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Institutional Review Boards:

Promising Approaches

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OFFICE OF INSPECTOR GENERAL

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EXECUTIVE SUMMARY

PURPOSE

To identify promising approaches that institutional review boards use to enhance their effectiveness and efficiency in protecting human subjects.

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.

In carrying out their responsibilities, IRBs face challenges posed by a changing research environment. Advances in genetics research, a proliferation of large-scale trials, and the blurring definitions of research and therapy make research increasingly complex to review and oversee. Across the country IRBs are inundated with research plans and are under enormous pressure to review them quickly. At the same time, many are finding it difficult to recruit and maintain members. Despite these challenges, many IRBs have developed innovative strategies for reviewing research plans and for providing educational outreach. Yet, in this environment there is little time for the sharing of promising approaches among the thousands of IRBs in existence.

Promising Approaches: The Focus of this Report

This report focuses on promising approaches of IRBs. One of 4 reports we are issuing on IRBs, it draws on interviews and group discussions with representatives of about 75 IRBs; site visits to IRBs in 6 academic health centers where extensive clinical research is taking place; reviews of Federal records and pertinent literature; and attendance at IRB meetings.

The promising approaches included here address six key areas of responsibility for IRBs. Within each area, we have chosen promising approaches that seem to have potential for multiple IRBs. We recognize, however, that what works well in one IRB may not necessarily work well in another.

PROMISING APPROACHES

Managing the Workload

To reduce workload pressures, many institutions are creating multiple IRBs and/or increasing the number of IRB meetings. Some institutions are creating specialty IRBs, such as dental, medical or social science IRBs to ensure that board members have sufficient expertise to assess research plans. Other institutions maintain general-purpose IRBs but stagger their meetings. One IRB staggers its four board meetings so that there is an IRB meeting every week. A research investigator submitting a research plan to this IRB will have his or her plan reviewed by the first available board. The waiting period is generally no longer than one week.

Providing Educational Outreach to Research Investigators

To ensure that all research investigators receive minimal training about human-subject protections, some institutions require their research investigators to attend mandatory training programs. A dean at one institution will not sign off on approved research until investigators have attended a 2-day workshop. According to IRB staff, this method provides a powerful political message to all investigators about the importance of human-subject education. Another institution requires all of its investigators to complete an on-line tutorial about human-subject protections. This tutorial, which takes an hour to complete, provides a base level of education for a nominal fee to the institution.

Reviewing Approved Research

Using a third party to oversee research is an effective technique for IRBs that do not have the time to observe the research process themselves. One IRB requires a research intermediary to interact with all psychiatric patients involved in research projects. Among other things, the research intermediary discusses the consent form with patients after the form has been signed to ensure that upon reflection, patients continue to want to participate in the research. Every few months, the research intermediary reports to the IRB about patients' concerns and the ways in which the consent process and/or research could be made more efficient and less obtrusive for patients.

Providing Educational Outreach to IRB Members

Educating IRB members is an important strategy for ensuring that they have adequate expertise to assess research plans. One IRB sends its members literature relevant to the research plan being discussed. This approach has been particularly beneficial to help orient new members to the ethical issues they should consider when reviewing protocols. Another IRB devotes a portion of each meeting to education. A benefit of this type of education, according to the IRB director, is the ripple effect it can have with other researchers in the institution. For example, after a recent meeting where AIDS trials were discussed, two of the physician members shared the discussion with their residents.

Broadening Perspectives in the IRB Review Process

A strategy for providing thoughtful, fair review is to continually maintain contact with the community in which the research takes place. One IRB established an Office of Ethnic Diversity in Research to help it identify barriers the community faces when participating in research and potential strategies to overcome these barriers. For example, many in the community are unaware of what being a research subject entails and they associate the hospital with treatment rather than research. Through community outreach, the IRB has become sensitive to the need to further simplify consent forms in order to impress upon potential subjects that they are participating in research.

Evaluating IRB Effectiveness and Efficiency

To improve its operations, one IRB performed a two-pronged self-evaluation. First, it convened a group of faculty members to perform a month-long evaluation of its operations. Second, it hired an outside monitor to assess research protocols for regulatory compliance and to interview investigators about their interactions with the IRB and their experiences with the review process. Both evaluations were helpful in highlighting areas that needed improvement, such as increased resources for the IRB, changes in the reporting structure, and more support from the University. The resultant changes have also helped to create better relations between researchers and the IRB.

CONCLUSION

Despite the challenges posed by the new research environment, IRBs have employed many promising approaches to enhance their effectiveness and efficiency. A key challenge to the Federal government is to find ways of giving IRBs the flexibility to develop innovative approaches while at the same time holding them accountable for performance. This is a matter we address in our summary report entitled, *Institutional Review Boards: A Time For Reform.*

COMMENTS ON THE DRAFT REPORTS

Within the Department of Health and Human Services, we received comments on our four draft reports from the National Institutes of Health, the Food and Drug Administration and, jointly, from the Assistant Secretary for Planning and Evaluation and the Assistant Secretary for Health. We also solicited and received comments from the following external parties: the Applied Research Ethics National Association, the American Association of Medical Colleges, the Consortium of Independent Review Boards, and Public Citizen's Health Research Group. We include the detailed text of all of these comments and our responses to them in appendix D of our overview report, *Institutional Review Boards: A Time for Reform* (OEI-01-97-00193). In the executive summary of that report, we summarize the thrust of these comments and our responses.

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INTRODUCTION

PURPOSE

To identify promising approaches that institutional review boards use to enhance their effectiveness and efficiency in protecting human subjects.

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.

Establishment of Institutional Review Boards

In the 1970s, in the aftermath of some widely publicized abuses involving human subjects in clinical research, the Federal government began establishing a set of requirements calling for institutional reviews boards (IRBs) to protect human subjects. The IRB system was originally envisioned as a decentralized system in which research was to be overseen at the local level. Most of the early IRBs were established in the large teaching hospitals and medical centers, where nearly all clinical research was conducted.[1] At the time that the regulations were established, research studies were typically conducted by a single research investigator[2] with a few subjects.

Challenges Facing Institutional Review Boards

The environment in which IRBs operate has changed significantly in the past two decades. Managed care, with its emphasis on cost control, is squeezing research support at academic health centers and limiting providers' time for administrative duties such as IRB participation. The proportion of research that is commercially sponsored has grown.[3] The locus of clinical research has shifted from single-site trials to large multi-site trials conducted across the country, even the world.[4] Biomedical research is constantly expanding into new frontiers such as gene testing and gene therapy. Many of these new research directions raise complicated questions about human-subject protections and challenge our notions of informed consent. When IRBs were first established, research was viewed as burdensome rather than beneficial to human subjects and something to be protected from. Now, many people with lethal diseases are demanding access to the most advanced treatments, even when these treatments are experimental.

