

Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards

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Clinical research has undergone remarkable and beneficial expansion in the past 25 years, but with this growth has come an unprecedented increase in workload for the human subjects protection system. Recently, a major change in federal oversight of local Institutional review boards (IRBs) became evident. Although it was not announced publicly, in 1998 and 1999 federal regulatory actions against local IRBs increased threefold. Particularly notable was the marked increase in regulatory actions taken against the IRBs of academic medical centers (1 in 1997 compared with 14 in 1999). Ironically, this apparent federal crackdown began at the same time that two federal review panels called for major changes in the regulations governing local IRBs. A key factor in the current crisis in the function of local IRBs is the ascendance of multicenter clinical trials as the dominant form of

clinical research. Local IRBs were not designed to handle the initial evaluation and ongoing review required by the rapidly increasing number of multicenter clinical trials. Furthermore, local IRB review of the thousands of safety reports from multicenter clinical trials monopolizes resources without promoting patient safety. Instead of rigid enforcement of outmoded regulations that do not contribute to patient safety, the responsibilities of the local IRB in the oversight of multicenter clinical trials must be systematically evaluated.

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In September 1999, all human studies were suspended at our medical center, the University of Colorado Health Sciences Center. This action was taken by the U.S. Food and Drug Administration (FDA) and the Office for Protection from Research Risks (OPRR) because issues raised in a previous audit of the local institutional review board (IRB) had not been adequately addressed. As clinical investigators, we were shocked to find our institution in this situation. Clinical trials evaluating innovative treatments were interrupted for 4 months, and even now, the effects of the suspension linger.

Our purpose is not to contest the specifics of the suspension at our institution. Although we disagree with some aspects of the present IRB system, our institution had a responsibility to follow that system and failed to do so. The IRBs of other medical centers have also had similar suspensions or warnings in the past few years. Our purpose is to examine the problems underlying recent federal regulatory actions against IRBs.

FEDERAL OVERSIGHT OF LOCAL IRBS

All federally sponsored human studies, except those meeting specific criteria for exemption, and human studies of drugs or devices regulated by the FDA must be reviewed by an IRB. The IRB system was developed

in the 1970s in response to studies with reprehensible disregard for the safety and autonomy of patients (1, 2). Most IRBs in the United States exist locally, at the 3000 to 5000 academic medical centers, hospitals, and clinics carrying out clinical research (3). Because there is no central registry, details on the number and types of IRBs in the United States are not available (4).

Federal regulations, which are administered by FDA and OPRR (recently reorganized as the Office for Human Research Protections), specify the composition and function of IRBs (5-7). The required components of IRB activity include review of fundable federal grant proposals (8), review of research protocols involving humans, approval of consent forms, and monitoring of ongoing studies ("continuing review") at least annually (7).

MULTICENTER CLINICAL TRIALS AND LOCAL IRBS

Clinical research has undergone remarkable expansion in the past 25 years. According to one estimate, the number of protocols submitted to local IRBs increased 42% in just 5 years (3). Most of the expansion in clinical research has been in the form of multicenter trials (3), which present major problems for a local IRB. In addition to the sheer volume of protocols to consider, multicenter trials generate thousands of safety reports (on death and hospitalization, for example) because of

the treatment, the severity of the disease, or the large numbers of participants.

These protocols and safety reports are reviewed by an organization analogous to a jury. Local IRBs must include members from outside the institution, science, and medicine; in fact, no action of a local IRB is valid unless at least one designated "nonscientific member" is present (7). Although the IRB staff may devote their full attention to oversight of research, the members themselves, by design, do not. Given this constraint, simple mathematics illustrates the "pressure cooker atmosphere" (9) faced by local IRBs.

Assume that an academic center has 500 new and 1000 ongoing studies per year (3, 9). All of these studies are to be reviewed by two IRBs, each of which meets 22 times per year for 3 hours per meeting. Assuming that new protocols require twice as much time to review as continuing studies, the IRB has 8 minutes per new study (11.4 per meeting) and 4 minutes per continuing review (22.7 per meeting). This simple analysis does not allow for time spent on any activity other than consideration of protocols requiring full committee review and probably overestimates the time available for protocol review. Indeed, a recent federal review found that the average local IRB meeting lasted 2.5 hours and included 18 initial reviews, 9 expedited reviews, 43 amendments, and 21 safety reports (3).

FEDERAL REGULATORY ACTIONS AGAINST LOCAL IRBs

Although it was not announced publicly, federal oversight of local IRBs recently underwent a major change (4). The number of regulatory actions by FDA and OPRR tripled from 1997 to 1999, and regulatory actions against academic medical centers increased even more sharply (1 in 1997 compared with 14 in 1999). Given the problems of local IRBs, some might suggest that the increase in regulatory actions is fully justified, even overdue. We counter that they represent the cracks in a system overloaded by outmoded regulations.

