducted at small community hospitals.

13. Comments of Dr. Jim Childress, meeting transcript of the National Bioethics Advisory Commission, 9 January 1997, (Eberlin Reporting Service: Silver Spring, MD), p. 21.

14. Between 1974 and 1975, IRBs reviewed an average of 43 proposals per annum. (*Institutional Review Boards: Report and Recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, 43 Federal Register, 10 November 1978, p. 56186.)

15. Barbara Mishkin, "Ethics, Law and Public Policy", *Professional Ethics Report* (a publication of the American Association for the Advancement of Science), Vol. 7, (Spring 1994), No. 2, pp. 4-6.

16. U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996, p. 17.

17. The FDA reports, however, that it is in the process of revising its policies on disclosure of such information.

18. We do not claim that this practice is widespread, but IRB representatives we spoke with did identify situations where such information was not conveyed. These representatives emphasized a certain vulnerability they felt about not being sufficiently informed about any prior IRB reviews. Some of the independent IRB officials we spoke with were particularly concerned about this practice.

The FDA cites 21 C.F.R., sec. 812.150(b) when this situation occurs: "A sponsor shall upon request by a reviewing IRB or FDA, provide accurate complete, and current information about any aspect of the investigation." We believe, however, that the rules regarding notification should be made more explicit.

19. The FDA and OPRR also offer frequent interpretations in more informal ways: over the telephone, by electronic mail, fax, or in person. Many IRB officials we spoke with stressed that these clarifications were helpful to them.

20. Charles Marwick, "Institutional Review Boards Under Stress: Will They Explode or Change?" *Journal of the American Medical Association*, Vol. 276, (27 November 1996), No. 20, pp. 1623-1626.

21. Contract Research Organizations manage clinical trials for drug and device manufacturers.

22. For more information about the independent, for-profit IRBs, see our companion report Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: The Emergence of Independent Boards* (OEI-01-97-00192) June 1998.

23. Gregory J. Hayes, Steven C. Hayes, and Thane Dykstra, "A Survey of University Institutional Review Boards: Characteristics, Policies, and Procedures", *IRB*, Vol. 17, (May-June 1995), No. 3, pp. 1-6.

24. The National Service Research Award Act of 1974 established the assurance as the primary mechanism by which the Department was to oversee research involving human subjects. (National Service Research Award Act of 1974, Public L. No. 93-348, sec. 474, 88 Stat. 342.)

25. We use NIH and FDA as the two focal points because they are parallel constituent agencies of HHS. We add OPRR to the NIH side because in the IRB community, OPRR, a component of NIH, is typically viewed as the focal point for IRB oversight.

26. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: Promising Approaches* (OEI-01-97-00191) June 1998.

27. HCFA Press Office, "New Results-Oriented Medicare Rules Proposed For Hospitals," December 19, 1997. Available on the world wide web at www.dhhs.gov.

28. The suggested revisions to the IRB expedited review list move in the direction we call for here. (Federal Register, Vol. 62, No. 217, 10 November 10 1997, p. 60604.)

29. Advisory Committee on Human Radiation Experiments, *Final Report,* (Washington DC: U.S. Government Printing Office, 1995), Chapter 18, Recommendation 13(1).

30. Ruth Ellen Bulger, Elizabeth Meyer Bobby, and Harvey V. Fineberg, Editors, *Society's Choices: Social and Ethical Decision Making in Biomedicine*, (National Academy Press: Washington, DC, 1995) p. 182.

31. In reviewing our reports, the group Public Citizen suggested that the following types of evaluations would provide useful information about IRBs. While these suggestions were not directed per se to NIH/OPRR or FDA, we felt that they might help to stimulate discussion. The suggestions include: (1) assessing the differences between IRBs based on a review of a standardized protocol; (2) collecting data on differences between IRBs in rejection rates or rates of requiring serious modifications in protocols; (3) analyses of close votes at IRBs to see if and why those protocols got approved; and (4) retrospective analyses of IRB meetings which approved trials now considered unethical.

32. 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 changes that the IRB called for in the informed consent document, and the continuation of a research project for six weeks beyond when the IRB had suspended it Department of Health and Human Services, Office of Inspector General, *Investigational Devices: Four Case Studies* (OEI-05-94-00100), April 1995.

33. Comments of Dr. Jim Childress, meeting transcript of the National Bioethics Advisory Commission, January 9, 1997, (Eberlin Reporting Service: Silver Spring, MD), p. 20.

34. At some large research institutions, multi-site trials now account for about one-half of all active research protocols.

35. There is one regulation which requires the establishment of an independent data monitoring committee. The FDA regulation that provides for an exception from the informed consent requirements in certain emergency research (21 C.F.R., sec. 50.24) requires that a study conducted under the exception have established an independent data safety monitoring board to review data during the study in order to exercise oversight of the study.

