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Institutional Review Boards:

The Emergence of Independent Boards

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EXECUTIVE SUMMARY

PURPOSE

To describe the role of independent institutional review boards in ensuring protections for human subjects of clinical research.

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 give their 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.

Over the past 25 years, thousands of IRBs have formed to help ensure human-subject protections. At first, most were in large academic centers, where most of the federally funded research still occurs. As research spread to other settings and as commercially sponsored research increased, IRBs arose in different environments such as community hospitals, managed care organizations, and government agencies. A few emerged as independent entities working outside of institutions where research is performed.

Independent Boards: The Focus of This Report

This report focuses on independent IRBs, about which little has been published. One of 4 reports we are issuing on IRBs, it draws primarily on the interviews we held with representatives of 11 independent IRBs. In addition, it relies on information gathered from interviews and group discussions with representatives of about 60 other IRBs; site visits to 6 IRBs; reviews of Federal records; and attendance at IRB meetings.

FINDINGS

Independent IRBs Are Playing an Increasingly Prominent Role in the Research Community.

While There are Relatively Few of Them, Their Number has been Growing. Although one dates back to 1968, most were established in the 1980s and '90s. It appears that at least 15, and perhaps quite a few more, are now operating.

They Oversee an Increasing Number of Research Plans. In the last 2 years, independent IRBs we contacted reported an average increase of approximately 36 percent in initial protocols reviewed. The largest and oldest of the independent IRBs reviewed more initial protocols in 1997 than did many IRBs in academic health centers.

They are Now Reviewing HHS-Sponsored Research. Prior to 1995, all such research was being overseen by IRBs at the institutions where the research occurred. In that year, some HHS grantees first gained Federal approval for an independent board to serve as their IRB. At present, independent boards are responsible for at least 12 HHS-funded projects.

They are Becoming More Involved with Hospital-Based Research. Some act as the IRB of record for hospitals. Some provide consultation to hospital-based IRBs. One has contracted with a major medical center to review all commercially sponsored protocols for that center's IRB.

Independent IRBs Offer Advantages That Institutional IRBs Find Difficult to Match.

They Are Geared to Quick Decisions on Research Plans. Independent IRBs are organized to respond to commercial sponsors' expectations for timely reviews. On average, those we interviewed reported that they could provide initial research protocol decisions in about 11 days. For the academic health centers we reviewed, the average was about 37 days.

They Provide a Detached Source of Expertise. Independent IRBs are not affiliated with the institutions whose research they review and are unlikely to have collegial relationships with the investigators. This detachment facilitates research plan review without institutional or collegial biases.

They Can Provide Unified Reviews for Multi-Site Trials. For such trials, an independent IRB can serve as a single entity reviewing the applicability of a specific research plan to various sites. This eliminates the complications that result from multiple, local IRB reviews. It also facilitates analysis of adverse-event reports from various sites.

Yet, The Use of Independent IRBs Raises Concerns.

They Are Not Local Review Bodies. Local review is a long-established principle of human-subject protection. Familiarity with the conditions of the institution, the investigators, and the local community have been viewed as vital to effective human-subject protection. Concerns about independent IRBs' ability to provide local review have inhibited their participation in federally sponsored research. The independent IRBs

have sought to ease such concerns by keeping abreast of the research site's circumstances through site visits, local contacts, newspaper clipping services, and other means.

They May Be Subject to Conflicts of Interest. Some IRB officials are concerned that independent IRBs, almost all of which are for-profit enterprises, may compromise the review process to please their sponsors/customers and to advance their financial well-being. Yet, these officials also express concern that in an increasingly competitive environment, all IRBs are subject to conflicting pressures that could compromise their core mission.

They Heighten Concerns about IRB Shopping. Sponsors who are unhappy with the reviews of one independent IRB may seek out another that they expect to be more accommodating. The independent IRBs themselves may not know if a sponsor's research plan has been turned down, or found lacking, by another IRB.

