

**Department of Health and Human Services**

**OFFICE OF  
INSPECTOR GENERAL**

**Institutional Review Boards:  
Their Role in Reviewing Approved Research**



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# EXECUTIVE SUMMARY

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## PURPOSE

To review the performance of institutional review boards in reviewing ongoing research involving 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.

### Continuing Review: The Focus of This Report

Continuing review can serve as a key safety net for human subjects. This protective role has become especially significant as many individuals have signed up to participate in research trials with little understanding of the risks involved or of the distinction between research and established therapy. Its importance has also been heightened as the research environment has become increasingly affected by marketplace pressures and as some protection lapses have occurred, causing harm to human research subjects.

In this report, which is one of four we are issuing on IRBs, we address the IRBs' continuing review function. Given our focus on the overall system of protections provided to human subjects, 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 Continuing Review Conducted by IRBs Is of Limited Scope and Significance.

**Minimal Substantive Review of Reports.** Once IRBs complete their reviews of initial research proposals, they often have little time left for continuing reviews. Thus, their

reviews of the annual reports, adverse-event reports, and protocol amendments submitted by research sponsors are often hurried and superficial.

**Minimal Field Presence.** The continuing review that IRBs carry out is limited almost entirely to paperwork reviews. They rarely visit the research site to determine how the consent process is actually working or to review the records of active protocols. To varying degrees other parties do conduct on-site monitoring, but unlike the IRBs, they do not have a central mission of protecting human subjects.

### **A Number of Factors Limit IRBs' Capacity to Conduct Continuing Review.**

**Heightened Workload Pressures.** IRBs are inundated with research proposals. Working in competitive environments with major institutional cost pressures, many of them have been unable to add the staff and other resources to keep up with the workload increases. At the same time, volunteer IRB members, pressed to concentrate their time on revenue-enhancing clinical activities, find it more difficult to devote time to the boards.

**Limited Useful Feedback on Multi-Site Trials.** A significant portion of the research being reviewed by IRBs is now part of multi-site trials. These trials often include an active monitoring component carried out by Data Safety Monitoring Boards (DSMBs) and/or by clinical audit teams. Such monitoring involves expert peer review of IRB-approved research. But, the DSMBs and audit teams rarely report their findings to IRBs.

**Limited Feedback on FDA Actions Against Investigators.** Correspondence regarding FDA actions against research investigators is not routinely disclosed to IRBs. A number of IRB officials reported to us instances in which they heard about an FDA action indirectly, from other (often media) sources. Officials at FDA indicated that they are precluded from routinely disclosing such information by legal concerns under the Privacy Act.

**Limited IRB Expertise.** IRBs find that they often have insufficient scientific expertise to assess the results of active protocols. This can present particular vulnerabilities in the case of protocols that are not subject to peer review by other bodies.

**Limited Nonscientific and Noninstitutional Input.** IRBs typically have minimal "outside" representation. This limitation deprives them of a valuable counterbalance during the continuing review process when important questions can be raised concerning the interests of human subjects.

**The Trust Factor.** The IRB process is rooted in trust, assuming the best of intentions of investigators and sponsors. This tradition makes substantive continuing review suspect. It holds that the IRB's job is to ensure protections upfront, not to serve as "watchdogs" or "police."

## **Federal Oversight of IRBs Provides Little Basis for Determining the Effectiveness of IRBs' Continuing Review of Approved Research.**

Two agencies within the Department of Health and Human Services are responsible for the oversight of IRBs: the National Institutes of Health (NIH), through its Office for Protection from Research Risks (OPRR), and the Food and Drug Administration (FDA).

**The OPRR Oversight Focuses on Upfront Assurances. Only Rarely Does Its Oversight Involve On-site Assessments of IRB Performance.** The assurance is an upfront document of an institution's commitment to human-subject protections. It does not involve an assessment of performance. The OPRR is in a better position to make such assessments when it conducts for-cause site visits, but because of resource constraints it conducted only one such visit between April 1997 and May 1998.

**The FDA Oversight Focuses on Inspections. Its Reviews, However, Stress Procedural Compliance, with Only Minimal Attention Given to IRB Effectiveness.** The FDA conducted just under 200 inspections in 1997. These inspections aim to ensure IRB adherence to Federal requirements and frequently result in deficiency notices to the IRBs. But here, too, there is little attention to assessing results. For instance, while FDA calls for IRBs to ensure that subjects understand the implications of their participation in research, FDA's own inspection process does not enable it to determine how well IRBs are able to do that.

## **CONCLUSION**

The IRBs' limited efforts in conducting continuing review of active research is a serious national issue because it compromises their protection of human subjects. It inhibits their capacity to identify and address situations where unacceptable risks emerge, or research results prove to be too favorable to continue, or protocols stray beyond approved limits. It also inhibits their capacity to ensure that the subjects have sufficient understanding of the risks they may incur in the research process.

With this conclusion, we do not claim that widespread abuses exist. We recognize the important contributions that IRBs have made and continue to make. The system of protections they provide is supported by many conscientious investigators committed to protecting human subjects and by many dedicated IRB members and staff doing their best under trying circumstances. But, our inquiry offers an important warning signal--one that could get stronger in view of current developments. These include Federal plans to increase significantly the numbers of subjects in clinical trials and various proposals that would give IRBs increased responsibility in the areas of genetics and confidentiality. This warning signal warrants a Federal response. We address the elements of such a response in our parallel inspection 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

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## PURPOSE

To review the performance of institutional review boards in reviewing ongoing research involving 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 (HHS). Appendix A offers further background on the Federal requirements that apply to these boards, particularly with respect to their continuing review function.

