POLICY FORUM: MEDICAL RESEARCH

Oversight Mechanisms for Clinical Research

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The mounting reservoir of biomedical research discoveries applicable to health, the rapid expansion of the pharmaceutical and biotechnology industries, and the movement toward evidence-based medicine have ensured that clinical research in the United States will play an increasingly dominant role in the future of medical practice. However, the need to conduct clinical research has far outpaced its research support infrastructures, training programs, and potentially the means for assuring the protection of human subjects.

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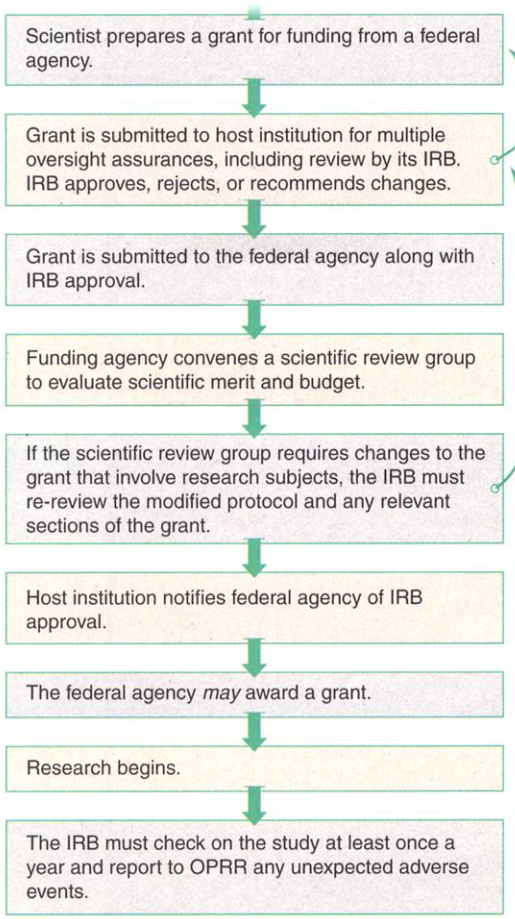
Challenges

Several forces impinge upon the ability of researchers to conduct clinical investigations, including the existence of increasingly complex and costly oversight mechanisms. The historic Tuskegee and Willowbrook (*1*) studies, the recent report on radiation experiments done without participant consent (*2*), and the tragic death of the participant in a recent gene therapy trial have heightened public concerns and have resulted in increased scrutiny of clinical research. The atmosphere of mistrust has been further aggravated by media coverage of physicians who supplement their incomes through inappropriate recruitment of subjects for clinical trials (*3*) and, more generally, of the potential conflict between patients' interest and the financing of clinical research (*4*).

As our understanding of human therapeutics has evolved, clinical trials have become increasingly complicated. The desire to ensure the validity of clinical trials combined with the need to protect human subjects has led to the proliferation of regulatory requirements and documentation. Because of the complexity of the conduct and regulation of clinical research, clinical investigators need formal training in this area, and an infrastructure must be developed and maintained that will assure protection of human subjects (*5*).



Lengthy path toward clinical research.

History of Regulation

Given the explosive growth of clinical research in the last two decades, it is not surprising that the development of uniform standards for patient protection, at both the oversight level and at research institutions, has lagged behind the expanded need. The Office for Protection from Research Risks (OPRR) was established in 1972, a time when most clinical research studies were conducted by individual or small groups of investigators dealing with small groups of subjects. This office, with a current annual budget of only $2.7 million, is now responsible for studies at more than 4000 federally funded universities, hospitals, and other medical and behavioral research institutions, both in the United States and abroad. The responsibility for these issues in industry-sponsored research is handled by the Food and Drug Administration (FDA) divisions dealing with specific clinical trials. All research involving human subjects is also reviewed at the local level by the Institutional Review Board (IRB), in addition to oversight provided at the national level by OPRR or FDA. For clinical research not involving investigational drugs, biologics, or devices, and which is not federally funded, the local IRB alone bears all of the oversight responsibility.

Although all federal agencies operate under the 1971 U.S. Department of Health, Education, and Welfare Guidelines (codified into Federal Regulations in 1974), which guide all research on human subjects, the majority of federally sponsored clinical trials are funded by the Department of Health and Human Services (DHHS), which includes the National Institutes of Health (NIH) and the Agency for Health Care Policy and Research (AHCPR). In many instances, both OPRR and FDA oversee the same trial. This parallel development of oversight bodies has led to duplication of reviews and some variance in the interpretation of regulations. For example, OPRR requires that IRBs review the entire NIH grant along with the clinical research protocol, and the FDA does not.

Growth of Clinical Research and the Experience at Duke University

Although the proportion of clinical research done at academic health centers (AHCs) has declined relative to the private sector, the absolute amount has skyrocketed, with about $5 billion per year going to academic institutions. Indeed, nearly 40% of sponsored research at AHCs is funded by industry and other nonfederal sources, and most of this represents clinical research. The growth rate of clinical research at Duke University exceeds the national numbers. In 1974, the year Duke's IRB was established, clinical research accounted for only a small fraction of overall research funding. Today, that figure is in excess of $100 million per year. Similarly, 400 protocols were reviewed in 1974; today, about 2200 protocols are reviewed annually.

