Oversight of Human Participants Research: Identifying Problems To Evaluate Reform Proposals

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The oversight of research involving human participants is widely believed to be inadequate. The U.S. Congress, national commissions, the Department of Health and Human Services, the Institute of Medicine, numerous professional societies, and others are proposing remedies based on the assumption that the main problems are researchers' conflict of interest, lack of institutional review board (IRB) resources, and the volume and complexity of clinical research. Developing appropriate reform proposals requires carefully delineating the problems of the current system to know what reforms are needed. To stimulate a more informed and meaningful debate, we delineate 15 current problems into 3 broad categories. First, structural problems encompass 8 specific problems related to the way the research oversight system is organized. Second, procedural problems constitute 5 specific problems related to the operations of IRB review. Finally, performance assessment problems include 2 problems related to absence of systematic assessment of the outcomes of the oversight system. We critically assess proposed reforms, such as accreditation and central IRBs, according to how well they address these 15 problems. None of the reforms addresses all 15 problems. Indeed, most focus on the procedural problems, failing to address either the structure or the performance assessment problems. Finally, on the basis of the delineation of problems, we outline components of a more effective reform proposal, including bringing all research under federal oversight, a permanent advisory committee to address recurrent ethical issues in clinical research, mandatory single-time review for multicenter research protocols, additional financial support for IRB functions, and a standardized system for collecting and disseminating data on both adverse events and the performance assessment of IRBs.

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The oversight of research involving human participants is widely believed to be inadequate (1). The U.S. Congress, national commissions, the Department of Health and Human Services (DHHS), the Institute of Medicine, numerous professional societies, and others are proposing remedies (1–4). Despite a paucity of data, these efforts are proceeding largely from the assumption that the "primary threats to the system's effectiveness" are researchers' conflict of interest, lack of institutional review board (IRB) resources, and "increasing volume and research complexity" (5). This characterization, however, fails to capture the full range of problems (6). Clearly, to know what reforms are needed and to critically assess the adequacy of current reform proposals, it is necessary to carefully delineate the problems of the current human participants research oversight system. Therefore, to stimulate a more informed and meaningful debate, we delineate 15 current problems into 3 broad types and critically assess proposed reforms according to their relevance to these specific problems. Finally, on the basis of this inventory of problems, we outline 5 fundamental components of a more effective reform proposal, including bringing all research under federal oversight, a permanent advisory committee to address recurring ethical issues, mandatory single-time review for multicenter research protocols, additional financial support for IRB functions, and a standardized system for collecting and disseminating data on both adverse events and performance assessment of IRBs.

Problems with the Current System

In the mid-1970s, the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended a regulatory system based on research review by institutional review boards (IRBs) and individual informed consent. These 2 protections formed the core of federal regulations governing research with human participants, codified in 1981 as 45 CFR 46 (7, 8). In 1991, when many federal agencies adopted subpart A of the regulations, they became known as the "Common Rule" (9). The U.S. Food and Drug Administration (FDA) uses separate but similar regulations for clinical research submitted for approval of drugs, devices, or biological agents (10, 11).

Through years of operation, the deficiencies of this oversight system have become increasingly apparent and worrisome (1, 12, 13). Recent deaths of research participants, the temporary suspension of research at prominent academic centers, and other publicized events have undermined the public trust and focused attention on the need for reform (12). As the IOM concluded: "The evidence is abundant regarding the significant strains and weaknesses of the current system" (1). To inform public deliberation on the research oversight system, we have identified 15 problems and grouped them into 3 broad categories: 1) structural problems deriving from the organization of the system as established by the federal regulations, 2) procedural problems stemming from the ways in which individual IRBs operate, and 3) performance assessment problems resulting from the absence of systemic assessment of cur-

rent protections (**Table 1**). There is a paucity of data quantifying these problems; as the IOM noted, however, the absence of systematic data is not indicative of the absence of problems but is a serious problem in itself (1).

STRUCTURAL PROBLEMS

Some problems with the current oversight system stem from its basic structure. First, as noted by many commentators, the federal regulations do not apply to all research involving humans (1, 13). Only Maryland has a state law requiring that all research with humans adhere to the federal regulations. Otherwise, current regulations apply only to federally funded research or research involving drugs, biological agents, or devices subject to FDA approval (14). While many institutions adhere to the regulations through voluntary agreements, numerous controversial and potentially dangerous types of studies—research on reproduction, the cloning of embryos, dietary supplements, and surgical innovations not testing a device—are performed without federal safeguards (15–17).