### Prior Inquiries

For about a quarter of a century, IRBs have been playing an important part 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.<sup>1</sup> 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.<sup>2</sup> In the following year, the General Accounting Office issued a report reinforcing these points and identifying numerous factors inhibiting IRB performance.<sup>3</sup>

We, too, found particular reason to be concerned about IRB oversight in a recent inquiry of our own. In examining clinical trials involving four investigational medical devices, we discovered inadequacies related to IRB continuing review 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 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.<sup>4</sup>

### 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.<sup>5</sup> This report is one of four that has resulted from our overall inquiry. A



second report, *Institutional Review Boards: Promising Approaches*, presents innovative approaches that IRBs have undertaken in six key areas of responsibility. A third, *Institutional Review Boards: The Emergence of Independent Boards*, indicates how those IRBs that are separate from research institutions are a growing force; it addresses the advantages and disadvantages associated with independent boards. A fourth report, *Institutional Review Boards: A Time For Reform*, serves as the big picture report, viewing the overall functioning of IRBs and presenting recommendations emerging from our inquiry.

In this report, we focus on the continuing review function of the IRBs--that is, on the review activities they undertake subsequent to their initial approval of research protocols. We examined these review activities because of the concerns we noted in the previous section and because, as our inquiry progressed, we became increasingly aware of continuing review's importance as a human-subject protection. We elaborate on that importance in the following section before we present our findings on the extent of continuing review that takes place, the factors inhibiting that review, and the nature of the Federal oversight of this process.

Our 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;<sup>6</sup> government documents and national commission reports produced over the past 25 years; articles and books addressing human-subject protections; Federal records on IRBs; issues raised on an electronic e-mail forum by those associated with IRBs; attendance at IRB meetings; site visits with FDA inspectors; and site visits to 6 IRBs based in academic health centers.<sup>7</sup> At these centers, which are among the most heavily funded biomedical research centers in the country,<sup>8</sup> we interviewed not only IRB administrators and members, but also many others in the parent institutions whose functions 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.

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 B.

# IMPORTANCE OF CONTINUING REVIEW

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The IRBs' ongoing review of research involving human subjects can serve as an important safety net for human subjects.<sup>9</sup> It provides a means of addressing vulnerabilities that may not have been adequately identified and/or corrected during the initial review process. It also offers a way of addressing vulnerabilities that may have emerged during the course of the approved research.

In recognition of the importance of continuing review, Federal regulations call for IRBs to conduct reviews "at intervals appropriate to the degree of risk, but not less than once per year," and specify that IRBs have the authority "to observe or have a third party observe the consent process and the research."<sup>10</sup> On January 10, 1995, the Office for Protection from Research Risks (OPRR) in the National Institutes of Health reaffirmed this IRB responsibility through the issuance of a "Dear Colleague" letter to IRBs. That letter noted that continuing review must be "substantive and meaningful," and elaborated on associated operational matters, most especially that the annual reviews must be completed within 1 year of a previous IRB review.<sup>11</sup> Similarly, on October 1, 1995, the FDA issued an Information Sheet to IRBs and clinical investigators that reinforced the importance of continuing review and sought to clarify the minimum requirements that IRBs have in that regard.<sup>12</sup>

In recent years, the safety net role that continuing review represents may have become more important than ever. Four factors lead us to this conclusion. We wish to emphasize the importance of continuing review before presenting our findings. These factors are as follows:

## **The Limits of Informed Consent**

Individuals who consent in writing to participate as a research subject do not necessarily understand the implications of their decision.<sup>13</sup> They may not realize that the primary mission of research is to advance medical knowledge rather than to provide subjects with medical treatments. Further, they may develop unrealistic expectations about both the potential benefits and risks associated with their participation.<sup>14</sup> The 1995 presidential advisory commission concluded that there was, indeed, "reason to worry" that such misunderstandings may be common.<sup>15</sup>

On the front lines, the informed consent process is much more about forms--determining their content and making sure they are signed--than it is about ensuring understanding by the potential subjects. This limitation is widely corroborated in the literature,<sup>16</sup> in convenings of IRB officials, and in our own discussions and site visits.<sup>17</sup> Many IRBs strive to see that consent forms are as informative and clear as possible. But these efforts often run against the grain as the forms become longer and more complex, serving more

as documents to protect the institutions and the sponsors rather than the human subjects. Some IRBs also strive to encourage researchers to interact with potential subjects in ways that facilitate understanding. But, they generally have little basis for knowing how well they succeed in that regard.<sup>18</sup>

## **The Blurring of Research and Treatment**

It is also the case, as the 1995 Advisory Commission underscored, that individuals who consent to participate as human research subjects do not necessarily distinguish research from standard therapy or treatment. In a survey of 1,882 randomly selected patients in the waiting rooms of 16 hospitals, the Commission found that 371 had been research subjects. Yet, almost 20 percent of these research subjects incorrectly stated that they were not and never had been research subjects. Worse yet, about 40 percent of the studies reviewed involving these individuals were experiments that posed greater than minimal risk.<sup>19</sup>

In recent years, potential human subjects themselves have often been the ones blurring the distinctions between research and treatment. Patients, especially those with life-threatening diseases, have often placed more emphasis on gaining access to experimental efforts than on being protected from the harm they can cause.<sup>20</sup> Yet some researchers have also been contributing to this blurring through their own tendency to emphasize the personal benefits rather than the risks of research (see appendix C) and/or through use of their own patients as human subjects. One researcher, who is also a member of an IRB, told us that over the years his own patients accounted for nearly all the subjects in his many studies and that this did not prove to be a problem because they trusted him. In contrast, another researcher, who was a participant in one of the commissions addressing human-subject protections, told us that physicians' own patients represented one of the most vulnerable categories of subjects.

## **The Changing Research Environment**

The research culture in which IRBs function has been significantly transformed over the past 20 years. As the proportion of industry sponsored research has increased, this culture has been increasingly shaped by the realities of the marketplace. Sponsors, with significant amounts of money at risk, emphasize the rapid development of products and seek to work with IRBs that will conduct their reviews quickly. At the same time, the parent institutions of many IRBs are eager to gain the revenue associated with large industry sponsored projects.<sup>21</sup> While they tend to be careful not to jeopardize the role of the IRBs, they also expect them to respect the sponsors' need for quick turnaround.