36. One large academic health center we visited reported that it has requested and regularly receives feedback from DSMBs. But this is contrary to the experience of other IRBs we had contact with.

37. A cooperative group is a formal, free-standing government-sponsored entity responsible for conducting multi-site trials. There are, for example, 11 such groups associated with the National Cancer Institute (NCI). According to Federal requirements, NCI cooperative groups are required to monitor their research sites once every 36 months.

38. Periodically, when the cooperative group believes that its monitoring has identified information that may be pertinent to the IRB, it will inform OPRR, which, in turn, will inform the IRB. In addition, the IRBs sometimes will obtain information from the on-site principal investigators.

39. The FDA cites 21 C.F.R., sec. 812.50(b) when this situation occurs: "A sponsor shall upon request by a reviewing IRB or FDA, provide accurate complete, and current information about any aspect of the investigation." We believe, however, that the rules regarding notification should be made more explicit.

40. The National commission that developed the current system of human protections in the 1970s, envisioned a more proactive role for IRBs. In its report, it noted that IRBs may interview human subjects about their research experience or require that investigators provide subjects with a form through which they may report to the IRB their research experiences. It cautioned about observing the consent process, but noted that "certain research will warrant observation to assure the protection of subjects and in such cases IRBs have an obligation to take suitable measures." It further noted that the documentation of informed consent should not be confused with the substance of informed consent and that in certain cases the IRB may well require that a neutral party be present to assist a potential human subject considering participation in a research effort. (Institutional Review Boards: *Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, 43 Federal Register, 10 November 1978, p. 56174.)

The IRB regulations, which were adopted in 1981, provide IRBs with the authority to "observe or have a third party observe the consent process and the research. (45 C.F.R., sec. 46.109(e) and 21 C.F.R., sec. 56.109(e))

41. Some cancer centers and clinical research centers are particularly active in auditing investigators and assuring that protocols are being conducted as approved. Many IRBs do attempt from time to time to visit research sites to obtain first-hand knowledge about research practices. But, certainly, the workload pressures and other barriers we noted in our report on continuing review significantly limit the frequency and effectiveness of such efforts.

42. Remarks by the President in Apology for the Study Done in Tuskegee, White House Press Release, May 16, 1997.

43. See Alicia K. Dustira, "The Federal Role in Influencing Research Ethics Education and Standards in Science," *Professional Ethics*, Vol.5, Nos. 1 & 2, pp. 143-4; and Office of Research Integrity, "NIH Strengthens Responsible Conduct of Research Requirement in Training Grant Applications," *Office of Research Integrity Newsletter,* Vol.1, No.2, April 1993, pp.1 and 8.

44. The Commission on Research Integrity. *Integrity and Misconduct in Research*, (Washington, DC: U.S. Government Printing Office, November 1995.)

45. In the "Statement of Investigator" (FDA Form 1572), the investigator is asked to make a number of attestations (or as the form states, "commitments"). These include the following:

1. "I agree to inform any patients or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 C.F.R., sec. 50 and institutional review board (IRB) review and approval in 21 C.F.R., sec. 56 are met."

2. "I will ensure that an IRB that complies with the requirements of 21 C.F.R., sec. 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects."

46. For example, the NIH has developed a computer-based tutorial about human-subject protections. It is available to the public and can be downloaded from the NIH web site.

47. Harold Edgar and David J. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation," *The Milbank Quarterly*, Vol. 73, 1995, No. 4, pp. 489-506.

48. In that statement, the President said: "We commit to increase our community involvement so that we may begin restoring lost trust. The study at Tuskegee served to sow distrust of our medial institutions, especially where research is involved." (Remarks by the President in Apology for the Study Done in Tuskegee, White House Press Release, May 16, 1997.)

49. *Institutional Review Boards: Report and Recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, 43 Fed. Reg., 10 November 1978, p. 56178.

50. At present the HHS regulations for IRBs address this issue by calling for research institutions engaged in federally funded research to assure that "provisions are made for meeting space and sufficient staff to support the IRB's review and record keeping duties." (45 C.F.R., sec. 46.103(2))

51. In such cases, OPRR has been quite explicit in informing an IRB of its lack of adequate staff support and in calling for an increased commitment of staff and other resources. It has also called for the parent institutions to give greater recognition to IRB members for the critical services they provide.

52. Such a reorientation would be in accord with the directive set forth in the House Appropriations Committee report on the 1998 Balanced Budget Act to lessen the regulatory burden associated with extramural scientific research.

53. This parallels a recommendation called for by a Presidential advisory commission 15 years ago: "A broad educational and monitoring program covering the protection of human subjects and designed to reach investigators, IRB members, research administrators should be conducted. Among the various activities included in the program should be site visits of research institutions using experienced IRB members and staff as site visitors." (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Implementing Human Research Regulations: Second Biennial Report in the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subjects*, Washington, DC: U.S. Government Printing Office, 1983, pp. 135-137.)