Second, current regulations and guidelines for protection of human research participants are inconsistent. While there are on-going efforts at harmonization, for many issues, such as reporting adverse events, conflicts of interest, and the operation of data safety and monitoring boards, the rules issued by the FDA and the National Institutes of Health (NIH) diverge or even conflict (**Table 2**) (13, 18–24). Furthermore, FDA and NIH regulations are not always consistent with regulations issued by other federal agencies that sponsor and oversee human participants research or with regulations in foreign countries where U.S. investigators conduct research (13).

Third, there is no effective mechanism for addressing fundamental and recurring ethical issues in clinical research, such as payment of research participants, use of stored biological specimens, or use of placebos. While numerous national bodies have addressed such ethical issues, their efforts have been sporadic and unsystematic and their recommendations rarely implemented (1, 25–27). Institutional review boards frequently consider these issues in the context of an individual study but generally lack the time, research capacity, deliberative mechanisms, and expertise to authoritatively consider ethical issues and their social implications (13). Consequently, researchers are uncertain about what to do, practices diverge widely, and research projects are charged with abuse of participants, all of which hinder research and endanger participants.

Fourth, institutional conflicts of interest are inherent in the current system of review. Each IRB is funded by and operates under the auspices of the very institution conducting the research the IRB reviews (28). Moreover, researchers submitting proposals for review often have IRB members as colleagues (29). Whether the conflicts inherent in these arrangements are appropriately managed—or are even manageable—remains an open question.

Fifth, there are multiple, incompatible guidelines for managing conflicts of interest on the part of either IRB members or investigators (21–23, 30). The role of the IRB in overseeing investigators' conflicts of interest is unclear (31). Furthermore, few rules govern conflicts of interest on the institutional level (32).

Sixth, the review process for many studies is repetitive. Years ago, clinical research studies were usually conducted at a single academic center; now, a single study, whether funded by biopharmaceutical companies or the government, is commonly conducted at multiple sites (33). Scores of IRBs may have to review a single multisite study, a process that consumes considerable time and resources without evidence that these multiple reviews enhance safety (1, 34). The system of local review may foster local efforts to uphold ethical standards for research and capitalizes on the IRB's knowledge of the local research environment and community standards (35). However, no data substantiate the value of such local knowledge or whether it can only be—or is best—gained through institution-based review.

Seventh, IRBs have historically operated with few resources (36–45). Academic institutions typically do not have a separate source of funds for IRBs; support comes from indirect costs on grants and, increasingly, charges to commercial sponsors (41). Many IRB members are not compensated for their efforts, and resources for staff, computerization, and other infrastructure needs are believed to be inadequate, although clear metrics for what constitutes adequacy in this area have not been established (1). While some academic institutions have increased their financial support of IRBs, and the NIH is now providing one-time grants to augment resources for IRBs, there remains no sustained source of IRB funding (46, 47).

Finally, education in research ethics is haphazard (13). The NIH recently established a research ethics education requirement for investigators and other key research personnel involved in NIH grants (47, 48). However, the NIH has not specified curricular requirements, and the adequacy of the education has not been verified. Similarly, there are no federally mandated educational requirements for non-NIH IRB members. At the NIH intramural program, IRB members must complete computer-based training, but again, there is no assurance that this training is adequate (49).

REVIEW PROCEDURE PROBLEMS

Additional problems undermining the protection of research participants derive from the way that individual IRBs operate. First, the process of review is time-consuming, partially because protocols frequently require prior review by scientific and other committees (50, 51). Also, the federal regulations state that the entire IRB, rather than only the chair or designee, must review modifications to protocols not eligible for expedited review (52, 53). Be-

Table 1. **Do the Proposed Reforms Address Key Problems with the Human Research Participants Protection System?***