These pressures to accelerate initial IRB reviews heighten the importance of continuing review as a safety net. So, too, does the emergence of newer kinds of research that have major implications for human subjects. This is especially true for genetics research which can produce sensitive and troubling information pertinent not only to a subject directly, but to a subject's relatives, potential offspring, insurers, employers, and others.

How access to such information is controlled and how well subjects are informed and counseled about it are vital matters that are certain to warrant continuing attention during the course of a research effort.

## **The Protection Breakdowns Involving IRB-Approved Protocols**

The system of protections now in place is certainly much better than that which existed when the Federal requirements were first established in the 1970s. But even with these protections, lapses do occur and they serve to reinforce the need for continuing review. A few of these lapses have been highly publicized ones that resulted in significant harm, even death, to human subjects or have exposed them to unnecessary risks.<sup>22</sup> Other lapses may remain unnoticed. In fact, in our previous study on investigational devices, we found reason for concern in 11 of the 20 sites we visited. These involved 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.<sup>23</sup>

A number of the IRB officials we spoke with mentioned a continuing concern they have with "protocol creep," wherein the number of human subjects, the drug doses, or some other aspect of the research ventures beyond that approved by the IRB. Some also expressed concern about whether, in research involving placebos, the IRB is getting sufficient up-to-date information about investigational treatments to ensure that the use of placebos remains justified.

# FINDINGS

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## The Continuing Review Conducted by IRBs Is of Limited Scope and Significance.

### Minimal Substantive Review of Reports

In accord with Federal regulations, IRBs receive and must review significant amounts of paperwork on active research projects. They must review annual reports, adverse-event reports, and amendments to research protocols. In each case, however, little substantive review tends to take place.

**Annual Reviews.** The OPRR's 1995 Dear Colleague letter on continuing review has had the intended effect of getting IRBs to pay more attention to annual reviews, but the attention has focused much more on complying with procedural requirements than on conducting substantive continuing review. Many IRBs find that with significant increases in the quantity of new research protocols to review, they have little time left for annual reviews. Not at all uncommon is the situation we found at one IRB meeting where the board relied on prior reviews of a primary reviewer and administrative staff and quickly approved several annual reviews in the last 15 minutes of 2½ hour meeting.<sup>24</sup>

Many board members regard the annual review requirement as unproductive unless it has become apparent that there are significant problems concerning a protocol. Otherwise, they say it is unnecessarily duplicative of the initial review and even undermines the voluntary commitments that busy board members make to the IRB.<sup>25</sup> Along this line, some board members we spoke with regarded annual reviews as essentially a staff responsibility and gave little if any time to reviewing the annual reports prior to the board meetings.

**Adverse-Event Reports.** The FDA requires that sponsors and investigators report to the FDA and participating IRBs any adverse events involving both serious and unanticipated effects on human subjects. As with the continuing review requirement, the Federal intent was to foster substantive review. But here, too, the reality has been quite different. The IRBs have, indeed, been receiving adverse-event reports (AERs). In fact, those IRBs that oversee projects that are part of large, multi-site trials are being inundated with them, as sponsors, eager to minimize liability exposure, choose to err on the side of reporting rather than not reporting. One IRB we visited had received several boxes of AERs within the past few weeks. Another indicated that it was receiving an average of 200 AERs a month.

The IRB officials equate the review of AERs to that of looking for a needle in a haystack.<sup>26</sup> They say that the reports seldom inform them of how many patients are enrolled in a multi-site trial and tend to include little if any analysis of the significance of

the adverse event reported. Thus, the IRBs find themselves hard-pressed to use AERs as a tool of substantive oversight. Rarely does an AER lead to any IRB intervention concerning an active protocol. On the few occasions when it does, it is likely to involve some change in the way risks are explained on an informed consent form. In reviewing the last two meetings of the IRB, one IRB official calculated that the members had reviewed 32 AERs in one meeting and 21 in the other, none of them leading to any changes. This experience was not at all unusual at that IRB or at the others we contacted.

**Protocol Amendments.** Federal regulations also call for sponsors and investigators to obtain IRB approval for any changes that they wish to make in research protocols. This results in a steady stream of amendments submitted to and reviewed by IRBs. Occasionally these changes will trigger a substantive review of a project but, they typically involve minor matters that are routinely processed. It is important to recognize that the IRB is highly dependent on investigators and sponsors to be attuned to changes in the course of a research project and to call for amendments when necessary.

### **Minimal Field Presence**

The continuing review that IRBs do carry out is limited almost entirely to paperwork reviews by IRB members and staff. Although the IRBs have the authority to visit the research site as part of their continuing review, our inquiries and other studies indicate that they rarely visit the research site to determine how the informed consent process is actually working or to review the data and records of active protocols.<sup>27</sup> This may be particularly worrisome with regard to independent IRBs, which are often located far from the research site. Five of the eleven independent boards we interviewed reported that they have no routine policy for visiting the research sites under their purview.

On those few occasions when IRBs do become more directly involved in reviewing a research practice, the action tends to be triggered more by particular concerns that have come to their attention than by random reviews.<sup>28</sup> As a result, IRBs typically have little basis to know for themselves how research teams approach the informed consent process, how well human subjects understand the implications of their participation in research, and how fully research teams remain true to the research design set forth in their approved protocols.<sup>29</sup>

In this context, it is important to recognize that to varying degrees other parties do conduct reviews at the research site. These include commercial sponsors and/or the contract research organizations representing them, clinical research centers and/or other parts of the institution to which an IRB belongs, and, as we note in a subsequent section of this report, the monitoring bodies associated with multi-site clinical trials and federally funded cooperative-group trials. Unlike the IRBs, however, none of these parties has the protection of human subjects as its central mission.