These changes have had a significant effect on IRBs across the country. Many are inundated with research proposals[5] and are overwhelmed by adverse-event reports from sponsors. Many IRBs are not sufficiently supported by their institutions. A number of IRBs are having difficulty recruiting and maintaining members, particularly physician

members. At the same time, they are under enormous pressure to review protocols quickly. Despite these challenges, many IRBs have developed innovative approaches to improve their effectiveness and efficiency. Yet, in this environment there is little time for the sharing of promising approaches among the thousands of IRBs in existence.[6]

This Inquiry and this Report

In the wake of many changes transforming the world of clinical research, there is renewed interest in human-subject protections and the role of the IRB. A 1995 report issued by the Institute of Medicine (IOM) recommended a study on lessons learned about effective IRB functioning.[7] The National Bioethics Advisory Commission (NBAC) is currently examining the state of these protections and is pursuing information about IRBs.[8]

This report, which is one of four we are issuing as part of a broad inquiry of IRBs, focuses on promising approaches of IRBs.[9] In determining what to characterize as a promising approach, we depended on the judgements of IRB members and administrators, consultations with IRB experts, and our own judgement of whether the approach was significantly different and important to warrant attention. The promising approaches included here appear to have potential in numerous IRBs, although we recognize that what works well in one IRB may not necessarily work well in another. It is important to acknowledge that our highlighting a promising approach at one institution does not necessarily mean that other institutions have not developed similar approaches.

Many of the issues raised in this report are addressed more fully in our parallel reports. One report, *Institutional Review Boards: Their Role in Reviewing Approved Research,* finds that IRBs are devoting minimal attention to their continuing review responsibilities and identifies key obstacles responsible for that situation. Another, *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. A third, *Institutional Review Boards: A Time For Reform*, provides an overview of IRB functioning and presents recommendations emerging from our inquiry.

Our overall inquiry draws on a rich variety of sources. These include interviews and group discussions with representatives of about 75 IRBs of varying sizes and auspices;[10] government documents and national commission reports produced over the past 25 years; articles and books addressing human-subject protections; Federal records on IRBs; attendance at IRB meetings; site visits with FDA inspectors; site visits to 6 IRBs based in academic health centers[11] where extensive research is taking place;[12] issues raised on an e-mail forum by those associated with IRBs. We focused on the IRB system as a whole and on the environment in which IRBs 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 study 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).

Management of the Workload

Issue

IRBs across the country are inundated with research proposals and related documentation. The number of proposals being submitted to the IRB has grown significantly. With the emergence of large, multi-center trials, the number of adverse-event reports submitted to the IRB has also risen dramatically. The escalating volume of work, combined with the increase in adverse-event submissions has greatly added to the paperwork burden that IRBs face. As the field of clinical trials becomes increasingly competitive, IRBs are under enormous pressure to review protocols quickly. The challenge for these boards is to find mechanisms to review protocols thoroughly and efficiently in a way that does not place the thrust of the increased burden on volunteer members' time.

> One IRB we visited reported that between 1986 and 1996 the annual number of full-board reviews increased from 1450 to 2659, expedited reviews from 301 to 581, amendments from 435 to 1011, and adverse-event reports from 50 to 200.

Federal Reference Points

The HHS regulations, which are overseen by the Office of Protection from Research Risks (OPRR) in the National Institutes of Health (NIH), require that institutions make provisions for meeting space and sufficient staff to support the IRB's review and record keeping duties.[13] The Food and Drug Administration (FDA) regulations have no such counterpart. Both sets of Federal regulations require that an IRB be composed of a minimum of five members. There is no maximum size.[14] However, OPRR cautions that while an IRB can have as many members as is necessary to perform its duties effectively, care should be taken that the board does not become so large that its management becomes cumbersome.[15] In their written guidance to IRBs, neither FDA nor OPRR go beyond staffing and membership requirements to address measures of efficiency, such as turnaround time or the ratio of protocols to reviewers.

Promising Approaches

Develop an Institutional Infrastructure to Assist Research Investigators

Support for clinical investigators, which can range from minimal assistance to formal protocol management, occurs at the departmental level at many institutions. The Massachusetts General Hospital Cancer Center in Boston has developed a comprehensive centralized protocol management office to assist researchers with all aspects of the clinical trial. Sixteen research associates assist investigators with protocol development, submission to appropriate departments, and management. The office also provides

education for investigators, and includes a quality-control function to ensure regulatory compliance. The IRB told us that protocol management by the cancer center has dramatically improved IRB efficiency. Officials in the cancer center say it has been vital to improving investigator awareness of how to run a good clinical trial.

In an effort to strengthen the role of clinical research, many institutions are developing clinical research programs intended to increase coordination among offices responsible for clinical research, provide training for investigators, and strengthen biostatistical support and scientific review. It is too early to analyze the returns of these programs. It is expected, however, that these programs should help the mission of the IRB through ensuring that protocols submitted to the IRB are more complete and have gone through appropriate review channels.

Pre-review Research Protocols

Many institutions are beginning to initiate methods of pre-review in an effort to ensure that protocols reviewed at full-board meetings are as complete as possible. A recent survey found that IRBs most commonly reject proposals because of improperly designed consent forms (54 percent), poor study design (44 percent) and scientific merit (14 percent).[16] New protocols at Roswell Park Cancer Institute in Buffalo are assigned to two members of the Scientific Review Committee who check for missing information, scientific originality and significance, and for overall scientific merit.[17] If the reviewers find problems with a protocol, they contact the investigator for clarification. These problems must be resolved before the protocol can be presented to the full board. Protocols have improved, as has efficiency, since the Scientific Review Committee was established a decade ago. Staff at Roswell Park Cancer Institute believe that such a committee would be an asset at many institutions, yet they warn that it would require resources, committee member time, and an another layer of review for investigators.

Pre-review can also be done by IRB members or outside experts. At Albany Medical Center in New York, an IRB subcommittee composed of three persons (two primary reviewers and a staff member) resolves issues with investigators prior to a full-board meeting. This process greatly reduces the meeting length by eliminating fact-finding and one-on-one discussions between the investigators and IRB members. Using this system, they have reduced the length of the IRB meeting by half, increased IRB member attendance, and increased the time spent on human-protection issues. The Toledo Hospital in Ohio relies on a statistician to pre-review protocols for methodological rigor and to help with the consent form.

Develop Well-focused Applications

Many IRBs are revising their protocol application forms in an effort to elicit clearer and more complete explanations. Protocols that contain complete information regarding the conduct of a clinical trial are most meaningful to IRB reviewers and allow the board to function with maximum efficiency. Massachusetts General Hospital in Boston has

revised its form so that investigators are required to check off information detailing when informed consent will be obtained, by whom, and from whom. Children's Hospital of Boston has also successfully revised their application form (see box). Other institutions use techniques such as including sample consent forms in the application form, providing checklists of information that must be included with the protocol application, and creating a single form that can accommodate a variety of types of research.

