Sounding Board

A Central Institutional Review Board for Multi-Institutional Trials

THESE are difficult times for the nation's system of protection for human subjects in research.[1-10] On the basis of a series of reports, the Office of the Inspector General of the Department of Health and Human Services concluded that institutional review boards (IRBs) are now forced to "review too much, too quickly, with too little expertise," and with inadequate resources.[6] One consequence is that there is minimal, often perfunctory, review of ongoing research. In addition, IRB members have become disillusioned as a result of both public criticism concerning the perceived failures of the boards and the increasing amount of time required to perform duplicative tasks that add little to the safety of patients.[11,12]

We believe that the effectiveness of IRBs has been undermined by many factors that are, in part, the consequence of a system that has failed to adapt to major changes that have occurred in the research environment since the IRB system was established in the 1970s. These changes include a shift from predominantly federally funded studies performed at single academic centers to large multicenter trials of complex treatments involving both federal and private sponsors.[1,6,7,13-15] The Bell Report for the National Institutes of Health described the staggering annual workload facing 491 IRBs, including an estimated 284,000 reviews: 105,000 initial reviews, 116,000 annual reviews, and 63,000 amendments. It also noted that the annual full-board meeting time ranged from 9 to 50 hours and that the average time devoted to discussion of the initial review of a protocol was 21 minutes for low-volume IRBs and 3 minutes for high-volume IRBs.[2] Elsewhere in this issue of the *Journal,* Steinbrook discusses many of the problems that must be solved to improve the protection of research subjects.[16] We describe a possible solution to some of these problems — namely, a novel model, now in the pilot phase, for the review of multicenter phase 3 trials that involves the use of a central IRB (CIRB) and a facilitated review process. The model was developed by the National Cancer Institute (NCI), in collaboration with the Office for Human Research Protections, as part of a larger initiative to improve the NCI's clinical-trials program.

ORIGINS OF THE CENTRAL REVIEW BOARD

The CIRB project arose as a means of increasing patients' access to and enrollment in NCI-supported clinical trials. NCI is the largest sponsor of clinical trials of treatment for cancer in the United States, but only 2 percent of patients with newly diagnosed cancer (30,000) participated in NCI-sponsored cancer-treatment trials in 2001. Patients are more likely to participate in a trial if their physicians are investigators, but physician-investigators argue that the burdens associated with securing approval from the local IRB for these studies limit their interest in participation, particularly if only a small number of patients will be enrolled at a particular site. These burdens include long and complex application and review processes and the substantial time required to obtain approval, estimated to be 5 to 14 hours.[2] The recent imposition of fees for review by some IRBs creates yet another obstacle.[13,17]

The burdens that IRB review places on investigators are neither unique to the NCI program nor necessarily persuasive that change is needed. Nonetheless, in the context of large multicenter trials, they call attention to serious problems of duplication of effort and inefficiency associated with numerous local reviews of the same trial — problems that have also been noted by others.[11,12] For example, the NCI has a total of more than 10,000 registered investigators at almost 3000 individual sites. Each year, there are approximately 160 ongoing phase 3 trials, of which 30 are new trials. Conservatively estimated, the average number of clinical sites participating in each trial is about 100 (range, 4 to 809), although many trials have several hundred sites; thus, at a minimum, 16,000 IRB reviews of NCI phase 3 trials are conducted each year (3000 initial reviews and 13,000 annual reviews of ongoing trials). In addition, IRBs perform an estimated 20,000 reviews of protocol amendments and thousands of reviews of adverse events each year. These numbers will only increase as the NCI implements additional initiatives designed to expand patients' access to clinical trials. At a time of growing concern about the adequacy of an overburdened system for the protection of research subjects, the benefit of these obviously duplicative and seemingly wasteful efforts must be weighed against the cost, especially the distraction of local IRBs from the essential task of effectively monitoring local research. The CIRB project has been structured to address many of these concerns.

THE CENTRAL REVIEW BOARD AND FACILITATED REVIEW

The CIRB pilot project provides an expert IRB review of NCI-sponsored trials at the national level before protocols are distributed to local investigators. Local IRBs can then approve the protocols rapidly, using a facilitated review process based on the CIRB review. A number of regulatory agencies, including

the Food and Drug Administration (FDA) and the Office for Human Research Protections, have agreed that this approach is in compliance with relevant federal regulations. Furthermore, the Office for Human Research Protections has made the important determination that a facilitated review may be conducted by the chairperson of the local IRB or by an IRB subcommittee after the CIRB materials have been reviewed. Thus, the protocol can be approved quickly and efficiently. Locally, facilitated review could make it possible for many more physicians and their patients to participate in trials by making them accessible within days rather than months. If this approach were instituted throughout the national IRB system, it would reduce vast amounts of duplication of effort and allow IRBs to address truly local matters, such as oversight of local studies.