# A Number of Important Factors Inhibit IRBs' Capacity to Conduct Continuing Review.

## Heightened Workload Pressures

IRBs of all sizes are facing major workload demands. These are generated in part by the significant numbers of adverse-event reports and protocol amendments submitted to them for review. But, the key force is a dramatic increase in the number of research protocols being submitted for initial review. 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.<sup>30</sup> This finding is in accord with that of a recent survey of academic health centers which found that their IRBs were reviewing an average of 297 proposals a year. Ten percent of them were reviewing 1,000 to 2,500 proposals annually.<sup>31</sup>

### No Time for Chit-Chat

The agendas of the IRB review meetings at academic centers 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, the meetings typically lasted about 2½ hours and included an average of 18 initial reviews, 9 expedited reviews, 43 protocol amendments, and 21 adverse-event reports.

Most IRBs appear to be struggling to keep up with these demands. In increasingly competitive environments where market developments are triggering greater cost pressures on health care institutions, many IRBs report that they have not been able to add the staff needed to respond to the demands. At the same time, IRB members, particularly in the large medical centers, find themselves increasingly pressured to concentrate their time on revenue-generating clinical activities, with the result that voluntary commitments to IRB work have become more difficult to meet.<sup>32</sup> The IRBs cope with these developments, sometimes in innovative ways,<sup>33</sup> but with a steady increasing flow of protocols to review, the time demands on members continue to mount.<sup>34</sup> Summing up this situation, one experienced, well-informed IRB official commented: "Many IRBs, especially in large institutions, are on the verge of imploding."

These workload pressures jeopardize the protections afforded by IRBs. The General Accounting Office provided an alert in this regard when it noted in its 1996 report that IRBs may spend only one to two minutes of review per study, relying mainly on reviews conducted by primary reviewers prior to a board meeting.<sup>35</sup> Our own inquiry reinforces this concern and makes it especially clear that little time is left for conducting substantive continuing review or for educational outreach that can help the research community become more knowledgeable about the obligations and importance of human-subject protections. Such outreach, IRB officials note, can help ensure that investigators themselves serve as a continuing source of protection for human subjects and that applications submitted to the IRBs are properly completed. Many IRBs report that they spend a considerable amount of time on research protocols and informed consent forms that are flawed in various ways and must be sent back to the investigators for corrections.



## **Limited Useful Feedback on Multi-Site Trials**

More and more of the research being reviewed by IRBs is part of national or even international multi-center trials funded by the Federal government or commercial sponsors.<sup>36</sup> Many are vast, far-reaching operations. For example, the Pediatric Oncology Group funded by the National Cancer Institute conducts trials through more than 1,000 researchers from over 100 sites in the U.S., Canada, and a few as far away as Europe.<sup>37</sup> Each of our study sites reported significant increases in the number of multi-center trials. At two sites, these trials constitute about one-half of the research overseen by the IRB.<sup>38</sup>

These trials typically include an active monitoring component. For instance, since 1992, some of the cooperative-group projects funded by the National Cancer Institute (NCI) have required a Data Safety Monitoring Board (DSMB).<sup>39</sup> These are independent bodies that include scientists expert in the area being investigated, statisticians, ethicists, and sometimes subject advocates. Their role is to analyze study data on a regular basis and to ensure patient safety through the analysis of adverse-event reports among other things. Many commercially sponsored trials also include DSMBs, especially if they involve large numbers of subjects. In these cases, however, there is no Federal requirement for a DSMB.

The monitoring of multi-site trials also tends to involve on-site reviews. Sites participating in cooperative-group projects funded by the National Cancer Institute must be audited once every 36 months.<sup>40</sup> These are highly substantive audits typically involving scientists, statisticians, and others. Other federally funded cooperative groups have similar requirements. Commercial sponsors also have an on-site review component (according to FDA requirements).<sup>41</sup>

These monitoring efforts by DSMBs and audit teams represent substantive ongoing oversight of IRB-approved research. But, strikingly, little of what is learned is shared with IRBs. Neither the DSMBs nor the audit teams report their findings to the IRBs.<sup>42</sup> Their orientation and feedback is to the research sponsors and investigators. Only rarely do any of the results of this valuable peer review get to the IRBs to support their own continuing review responsibilities.<sup>43</sup>

## **Limited Feedback on FDA Actions Taken Against Investigators**

The FDA conducts routine and directed inspections of research investigators. Directed inspections may be initiated as a result of complaints from subjects or others about human-subject violations, concerns about an investigator, or questions that arise from a review of the study data. Inspections can result in a variety of actions, such as the rejection of study data, letters to an investigator, or, at the extreme, a disqualification from participating in pre-market research. The FDA does not, on a routine basis, affirmatively disclose all correspondence to sponsors and IRBs. A number of IRB officials pointed this out to us and reported instances in which they heard about an FDA action indirectly, from other (often media) sources, about an action taken against a

research investigator involved in one of their approved research plans. Officials at FDA indicated that legal restrictions under the Privacy Act preclude FDA from routinely disclosing all investigator-related correspondence to sponsors and IRBs on a routine basis. However, certain information, such as warning letters purged of trade secrets and confidential commercial information and the names of disqualified or restricted investigators, are available to the public on the FDA web site. In addition, certain information about the inspections, including classifications of FDA's inspections, is available to the public through the Freedom of Information Act (FOIA). But overworked IRBs generally do not have the available time to regularly scan the web site to see if any of their investigators, often numbering in the hundreds, have been disciplined. Likewise, they might not know when to make a FOIA request to 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.

### **Limited IRB Expertise**

The IRBs find that they often do not have sufficient scientific expertise on their boards to deal with the increasingly complex areas of research. They also often lack staff to adequately assess the results of an active protocol. In contrast, the expertise represented on a DSMB or audit team tends to be geared specifically, at least in part, to the protocol under review. From time to time, IRBs will seek consultant assistance to fill the gap, but this can be costly and slow down a review process that is already overburdened. This deficiency is a significant source of concern to a number of IRB officials we met with. For the cooperative and commercial projects subject to peer review, these officials at least know that substantive continuing review is occurring in other places. But for the significant amount of IRB-approved research for which no such peer review takes place, this safety net does not exist.