Outline of Points to be Covered in the Research Protocol
Item #2: Specific Aims/Objectives

Old protocol application: " In outline form, state clearly the objectives of the research."

Revised protocol application: " The objectives should give a concise statement of the hypotheses. The study design should be capable of answering these hypotheses. In short, the question: "What will be learned from the proposed study?" should be answered. Objectives should appropriately correspond to the phase of the study. For each objective listed, the protocol should adequately address how the answers are to be obtained. Often questions arise because protocols are submitted with objectives that are not answerable by the research proposed."

From Children's Hospital of Boston Protocol Application, Committee on Clinical Investigation

Increase the Number of IRBs and/or the Number of Meetings

The mounting workload can be too much for one IRB to handle. For example, the University of Rochester in New York used to have one IRB to review 1,700 active protocols. The institution recently created four boards (two medical, one behavioral, and one dental) from the original IRB to divide up the workload and to ensure greater reviewer expertise. Another option is to have multiple, general-purpose IRBs and stagger the meetings. For example, Washington University in Saint Louis staggers the meetings of its four IRBs so there is an IRB meeting every week. Yet another approach is to rely on alternative members. At the University of Kentucky in Lexington, each IRB member on the medical IRB has an alternate who has a similar medical background. Between the members and the alternates, the University of Kentucky is able to hold an IRB meeting four times a month.

There are, however, some concerns with using these approaches. Many of these institutions are struggling with issues of how to ensure consistency among the various IRBs, how to attract a sufficient number of qualified IRB members and alternates, and how to ensure that specialty IRBs do not focus solely on the behavioral or medical aspects of a research proposal at the exclusion of other concerns.

Require Research Investigators to Assess the Importance of Adverse-Event Reports

IRBs are deluged with adverse-event reports from the multi-center clinical trials they oversee. Many of these reports are difficult to interpret because they are sent to IRBs as individual action reports and convey no trend information. The University of Nebraska

Medical Center IRB at Omaha is one of a number of IRBs that require investigators to fill out an accompanying adverse-event report form to assist the IRB in performing a risk assessment. These forms seek investigators' advice concerning the relationship of the adverse event to the intervention, whether or not a change in a protocol is necessary, and whether or not information about the adverse event is germane to consent and/or re-consent. The thinking behind these forms is that investigators are in the best position to determine the significance of adverse-event reports. Furthermore, it forces the investigators to stay abreast of all adverse-events that they submit to the IRB.

Employ Technology to Relieve Burden on IRB Staff

Using an electronic database can minimize clerical work, assist the IRB in keeping track of studies, and allow for coordination among multiple IRBs. Although we found no IRBs that have the capability to allow investigators to submit protocols electronically, many IRBs told us they are moving in that direction. New database technology will allow for efficiencies such as on-line adverse-event reporting, electronic interaction with other clinical departments, and on-line updates for research investigators on the status of their protocols. The hope is that by giving investigators better tools, IRBs will receive better protocols thus allowing for more time to be spent at full-board meetings on human-subject protection issues. While many institutions embrace the idea of employing technology to relieve the burden on IRB staff, many cite the necessary financial investment as a barrier.

Educational Outreach to Research Investigators

Issue

Research investigators and their staff[18] must be well-informed of the IRB's role and significance for the system of human-subject protections to work effectively. However, education about human-subject protections is not necessarily part of an investigator's formal education. Investigators often have incomplete knowledge of when and how research protocols must be submitted. In some cases, they may not be aware of what constitutes adequate informed consent or they may have difficulty in distinguishing between clinical care and research. Since the late 1970s, a number of national commissions and groups have called for a greater emphasis on investigator education.[19]

Federal Reference Points

The OPRR Multiple Project Assurance requires the institution to make a copy of the assurance available to investigators and staff. In a "Dear Colleague" letter, the OPRR suggests that IRBs make investigators aware of policies regarding continuing review and women and minorities in research, but does not specify how this educational outreach should occur.[20] The FDA Information Sheets for IRBs and Clinical Investigators provide no guidance to IRBs on educational outreach to investigators and their staff.

Promising Approaches

Lectures, Conferences and Workshops

At the University of Washington in Seattle, the IRB director conducts 25-30 presentations annually to persons involved with human-subjects research. Compared with many of the IRBs we interviewed, this represents a high volume of educational outreach. Approximately one-third of these presentations are oriented toward faculty members and research staff, the remaining two-thirds toward graduate and post-doctoral students. Each seminar, which lasts up to one and a half hours, addresses the history of the IRBs, major principles of the Federal regulations, and specifics the IRBs look for when reviewing protocols. The sheer number of presentations conducted means that most research investigators interested in attending a presentation will, most likely, find a convenient time to do so. Ensuring this convenience demands a significant commitment from the director, because each presentation entails five to six hours of work between the preparation, and the presentation itself.

At the University of Minnesota Academic Health Center, research investigators attended a mandatory 2-day course on the responsible conduct of research, a component of which

is human-subjects protections. The Dean of Medicine will not approve an investigator's protocol unless he or she has fulfilled this requirement. One IRB administrator told us that this type of education sends a powerful political message to all investigators.

The University of Minnesota also employs a full-time education coordinator. Working with the various departments and deans to determine the education needs of investigators, she assesses, plans, and evaluates appropriate educational programs. A large number of investigators attend these educational sessions. As a result of these requirements, the IRB has seen a heightened awareness among researchers about the need to submit research proposals to the board.[21] The IRB has also noted an improvement in important aspects of the submitted protocols, for example, the consent document.

At many institutions, clinical coordinators handle the daily tasks of research, (*e.g.*, obtaining informed consent, maintaining records, etc.) As such, their education is crucial to human subjects' protections. However, in many cases, coordinators have little understanding of what human-subject regulations are or why they exist. To address this problem, Massachusetts General Hospital (MGH) has recently begun offering a 2-day course for coordinators through its Clinical Research Program. Topics include: roles and responsibilities of the investigator, sponsor, research staff, and coordinator; U.S. regulations and guidelines, research documentation, recruiting subjects, and obtaining informed consent. Currently, data does not exist to show the impact of the program, but people at MGH are enthusiastic about it and are planning to offer more courses for clinical coordinators.

