

[Memo Report]

October 23, 1998

June Gibbs Brown
Inspector General

Final Report on Low-Volume Institutional Review Boards (OEI-01-97-00194)

See Addressees Below

In this memorandum, I would like to share with you the results of a brief review we conducted of low-volume institutional review boards (IRBs). We did this as a follow-up to our recent study of challenges facing IRBs.

In general, in our June 1998 summary report, we concluded that the IRB system is in jeopardy and made numerous recommendations for reforming the system.¹ While the findings and recommendations of these reports applied to all IRBs, they had particular relevance to academic health centers whose primary focus is research.

While conducting the research for these reports, we became aware that there are some unique challenges facing hospital-based IRBs outside of the academic health centers. Because these IRBs tend to oversee considerably fewer research protocols than those at the large research centers, we refer to them as “low-volume” IRBs; in this memorandum, we define low-volume IRBs as those that conduct less than 125 initial reviews annually. This definition most likely encompasses a majority of the 3,000-5,000 IRBs in this country. However, given their smaller caseloads, low-volume IRBs probably oversee the minority of protocols subject to IRB review. These IRBs typically reside in hospitals that are community-focused and lack a research culture.²

In brief, our results indicate that low-volume IRBs, like others, face significant threats to their effectiveness; they review too much, too quickly, with too little expertise and conduct minimal review of approved research. In addition, they face conflicts that threaten their independence, provide little training for investigators and board members, and devote little attention to evaluating IRB effectiveness. Finally, they face major changes in the research environment. We conclude that the same recommendations set forth in our prior report apply to low-volume IRBs. In implementing these recommendations, we suggest that oversight agencies pay special

attention to the particular needs of low-volume IRBs. Specifically, we recommend that the Office of Protection from Research Risks (OPRR) and the Food and Drug Administration address low-volume IRBs' relative isolation from the rest of the IRB community by fostering collaborations between low-volume IRBs and others.

Methodology

We developed an awareness of the special challenges facing low-volume IRBs through our contacts with various IRB officials, as well as through our review of a recent Canadian commission report that addressed issues specifically pertaining to low-volume IRBs.³ We decided to conduct a limited follow-up inquiry to assess more fully the applicability of the findings from our earlier IRB reports to low-volume IRBs.

We based this inquiry primarily on a judgmental sample of 12 low-volume IRBs. We identified these IRBs through references from participants in our prior IRB research. In choosing the IRBs to include in our sample, we attempted to attain both geographical diversity and a range of hospital types in order to broaden the applicability of our findings. Our sample of IRBs conducted a median of 44 annual initial reviews, ranging from a low of 5 to a high of 124.⁴ We obtained data and conducted interviews with representatives from each IRB in our sample. In addition, we interviewed several experienced IRB officials who offer educational consulting to low-volume IRBs. Finally, we analyzed the data in a recent IRB-related National Institutes of Health (NIH) report.⁵

Low-Volume IRBs, Like Other IRBs, are At-Risk

Our prior report identified six basic factors that jeopardize the effectiveness of IRBs. In this follow-up probe, we have found further confirmation that these factors apply to low-volume IRBs. In interviewing low-volume IRB members and staff, we were impressed by the integrity and dedication that they have brought to the task of protecting human subjects. They have made, and continue to make, important contributions. However, systemic weaknesses exist and may be intensifying. In Table 1 and the text below, we list five of the factors presented in our prior report and review their applicability to low-volume IRBs. Subsequently, in Table 2, we address the sixth factor concerning the changing research environment.

TABLE 1: APPLICABILITY OF KEY FINDINGS FROM OUR PRIOR REPORT	
FINDING	APPLICABILITY TO LOW-VOLUME IRBS
IRBs review too much, too quickly, with too little expertise.	Moderate. Though their protocol volume has increased only slightly, workload pressures still exist due to insufficient resources. Furthermore, these IRBs tend to be isolated, with limited expertise in both scientific and ethical areas. Because they review so few protocols, reviewers’ breadth of experience with human-subject protection issues is lacking, potentially affecting their ability to discern subtle issues/violations.
IRBs conduct minimal continuing review of approved research.	Substantial. They tend to devote only a small proportion of IRB meetings to continuing review. Their isolation and limited expertise may make them less likely to identify problems; they tend to raise fewer questions and require fewer modifications. Continuing reviews are virtually all paper-based.
IRBs face conflicts that threaten their independence.	Substantial. Commercial sponsorship provides an increasingly significant source of revenue for many hospitals. This situation can intensify pressures to accommodate a hospital’s financial interests. Conflicts of interest may arise from these IRBs having one staff person acting in multiple conflicting roles. They have few community members, though they seem to have an easier time attracting nonaffiliated and nonscientific members than high-volume IRBs.
IRBs and their institutions provide little training for investigators and board members.	Substantial. Low-volume IRBs are often isolated, underfunded, and unable to provide training. Few have the funding to access outside training for members, unless they charge sponsors for reviews. Training of investigators is minimal or non-existent.
IRBs devote little attention to evaluating IRB effectiveness.	Substantial. Few perform any self-evaluation, though many were receptive to this idea. A small number have hired outside consultants.