### **Limited Nonscientific, Noninstitutional Input**

The HHS and FDA regulations require that all IRBs have a minimum of five members. The regulations further stipulate that there be at least one member whose primary concerns are nonscientific and one who is not affiliated with the parent institution. Boards can satisfy both requirements with the appointment of a single individual who is not affiliated with the institution and who is not a scientist. The IRBs we spoke with typically had more than five members but seldom maintained a 1 to 5 ratio of "outside" members.<sup>44</sup> More importantly, few seem to seek or be able, on a consistent basis, to recruit and maintain lay and/or nonaffiliated members who play an active, effective role in helping the IRB stay closely attuned to the perspectives and experiences of human subjects. Such members, once sufficiently experienced and trained, can provide an important counterbalance to scientific and institutional interests. This may be especially important during the continuing review process when important questions (including how the informed consent process is approached, whether human subjects understand

sufficiently the risks associated with the research, and the adequacy of outreach efforts to diverse populations) can be raised concerning the interests of human subjects.

### **The Trust Factor**

The IRB process is rooted in trust. The IRB reviews traditionally have been approached in a collegial manner assuming the best of intentions on the part of researchers and sponsors. This tradition makes substantive IRB continuing review suspect at best and counterproductive at worst. As one IRB member said: "Our job is to ensure human-subject protections upfront; we are not watchdogs." Many IRB officials and much of the literature on IRBs warn that any movement toward "policing" could undermine the credibility that IRBs have developed over the years.<sup>45</sup> These considerations are extremely important. The trust that exists is a strength of the system. Any erosion in it could, indeed, threaten human-subject protections.

Yet, in subtle, but significant ways, this tradition of trust inhibits effective continuing review. It inhibits IRBs from identifying deviations in approved research plans, as we found in our previous study on investigational medical devices;<sup>46</sup> or from learning that many human subjects have little understanding of the informed consent forms they sign, as the Advisory Commission found in its 1995 review;<sup>47</sup> or from finding maverick researchers who have not even submitted their research for IRB review, as one IRB found through the use of computer-assisted literature monitoring.<sup>48</sup> How to achieve substantive continuing review along the lines represented by these examples while maintaining a core of trust with the research community may well be the most significant challenge facing IRBs.

## **Federal Oversight of IRBs Provides Little Basis for Determining the Effectiveness of IRBs' Continuing Review of Approved Research.**

As noted in our IRB primer on page 3, two agencies in the Department of Health and Human Services are responsible for the oversight of IRBs: the National Institutes of Health (NIH) through the Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA). These two agencies enforce what is essentially a common set of regulations. Appendix B provides an overview of their oversight mechanisms.

### **The OPRR Oversight Focuses on Upfront Assurances. Only Rarely Does Its Oversight Involve On-site Assessments of IRB Performance.**

In the early years of Federal oversight, the assurance documents were relatively brief and the process of negotiating them was highly educational in nature.<sup>49</sup> Over the years as the number of assurances (especially single project assurances) has grown and as IRB workloads have increased, the assurance documents have become much more extensive and the process more routinized. At present, the overall value of this process remains

questionable. In institutions with multiple project assurances (MPAs), where about 75 percent of NIH-funded research takes place, many of the IRB officials we spoke with reported that the assurance process does little to foster institutional commitments to IRB operations. At the same time, OPRR officials recognize that if they were to use this process to press for further institutional commitments to IRBs, the institutions might be much less likely to include all non-HHS funded research under their assurance.

This assurance process, as it now functions, does not yield much information about the actual effectiveness of IRBs in providing continuing protections to subjects enrolled in approved protocols. The OPRR is in much better position to obtain such information when it conducts on-site reviews, either as part of a technical-assistance visit or noncompliance investigation. Indeed, the most substantive assessments of performance and the most forceful recommendations for improving performance that we have identified during our inquiry have occurred as part of investigations of IRBs that have been responsible for and/or involved in a significant and highly publicized lapse in human-subjects protections. Yet, OPRR informs us that because of resource limitations it conducted only one such visit between April 1997 and May 1998. Its investigations, of which about 75 are open at the current time, are almost always conducted from a distance.

**The FDA Oversight Focuses on Inspections. Its Reviews, However, Stress Procedural Compliance, with Only Minimal Attention Given to IRB Effectiveness.**

The FDA estimates that there are about 1,500 to 1,700 IRBs involved in reviewing research of FDA-regulated products, mostly pharmaceuticals.<sup>50</sup> For this universe of IRBs, which includes most of the IRBs having assurances with OPRR, FDA conducts periodic inspection visits. In 1997, the FDA conducted just under 200 site visits (see appendix B). They are carried out by FDA inspectors who also have responsibilities for inspections focusing on food products, research sponsors, and even investigators.

The on-site inspections focus almost entirely on determining IRB compliance with FDA regulations. They involve some interviewing of IRB leadership, but mainly a review of IRB records, including those of three IRB-approved studies. They examine the IRB's conformance to discrete Federal mandates concerning matters such as attendance at board meetings, completeness of board-meeting minutes, annual protocol reviews, and informed consent forms. These and many other compliance issues examined can be important indicators of IRB performance, but they provide FDA with little direct feedback on the actual effectiveness of the IRB in protecting human subjects. For instance, FDA has issued an information letter to IRBs calling for them to make sure that individuals understand what they are consenting to when they agree to participate in a research effort. Yet, the FDA's inspection process affords it little basis for determining if such understanding takes place; nor does it even review the adequacy of the IRB's own mechanisms for making such a determination.