Problems	Accreditation	Credentialing IRB Professionals	Central IRBs	Legislative Proposals	OHRP Initiatives	IOM Report
Structural problems						
1. Federal regulations do not apply to all research Federal regulations apply to research funded by the 17 federal government departments or agencies that have adopted the "Common Rule" and to research seeking FDA approval of drugs, biological agents, or devices. Most clearly, they do not cover much research regarding reproduction and dietary supplements.	No	No	No	Yes	No	Yes
2. Inconsistencies in various federal regulations NIH and FDA regulations regarding conflicts of interest, DSMBs, and adverse event reporting are divergent and contradictory. Federal regulations and regulations in other countries also conflict.	No	No	No	No	No	No
3. No effective mechanism for IRBs to address major ethical issues IRBs lack time and expertise, and there is no other body to establish authoritative policies regarding persistent ethical issues, such as payment to research participants, use of placebos, and the social value of research.	No	No	No	No	No	No
4. Inherent institutional conflicts of interest Institution that funds the IRB also conducts and oversees the research the IRB reviews.	No	No	Partially	Partially	No	Partially
5. No systematic management of conflicts of interest Current management of investigators' and IRB members' conflicts of interest is complex and contradictory. IRBs' role overseeing conflicts is poorly defined.	Partially	No	No	Partially	Partially	Yes
6. Repetitive IRB reviews Multisite research is reviewed at each institution, dissipating limited resources.	No	No	Partially	Partially	No	Partially
7. Absence of resources devoted to IRBs IRB support is a combination of funds from fees on sponsors and indirects on grants. Limited resources compromise administrative support and development of infrastructure and policies.	Partially	No	No	Partially	Partially	No
8. Inadequate education Educational requirements for clinical investigators and IRB members exist only for NIH-funded research institutions and their IRBs. The requirements and curricular content are poorly defined.	Partially	Partially	No	Yes	Partially	Partially
Procedural problems						
9. Time-consuming review process Multiple reviews, including by scientific, biosafety, and other committees, infrequent IRB meetings, and the need for revisions to be rereviewed by the full IRB create a lengthy review process.	No	No	Partially	Partially	No	Partially
10. Poor quality control of IRB review IRBs may review research for which they lack expertise and rely on information given by investigators without corroboration.	Yes	No	Partially	No	Yes	No
11. Inadequate guidance on IRB operations Aside from basic IRB composition requirements, there is little guidance on how members should be selected, how decisions on research should be made, and how to communicate decisions to investigators.	Partially	No	No	Partially	No	Partially
12. Excessive focus on informed consent forms IRBs devote substantial time to the informed consent forms at the expense of serious consideration of other important ethical issues.	No	No	No	No	No	No
13. Ineffective adverse event reporting The process of adverse event reporting is vague; definition of "adverse event" varies within FDA regulations and between FDA and NIH regulations. IRBs receive notification of adverse events without full appreciation of magnitude of problem.	No	No	Partially	No	No	Yes
Performance assessment problems						
14. No validated measures of IRB performance No validated performance measures for human participants protections and no systematic collection and evaluation of the quality of IRBs. Consequently, unjustified variability cannot be corrected.	Partially	No	No	Partially	Partially	Yes
15. No systematic collection and dissemination of clinical research performance data No organization collects and disseminates data on the rates of participation by and risks to human participants in clinical research or on specific aspects of that research.	No	No	No	Partially	No	Yes

* DSMB = Data and Safety Monitoring Board; FDA = U.S. Food and Drug Administration; IOM = Institute of Medicine; IRB = institutional review board; NIH = National Institutes of Health; OHRP = Office for Human Research Protections.

Table 2. **Differences in Regulations between the Office of Human Research Protections and the U.S. Food and Drug Administration***