CONCLUSION

We offer two concluding observations that have broad significance for the Federal system of human-subject protections.

First, independent IRBs have become a noteworthy part of the IRB landscape. They provide some competition to IRBs in academic health centers and other settings and, in so doing, contribute to a marketplace ethic--one that is quite different from that 20, or even 10 years ago. This development presents opportunities in that it encourages more timely and innovative approaches to review. At the same time, competitive pressures on IRBs present dangers that can compromise human-subject protections.

Second, independent IRBs raise important questions for Federal oversight. How can the Federal government best ensure that independent IRBs help protect human research subjects? That the emerging competition does not compromise safeguards? That independent IRBs' advantages and efficiencies are not undercut by unnecessary Federal regulation? Such questions underscore the importance of understanding the effectiveness of IRBs--whether they are independent or part of research organizations. We address this matter in our summary report, *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 describe the role of independent institutional review boards in ensuring protections for human subjects of clinical research.

BACKGROUND

On page three we provide a primer on institutional review boards (IRBs). We explain why they were established, what roles they perform, how they are organized, where they are located, and how the Department of Health and Human Services (HHS) oversees them.

A number of studies of IRBs have been undertaken, the most thorough of which was published in 1978.[1] Since then, however, sweeping changes have transformed the economics and organization of clinical research. An increase in the commercial funding of clinical research has changed the culture of research and has driven the demand for independent IRBs. Research has evolved from the single-site model--with one hospital-based clinical investigator and a few subjects--to multi-site projects involving numerous private-practice or clinic-based physicians and, sometimes, thousands of subjects.[2]

Independent IRBs

These boards are not part of any organization in which research is conducted.

They are hired by research sponsors (most often pharmaceutical and device manufacturers) and investigators to review research plans.

Most are for-profit entities.

Some are owned by other organizations (such as contract research organizations that place clinical studies for research sponsors).

Some offer consultation, training, and other services in addition to traditional IRB services.

Board members are paid for their work, either on a per-meeting basis, an hourly basis, a per-protocol-reviewed basis, or some combination thereof.

In the midst of the many changes that are transforming the clinical research environment, a renewed interest in human-subject protections and the role of the IRB has arisen. A 1995 report issued by the Institute of Medicine (IOM) called for an examination of the effectiveness of the IRB system.[3] Another 1995 report, issued by a Presidential advisory committee, raised a number of concerns about the performance of IRBs.[4] A 1996 report from the U.S. General Accounting Office suggested that "continued vigilance over human subject research should remain a priority for the research community and agencies charged with oversight."[5] The National

Bioethics Advisory Commission is examining the current state of human-subject protections and has pursued information about IRBs.[6] These and other reviews, however, have given only passing attention to independent IRBs.

This Inquiry and This Report

This report, which is one of four that we are issuing on IRBs, focuses on the independent IRBs. It describes their growing presence and the major advantages and disadvantages attributed to them. The report is designed to complement its three companion reports. One, *Institutional Review Boards: Their Role in Reviewing Approved Research*, finds that IRBs devote minimal attention to continuing review and identifies key obstacles to such review. Another, *Institutional Review Boards: Promising Approaches*, presents innovative efforts that IRBs have undertaken in six key areas of responsibility. A third, *Institutional Review Boards: A Time For Reform*, provides a summary of IRB functioning and presents recommendations.

Our inquiry draws on a variety of sources. Of particular relevance to this report were our interviews with independent IRB officials. We held a group discussion with members of the Consortium of Independent IRBs (CIRB) and conducted telephone interviews with representatives of the 10 IRBs that are CIRB members and 1 independent IRB that is not a CIRB member. We also drew on interviews and group discussions with representatives of about 60 additional IRBs;[7] 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.

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).

FINDINGS

Independent IRBs are Playing an Increasingly Prominent Role in the Research Community.

While There are Relatively Few of Them, their Number has been Growing.