The IRB inspections often do result in deficiency notices to the IRB. The most frequent of these concern inadequate compliance with various written procedures and with

continuing review procedures. Most of these are not regarded by FDA as being of major significance and thus result in a request to the IRB to take corrective action. In those instances where FDA identifies what it regards as a significant deficiency, it issues a warning letter to the IRB. The warning letter calls for an immediate IRB response to FDA, spelling out how the identified problem will be corrected.

## CONCLUSION

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The IRBs' limited efforts in conducting continuing review of active research is a serious national issue because it compromises their protection of human subjects. It inhibits their capacity to identify and address situations where unacceptable risks emerge, or research results prove to be too favorable to continue, or protocols stray beyond approved parameters. The IRBs may not be vigilant enough to notice and to intervene on behalf of the subjects. It also inhibits their capacity to ensure that the subjects have adequate understanding of informed consent forms they have signed and that they recognize the distinctions between research and established therapy.

In offering this conclusion, we do not claim that widespread abuses exist. We recognize the important contributions that IRBs have made and continue to make. The system of protections they provide revolves around the participation of many conscientious investigators committed to protecting human subjects and many dedicated IRB members and staff doing their best under trying circumstances. But, our inquiry provides an important warning signal, especially given the scope of the changes occurring in the IRB environment. These include current Federal plans to raise the level of NIH funding, 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.<sup>51</sup> The signal we present warrants careful attention and a Federal response. In our summative report, *Institutional Review Boards: A Time For Reform*, we present recommendations on how the National Institutes of Health and the Food and Drug Administration could respond to the findings presented in this report and that emerge from our overall inquiry.

## **Federal Requirements on IRB Continuing Review**

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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.<sup>1</sup> 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."<sup>2</sup> This interval has been interpreted as no less than 12 months from the date of initial review.<sup>3</sup> 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.<sup>4</sup> 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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<sup>1</sup> 45 C.F.R., sec. 46 (HHS/OPRR) and 21 C.F.R., sec. 56 (FDA)  
Currently, 16 Federal departments and agencies abide by these regulations through the Common Rule for the protection of human subjects in research, effective August 19, 1991.

<sup>2</sup> *Ibid.*

<sup>3</sup>OPRR "Dear Colleague Letter", 10 January 1995, Continuing Review--Institutional and Institutional Review Board Responsibilities.

<sup>4</sup>*Ibid.*, FDA Information Sheets, 1995.

## Modifications and Adverse Event Reports

Periodically, the IRB may receive amendments/modifications to 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 continuous task for IRBs. An adverse event is 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. See 21 C.F.R., sect. 312 (for drug research) and 21 C.F.R., sec. 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.<sup>5</sup> 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.<sup>6</sup>

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<sup>5</sup> 45 C.F.R., sec. 46 (HHS/OPRR)  
21 C.F.R., sec. 56 (FDA)

<sup>6</sup> Changes may be initiated before IRB approval if they are necessary to eliminate immediate hazards to subjects. See *Ibid.*



## Federal Oversight of IRBs

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There are an estimated 3,000-5,000 IRBs across the country. Two agencies within HHS are responsible for the oversight of IRBs: OPRR and FDA. Each agency has its own set of IRB regulations. Although there are many similarities between the two sets of regulations, the agencies' 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 an IRB 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 and approved the protocol and the researchers are awaiting NIH funding. 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 of IRBs is uncertain, the FDA acknowledges that it is 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. An institution must apply for an SPA for each project it wishes to conduct. 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup>

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<sup>1</sup>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.

<sup>2</sup>Less frequently, investigations are conducted as a result of suggestions from Congress or the media.

<sup>3</sup>“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.<sup>4</sup> 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.<sup>5</sup>

**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, the use of the most current consent documents, the submission and review of adverse-event reports, and for

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<sup>4</sup> This is difficult to achieve because of workload constraints; IRBs found previously to be significantly deficient are inspected more frequently.

<sup>5</sup> Actions taken are classified according to the strength 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.

the presence of a quorum during 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 informed consent was signed and dated in a timely manner.

## **Advertising to Recruit Human Subjects**

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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."<sup>1</sup>

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.<sup>2</sup> 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 risks of research are easily overlooked. The advertisements cite an overwhelming array

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

<sup>2</sup> 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.

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

#### 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

#### Speed or Cocaine?

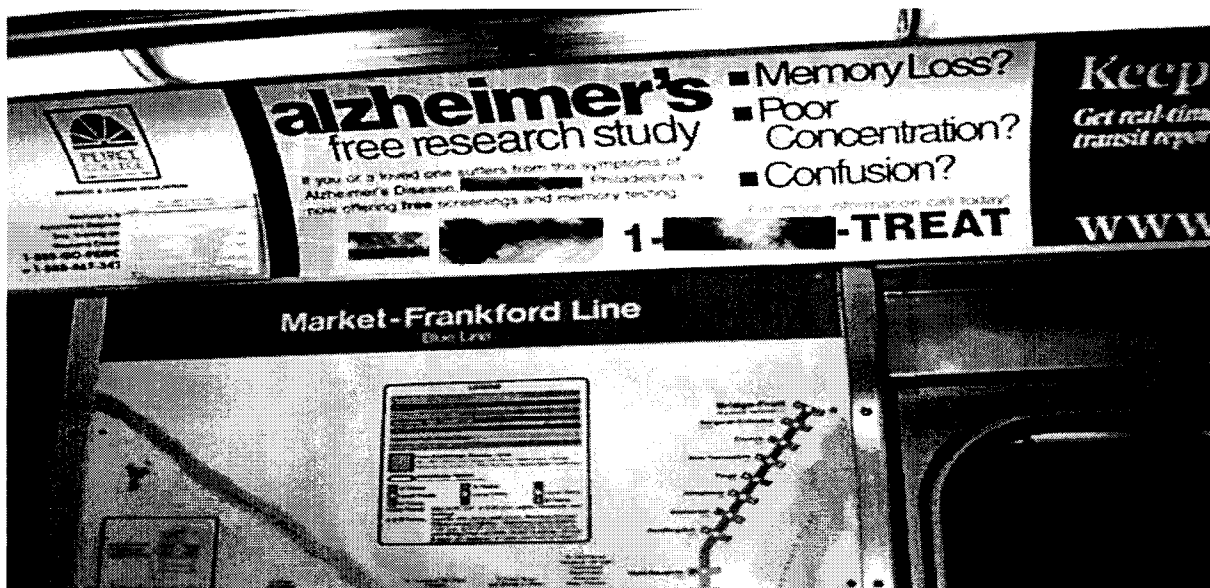
Need help getting clean?  
Free Treatment & Medication.  
Repeat Callers Welcome!!! Get Paid \$\$\$