On-line Tutorials

The NIH requires completion of an on-line tutorial for research investigators and all other individuals involved with human subjects research. The tutorial explains the purpose and history of IRBs and practical matters such as when research must be submitted to the IRB. This tutorial, which can be completed at an investigator's convenience, provides a base level of knowledge at low cost; the only significant cost associated with the tutorial is the initial development fee. Because of this practice, one official states, "ignorance of the regulations will never be an excuse [at NIH]." The disk is a "nuts and bolts" approach that any IRB could use. It is available on the internet at the NIH home page.[22]

Computer-assisted Literature Monitoring

An IRB's ability to protect human subjects is reliant on informed and compliant researcher investigators who are aware they must submit their protocols to the IRB. The University of California at San Diego (UCSD) recently initiated a computer-assisted literature monitoring program to detect maverick researchers. Every week the UCSD IRB runs a search of new publications containing the heading 'human' and an author address containing the words 'Diego' or 'Jolla'. Word matching algorithms are used to rank the similarity of each citation to the research projects in the IRB database. If a tentative

match of a publication to a project is made, a letter requesting confirmation of the match is sent to the investigator. Where no match can be made, a query letter is sent to the investigator requesting he/she contact the IRB office. The program has become so successful that investigators are now preempting the IRB by sending their abstracts before the IRB runs its search. To perform computer-assisted literature monitoring, an IRB does not necessarily need advanced computer capability. Private vendors offer low-cost search services; alternatively, IRB staff can run manual searches.

An Efficient Means of Improving Awareness and Compliance

Using computer-assisted literature monitoring, the University of California at San Diego was able to identify 132 recent publications by UCSD researchers. Thirteen of these had no record of being submitted to the IRB and resulted in counseling of the research faculty involved. According to the IRB, "this has been a valuable, low cost method of improving awareness of and compliance with human-subjects regulations among faculty members."

Websites and Manuals

An IRB's staff may not have the time to conduct conferences, seminars or other interpersonal education. Websites and manuals are an alternative. Once developed, they are effective and low cost educational tools. Websites have become a popular method for sharing information regarding policy, IRB memberships, meeting dates, deadlines, and events. At Baylor University in Texas, all investigators receive a manual from the institution that includes topics such as the definition of research, how to write protocols, and requirements of the IRB. According to the IRB administrator, the manual has been extremely helpful. For example, one anesthesiology resident called her to find out how to write a research protocol. She sent him the manual and four days later received back a "beautifully-written" research protocol. Responses from other users have also been positive. Making websites and manuals available for investigators and their staff also frees up time for the IRB staff as investigators are less dependent on them for information.

Use of Standardized Education Language

The University of Nebraska has developed standardized educational language for the review letters it sends out to investigators. They have categorized standardized statements into three broad areas: problems with protocols, problems with informed consent documents, and general-reminder language. A typical problem might be that an investigator has not clearly indicated how he/she intends to assess the subject's understanding of the research. In cases such as these, the IRB will send the investigator a letter with suggestions. These suggestions are all kept coded on a computer. At the stroke of a key, the administrator can insert the language into a customized letter. The use of standardized language can eliminate a page and a half of typing for the administrator. The University of Nebraska has been using this method for 15 years. Over

this time, the chair has been using fewer standardized statements as investigators are submitting more complete and well thought out protocols.

Use of Explicit Investigator Assurances

A research investigator's desire to be in compliance with Federal regulations can easily be frustrated by unclear explanations of what these requirements are. One institution, for example, had difficulties with investigators making modifications to approved research without IRB consent. Part of the problem was a vague statement investigators were required to sign verifying they met Federal regulations. The statement failed to explain explicitly what was entailed in compliance. To solve this problem, this institution created a form that clearly states the investigator will:

> "obtain voluntary and informed consent of subjects, submit to the IRB any adverse events, give progress reports, obtain prior approval from the IRB before amending or altering the project or before implementing changes in the approved consent form, maintain documentation of IRB approval for at least three years after the project has been completed, and treat subjects in a manner specified in this form."

According to the IRB administrator, this practice has been extremely beneficial in educating investigators. A greater number of investigators are now aware that changes to an approved protocol must also be reviewed by the IRB.

Continuing Review of Approved Research

Issue

Continuing review of approved research is vital to the protection of human subjects. The mounting workloads, new advances in biomedical research, and the growing public interest in experimental therapy as a way to access medical care make the continuing review function of IRBs increasingly important. Our inquiry and other studies indicate that due to heavy workloads and lack of institutional support many IRBs devote only minimal time to continuing review and to active oversight of the informed consent process.[23] The current system of adverse-event reporting contributes to the difficulty many IRBs face in adequately overseeing multi-center trials.

Federal Reference Points

The Federal regulations outline the minimum requirements for continuing review of approved protocols: IRBs must conduct periodic review of approved protocols at intervals appropriate to the degree of risk, but not less than once a year; and they have the authority to observe, or to have a third party observe, the consent process and the research.[24] As such, the regulations allow for great flexibility in the quantity, quality, and depth of continuing review. In an effort to strengthen the continuing review function, the FDA and OPRR have issued a number of guidelines in recent years. In a 1995 guidance, the OPRR called for continuing review to be "substantive and meaningful."

Promising Approaches

Involve a Third Party in Overseeing the Consent Process

Ensuring that subjects are adequately informed about participating in research is central to the mission of the IRB. Yet, our inquiry and other studies found that although IRBs have the authority to observe, or to have a third party observe, the consent process they rarely invoke this authority. IRB reviews of informed consent are limited almost entirely to paperwork reviews.[25] The following are examples of ways in which several IRBs, through the use of a third party, actively oversee the consent process. Many of these are in accord with the recommendations of the Advisory Committee for Human Radiation Experiments.[26]

A research intermediary interacts with all psychiatric research subjects at the University of Texas Health Science Center in Houston.[27] Because it might be considered obtrusive in the subject-researcher relationship, the research intermediary does not directly observe the consent process. Instead, she discusses the consent form with a subject after the form has been signed to ensure that the subject understood its terms and that upon reflection

the patient continues to want to participate in research. According to the IRB, patients who go through this process make better research subjects because they are sure of why they are participating and they are clear about their relationship to investigators.

Benefits of Using a Research Intermediary

The research intermediary at the University of Texas Health Science Center in Houston acts as a liaison between the subjects and the researchers. Every few months she reports to the IRB about patients' concerns and the ways in which the consent process and/or research could be made more efficient and less obtrusive for patients. The research intermediary also shares with the IRB how the consent process *really* works, which is something that many IRBs are unaware of.

Patient advocates provide additional oversight for subjects involved in risky and/or complex protocols at the Massachusetts General Hospital (MGH) in Boston. Typically they are involved in gene therapy protocols, Phase 1 studies,[28] and protocols in which decisions about participating in research must be made quickly. Patient advocates observe the consent process to ensure that subjects understand that they are voluntarily participating in research. Currently, most of the patient advocates are physicians. However, MGH is in the process of establishing an Office of Patient Advocates. The advocates, most of whom will be trained social workers, will be available 24 hours a day to oversee or participate in the consent process.