The CIRB is composed of 16 members with expertise in cancer from across the country. None are NCI employees, most attend the monthly CIRB meetings in person (some participate by teleconference), and each receives a $200 honorarium for attending meetings. Drawn from both academic and community organizations, the members include physicians, nurses, and pharmacologists with expertise in the treatment of cancer; ethicists; and patient advocates. The composition of the board satisfies federal regulatory requirements and the recommendations of the National Bioethics Advisory Commission, which specify that at least 25 percent of the membership should represent the perspective of research participants, be engaged primarily in nonscientific activities, or both.[8,18] The work of the CIRB is coordinated by an experienced NCI administrator and five full-time staff members. The pilot program initially involved 22 local institutions and is currently expanding to include 100. The division of responsibilities between the CIRB and each local IRB is spelled out in a formal agreement between the two entities and also in detailed standard operating procedures (available at http://www.ncicirb.org).

The CIRB has reviewed all NCI-sponsored phase 3 treatment trials involving adults with cancer that have been initiated since January 2001. The board's review functions are essentially identical to those of a local IRB. It performs an initial review of each new protocol; discusses any issues with the sponsor, coordinating cooperative group (an NCI-funded multicenter organization that develops protocols and conducts research), and study chair for the protocol; and makes a final decision whether to approve the protocol. The CIRB also reviews annual study reports, reports of serious adverse events, protocol amendments, reports by data and safety monitoring boards, and other documents. All review materials, including the application for approval of the study, protocol reviews, relevant correspondence, and minutes of meetings, are made available to the local IRBs participating in the pilot program.

The Office for Human Research Protections requires that IRB reviews of federally sponsored research involving human subjects, such as NCI trials, reflect an understanding of the local context in which the research occurs. This requirement must be met even if one IRB reviews protocols on behalf of another IRB. To comply with the local-context requirement, the CIRB uses a local-decision-maker approach, in which the local IRB decides, on a protocol-by-protocol basis, whether there are relevant issues involving the local context that must be addressed and whether a facilitated or full local review is warranted. A decision to perform a facilitated review makes the CIRB the review board of record responsible for annual reviews and for reviews of adverse events and protocol amendments. As appropriate, the local IRB may specify local restrictions, stipulations, or substitutions in protocols and informed-consent documents that have been approved by the CIRB. However, deletions or substantive changes that affect the meaning of CIRB-approved protocols or consent documents are not allowed. Changes in consent documents are monitored as part of periodic audits of NCI-sponsored trials.

The local institution and IRB are required to ensure that the research is performed safely and appropriately. They must assess the suitability of the local research environment for the proposed research; make sure that the investigators and other research staff receive training in the protection of human subjects and meet the institution's standards for the conduct of research; monitor the conduct of the study; review serious adverse events occurring at the local institution; and provide a mechanism for handling complaints by local subjects or others. The CIRB must be notified of steps taken to address problems in these areas.

In theory, the CIRB model should also substantially improve the review of adverse events in multicenter trials. In the current scheme, a local IRB must review reports of serious adverse events that occur at all participating sites; the sheer volume of these reports and the administrative burden may distract the IRB from the serious adverse events that actually require its attention.[11,12,19,20] In the CIRB model, the central board evaluates all individual adverse events in the context of the entire clinical trial and on the basis of supplemental toxicity information provided by the NCI. Such a comprehensive review is seldom possible at the local level.

EARLY EXPERIENCE WITH THE CENTRAL REVIEW BOARD

In its first year, the CIRB reviewed 20 protocols; 17 were approved with modifications, 2 required

substantive revisions before they were approved, and 1 is still being reviewed. For reasons unrelated to the CIRB program, most of these studies have not been initiated at the 22 local institutions participating in the pilot program. Because access to protocols has been based on membership in specific cooperative groups, local investigators have not sought approval from their local IRBs for many of the 19 approved protocols that were not developed by their cooperative group. As of March 2002, local IRBs had performed facilitated reviews 15 times (at six institutions) and had elected to conduct full reviews 25 times. With the planned expansion of the CIRB program to include 100 local sites over the next several months and the availability of all new trials to any cooperative-group investigator by June 2002, more useful data on the rate of utilization and on satisfaction with facilitated review should be available in 12 to 18 months. A formal evaluation of the process by the participating IRBs will be performed at that time.