The exact number of independent IRBs is not known, but the Consortium of Independent IRBs estimates that there are at least 15, and perhaps quite a few more. While 1 of these independent IRBs dates to 1968, at least 10 were established after 1980, and 4 of these were established after 1990. The increasing number of independent IRBs parallels an increasing number of research protocols being put forward by commercial sponsors.[8]

They Oversee an Increasing Number of Research Plans.

The number of research plans that the independent IRBs review is considerable and growing. In the last 2 years, independent IRBs we contacted reported an average increase in initial reviews of approximately 36 percent. In 1997, the independent IRBs we surveyed conducted an average of 256 initial reviews.[9] The largest and oldest of them reviewed over a 1,000 initial protocols and conducted over 4,000 continuing reviews in 1997, a caseload comparable with many IRBs in academic health centers.

The great preponderance of the research that independent IRBs oversee is sponsored by either pharmaceutical or device manufacturers and is conducted in physician offices outside of hospitals, medical clinics, or commercial-research facilities. A growth of research in such independent-investigator sites has contributed to the increase in the number of protocols that these IRBs review.[10]

They are Now Reviewing HHS-Sponsored Research.

Independent IRBs are increasingly being used for HHS-funded clinical studies. In these cases, a research institution must obtain a single project assurance from OPRR. It was not until 1995 that OPRR began granting assurances for projects that involved independent IRBs. It has continued this practice in subsequent years, so that at least 12 such assurances are now in place. The number is likely to increase in the years ahead.[11]

They are Becoming More Involved with Hospital-Based Research.

Independent IRBs become increasingly attractive to some hospitals as the quantity and complexity of their own IRBs' workloads increase. Four of the 11 independent IRBs with which we spoke already act as IRBs of record for one or more hospitals. One, in fact, had established a contract with a major academic health center IRB to review all commercially sponsored research plans for that IRB. A few other large research

institutions have separated their commercially sponsored research from the Federal assurance requirements that apply to all HHS-funded research, thereby giving the institution greater flexibility in contracting with independent IRBs if it so chooses. Many of the experienced IRB officials with whom we spoke noted that such separations are becoming increasingly likely and present good market opportunities for independent IRBs.

Independent IRBs Offer Advantages That Institutional IRBs Find Difficult to Match.

They Are Geared to Making Quick Decisions on Research Plans.

To commercial sponsors, time is money. Sponsors expect IRBs to do their work properly, but to do it quickly as well. Independent IRBs are organized to meet this expectation. It is widely recognized, by research sponsors and in the IRB community more generally, that they provide research sponsors with timely responses to their submissions.[12] Thus, for instance, the independent IRBs we contacted reported that, on average, they were able to provide research sponsors with an approval or disapproval decision for initial, non-expedited research protocols in an average of about 11 days. By contrast, the IRBs in academic medical centers that we visited reported decisions in an average of about 37 days.

Independent IRBs have an inherent advantage in meeting timeliness expectations because they hire their board members with the understanding that the members will be regularly available to conduct reviews.[13] Hospital IRB members, in contrast, are almost always volunteers with many competing demands for their time. Not surprisingly, independent IRBs tend to meet more frequently and can meet with minimal notice. The independent IRBs we contacted reported holding multiple board meetings each month. One independent IRB reported that it holds four meetings a week. Academic health centers and hospitals generally are hard-pressed to match that.[14]

They Provide a Detached Source of Expertise.

Independent IRBs are staffed by people who have no affiliation with the institutions whose research plans they review and who are unlikely to have collegial relationships with the investigators whose work they review.[15] Thus, the independent IRBs can operate without being influenced by concerns about the financial well-being or prestige of the institution that employs them or the career interests of colleagues. One hospital official, who has worked with independent and hospital-based IRBs, underscored the importance of such detachment, pointing out that it leads to greater objectivity. IRB officials in other settings, however, are wary of such a conclusion.

They Provide Unified Reviews for Multi-site Trials.