#### 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

## ENDNOTES

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

2. For more detailed explanations of these concerns see (a) 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. (b) The Advisory Committee on Human Radiation Experiments, *Final Report*, Washington D.C.: 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. The National Bioethics Advisory Commission 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 managements 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.

6. These IRBs are reviewing research at institutions receiving over 1.4 billion dollars of active 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.

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 six institutions alone account for over half a billion dollars of active 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.



9. It is important to note that while the IRB has a key responsibility for protecting human subjects, sponsors also have responsibility for the monitoring and oversight. According to 21 C.F.R., sec. 312, sponsors are required to ensure proper monitoring of investigations and they are also required to select a monitor to oversee investigations through site visits. In addition, the sponsor may require reports from investigators. There is, however, little information sharing between sponsors and the IRB.
10. See 45 C.F.R., sec. 46.109(e) and 21 C.F.R., sec. 56.109(e).
11. Dear Colleague letter from Office of Protection from Research Risks, "Continuing Review-- Institutional and Institutional Review Board Responsibilities," 10 January 1995.
12. FDA Information Sheets, "Continuing Review After Study Approval," 1 October 1995.
13. Several factors may contribute to the lack of understanding. In our previous study, where we conducted four case studies of medical devices, we found that the reading level of the informed consent documents related to each of the four medical devices ranged from college level to graduate level ability (Department of Health and Human Services, Office of Inspector General, *Investigational Devices: Four Case Studies* (OEI-05-94-00100), April 1995). Compounding the difficult reading level may be deficiencies in the informed consent documents themselves. The Center for Drug Evaluation Research, located with the FDA, has found an increasing number of deficiencies in informed consent documents at the IRBs it inspected. In 1995, it found 24 percent of IRBs inspected had informed consent documents deficiencies; in 1996, it found 28 percent had deficiencies; and in 1997, it found 41 percent had deficiencies.
14. A full and clear understanding of risks is especially important in Phase 1 clinical trials when relatively little is known about an intervention's effect in humans and the aim of the research may well be to determine how much of a medication can be tolerated by humans.
15. Advisory Committee on Human Radiation Experiments, *Final Report*, Washington, D.C.: U.S. Government Printing Office, 1995.
16. For example, see (a) 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; (b) U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996; and (c) Philip J. Hilts, "Psychiatric Research Under Fire," *New York Times*, 19 May 1998.
17. To a significant degree, we found that research investigators were quite removed from the informed consent process. In some of the larger departments, staff are primarily responsible for preparing the consent forms.
18. IRB and Federal officials typically recognize the importance of the interactive process, but find the consent form itself as a more practical tool for review purposes. Indicative is the following comment of a Food and Drug Administration official in her testimony before

Congress: “It is the interactive information exchange that is most important to the informed consent process. FDA focuses on the consent form during our inspections because it is the best evidence that we have of the basic information that was exchange during that process.”

(*Oversight of HHS: Bioethics and the Adequacy of Informed Consent*, Hearing before the Subcommittee on Human Resources and Intergovernmental Relations of the Committee on Government Reform and Oversight, U.S. House of Representatives, 8 May 1997, Testimony of Mary Pendergast.)

19. Advisory Committee on Human Radiation Experiments, *Final Report*, Washington, D.C.: U.S. Government Printing Office, 1995: Chapter 16, Section 3.

20. See (a) Paul McNeil, *The Ethics and Politics of Human Experimentation*, New York: Cambridge University Press, 1993. (b) “Don’t Let It Happen Again,” *The Economist*, 17 May 1997, pp. 27-28. (c) Michie Hunt, *The FDA: Promoting Access to New Drugs, Biologics, and Medical Devices*, National Health Policy Forum, The George Washington University, July 1997.

21. These projects tend to be part of national or even international multi-site projects involving research in out-patient settings. They are subject to oversight mechanisms carried out by the sponsors themselves. But, they do not tend to have the level of safeguards and monitoring typically provided to patients in inpatient settings.

22. See (a) Keith Epstein and Bill Sloat, “Drug Trials: Do People Know the Truth About Experiments?” *The Plain Dealer*, 15-18 December 1996, Special Sunday Insert, pp. 2-16; and (b) *Oversight of HHS: Bioethics, and the Adequacy of Informed Consent*, Hearing before the Subcommittee on Human Resources and Intergovernmental Relations of the Committee on Government Reform and Oversight, U.S. House of Representatives, 8 May 1997; and (c) Steve Stecklow and Laura Johannes, “Drug Makers Relied on Clinical Researchers Who Now Await Trial” *The Wall Street Journal*, 15 August 1997, pp. A1 and A6.

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

24. The GAO report also noted the limited attention to continuing reviews. It indicated that in their reviews, IRBs relied heavily on investigators’ self-assessments. (U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72, March 1996.)

25. The situation differs somewhat for the independent IRBs. Board members of these IRBs are paid for their time. Whether or not they are any more or less favorable toward annual reviews, we do not know.

26. Each report must be compiled, documented, and reviewed by the IRB. Also, the IRB must notify the investigator of any changes.

27. In its 1996 report, the GAO stated that “IRB reviews generally do not involve direct observation of the research study or of the process in which a subject’s consent is obtained.”