They review too much, too quickly, with too little expertise. It appears that low-volume IRBs have not been experiencing significant increases in protocol volume.⁶ However, the paucity of these IRBs’ resources may limit their effectiveness in protecting human subjects. One IRB administrator in our sample described her IRB as merely a “function”; the board had neither specific resources allocated for it nor specific office space devoted to it. Many of the IRBs in our sample had less than one full-time employee handling all of the IRB’s administrative tasks.

Many IRB officials and experts expressed concern as to whether low-volume IRBs have sufficient expertise to recognize complex scientific or ethical issues when they arise. One IRB consultant observed a low-volume IRB review a gene therapy protocol that she considered to contain controversial ethical issues; these were not addressed by the IRB. The IRBs that review extremely low volumes of protocols may be particularly lacking in expertise. Some experts believe that IRBs that review a very small number of protocols each year do not develop what one IRB official referred to as a “perception of risk,” an intuition as to how risky one protocol is relative to others.

They conduct minimal continuing review of approved research. Low-volume IRBs tend to devote only a small portion of their meeting time to continuing review, despite the smaller number of protocols they must review. Likewise, low-volume IRBs make few modifications to protocols during continuing review. As with high-volume IRBs, more than 80 percent of these IRBs' continuing reviews are approved as submitted.⁷ The IRBs may be less inclined to alter continuing protocols because they lack vital external information, including feedback from Data Safety Monitoring Boards (DSMBs) and meaningful adverse event reports, needed for judging the ongoing safety of the study. Because hospitals represented by low-volume IRBs often enroll just one or two patients in a given multi-center trial, this dearth of external information is especially detrimental to their IRB's continuing review process.

In addition, continuing review poses special problems for many low-volume IRBs, as they often do not have an adequate infrastructure for overseeing this process. Many have difficulty tracking continuing reviews because they lack adequate resources, such as a computerized protocol management system. The annual review requirement creates particular logistical difficulties for those IRBs that meet less than once per month.

They face conflicts that threaten their independence. Commercially-sponsored protocols can generate significant revenues for participating hospitals and investigators. As a result, IRBs may experience pressures to accommodate these interests while still upholding their responsibilities to protect human subjects. Such pressures are quite relevant to low-volume IRBs, as a high percentage of their research, a mean of 33 percent of our sample in 1997, is industry-sponsored (see insert). Many IRBs reported that they have experienced "IRB shopping" by commercial sponsors, and some have felt pressure to accept research because of its potential for generating hospital revenue.

Federal government as part of Cooperative Group Protocols	37%
Pharmaceutical manufacturers or their representatives	33%
Hospital's internal sources	14%
Device manufacturers or their representatives	4%
Other Federal sources	4%
Foundations	2%
Other	6%

In addition, the limited resources available to low-volume IRBs may result in one person being responsible for several conflicting duties. We spoke to one IRB administrator who had, at one point, simultaneously acted as the data manager, clinical coordinator, and IRB coordinator for a hospital. Another IRB in our sample included among its membership the entire hospital board.

Low-volume IRBs have few nonaffiliated members, though the low-volume IRBs in our sample seemed to experience less difficulty attracting and maintaining community members for their IRBs than the IRBs in our prior research. Nonaffiliated IRB members, as we noted in our prior report, can provide a helpful counter-balance to institutional interests.

They and their institutions provide little training for investigators and board members.

Training is especially important for these IRBs, particularly those overseeing a very low volume of protocols, because they tend to be relatively isolated from the rest of the IRB community. The minimal training primarily results from a lack of resources, since many of these low-volume IRBs are only budgeted to cover basic operational costs.

Many low-volume IRBs are removed from informal information networks, such as discussions with research colleagues, and other channels generally available to IRBs at larger academic health centers. This isolation is compounded by their occasional omission from more formal information networks, such as those facilitated by NIH’s OPRR; OPRR holds educational conferences almost exclusively at high-volume multiple project assurance (MPA) institutions and sends some educational materials only to MPA institutions. In addition, many of the IRB chairs and administrators in our sample had questions about IRB regulations, but were unaware of available resources for accessing this information, such as the Public Responsibility in Medicine and Research (PRIM&R), the Applied Research Ethics National Association (ARENA)⁸, or MCWIRB, an online IRB-focused discussion forum.

They devote little attention to evaluating IRB effectiveness. Few of the IRBs in our sample have conducted internal evaluations. However, many have discussed methods, such as performing on-site reviews of the consent process and bringing in consultants, for expanding upon the current paper-based review process. The IRBs in our sample reported that they have been hindered more by the cost of these undertakings than by lack of interest in pursuing them.