The key findings in the warning letters sent to local IRBs by the FDA (available at www.fda.gov/foi/warning.htm [accessed 12 November 2000]) and the OPRR (which can be obtained through a Freedom of Information Act request) in 1999 are summarized in the Table. Prominent among them are lack of substantive continuing review and inadequate review of safety reports.

Table. Reasons for Regulatory Actions by the U.S. FDA or the Office for Protection from Research Risks against Local IRBs during 1999*

Reason	Local IRBs Cited, n†
Inadequate documentation	17
Inadequate continuing review of previously approved protocols	16
Inadequate written procedures	15
Inappropriate use of expedited review or inappropriate waiver of consent	15
Deficient consent forms	12
Inadequate review of safety reports	8
Inadequate attention to vulnerable populations	7
Inappropriate voting procedures‡	6
Inadequate training of IRB members or investigators	6
Failure to review required changes	5
Other§	10

* FDA = Food and Drug Administration; IRB = institutional review board.

† Data are from 22 IRBs. All were cited for more than one infraction.

‡ Lack of quorum, lack of nonscientific member, and failure to assure that IRB members with a conflict of interest do not vote.

§ Includes inadequate staff, inadequate initial review, lack of diverse membership, and failure to review grant applications.

These actions are mandated in federal regulations and would seem to be critical to protecting patients in clinical trials. However, recent reviews by the Office of the Inspector General of the Department of Health and Human Services and a panel of the National Institutes of Health (NIH) concluded that the continuing review process should be completely reevaluated and that local IRBs should not be required to review off-site safety reports (3, 10).

LOCAL REVIEW OF SAFETY REPORTS FROM MULTICENTER CLINICAL TRIALS

The following example illustrates the problems of local IRB review of safety reports from multicenter trials. Adefovir, a drug with promising in vitro activity against HIV, hepatitis B, and several herpesviruses (11), was well tolerated in early clinical studies. However, when adefovir was given for more than 6 months, 17% to 35% of patients developed renal toxicity (12, 13). As a result, an FDA advisory panel recommended against approval, and the manufacturer stopped development of adefovir for HIV treatment. (Much lower doses are being evaluated for treatment of chronic hepatitis B.) The system worked: A promising agent was evaluated in a controlled fashion, and an unexpected toxicity was identified and appropriately managed. However, local IRB review played no role in this sequence of events. The

renal toxicity was identified at the data centers of the randomized trials, and warning letters were promptly sent to investigators.

Although some might take this example as further evidence of the need for local IRBs to perform substantive review of safety reports, the failure of local IRBs to detect renal toxicity of adefovir is inherent in the system. Even if given unlimited time and resources, local IRBs could not critically evaluate safety reports from multicenter trials because they lack the data elements needed for meaningful analysis: the denominators and study assignment. Without these key pieces of information, off-site safety reports become a flood of anecdotes with little meaning. For example, as clinical investigators, we reviewed and filed with the local IRB a stack of adefovir safety reports 10 inches thick; however, the aggregate was less informative than the two-page warning letter from the data centers. As summarized in the NIH review, "receipt of data that are neither aggregated nor interpreted does not provide useful information to the IRB to allow it to make an informed judgement on the appropriate action to be taken, if any" (10).

Patient safety in multicenter trials is monitored appropriately by central data management organizations and Data and Safety Monitoring Boards, which are composed of experts in the disease being studied and the conduct of clinical trials (14–16). All NIH-sponsored phase III trials are reviewed periodically by Data and Safety Monitoring Boards (10); this requirement could be extended to industry-sponsored studies.

The analysis of safety reports from multicenter trials illustrates an important theme of our concerns about research oversight: This function is critical, but it should not be a responsibility of the local IRB. The report of the Office of the Inspector General recognized this key point and recommended that federal agencies change the regulations governing local IRBs: "The NIH/OPRR and FDA should work with IRBs and others in identifying the specific Federal requirements to be eliminated or modified" (3).

LOCAL IRB REVIEW OF MULTICENTER CLINICAL TRIALS

Local IRB review of off-site safety reports from multicenter trials is an example of an unnecessary redundancy that ties up the current system. Are there other such redundancies? It is reasonable to ask whether local

IRBs play any meaningful role in multicenter trials. The content of federally sponsored multicenter protocols is extensively reviewed before development of a final version for study sites. As a result, it is unlikely that a local IRB will have substantive objections to the scientific content of such studies. We are uncertain whether the same considerations apply to industry-sponsored trials. There is certainly a need for IRB review of multicenter trials, but it is not clear that patient safety is enhanced by duplicating this process at the IRB of every study site.