The members of the CIRB are satisfied with the board's operation in its first year. The CIRB reviews only two or three new protocols each month. This workload allows for in-depth discussion of each protocol, annual reviews of ongoing trials and adverse events, and educational sessions during regularly scheduled meetings. The diverse perspectives and expertise of the board's members have resulted in a rich discussion of issues that is unmatched by many local IRBs. For each study it reviews, the CIRB has ready access to the study chair and to experts at the NCI who can answer questions during the review process. This level of access is rarely available to local IRBs, which must usually rely on information provided by local investigators who may have had little to do with developing the study and may therefore have a less thorough understanding of the rationale for the study, its design, or other issues that IRBs often address.

The logistic difficulties and complexity of communicating rapidly and effectively with all parties involved in large multi-institutional trials pose substantial challenges. The pilot experience has resulted in the implementation of a detailed communications plan to help ensure that the CIRB communicates as required with local IRBs, data and safety monitoring boards, local investigators, cooperative groups, the NCI as the sponsor of the trials, and others. A controlled-access Web site (http://www.ncicirb.org) has been developed to provide reliable electronic access to the many documents that the CIRB generates.

FUTURE CHALLENGES

A major challenge facing this new system is to define and adjudicate overlapping responsibilities. All proposed NCI protocols undergo several layers of scientific and ethical review by committees within the cooperative group and the NCI, as well as by the FDA (if an investigational agent is involved). These reviews address the scientific hypothesis, the study design, ethical issues, and the informed-consent document. In addition, all NCI-sponsored phase 3 trials are monitored by independent data and safety monitoring boards. These boards and the IRBs explicitly share responsibility for ensuring the safety and well-being of enrolled subjects, though the data and safety monitoring boards have a more comprehensive view of accumulating data, since they have exclusive access to unblinded data on efficacy, as well as data on adverse events and safety. The data and safety monitoring boards have a key role in ensuring the safety of subjects and assessing the relative risks and benefits of participation throughout the clinical trial. Lack of clarity about the appropriate division of responsibility between IRBs and data and safety monitoring boards is an important issue[12,20] that has not been fully resolved. In any case, the hope is that better communication between the data and safety monitoring board for a particular study and the CIRB will address the problem of overlapping responsibilities, further improve the protection of subjects, and ensure that informed-consent processes and protocols are modified appropriately to reflect relevant new knowledge.

The scientific expertise of many of the CIRB members raises the question of the boundary between a review of the scientific aspects of a study and a review of the ethical aspects. Some believe that the CIRB should address only safety and ethical issues, because all NCI-sponsored trials of cancer treatment pose reasonable scientific questions and have reasonable designs or they would not have survived the extensive scientific review to which they have already been subjected. Others argue that scientific merit and trial design are directly related to the risk–benefit assessment and are appropriate areas for review by either a local IRB or a CIRB. Although the CIRB should avoid imposing its views when dealing with issues about which reasonable people may disagree, the disease-specific scientific expertise of the board members increases the likelihood of controversies in the gray zone between safety and science. During its first 16 months of operation, the CIRB has already confronted these issues (as well as conflict over its role in ongoing reviews versus that of a data and safety monitoring board). Because the CIRB is the final committee through which all NCI-sponsored phase 3 trials must pass before they are activated, it has unprecedented power and authority. It will be crucial to pay careful attention to these issues. The selection of CIRB members with extensive IRB experience may help diminish conflicts in this realm.

The success of the CIRB pilot program ultimately

depends on the extent to which local IRBs use the facilitated review process; at present, their willingness to do so is uncertain. If large numbers of local IRBs decide to perform full rather than facilitated reviews, the CIRB will simply be another layer of review in an already multilayered process. In the increasingly complex regulatory environment of clinical research, local IRBs, or the institutional officials responsible for them, may be reluctant to relinquish responsibility to an independent body. Institutional concern about legal liability and indemnification may work against full participation in the new program, even though it is clear that fundamental changes in the system for the protection of research subjects are necessary.

As Steinbrook points out, a high-quality IRB review, although necessary, is unlikely to guarantee the full protection of research subjects.[16] This responsibility is truly shared, depending on the efforts of tens of thousands of persons throughout the country. The extent to which the many parties involved acknowledge this shared responsibility and work collaboratively may ultimately determine whether the complex review system actually improves the protection of research subjects. Local IRBs will remain a key component of the system, however, and it is clear that we need a more effective approach than the current one, which places too large a burden on local IRBs. We believe that the facilitated-review model for large national trials is a promising approach that preserves local autonomy and responsibility with regard to local matters, reduces the workload of local IRBs, and eliminates duplication of effort. An expert, central review of planned and ongoing research frees local IRBs to oversee the performance of studies at the local level, thus capitalizing on the strengths of both the central and the local systems and improving the overall protection of research subjects.

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