Some IRBs have begun to require or recommend counseling of research subjects to ensure that they understand the consequences of research. Roswell Park Cancer Institute in Buffalo requires genetic counselors for cases in which the implications of genetic testing are not fully addressed in the consent form. The University of Washington recommends financial counseling for Phase 1 oncology protocols, where study expenses are often not covered by the research sponsor or the subject's insurer.

Review Recent Copies of Signed Consent Forms

At the reapproval stage, investigators at the University of Kentucky in Lexington are required to submit to the IRB copies of signed consent forms for the two most recent subjects. This allows the IRB to check if the consent forms being used are the most updated and if they have been properly signed. The best indicator of the efficacy of this approach, according to the IRB director, is that the IRB has found problems with several investigators' consent forms. A downside, however, to this approach is that subject confidentiality is broken. The IRB members reviewing consent forms for an AIDS trial know that those consenting are HIV positive.[29] The IRB director believes that this practice is a particularly useful tool for large IRBs which are unable to review all consent forms for each approved protocol.

Develop a Comprehensive Continuing Review Form

A well-focused application can assist an IRB in providing a thorough and efficient initial review. Likewise, a well thought-out continuing review form can assist an IRB in identifying potential problems or concerns in approved protocols. The University of

Nebraska Medical Center IRB at Omaha recently revised its continuing review form so that it asks more probing questions (see box).[30] The revised form requires that the investigator, who is most familiar with the protocol, assist the IRB in assessing the recruitment of subjects, problems and complications, the process of consent, and the risk-benefit relationship. As a result of using this form, the IRB has been able to detect, and avert, problems at the reapproval stage.

IRB Application for Continuing Review of Therapeutic Research

Old continuing review application:

- Did any subject suffer an unanticipated adverse event or injury during the study? ___ Yes ___ No

New continuing review application:

- Did any subject suffer an unanticipated adverse event which was reported to the IRB since the last IRB review? If the answer is yes, specify the number of reported events and describe briefly their nature and significance.
- Did any subject suffer an unanticipated adverse event which has not yet been reported to the IRB. If the answer is yes...
- Was there any increase in the frequency of serious but expected adverse events? If the answer is yes...
- Since the last IRB review were any serious external adverse events reports submitted to the IRB? If the answer is yes...

From the University of Nebraska Medical Center at Omaha

Establish a "Re-review" Mechanism

The Federal regulations require that IRBs review approved protocols at intervals appropriate to the degree of risk but not less than once a year.[31] Yet, our inquiry and other sources found that IRBs typically carry out the continuing review requirement in a hurried manner, generally relying on administrative staff and on investigators' self-assessments.[32] Unless there is cause for a thorough review, the IRB generally spends minimal time discussing approved protocols. To enhance the continuing review function, several institutions have established a "re-review" mechanism. Children's Hospital of Boston requires that on the third anniversary of a protocol's initial approval investigators submit the protocol to the IRB as an initial protocol. This system forces investigators to revise the protocol, where necessary, and to compile all amendments and adverse events into one document. This approach can help IRB members stay abreast of rapidly changing protocols. The re-review system is not a substitute for meaningful continuing review, but it helps to ensure that long-term protocols receive scrutiny at regular intervals.

Educational Outreach to IRB Members

Issue

With the mounting workload pressure, few IRBs have the time or resources for educational outreach to IRB members. Most IRBs provide minimal orientation for new members, usually covering just the Federal regulations and IRB procedures. Yet given the growing complexity of protocols, ongoing training is increasingly critical for both the physician and lay member. New areas of research, such as xenotransplantation and gene therapy, raise complicated ethical questions that may not be immediately apparent to many reviewers. Several IRBs told us that when they do offer ongoing member training, few physicians have the time to attend.

Federal Reference Points

The OPRR guidebook states that IRB members and others charged with the responsibility of reviewing and approving research should receive detailed training in the regulations, guidelines, and policies applicable to human-subject research.[33] The OPRR and FDA sponsor a number of conferences for IRB members and administrators.[34] The OPRR guidebook explicitly encourages IRBs to support their members in attending workshops focused on IRB functioning.[35] The FDA Information Sheets for IRBs and Clinical Investigators provide no guidance on educational outreach to IRB members.

Promising Approaches

Provide Protocol Specific Education

Staff at the University of Kentucky in Lexington believe that an IRB gets the best results by tying educational outreach to the specific protocols being reviewed. When complex protocols come up for review--for example, those involving genetic testing, AIDS, or children--staff members copy relevant pages of the OPRR guidebook and send them to members. According to the IRB director, this approach is particularly beneficial to help orient new members to the ethical issues they should consider when reviewing protocols. A downside, however, of this type of education is the requisite resources and staff. For this approach to work, staff need to pre-screen protocols, determine relevant literature, photocopy and distribute the necessary materials.

Independent Review Consulting in California routinely includes several articles in each members' agenda packet. Designed to stimulate thought and discussion on a broad range of topics, the articles are culled from both the lay and medical press. Topics have included health care management, medical devices, and the inclusion of women and minorities in clinical trials, as well as consent and protocol issues. According to the IRB

director, this approach has helped facilitate openness among members and raise awareness.

Use Portion of IRB Meeting to Educate Members

At the University of Texas Health Science Center in Houston, the first ten minutes of each IRB meeting is devoted to the continuing education of IRB members. Recent topics have included problems in the designs of AIDS studies, statistical issues in study design, and ways of improving the IRB's efficiency. One benefit of this type of education is the ripple effect it can have with other researchers in the institution. For example, after a recent meeting where AIDS trials were discussed, two of the physician members shared the discussion with their residents. According to the IRB coordinator, the ongoing education has been helpful in increasing members' awareness of human-subject protections and in maintaining their tenure on and interest in the IRB.

Host Annual Trainings for IRB Members

Western Institutional Review Board of Olympia has hosted annual trainings for 14 years. Originally the trainings were intended for Western board members only. Now they have been opened it up to other IRB members. Last year, about 200 people attended the all day training seminar. Speakers at the seminars vary, but they generally address the following topics: someone from FDA provides an update on the regulations, someone speaks on the ethical aspects of research, an investigator speaks about the impact of IRB decisions on research, and someone from a pharmaceutical or device company speaks about how IRB rules and regulations affect their business practices.

According to the IRB director, the annual training sessions have been helpful in making members feel secure in their decisions. The sessions give members a chance to ask their questions of someone knowledgeable and then allows them to go back to their IRB with confidence. The training sessions are also helpful for giving members a well-rounded picture of the role of the IRB and how its decisions effect the parties involved.