Variable	FDA (21CFR.50 and 56)	OHRP (45CFR.46)
Scope of the regulations	Covers research on products regulated by the FDA, including food and color additives; drugs, medical devices, or biological agents for human use; and electronic products (50.1 and 56.101).	Covers all research with human participants conducted or supported by DHHS or conducted in an institution that agrees to comply with 45CFR.46 for all research (46.101).
Assurance	Does not require prospective assurances. Evidence from sponsor or investigator of compliance with the regulations is submitted with data for FDA review and approval.	Requires prospective assurance of compliance with the regulations from grantee institutions for any research conducted or supported by federal agencies (46.103).
Exemptions from IRB review	Allows exemption only for the initial emergency use of a test article (must be reported to the IRB within 5 days), and for taste and food quality evaluation (56.104[c] and [d]).	Allows exemption for certain research, including research conducted in educational settings; research that uses educational tests, surveys, interviews, or observation of public behavior; uses existing data or publicly available unidentified specimens; evaluates taste and food quality; and evaluates public benefit or service programs (46.101[b]).
Cooperative or multi-institutional research	For multi-institutional studies, institutions may use joint review, the review of another qualified IRB, or similar arrangements aimed at avoiding duplication of efforts (56.114).	"In the conduct of cooperative research projects each institution is responsible for safeguarding the rights and welfare of human subjects and complying with this policy" (46.114). Institutions may use joint review, the review of another qualified IRB, or similar arrangements with the approval of the department or agency head (46.114).
Exceptions from the requirements for informed consent	Exceptions to informed consent only allowed for: 1. Emergency use of a test article, detailed criteria (50.23[a]–[c]). 2. Military use of an investigational drug under certain conditions when decided by the President (50.23d). 3. Emergency research (50.24).	IRB can waive or alter requirements for informed consent when 1. Project is subject to approval by state or local officials and designed to study public benefit or service programs (46.116[c][1]) 2. Research is no more than minimal risk, the waiver will not adversely affect the rights and welfare of participants, research cannot practicably be done without the waiver, and participants will be provided with pertinent information after the study (46.116[d]).
Documentation of informed consent	Regulations require signed consent forms as documentation of informed consent (50.27), except when informed consent is waived (as above) or the IRB waives the requirement for signed consent for research that is no more than minimal risk and involves procedures for which consent would not normally be sought (56.109[c][1]).	IRB can waive requirements for signed consent forms when it would be the only link between the participant and research and harm could result from breach of confidentiality, or when the research presents no more than minimal risk and involves no procedures for which consent would normally be sought (46.117[c]).
Conflicts of interest†	Regulations require certification and disclosure of financial conflicts with every marketing application (21CFR.54).	
Reporting adverse events	Regulations require written procedures for ensuring prompt reporting to the IRB, appropriate officials, and the FDA regarding any unanticipated problems involving risk to participants or others or any serious or continuing noncompliance with regulations or IRB requirements (21CFR 56.108[b] and 21CFR 312.53[c][1][vii]). Specific guidance is provided regarding adverse event reporting, including definitions, time frame, and to whom reports go. Types of adverse events are defined (21CFR 312.32[a]). Investigators are required to report to the sponsor any adverse event that may "reasonably be regarded as caused by, or probably caused by, the drug" being studied (312.64[b]); and to the sponsor and IRB any unanticipated adverse device effect (812.150[a][1]). Sponsors are required to keep every participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safety (21CFR 312.55[b]). A sponsor who determines that its investigational drug presents an unreasonable and significant risk to participants shall discontinue those investigations that present the risk and notify the FDA, all IRBs, and all investigators (21CFR 56[d]).	Regulations require written procedures for ensuring prompt reporting to the IRB, appropriate officials, and the department or agency head regarding any unanticipated problems involving risk to participants or others or any serious or continuing noncompliance with regulations or IRB requirements (46.103[b][5]), but offer no specifications regarding those procedures. NIH guidelines require reporting adverse events to the IRB but are nonspecific with regard to definitions or timeframes.
DSMB	Regulations require the IRB to ensure that "when appropriate the research plan makes adequate provision for monitoring the data to ensure the safety of subjects" (21CFR 56.111[a][6]). All clinical trials require safety monitoring and by regulation, sponsors have specific requirements regarding monitoring and reporting (312.32) FDA issued draft guidance for sponsors on establishing DSMBs in late 2001. Guidance is found at www.fda.gov/ohrms/dockets/98fr/010489gd.pdf.	Regulations require the IRB to ensure that "when appropriate the research plan makes adequate provision for monitoring the data to ensure the safety of subjects" (46.111 [a][6]). NIH requires a data and safety monitoring plan for all clinical trials, including phase I and II studies, and requires the use of a DSMB for multisite clinical trials (http://grants.nih.gov/grants/peer/tree_dsm_plans.pdf). No regulations guide the composition or function of a DSMB.

* CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DSMB = Data and Safety Monitoring Board; FDA = U.S. Food and Drug Administration; IRB = institutional review board; NIH = National Institutes of Health; OHRP = Office for Human Research Protections.
† DHHS published guidance for managing financial conflicts of interest in research that would apply to both OHRP and FDA. The final guidance is titled "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection" (31 March 2003), OHRP, http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finalguid.pdf.

cause they seem bureaucratic and time-consuming without enhancing safety, these additional requirements frequently frustrate and alienate from research ethics and safety concerns the very researchers who ultimately must ensure the welfare of research participants. Consequently, researchers frequently view IRB review as a barrier to be overcome rather than a constructive process that will minimize risks and enhance safety (13, 46). This does not help foster a culture of research excellence and concern (1).