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

Edgar and Rothman stated that “it is rare for an IRB to leave the confines of its committee room and 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.) These sentiments are echoed by McNeil in his book. (Paul McNeil, *The Ethics and Politics of Human Experimentation*, New York: Cambridge University Press, 1993, p. 244.)

28. The National Commission that developed the current system of human protections in the 1970s, envisioned a much 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)).

29. Of particular note here is the Federal informed consent requirement which calls for investigators to seek informed consent “only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.” (See 21 C.F.R., sec. 50.20 and 45 C.F.R., sec. 46.116) Without any direct observation or feedback by independent parties, it is extremely difficult for IRBs to ascertain that such circumstances exist at the time that human subjects provide their written consent.

30. Three sites with 10 year data reported increases of over 80 percent. One reason for the escalating numbers may be that investigators, claiming that it is increasingly difficult to receive grants, are submitting more research protocols. The NIH requires IRB approval prior to funding decisions so IRBs may review a significant number of protocols that will not go on to be funded.

31. Hayes et al., “A Survey of University Institutional Review Boards: Characteristics, Policies, and Procedures,” *IRB*, Vol. 17 (May-June 1996), No. 3, pp. 1-6.

This highlights the importance of academic medical centers to human-subjects research when compared to another survey of all hospitals with at least 400 beds which reported an average of

84 proposals per year. (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.)

32. One former IRB member indicated that these pressures are particularly intense on physicians whose fields involve a significant amount of patient contact. As a result, IRBs are finding it especially difficult to recruit and retain physician members who regularly interact with patients and may be more attuned to their concerns.

33. For a more detailed explanation, see our companion report: Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: Promising Approaches*, OEI-01-97-00191.

34. These demands apply both to the time spent outside of meetings in reviewing proposals and to the time spent during meetings discussing them.

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

36. Since the 1950's trial of poliomyelitis vaccine involving over a million school-age children, large randomized clinical trials conducted simultaneously at a network of sites across the country have become a standard in determining treatment effectiveness. These multi-center trials are becoming even more important as scientists' and physicians' knowledge of disease improves. Specific subpopulations of patient groups are being identified and are required to test more targeted treatments and drugs. Any one institution may only have a few patients in each group, rarely enough to statistically determine effectiveness. Therefore, data from small patient groups at sites around the country, or even the world, must be combined.

37. Brad H. Pollock, "Quality Assurance for Interventions in Clinical Trials: Multicenter Data Monitoring, Data Management, and Analysis," *Cancer Supplement*, Vol. 74, (1 November 1994), No. 9, pp. 2647-2651.

Furthermore, NIH funding alone for such cooperative group projects has increased almost ten-fold in the past decade, from \$49.2 million in 1985 to \$419.2 million in 1994. (*NIH Extramural Trends--FY 1985-1994*).

Data available on the NIH website at <http://www.nih.gov/grants/award/trends94/chapter1.htm>

38. Multi-center trials may represent even larger percentages of active research at smaller institutions that do not have the patient base to support single-investigator studies.

39. There are 11 cooperative research groups associated with NCI alone. Each is a formal, free-standing entity which has its own board of directors, but is responsible for following federal guidelines. Each cooperative group oversees multiple protocols, ranging in number from 20 to well over 100. Other institutes at the NIH also have cooperative research groups with which they are associated.

40. Approximately 700 to 800 audits of project sites are conducted annually. As another example, the Division of AIDS at the National Institute of Allergy and Infectious Disease at NIH contracts with a CRO to monitor, four times a year, each clinical site it sponsors.

41. Beyond these, some academic health centers, particularly in their cancer programs, are carrying out their own audit component. See the section entitled “Management of the Workload” in our companion report: Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: Promising Approaches*, OEI-01-97-00191.

42. The IRB at one large academic health center we visited reported that it has regularly been requesting DSMB data from the research sponsors and to this point has not been refused access to the data. We have not heard of others making such requests and having similar success.

43. From time to time, the DSMBs and audit teams associated with cooperative-group projects will provide some information to OPRR if they have information they find to be particularly relevant to the IRB. The OPRR will then share the information with the IRB. Similarly, from time to time, some investigators or sponsors will share with the IRBs information or instructions they received from the DSMBs or audit teams.

44. The IRB regulations require that “each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.” Since 1994, the FDA’s Division of Scientific Investigations in CDER began to put forth in some post-inspection letters and a few conference presentations the benefits of interpreting this regulation as a ratio.

The independent IRBs tend to have more “outside” review members on their boards. While these members are paid for their review services, the great majority are not otherwise affiliated with the IRB or its parent institution and many are nonscientific members.

45. “The presumption that informs the current so-called monitoring activities of most IRBs is that members of the institution are to be trusted until some contrary evidence is brought forward. If the IRB is obliged to function as a police force, it can only indicate to the community of investigators that it is operating from presumptions of distrust. Presumptions of distrust cost a lot of time and energy of IRB members, most of whom have no training in police work in the first place.” (Robert J. Levine, *Ethics and Regulation of Clinical Research*, Baltimore: Urban & Schwarzenberg, 1986, p. 348-349.)

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

47. See Advisory Committee on Human Radiation Experiments, *Final Report*, Washington, D.C.: U.S. Government Printing Office, 1995: Chapter 16, Section 3.

48. For more information see Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: Promising Approaches*, (OEI-01-97-00191).

49. 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, P.L. No. 93-348, sec. 474, 88 Stat. 342.)

50. IRBs subject to FDA oversight only become known to the agency after an IND or IDE has been filed. Thus, the IRB has been operating for some time before the FDA becomes aware of its presence. The FDA has told us that the uncertainty in the number of IRBs subject to regulatory oversight is part of the problem in exercising that oversight.

51. 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 for the development of genetic 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, S. 1921, would rely on the IRB to determine measures of confidentiality, such as whether subject identifiers should be retained. (S.1921, 105<sup>th</sup> Congress, sponsored by Senators Jeffords and Dodd)