Broadening Perspectives in the IRB Review Process

Issue

Scientific knowledge is necessary but not sufficient for the IRB review process. The large number of scientists who serve on IRBs ensure ready access to medical and methodological knowledge that is of great value to the IRB in assessing the risks and benefits of research protocols submitted to it. This specialized knowledge, however, can have a downside. Investigators may inadvertently express a tendency to stress the benefits rather than the risks of research, overlook just how well subjects understand the informed consent document, or give insufficient attention to the diversity of subjects recruited. The inclusion of nonscientific members, noninstitutional members, and bioethicists on IRBs can be an important counterbalance to these tendencies. These members can help ensure the IRB remains sensitive to the needs and concerns of subjects and thereby assists the IRB in its goal of protecting human subjects.

Federal Reference Points

Of the five IRB members required by Federal regulations, there must be at least one whose primary concerns are in nonscientific areas and one who is not otherwise affiliated with the institution. In many IRBs, one member fills both roles. The OPRR guidebook suggests that the nonaffiliated member should represent the local community, "should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB."[36] The importance of the nonscientific and nonaffiliated members has been heightened by recent guidance concerning the inclusion of women and minorities in research.[37]

Promising Approaches

Enable Nonscientific and Noninstitutional Members to Play a Significant Role

Given the importance of achieving a balance as noted above, we searched widely for examples of IRBs with innovative approaches to recruiting, training and supporting their nonscientific and noninstitutional members.[38] Few came to our attention.

We found that many IRBs achieved some broadening of perspectives by reaching out within their hospital communities to social workers, attorneys, hospital executives, and even IRB administrative staff. These individuals, however, are affiliated with their research institutions and strictly speaking, are not unbiased "outsiders". Some of these same IRBs indicated they sought more outside members but with little success, noting the difficulties of finding persons who were willing to work long uncompensated hours.[39]

Through our research, we found several examples of nonscientific, noninstitutional members (that is, a single member who satisfies the requirements for having a nonaffiliated and a nonscientific perspective on the board) who had come to play an important continuing role in helping the IRB broaden its perspective. In one case, the IRB contributed significantly to this development by funding the member's participation at an IRB conference. More typically, the members drew on the knowledge and skills they brought with them to the IRB and lessons they learned during the course of their IRB service. These nonscientific, noninstitutional members told us they brought a very different voice to the IRB's deliberations, particularly when they raised nettlesome issues such as confidentiality or the adequacy of researcher's efforts to reach out to diverse populations. As non-researchers, they also tend to assess the risk/benefit ratio more critically. They may view research more from the vantage point of a subject. Consequently, they are able to understand the vulnerability subjects often feel.

The other IRB members and staff we spoke with also stressed the importance of the balancing role played by these pro-active community members. Yet, along with expressions of appreciation, they voiced some apprehension that these members can slow the deliberation process--not an insignificant consideration given the substantial number of research protocols that IRBs must review.

Include a Bioethicist on the IRB

Bioethicists, although not a substitute for nonscientific/nonaffiliated members, also help to broaden an IRB's perspective. For many years, bioethicists have participated on the National Institutes of Health IRBs. Through their training,[40] they have become sensitized to subtle yet significant ethical issues pertaining to human-subjects research. Because of this, they can assist other IRB members in identifying and deliberating on ethical issues. Indeed, a recent survey highlighted the usefulness of this program.[41]

As one bioethicist we spoke with noted, "It's not everyone's job to be up on research ethics, but bioethicists are trained to do that." For example, bioethicists at NIH have raised issues about the clarity of the informed consent document and its treatment of the risk/benefit ratio, about the distinction of clinical care from research, and about balancing attempts to bring more women and minorities into research without undue inducements. Some pointed out, however, that the specialized education of bioethicists is both a benefit and a drawback. While on the one hand it makes them more efficient in discovering subtle ethical issues, it also makes them more likely to focus on obscure ethical concerns which are not necessarily a consideration in human-subject protections. One person we spoke with at NIH also mentioned the possibility that other IRB members will feel less compelled to bring up ethical concerns when the bioethicist is present.

Provide Community Outreach

In response to the 1993 NIH guidelines on the inclusion of women and minorities in research, the University of Texas Health Science Center IRB in Houston developed and

established an Office of Ethnic Diversity in Research (OEDR). The OEDR's mission is to broaden the community's understanding of health-care research, to help eliminate cultural and practical roadblocks to participation in research studies, to establish and maintain rapport with community leaders, and to ascertain the areas in which the community would like to see additional research. About twice a month, a member of the OEDR makes presentations to the community. She is usually accompanied by a health educator, an IRB member, and/or an investigator from the University. Feedback from the OEDR's field visits is reported to the IRB, via the IRB coordinator. The OEDR has helped the IRB to identify barriers to participating in research and potential strategies to overcome these barriers. According to the IRB coordinator, many in the community are unaware of what being a research subject entails and they associate the hospital with treatment rather than research. This has made the IRB sensitive to the need to further simplify consent forms in order to impress upon potential subjects that they are participating in research.

Sample Questions Asked of the Community

1. If you did participate in a research activity, what kinds of problems did you encounter?

2. What could the University of Texas Health Science Center do to address the problems you have identified?

3. What type of healthcare research would you like us to study that would be beneficial to you, your community, and/or your organization?

4. Please list three things that you could think of that would improve how people in your community feel about participating in research.

Questionnaire by the Office of Ethnic Diversity in Research at the University of Texas Health Science Center in Houston

Evaluation of IRB Efficiency and Effectiveness

Issue

The IRB process is too important not to undergo periodic evaluation. Evaluations can help an IRB to determine whether it is effectively protecting human subjects, whether it is operating efficiently, and whether it has adequate authority.[42] The answers to these questions are important not only for protecting human subjects, but also for protecting institutions and investigators against liability. Many of the IRBs we spoke with expressed an interest in improving their effectiveness and efficiency. However, given the time and resource constraints they face, few are able to engage in evaluation activities. One IRB administrator remarked that, unfortunately, many IRBs and their institutions only become proactive about ensuring the integrity of the process once a concern has been brought to their attention.

Federal Reference Points

Institutions have some obligation, though not extensive, to perform self-assessments. The OPRR multiple project assurance requires offices of research administration to perform procedural and record-keeping audits not less than once a year.[43] The FDA and OPRR do not require IRBs to perform evaluations of their effectiveness or efficiency, although both encourage such activities. The FDA Information Sheets for IRBs and Clinical Investigators include a checklist to help institutions evaluate their own policies and procedures; the OPRR guidebook offers some points for IRBs to consider.[44] By contrast, evaluation requirements are much stronger for research involving animals. All Institutional Animal Care and Use Committees are mandated to conduct reviews of institutional programs and of animal facilities at least once every six months.

Promising Approaches

Perform a Full-scale Evaluation of the Clinical Research Process

In response to FDA and OPRR concerns about alleged non-compliance with regulations, the University of Minnesota commissioned two evaluations. The first evaluation was performed by an internal faculty advisory committee composed of several researchers, an IRB member, an administrator from Grants and Contracts, and a representative from legal counsel. The faculty advisory committee spent a month speaking with IRB administrators and chairs, researchers, legal counsel, and external consultants about IRB operations and resources. Based on their evaluation, they recommended changes in nine strategic areas.