Second, IRB members may lack expertise in the science of a research study under review (34). For example, an individual IRB might review research related to liver transplantation without any member or consultant having expertise in the area. This may compromise the IRB's knowledge of the importance of the research, its scientific validity, or the latest unpublished data about the risks for the intervention. Rather than relying entirely on information provided by the investigator, IRBs can and do consult outside sources or experts, but this requires time and resources, and appears to be done only sporadically (46). The nonscientific perspective of lay representatives can also be marginalized (1, 54).

Third, aside from the regulatory requirements for a quorum and a majority vote, IRBs lack substantive guidance on their operations, such as criteria for appointment or dismissal of members, and how they should communicate their decisions to investigators (11, 55).

Fourth, IRBs often spend much time scrutinizing informed consent documents and producing excessively long detailed forms, even for relatively simple, minimal-risk research. This focus on informed consent documents negates the widely accepted notion that informed consent is a process, does not always improve the informed consent process, and diverts limited IRB time from consideration of other serious ethical issues (13).

Finally, the process for reporting adverse events is confusing and repetitive and may not promote the safety of research participants. While the FDA has strict criteria, timelines, and procedures for reporting adverse events, the NIH guidelines are less clear (**Table 2**) (13, 19, 20). More important, in multisite studies each adverse event is reported to each local IRB, which often lack any context for understanding this information (such as how many people have enrolled in the trial and the reported frequency of the event) (13). Moreover, without a centralized reporting system, unusual and unexpected events are frequently not identified.

Performance Assessment Problems

The current system does not systematically assess performance or outcomes (1). No one can authoritatively report how many or what types of research studies are being conducted, how many people are enrolled in each type of study, how many serious (grade III and IV) and unexpected adverse events occur annually, how many participants die of research-related causes, and so on. There are 2 reasons for the paucity of data. First, no validated measures for evaluating the performance or outcomes of the system exist (1). Second, while individual institutions may collect data on outcomes, no one systematically monitors the entire research enterprise; this lack of oversight precludes assessments of the overall safety of clinical research. To date, regulatory agencies have not provided such data for certain segments of research. Without such data, it is impossible to identify and correct inconsistent practices and determine the extent to which the current system enhances protection of research participants (1).

Each of these problems can exacerbate the others. For instance, repetitive review of multisite studies dissipates limited IRB resources, which otherwise could be devoted to developing educational materials or tracking adverse events.

Proposed Solutions

Six major reforms of the current system for protecting research participants have been proposed or enacted (**Table 1**). It is important to evaluate how well each of these proposals addresses this constellation of 15 problems.

Accreditation of IRBs and Institutional Protections

Currently there are 2 voluntary accreditation processes, and 1 mandatory accreditation process limited to Veterans Affairs (VA) medical centers. Accreditation signifies that an institution's system for protecting research participants meets certain standards (56–58). Accreditation programs can help solve problems in the review process by facilitating the development of standard operating procedures; this can encourage IRBs to focus on issues beyond informed consent documents. They can also ensure that IRBs obtain outside expertise when needed and that investigators, IRB members, and staff receive appropriate training and resources.

The Department of Veterans Affairs requires that all VA medical centers be accredited by the National Committee for Quality Assurance (NCQA). In December 2002, after an initial set of standards were withdrawn because of "negative feedback" from the first VA center reviews, new draft guidelines that focus more on self-evaluation by the participating site and reduce the number of standards were released (59). In January 2003, NCQA and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) announced the formation of Partnership for Human Research Protection (PHRP) to offer voluntary accreditation to non–VA protection programs mainly through a Web-based self-assessment tool and subsequent PHRP review (57, 61). As of June 2004, PHRP accredited just 4 organizations, including 1 hospital and 1 independent IRB.