They face major changes in the research environment.

TABLE 2: A CHANGING ENVIRONMENT FOR IRBS	
CHANGES IDENTIFIED IN PRIOR OIG REPORT	RELEVANCE OF THE CHANGES TO LOW-VOLUME IRBS
Increased Commercialization of Research	Substantial. Many have experienced “IRB shopping” and pressures from their institutions and/or sponsors for quick reviews for commercial sponsors.
Proliferation of Multi-Center Trials	Substantial. Adverse-event reports are difficult to interpret and sponsors provide little additional information about ongoing trials.
New Types of Research	Moderate. Though generally not involved in “cutting edge” research, many of these hospitals are expanding into new arenas of research. This research often requires new, specialized expertise and introduces new ethical issues.
Expansion of Managed Care	Moderate. Managed care is a limited, but growing presence in these hospitals. Where it exists, managed care cost pressures limit the allocation of personnel and other resources for IRB-related activities.
Increased Number of Proposals	Moderate. While these IRBs are not facing significant increases in protocol volume, lack of sufficient IRB resources may preclude them from conducting a complete and timely review of their existing workload.
Rise of Patient Consumerism	Minor. Some IRBs have encountered patient demands for certain unproven “therapies,” though most have experienced little or no patient consumerism.

Low-volume IRBs have been particularly affected by the proliferation of multi-center trials and the increased commercialization of research. These changes have introduced research into new settings, including hospitals traditionally focused on clinical care. This research often exposes IRBs to new ethical and scientific issues that may exceed their current realm of expertise. Managed care has not yet penetrated many of the hospitals in our sample and therefore has not affected their IRBs as much as IRBs housed in large academic health centers. However, almost all of the hospitals in our sample have experienced the effects of shrinking budgets and, consequently, a shortage of IRB resources. Some changes, such as patient consumerism and new types of biomedical research are not yet having a significant impact on low-volume IRBs.

Though all of the aforementioned changes have affected low-volume IRBs, these changes have had a slower and less intense impact than they have had on large academic health centers.

Conclusion

We have determined in this follow-up inquiry that the findings of our prior report are generally quite applicable to low-volume IRBs. Therefore, we reiterate the importance of the recommendations stated in that report. Although there are some differences in how and to what degree these findings apply, the overall picture that emerges clearly indicates that the call for reform we issued in our prior report applies to the broad universe of IRBs. In essence, these recommendations are as valid for community hospital IRBs responsible for reviewing a few dozen protocols a year as they are for academic health center IRBs responsible for reviewing a few thousand.

This similarity, however, does not alter the fact that low-volume IRBs have some distinctive characteristics that warrant special attention in carrying out these recommendations. The most notable of these characteristics is a sense of isolation. Although we recognize the limited resources that FDA and OPRR have to conduct educational outreach, we suggest that they pay special attention to low-volume IRBs and the issue of isolation when conducting this outreach. Such outreach could be accomplished through the issuance of FDA informational letters and OPRR "Dear Colleague" letters, the inclusion of additional material on web-sites, the preparation and distribution of special video material, or the use of existing networks, such as ARENA, PRIM&R, and cooperative research groups.

As part of these efforts, we suggest that OPRR and FDA focus on fostering collaborations between low-volume IRBs and other IRBs. Closer linkages with more experienced IRBs would strengthen their participation in the broader research community. Such collaborations might involve more experienced IRBs assisting low-volume IRBs by conducting training sessions, providing advice in special circumstances, and even in carrying out protocol reviews. We believe that the isolation of low-volume IRBs can be addressed more effectively through joint efforts among IRBs than through central initiatives by the Federal Government.

Page 7 - See Addressees Below

If you have any questions about this memorandum report, or about our work on IRBs in general, please feel free to call me or George Grob or have your staff contact Mary Beth Clarke at (202) 619-2481.

Attachment

Addressees:

Harold E. Varmus, M.D.
Director
National Institutes of Health

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration

Appendix A: Low-Volume IRB Promising Approaches

In conducting interviews with IRB chairs and administrators, we encountered a number of promising approaches for handling the substantial responsibility of low-volume IRBs. We present some of them in this appendix. In determining what to characterize as a promising approach, we depended on the judgements of IRB members, administrators, and consultants, as well as our own judgement of whether the approach was significantly novel and important to warrant attention. The innovative practices included here are specifically geared towards combating the isolation of low-volume IRBs. In addition to the promising approaches listed here, we devoted an entire prior report, *Institutional Review Boards: Promising Approaches* (OEI-01-97-00191), to describing innovative IRB practices. While most of the ideas and techniques identified in that report were found in large academic health centers, we believe that many of those promising approaches could also be applied to low-volume IRBs.