To further assure itself that the process was functioning well, the University of Minnesota hired an outside monitor to assess protocols that met internal criteria for risk. These protocols were assessed for their level of regulatory compliance. In addition, the monitor interviewed research investigators about their interactions with the IRB and their experiences with the IRB process. The monitor reported all results to the IRB, including a set of recommendations. While the IRB had the option of using an internal auditor for this task, they felt it was critical to bring in an external monitor. They felt that an external monitor provided a greater level of objectivity. According to the IRB, responses to the monitor were extremely positive. In fact, resource-permitting, the IRB would like repeat this process in the future.

The two evaluations were helpful in highlighting areas that needed improvement, such as increased resources for the IRB, changes in the reporting structure, and more support from the University. The resultant changes have helped to create better relations between researchers and the IRB. In retrospect, IRB staff felt that if such an evaluation had happened earlier it might have prevented difficulties the IRB was experiencing.

Evaluate a Specific Aspect of IRB Functioning

Santa Rosa Health Care conducted a year-long evaluation of its continuing review procedures to ascertain its compliance with OPRR guidance and to ensure that subjects were receiving updated toxicity information in the informed consent document.[45] As protocols came up for reapproval, the IRB performed an item-by-item comparison of toxicities contained in the local consent form to the toxicities contained in the consent form supplied by the research base. They also performed a comparison of interim reports to the toxicities contained in the local and sample consent forms, a review of drug profiles, and a review of product labeling for approved drugs.

The Santa Rosa Health Care IRB discovered that the majority of protocols had incomplete informed consents, that it had been lax in the critical review of initial submissions, and that some interim reports failed to provide necessary information so that potential risks to study participants could be adequately assessed. As a result, the IRB revised the stringency of its initial review of consent forms to include a more thorough review of the toxicities listed. The IRB also compiled a reference binder containing a list of the more commonly used chemotherapeutic drugs. According to the IRB chair, these steps were helpful in strengthening the IRB review process and were also instrumental in heightening investigator awareness of the need to submit accurate informed consent documents. The evaluation was, however, extremely resource-intensive. The IRB chair pointed out that because his IRB had a small workload it was able to put such an extensive amount of time and effort into the evaluation--something that larger IRBs might not have time for.

CONCLUSION

As we noted in the introduction, many IRBs are struggling to keep pace in the rapidly changing research environment. Yet, despite the challenges posed by the new research environment, a number of IRBs have developed innovative approaches to enhancing their effectiveness and efficiency. Many of these approaches are catalogued in this report.

We did not independently evaluate any approach highlighted in this report. An approach's inclusion does not necessarily mean that it receives our stamp of approval, or that it is occurring only at the institution we highlighted. We intend to provide a snapshot in time; it is not a definitive study of all IRBs. The report is intended to stimulate discussion among the Department, IRBs, and those groups interested in IRB functioning. While we have highlighted the work of many IRBs, we may have omitted some promising approaches.

A key challenge to the Federal government is to find ways of giving IRBs the flexibility to develop promising approaches while at the same time holding them accountable for performance. This a matter we address in our summary report entitled, *Institutional Review Boards: A Time For Reform.*

Endnotes

1. Over time, as clinical research activities spread to other settings, IRBs were established in these settings as well. Institutional review boards now exist in a variety of institutions--including State governments, the National Institutes of Health, universities, managed care organizations, contract-research organizations, and hospitals (of all kinds). Independent IRBs have also arisen to review research protocols.

2. Throughout this report, the terms "research investigator" and "investigator" are used interchangeably. They are used to denote persons leading clinical research studies.

3. The clinical research market is roughly a 4 billion dollar market. It is estimated that about 75 percent of clinical research is industry-sponsored. (Telephone conversation with Kenneth Getz, Director of Center Watch, 26 May 1998.)

4. 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.

5. Throughout this report, the terms "research plans", "research proposals", and "protocols" are used interchangeably. They are used to denote proposals submitted by research investigator to the IRB for review.

6. The primary sources of interaction among IRBs, for those who can afford the fees, are annual meetings hosted by Public Responsibility in Medicine and Research (PRIM&R) and Applied Research Ethics National Association (ARENA), and FDA- and NIH-sponsored conferences and guidance letters. One successful forum for communication has been an electronic mailing list sponsored by the Office of Research, Technology and Information at the Medical College of Wisconsin. The goal of the forum is to promote discussion of ethical, regulatory, and policy concerns with human-subjects research. This has provided an opportunity for over 720 IRBs to raise issues they are struggling with and to learn from one another.

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

8. The National Bioethics Advisory Commission (NBAC) was established by Executive Order 12975 on October 3, 1995. Section 5 of the executive order establishing NBAC states that as a first priority, NBAC shall direct its attention to consideration of protection of the rights and welfare of human research subjects.

9. Some of the promising approaches we address are carried out, not by the IRB, but by other parts of the institutions of which the IRB is a part.

10. 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.

11. 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.)

12. 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.

13. 45 C.F.R., sec. 46.103(b)(2).

14. 45 C.F.R., sec. 46.107(a) and 21 C.F.R., sec. 56.107(a).

15. Office or Protection from Research Risks, *Protecting Human Research Subjects: Institutional Review Guidebook* (U.S. Government Printing Office, 1993), ch. 1, sec. B, p. I-4.

16. Jeffrey S. Jones et al., "Structure and Practice of Institutional Review Boards in the United States," *Academic Emergency Medicine*, vol. 3 (August 1996) no. 8, pp. 804-809.

17. This is in addition to determining that the scientific design and methods are adequate for achieving the stated objectives.

18. From here on, references to "researchers" and "investigators" will apply to staff as well. The education of research staff is critical as it is often the staff, not the investigators, who conduct the daily business of administering research.

19. These bodies include the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the Commission on Research Integrity, Applied Research Ethics National Association (ARENA), and the President in his 1997 remarks in apology for the study done in Tuskegee.

20. Dear Colleague letter from the Office of Protection from Research Risks, Subject: "Continuing Review -- Institutional and Institutional Review Board Responsibilities", 10 January 1995, and Dear Colleague letter from the Office of Protection from Research Risks, "Subject: Inclusion of Women and Minorities in Research," April 25, 1994.

21. According to the IRBs we interviewed, investigators can be confused about what types of research need to be submitted to the IRB. The growth of managed care research, and

particularly quality improvement and outcomes research, is fueling this confusion.