Some multi-site trials involve research sites that do not have their own IRBs or do not require that all local research be overseen by the site's own IRB. In such cases, independent IRBs can serve as a single entity reviewing the applicability of a specific research plan to various sites.[16] This unified review eliminates the complications that result from multiple, local IRB reviews of a sponsor's research plan. It also facilitates analysis of adverse-event reports submitted from individual sites and, in so doing, can enhance protections for human subjects.

Yet, the Use of Independent IRBs Raises Concerns.

They Are Not Local Review Bodies.

In the 1970s, when the current infrastructure of Federal protections for human research subjects was established and when relatively few national multi-site trials were underway, local review was regarded as essential. In one of its key reports, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research concluded:

> ...the rights of subjects should be protected by local review committees operating pursuant to federal regulations and located in institutions where research involving human subjects is conducted. Compared to the possible alternatives of a regional or national review process, local committees have the advantage of greater familiarity with the actual conditions surrounding the conduct of research. Such committees can work closely with investigators to assure that the rights and welfare of human subjects are protected and, at the same time, that the application of policies is fair to the investigators.[17]

The OPRR's recent decision to grant assurances involving independent IRBs is based largely on the IRBs' commitments to stay well-informed about local sites. In response to OPRR and other concerned parties, the independent IRBs point to a variety of ways in which they keep abreast of the site circumstances. These include site visits, local contacts, relationships with local IRBs, newspaper clipping services, and other means. Many in the IRB field remain unconvinced that such compensatory efforts allow for adequate local representation.

They May Be Subject to Conflicts of Interest.

Some IRB officials are concerned that an independent, for-profit IRB might compromise its review process to advance the financial well-being of the firm. Such concerns are heightened to the extent that corporate-equity owners or employees serve on the IRB review boards and are sustained to some extent by the fact that reviewers are paid for their services. The NIH policy for HHS-funded research reviews by for-profit IRBs is to prohibit equity owners from participating in the review process. There is no such policy

for industry-sponsored studies submitted to FDA. As we noted earlier, the great preponderance of research overseen by independent IRBs is sponsored by either pharmaceutical or device manufacturers.

A contrast is often made with the academic health center, where, some IRB officials say, a long established research culture allows for greater IRB independence. In an increasingly competitive research environment, however, in which those centers are seeking to maximize clinical research revenues, the IRBs in these centers can also experience conflicting pressures.

They Heighten Concerns about IRB Shopping.

For research that is not federally funded, sponsors have considerable discretion in their choice of an IRB. A problem here is that if one IRB finds fault with the sponsor's research plan, the sponsor might then contract with another IRB without informing it of the prior board's determinations. While applicable to all IRBs, this vulnerability is particularly germane to independent IRBs since nearly all the proposals they review are not federally funded. Some representatives of these boards emphasized this point to us and felt there was a good case for a Federal requirement that when submitting a research plan for review, sponsors must inform the IRB of any prior IRB reviews of that plan.

CONCLUSION

This report does not afford us a basis for assessing how well independent IRBs are performing. But, it does lead us to two concluding observations that have broader significance for the Federal system of human-subject protections.

First, independent IRBs have become a noteworthy part of the IRB landscape. They give research sponsors an alternative to the traditional, well-established IRBs. Particularly for non-federally funded research, they allow for these sponsors to engage in some shopping to determine what IRBs best meet their needs. In that sense, they serve as competition to the longer established IRBs, especially those in academic health centers, and contribute to a marketplace ethic--one that is quite different from the ethic of 20 or even 10 years ago when IRB activity was carried out within a more clearly defined research culture. This development presents both opportunities as well as dangers. On the one hand, it encourages IRBs to undertake more timely and innovative approaches to their review processes. On the other hand, the competitive pressures to satisfy research sponsors can lead some IRBs to be less vigilant in protecting human subjects.