Periodically, OPRR representatives evaluate research institutions by making site visits. In December 1998, during a routine visit to Duke University, reviewers identified 22 administrative deficiencies

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(*6*) (inadequate education of IRB members and clinical investigators, insufficient documentation in minutes of discussions during IRB meetings, potential conflict of interest of two IRB members, not recording quorum counts for votes on protocols, inadequate administrative support, failure to review the entire NIH grant along with the clinical trial protocol) in need of remediation. In February, a plan for corrective action that included addressing OPRR's points, as well as the addition of a second IRB and additional investments in IRB administrative infrastructure, was submitted to OPRR. We were corresponding with OPRR about implementation of that plan when, on 10 May, OPRR notified us that they were suspending our Multiple Projects Assurance (MPA) immediately. (An institution submits an MPA document for approval by OPRR as an assurance of the institution's commitment to comply with the regulations of the DHHS for the protection of research subjects.) Without an MPA, DHHS-funded multiple trials cannot be conducted (*6*).

We had not anticipated such an action by OPRR. Through much effort on the part of our faculty and administrative staff, and with the assistance of OPRR, we modified and accelerated our corrective action plan, and our MPA was reinstated 4 days later. As difficult and expensive as this experience was for our institution, we learned a great deal and have suggestions about how oversight can be improved.

Observations and Recommendations

We endorse oversight mechanisms that protect research subjects to the maximum degree possible. Nonetheless, it is our view that regulatory and compliance mechanisms are overly complex, difficult to interpret, and, at times, redundant or inefficient. Some regulations are ambiguous and may offer no added protection for subjects. Unnecessary procedural requirements increase costs and distract already overworked IRB members from focusing on the protection of human subjects. For example, current processes require IRBs to review fully all submitted grant proposals. As the success rate for new R01 grants was 20% in 1998 (*7*), the majority of proposals reviewed by IRBs are not carried out.

Little attention has been paid to the value of various oversight regulations, some of which may not contribute to fostering quality clinical research and appropriate study subject protection. An example of a questionable requirement is the need for the IRB to review the entire NIH grant (including budget) along with the clinical research protocol.

We recommend a comprehensive and broadly based review of federal regulations to protect human subjects, with the goal of creating a single set of effective federal regulations. Regulations that add additional work and/or cost without providing clear benefit should be eliminated. Periodic updating (e.g., biannual) and the development of methodologies to gauge effectiveness are also needed.

Multiple oversight agencies and lines of reporting (e.g., OPRR, FDA, the funding agency) can create duplication and ambiguity. For example, a multi-institutional clinical trial funded by NASA is regulated by the IRB at each participating institution, by NASA, and by OPRR. If a problem occurred that led to an OPRR audit of a participating institution, the FDA would conduct an additional audit of that institution. Conversely, if the FDA audited an institution for a problem, OPRR would be notified and would conduct their own audit of all DHHS-funded studies. We recommend that oversight for all clinical research subject protection be delegated to a single federal agency with a single reporting mechanism, regardless of funding source. This agency should be adequately funded and should work in collaboration with institutions and physician practices to establish a system of prospective review, accreditation, and continuing education to reduce the need for retroactive action.

Well-meaning individuals and institutions may interpret regulations differently. We recommend that mechanisms be established for entities to obtain prospective approval for standard operating procedures. For example, OPRR could provide examples of minutes that reflect the level of detail required, and variances should be well defined so that adherence to standards can be judged proactively rather than retrospectively. Where disagreements remain, an appropriate mechanism for review and appeal should be developed.

Institutions and investigators have varying levels of understanding of current clinical research regulations and procedures. We recommend ongoing certification of IRB members and clinical investigators and accreditation of institutions, including documentation of adequate knowledge of federal regulations, ethical issues in clinical research, and the organizational structure needed to document compliance. There should be discussion as to whether certification should be done by a federal agency or some impartial private entity.

Increases in clinical research, oversight, and other regulatory mechanisms have required institutions to fund an increasingly large infrastructure. Not-for-profit entities that subsidize clinical research are facing mounting financial pressures. The infrastructure costs directly attributable to IRB support at Duke University will significantly increase during the current academic year to well over $1 million per year. Additionally, the voluntary contribution of faculty time for IRB service represents another significant cost that is not reimbursed. Given the growing financial pressures in academic medicine, it is increasingly difficult to enlist faculty to serve on IRBs. We recommend that infrastructure costs for human subject protection be negotiated and built into the indirect cost recovery for both federally and privately funded research.

The inherent conflict of interest in clinical trials is mitigated by the dual protection of informed consent and independent review oversight. However, the issue of the ethics of physicians being remunerated by pharmaceutical companies for enlisting their own patients into clinical trials deserves greater focus. We recommend that rational guidelines be developed relating to potential conflicts of interest for physicians enrolling patients into clinical trials.

Considerable attention has been given to the need for greater oversight in clinical trials. However, it must be emphasized that they provide the only means available to validate new medical therapies and thereby to assure the public of safety and efficacy. Clinical researchers and health experts should educate the public and politicians about the need for policies to further health while affording appropriate protection. Given the expansion of clinical research, it is time for a comprehensive review of subject protection legislation and oversight that was developed in a far different era. The goal should be an effective, simplified system that is understandable, that works, and that is adaptable to change.

References and Notes

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8. The authors wish to acknowledge the contributions of R. M. Califf, J. M. Falletta, J. C. Farmer Jr., R. E. Kaufman, V. Y. Saito, and J. Sugarman.