The Association for the Accreditation of Human Research Protection Programs (AAHRPP) is an independent organization formed by the Association of American Med-

ical Colleges, the Association of American Universities, the Consortium of Social Science Associations, the Federation of American Societies for Experimental Biology, the National Association of State Universities and Land Grant Colleges, the National Health Council, and Public Responsibility in Medicine and Research. This organization began offering accreditation in February 2002, using 21 standards encompassing written policies and procedures regarding conflicts of interest, education of IRB personnel, and research teams in the protection of research participants; the provision of adequate resources for IRBs; and the specification that IRBs devote sufficient time to reviews but conduct them expeditiously (58). As of June 2004, AAHRPP has not revealed how many institutions have been reviewed but states that it has granted full accreditation to just 9 programs (6 medical centers and 3 independent IRBs) and qualified accreditation to 1 other organization (62).

Accreditation has 5 major problems. First, the underlying assumption that accreditation contributes to, ensures, or is correlated with quality is questionable. Indeed, a recent study showing that JCAHO accreditation of hospitals does not necessarily indicate improved quality of care casts doubt on the accreditation–quality link, even in domains with substantive performance measures (63). Second, accreditation predominantly addresses the procedural problems; it cannot address either structural or performance assessment problems. Third, since accreditation requires both time and money, IRB resources may be diverted from other important activities. Fourth, with voluntary accreditation, the more stringent the standards are the less likely institutions will volunteer for review. Finally, as suspension of the NCQA program illustrates, the efficacy of an accreditation program largely depends on its standards. Inappropriate or inadequate standards might actually compromise a system of protecting research participants.

The best evaluation may be the one issued by the IOM, which assessed the NCQA and the AAHRPP accreditation initiatives in 2001 at the request of the DHHS. The IOM said that they generally lacked specificity, with a clear emphasis on documentation (64). Overall, the IOM argued that because "the proposed standards are new and untested . . . these emerging accreditation programs are best viewed as pilot projects that will have to be evaluated in light of experience" (64).

Credentialing of IRB Personnel

In October 2000, the Council for Certification of IRB Professionals, affiliated with the Applied Research Ethics National Association, began offering IRB personnel a 4-hour examination with 400 questions "based on federal requirements, interpretations, and guidelines," not specific institutional policies (65). As of June 2004, slightly over 550 professionals successfully completed the requirements for certification (66).

By enhancing the education of IRB personnel, credentialing could streamline review and improve continuing review. Ironically, the process could also promote literalist adherence to regulations and increased emphasis on informed consent documents, creating additional delays in the research review process that do not necessarily result in improved participant protection. Even under the best circumstances, credentialing cannot address most of the structural, process, and performance problems with the oversight system.

Centralized IRBs

Recently, the National Cancer Institute and the Office for Human Research Protections (OHRP) created a central IRB to review multisite phase III oncology trials (33). Under this pilot program, local IRBs at participating institutions can defer review to the central IRB. Theoretically, a central IRB can eliminate repetitive reviews, minimize institutional conflicts of interest, ensure IRB expertise on the research under review, and centralize the reporting of adverse events. This approach might reduce local IRBs' workloads, allowing them to focus on research requiring a local perspective or local aspects of multisite research (33).

Critics contend that this pilot central IRB may lack essential knowledge relevant to the wide range of research topics reviewed. In addition, the central IRB suffers from concentration of power; without an appeals process, decisions not to approve research are final. Most worrisome, because deferring to the central IRB review is voluntary, institutions have been reluctant to defer to the central IRB. Consequently, rather than streamlining the review process, it has added an additional layer of review and delay (33, 67).

Even an effective central IRB could not resolve many of the system's problems, including the fact that not all research is subject to regulation and the lack of system-wide performance data.

Legislative Proposals

Over the last decade, numerous legislative reforms of protections for research participants have been proposed, but none have been enacted. In the 107th Congress, there were 2 proposals: the Research Revitalization Act of 2002 (Edward Kennedy) in the Senate and the Human Subject Research Protection Act of 2002 (Diana DeGette and James Greenwood) in the House (2, 3). Both would have required that all research with human participants conforms to federal regulations, that researchers receive training in the protection of human participants, that researchers' financial conflicts of interest be disclosed, that multisite studies be reviewed by a central IRB, and that basic performance data be collected (2, 3). Each bill also had unique provisions; Senator Kennedy's proposal required that within 6 years all research be reviewed by accredited IRBs (2), while the House bill emphasized harmonization between the FDA's regulations and the "Common Rule."