Even the much-touted role of local IRBs in assuring that consent forms be appropriate for the local population is questionable. Studies in the past 20 years demonstrate that most consent forms are written at an inappropriate reading level for most patients (17–19) and are not improved by local IRB review (20). A well-formulated central IRB with expertise in the communication of complex material may assure more appropriate consent forms than overburdened local IRBs can. For example, the National Cancer Institute used a multidisciplinary team to develop a template that markedly simplifies the language of consent forms (21). Moreover, OPRR guidelines appropriately point out that informed consent should be an ongoing process; patients should be promptly informed of changes as new information becomes available (22). The current system, in which all changes to consent forms must be reviewed by multiple local IRBs, impedes this important aspect of informed consent. Finally, the translation of consent forms into the native languages of the target patient populations, an important part of informed consent, would be dramatically easier if all study sites used a standardized consent form.

Local review of multicenter protocols certainly has negative effects (23, 24). A questionnaire-based study on the effect of birth weight on child development required submission of 1095 copies of the protocol, 1116 forms, and additional supporting documents to 145 IRBs in the United Kingdom (25). Responses to this remarkably duplicative process varied greatly, including diametrically opposed mandates (26), and 22% of the IRBs had not responded within 3 months. Comparable data have not been reported from the United States, but our experience suggests that valuable research is unduly delayed here as well.

Finally, we are concerned that involvement of local IRBs in all aspects of multicenter clinical trials overloads

the system, and as a result the local IRB cannot carry out the functions it uniquely can perform. Some of the most worrisome lapses in protection of human subjects in the past decade involved abuses in the process of obtaining informed consent, not the wording of informed consent documents (27). Preventing these kinds of abuses may require such actions as on-site monitoring of the process of obtaining informed consent, not additional paperwork.

ALTERNATIVES TO THE CURRENT SYSTEM

We believe that the information in the Table does not reflect a crisis in human subjects protection but rather a crisis in local IRB function brought on by the administrative burden of multicenter clinical trials. How can this crisis be resolved? Independent IRBs, which oversee geographically dispersed study sites, have become more common in the past decade and are increasingly being used for industry-sponsored studies (28). Independent IRBs probably work more quickly than local IRBs, but there are appropriate concerns about the conflict of interest that may occur when the IRB is paid directly by the sponsoring pharmaceutical company (28). Additional safeguards may be necessary to ensure that the members of such IRBs are insulated from pressure by study sponsors.

The United Kingdom instituted a two-tiered system in which regional IRB review of multicenter protocols is followed by expedited local review. In its first year of operation, this system had mixed results (29, 30), but it may improve oversight of multicenter trials. In the United States, regulations permit one IRB to delegate its oversight responsibility for a study to another IRB (5), allowing centralized review of multicenter clinical trials. The National Cancer Institute is undertaking a pilot evaluation of a central IRB (31). The optimal mix of central and local review of multicenter trials has not been identified, but the failings and inefficiencies of the current system demand innovation.

What, then, is the appropriate role of the local IRB? In our view, it includes training of investigators in performance of ethical clinical research (such as confidentiality and elements of informed consent), observation of methods used to recruit and enroll patients, and more detailed review of research performed solely within that institution. The safeguards built into the present system

for multicenter trials do not extend to intramural research. If unburdened of the meaningless aspects of oversight of multicenter trials, the local IRB should have the time and resources to do these tasks well.

THE IMPORTANCE OF CLINICAL TRIALS

Many controversies exist in the ethics of clinical research (32), but we do not regard any of the foregoing discussion as a disagreement over ethics. The issue is how best to assure patient safety and autonomy in clinical trials, not whether it is necessary to do so. Furthermore, we must remember that well-conducted research protects the general patient population from very real risks—those of unproven therapy.

A defining characteristic of western medicine is the willingness to subject appealing hypotheses and treatments to rigorous evaluation in clinical research. The history of medicine provides numerous examples of promising medical or surgical treatments that harmed rather than helped (33, 34). An additional lesson from medical history is that promising treatments will be implemented regardless of whether they have been rigorously evaluated. The medical profession and the public demand innovative approaches to human disease, and this demand will not be regulated out of existence (35). Several treatments and procedures that are commonly used today in the absence of data from controlled trials generate substantive concerns about patient safety (36, 37).

Therefore, from the standpoint of patient safety, the regulatory system should encourage more well-designed clinical research, not less. We are concerned that the long-term result of the federal crackdown on local IRBs will be a decrease in clinical research as the process becomes increasingly slow and burdensome. The effects of such a slowdown in clinical research could include increased use of off-label treatments that have not been rigorously evaluated in clinical trials.

We are in the midst of revolutionary developments in medical diagnostics and therapeutics, but these new tools must be evaluated in clinical trials. A critical but neglected part of the infrastructure to perform these trials is the IRB system. Local IRBs are in crisis, trapped between demands for more clinical research and the requirements of federal regulations that were not designed for multicenter trials. This problem will not be solved through more vigorous enforcement of outmoded regu-

lations; rather, we need a thorough overhaul of the system, in which the parts that monopolize resources and do not contribute to patient safety are modified or eliminated.

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