Second, independent IRBs raise important questions for Federal oversight. How can the Federal government best ensure that independent IRBs afford necessary protections? That the emerging competition does not compromise safeguards? That the advantages and efficiencies offered by independent IRBs are not undercut by unnecessary Federal prescriptions? Such questions underscore the importance of having a good understanding of the actual effectiveness of IRBs, whether they are independent or part of an organization that conducts research. This is a matter we address in our summary report, entitled, *Institutional Review Boards: A Time For Reform.*

Endnotes

1. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research contracted with the Survey Research Center of the University of Michigan to conduct a study that focused on IRB review procedures and research projects reviewed in 1974-1975 at a representative sample of 61 of the more than 420 institutions that had DHEW assurances. The study methodology entailed interviews with more than 3900 people involved with the IRBs (including IRB members, researchers whose protocols were reviewed by IRBs, and research subjects.) According to Paul M. McNeil, this study is still the most thorough of any on record in any country (Paul M. McNeil, *The Ethics and Politics of Human Experimentation*, Cambridge: Cambridge University Press, 1993, p. 86).

2. This evolution in research mainly applies to studies involving investigational drugs. In the case of medical devices some large, multi-site studies were already underway in the late 1970s.

3. 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.

4. Advisory Committee on Human Radiation Experiments, *Final Report,* Washington DC: U.S. Government Printing Office, 1995.

In that same year, a report from the HHS Office of Inspector General raised concerns about IRBs' ability to monitor ongoing clinical trials and about the extent to which effective linkages exist among hospital committees, offices, and departments to adequately provide protection for human subjects enrolled in clinical research. (Department of Health and Human Services, Office of Inspector General, *Investigational Devices: Four Case Studies,* OEI-05-94-00100, April 1995.)

5. U.S. General Accounting Office, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HHS-96-72, March 8, 1996, p. 3.

6. 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.

7. 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.

8. The FDA suggests that the reason for more independent IRBs stems from a change in FDA's regulations in 1981. For a further elaboration, see FDA's Comments on the Draft OIG Report (appendix D) in our summary report entitled, *Institutional Review Boards: A Time For Reform.*

9. A recent survey of academic health centers found that their IRBs were reviewing an average of 297 proposals a year. (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.) A second survey, this one of hospitals with at least 400 beds, reported that IRBs reviewed 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.)

10. "Independent IRBs: Subject Protection and Client Service Are the Keys," *Bio/Pharmaceutical Outsourcing Report*, (October 1997) Vol 2, Number 10, p.1.

11. The FDA has long accepted independent IRBs as part of the clinical research landscape and has audited independent IRBs.

12. "Independent IRBs: Subject Protection and Client Service Are the Keys," *Bio/Pharmaceutical Outsourcing Report*, (October 1997) Vol 2, Number 10, p.1.

13. Of the seven IRBs that provided us with information on this topic, four reported that they paid IRB members for each meeting attended; one paid members for each protocol reviewed; another compensated members a base amount for each meeting plus an additional amount for meeting agenda items that surpassed the fixed number; and the seventh used a mixed compensation system whereby most IRB members were paid for each meeting attended, but some members were paid an hourly rate for either meeting attendance or review of adverse event reports and Investigational New Drug safety reports.

14. Some of the independent IRB officials we contacted also suggested that the research protocols they receive, which are mostly from pharmaceutical and device manufacturers, tend to be carefully prepared and do not require much revision or clarification. The sponsors and their agents, hoping to bring products for FDA approval, tend to be well aware of FDA's requirements concerning IRB review and gear their submissions accordingly.

15. When an institution lacks its own IRB, researchers could be tempted to establish a board for the sole purpose of reviewing a few proposals. Such situations could jeopardize human-subject protections because these IRBs would lack sufficient expertise. Independent IRBs are an alternative in such instances.

16. Hospital IRBs that serve multi-hospital systems are also able to provide unified reviews for sites that are part of their system.

17. *Institutional Review Boards: Report and Recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*, 43 Federal Register, 30 November 1978, p. 56186.