We did not independently evaluate any practice highlighted in this appendix. Furthermore, a practice's inclusion does not necessarily mean that it receives our stamp of approval; nor are we claiming in highlighting a promising approach at one institution that other institutions have not developed similar approaches. We intend to provide a snapshot of the types of innovations taking place in IRBs in order to fuel discussion among interested parties; it is by no means a definitive study of all IRBs.

Using consultants

Procedural. Several IRBs have brought in outside consultants, generally people who have been IRB professionals at large, academic medical centers for many years, to advise on ways that the IRB could improve its efficiency and effectiveness. These consultants bring a broad perspective and a great deal of knowledge and experience to low-volume IRBs, both in substantive areas, such as the ethics of human-subject research, and in procedural issues relating to IRBs. These consultants' recommendations tend to be much more performance-based than those espoused by FDA inspectors. All of the IRBs in our sample who had hired consultants found them helpful.

Scientific. In order to ensure the quality and appropriateness of a protocol, one IRB chair often asks a hospital physician, who specializes in the same field as the investigator submitting the protocol in question, to review that protocol. He finds this to be an effective way to verify the robustness of the design, the accuracy of the specialized information, and the relevance of this study in light of current work in the field.

Training at nearby hospitals

Though low-volume IRBs tend to have little, if any, budget to provide training for investigators and/or members, many of these IRBs are located close to research hospitals which do sponsor such training. One IRB in our sample regularly provides opportunities for members and investigators to attend training sessions at a local large academic medical center.

Including an experienced member of a local high-volume IRB on a low-volume IRB

One way of combating the sense of isolation that many of these low-volume IRBs feel is to recruit someone who sits on the IRB of a nearby high-volume hospital onto their own IRB. Including a “dual” member on their IRB is a low-cost method for low-volume IRBs to stay abreast of ever-changing practices and regulations. The IRB in our sample that included such a member reported that this member added an unprecedented continuing education component to their meetings. Furthermore, she had invited any interested members to a meeting at the high-volume IRB on which she also serves, to observe their procedures and witness how they handle certain issues.

Charging commercial sponsors

Some have begun charging a small fee to commercial sponsors. IRBs have reported using this money for a wide array of IRB-related activities including education and training of members. However, we recognize that, although this generates needed funds for many of these IRBs, it places much of the financial burden on commercial sponsors. Although such a practice potentially could create tensions between investigators and commercial sponsors, the IRBs currently engaging in this practice report that charging a fee to commercial sponsors has not discouraged any research thus far.

Appendix B: Endnotes

1. The general recommendations from our prior report, *Institutional Review Boards: A Time for Reform* (OEI-01-97-00193), were directed jointly to NIH and FDA, and are listed below. Each of these was followed by a number of more specific operational recommendations.

- Recast Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable for results.
- Strengthen continuing protections for human subjects participating in research.
- Enact Federal requirements that help ensure that investigators and IRB members are adequately sensitized to human subject protections.
- Help insulate IRBs from conflicts that can compromise their mission in protecting human subjects.
- Recognize the seriousness of the workload pressures that many IRBs face and take actions that aim to moderate them.
- Reengineer the Federal oversight process.

2. There are a number of low-volume independent IRBs that are not part of a hospital organization. Although we do not consider independent IRBs in this memorandum, they are examined in our prior report, *Institutional Review Boards: Emergence of Independent Boards* (OEI-01-97-00192).

3. National Council on Bioethics in Human Research, “Protecting and Promoting the Human Research Subject: A Review of the Function of Research Ethics Boards in Canadian Faculties of Medicine,” *NCBHR Communique CNBRH*, Vol.6 (1995) No.1. This Canadian commission report raised concerns about low-volume IRBs, stating that those that oversee a very low number of protocols are unable to conduct reviews with adequate breadth and depth. The report recommended that IRBs which review less than 50 proposals annually should merge with an IRB from another institution.

4. Total annual initial reviews include both full board and expedited reviews.

5. NIH Office of Extramural Research, “Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects,” June 15, 1998. This is a broad, data-rich survey of 491 IRBs that held multiple project assurances (MPAs) in 1995.

6. For the IRBs in our sample, initial reviews increased by a mean of 16 percent between 1993 and 1997, in contrast to the 42 percent increase found at the 6 academic medical centers cited in our previous report.

7. NIH Office of Extramural Research, “Evaluation of NIH Implementation of Section 491 of the

Public Health Service Act, Mandating a Program of Protection for Research Subjects,”
June 15, 1998.

8. The Applied Research Ethics National Association (ARENA) is a subsidiary of the Public Responsibility in Medicine and Research (PRIM&R), which is a nonprofit organization dedicated to promoting the ethical conduct of research. ARENA is a professional association whose members include administrators and members of Institutional Review Boards and Institutional Animal Care and Use Committees.