22. The Internet address is http://helix.nih.gov:8001/ohsr/cbt/.

23. A 1996 report by the U.S. General Accounting Office asserted that continuing reviews "are typically either superficial or not done at all. According to OPRR officials, IRBs have not always understood the requirements for continuing review, and, in other cases, IRB workload demands have reduced the quality of this review. In some cases, IRB administrative staff with no scientific expertise--not IRB members themselves--review continuing review forms, ensuring only that the information has been provided. Heavy workload also necessitates that IRBs rely largely on investigators' self-assessments in conducting continuing reviews" (U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996, p. 17-18.) Our companion report also raises questions about the oversight process. For more information see, U.S. Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: Their Role in Reviewing Approved Research*, OEI-01-97-00190.

24. 45 C.F.R., sec. 46.109(e) and 21 C.F.R., sec. 56.109(e).

25. Several recent articles and reports have pointed out the limitations to the informed consent process. In 1995, Harold Edgar and David J. Rothman reported that IRBs rarely require third-party observers to oversee the consent process or to examine what actually occurs in the consent process. (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.) A 1996 U.S. General Accounting Office study found that IRB reviews generally did not involve the direct observation of the research study or the informed consent process. (U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996, pp. 17-18.)

According to Reiser and Knudson, the reasons for the infrequent inclusion of a third-party observer include: (1) that they would interfere with the consent process; (2) that their presence would imply that investigators are not trusted to obtain consent; and (3) that they would introduce into the research a new problem--that of finding qualified observers to handle oversight tasks such as gaining knowledge about the protocol, learning about the subject and the setting of research, and, most important, bringing an impartial view to the analysis. (Stanley Joel Reiser and Paula Knudson, "Protecting Research Subjects after Consent: The Case for the 'Research Intermediary'", *IRB*, March-April 1993, pp. 10-11.)

26. Recommendation 10, part 2 of the Advisory Commission on Human Radiation Experiments calls for "Mechanisms for ensuring that the information provided to potential subjects (1) clearly distinguishes research from treatment, (2) realistically portrays the likelihood that subjects may benefit medically from their participation and the nature of the potential benefit, and (3) clearly explains the potential for discomfort and pain that may accompany participation in research."

Recommendation 10, part 5 calls for "Mechanisms for ensuring that information provided to potential subjects clearly identifies the financial implications of deciding to consent to or refuse participation in research." (Advisory Committee on Human Radiation Experiments, *Final Report,* Washington DC: U.S. Government Printing Office, 1995).

27. For more information about the use of a research intermediary, see Stanley Joe Reiser and Paula Knudson "Protecting Research Subjects after Consent: The Case for the 'Research Intermediary'", *IRB*, March-April 1993, pp. 10-11.

28. Phase 1 studies are the first of several required clinical trials. Phase 1 trials test the safety of a drug or device on volunteer human subjects.

29. The IRB deals with this by requiring that investigators tell subjects up front that their consent forms may be reviewed by the IRB. If this causes a problem for a subject or investigator, the name of a subject can be deleted prior to IRB review.

30. For more information about this continuing review form, see Bruce Gordon and Ernest Prentice, "Continuing Review of Research Involving Human Subjects: Approach to the Problem and Remaining Areas of Concern", *IRB*, Vol. 19, March-April 1997, No. 2, pp. 8-11.

31. 45 C.F.R., sec. 46.109(e) and 21 C.F.R., sec. 56.109 (e).

32. Based on a 1993 survey of IRBs, Barbara Mishkin commented that "Probably the most troublesome problem--and the most frequent--was the absence of substantive review at the time of annual renewals. In a number of IRBs, the staff review annual review reports primarily to assure that one has been filed and that all spaces on an institutional form have been filled in. In some instances, even that review is poorly performed, and staff have submitted to the IRB, and the IRB has actually approved, submissions that are clearly incomplete. For example one IRB repeatedly re-approved protocols for which the principal investigator (PI) never provided the IND (investigational new drug) number assigned by the FDA for a new drug under study. Another IRB repeatedly processed forms on which the PI failed to indicate whether the risks to human subjects were minimal, moderate, or high." 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.

33. Office of Protection from Research Risks, *Protecting Human Research Subjects: Institutional Review Guidebook* (U.S. Government Printing Office, 1993), ch. 1, sec. B, p. I-7.

34. The OPRR sponsors an average of five national educational conferences per year.

35. Office of Protection from Research Risks, *Protecting Human Research Subjects: Institutional Review Guidebook* (U.S. Government Printing Office, 1993), ch. 1, sec. B, p. I-7.

36. Office of Protection from Research Risks, *Protecting Human Research Subjects: Institutional Review Guidebook* (U.S. Government Printing Office, 1993), ch. 1, sec. B, p. I-4.

37. The NIH guidelines are located in the Federal Register, (59 Fed. Reg. 14,508, March 28, 1994.) The institution's responsibility is expanded upon in the OPRR Dear Colleague letter, "Subject: Inclusion of Women and Minorities in Research", April 25, 1994. The FDA guideline can be found in a July 22, 1993 guidance entitled "Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs."

38. Federal regulations call for at least one IRB member whose concerns are primarily in nonscientific areas and one member who is not otherwise affiliated with the institution. Some IRBs rely on a single member to satisfy both requirements.

39. Many IRBs hold their review meetings during business hours.

40. Many of the persons chosen to serve as bioethicists have a background in science and/or ethics. At the NIH, education is provided for new consultants through a one day training session. Continuing education and dialogue occurs through group meetings held on alternate months.

41. A 1992 poll of 127 NIH IRB members found 63 percent of those polled believing the bioethicist on their board to be very helpful, 32 percent somewhat helpful and 5 percent not helpful. In response to the question, "Does the consultant assist you in elucidating or clarifying bioethics issues," 80 percent of the members and 100 percent of the chairpersons responded "yes." (Evan G. DeRenzo and Frederick O. Bonkovsky, "Bioethics Consultants of the National Institutes of Health's Intramural IRB System: The Continuing Evolution," *IRB,* May-June 1993, pp. 9-10)

42. According to Hayes: "If, in fact, IRBs make mistakes from time to time, a thorough, periodic evaluation, particularly one done externally, would help to refocus the group's mission and objectives.... The IRB process is simply too important not to include a carefully designed evaluation process, which can help boards stay on task and maintain the quality and objectivity of their decisions." (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)

43. OPRR Multiple Project Assurance, 1997, Part 2, Section II.

44. The encouragement for self-evaluation can be found in (1) the FDA Information Sheets for IRBs and Clinical Investigators, 1995, appendix H, and (2) the Office of Protection from Research Risks, *Protecting Human Research Subjects: Institutional Review Guidebook* (U.S. Government Printing Office, 1993), ch. 1, sec. B, pp. I-7 through I-8.

45. For more information about this evaluation, see Mary S. Adams and Dennis A. Conrad, "Annual Review: Observed Deficiencies and Suggested Corrections", *IRB*, vol. 18, November-December 1996, no. 6, pp. 1-4.