If enacted, such proposals might improve the protection of research participants, yet their effects would be limited in scope, their measures are largely untested, and the

implications of implementing them are unclear. For example, they call for increased resources for IRBs but fail to identify a funding source. Of note, the proposals do not establish a robust system for reporting adverse events. The specific provisions of any legislative initiatives are likely to change, and they may ultimately address more problems. However, like all previous efforts, the major hurdle has been passage; neither bill was enacted. Congresswoman DeGette reintroduced her bill with minor changes in November 2003 as the Protections for Participants in Research Act 2003, and Senator Kennedy plans to reintroduce his bill in 2004.

OHRP Initiatives

The Office for Human Research Protections is the federal regulatory agency charged with oversight of all DHHS-funded research with human participants (55). Institutions conducting DHHS-funded research must file a legally binding assurance with OHRP promising adherence to federal regulations (55). This agency can audit DHHS-supported research and suspend any noncompliant research. For instance, OHRP recently halted research at several institutions, including the Johns Hopkins University and Duke University School of Medicine (68). These actions have garnered attention from the academic world, have improved oversight at the targeted institutions, and have prompted other institutions to strengthen their programs for protecting research participants (46).

The other initiatives from OHRP include a simplified Federalwide Assurance (FWA) process, a voluntary quality-improvement program, and the issuance of guidance on various topics. As part of the quality-improvement program, OHRP offers a self-assessment tool for institutions to evaluate their human participants protection programs and offers site visits to provide specific advice (4). This process is designed to help institutions assess the workload of IRBs, the infrastructure and resources devoted to IRBs, and the skills and training of researchers and IRB personnel. The agency is developing guidelines for institutions to implement continuous quality-improvement programs.

The Office for Human Research Protections has also issued final guidelines for addressing financial conflicts of interest on 5 May 2004 (69). However, these guidelines are more a series of questions for IRBs and investigators to consider than clear rules of ethical practice. In addition, the guidelines will not help manage the inherent conflict of interest that arises because IRBs work for the institutions whose protocols they review. Indeed, while many federal agencies rely on OHRP-approved assurances, OHRP's overall authority is limited by statute, preventing it from addressing other key problems. Office for Human Research Protections cannot oversee or require compliance with federal regulations for all research, especially research at institutions that are not covered under FWAs. Furthermore, OHRP's enforcement actions may undermine efforts to streamline review because institutions may be inappropriately concerned about audits, liability, and compliance actions. In addition, it has not issued clear and definitive guidance on recurring ethical issues such as the use of placeboes and stored biological samples. Finally, little has been done to enhance adverse-event reporting or institute systematic collection of performance data.

IOM's "Responsible Research" Report

At the request of the DHHS, the IOM issued a report in October 2002 assessing the current protection system and recommending improvements (1). The IOM's revival of a 1982 recommendation by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research for a no-fault compensation system for research injuries has received substantial attention, as has the call for a comprehensive "clinical trials registry for public use" (1, 70). While these recommendations address deficiencies of the current system, they would not directly enhance protections for research participants. The IOM did make other recommendations, including that federal regulations should apply to all research and that research ethics review boards (ERBs) replace IRBs, while other bodies conduct scientific reviews and reviews for conflicts of interest. However, ERBs would be "vested with" integrating the considerations of these reviews for a final decision (1).

In addition, the IOM recommended a sliding scale of review "calibrated to a study's degree of risk," with federal agencies specifying what constitutes minimal-risk research for expeditious review (1). They also recommended improving safety-monitoring systems and called on federal agencies to standardize collecting and reporting adverse events. The IOM also suggested assigning one ERB primary responsibility for reviewing multisite research and granting other ERBs discretion to accept its determination. The IOM also called for "revitalizing informed consent" and reducing the liability focus of consent forms (1). Finally, the IOM decried "the lack of data regarding the scope and scale of current protection activities . . . [that] handicaps an objective assessment of the protection program performance" (1). Rather than delineating performance measures, the IOM called for another independent body to develop such measures and collect performance data.

The IOM acknowledges that its recommendations reflect "the current state of policy development, the present regulatory framework, and the efforts undertaken by others" rather than a far-reaching, innovative proposal (1). Applying federal protections to all clinical research, developing outcome measures, and collecting performance data are critical. Other IOM suggestions may not improve protections for research participants. As demonstrated by the National Cancer Institute's central IRB, discretionary review by one IRB for multisite studies does not necessarily streamline the review process or better protect participants (33, 67). Similarly, dividing scientific, conflict-of-interest,

and ethics reviews among separate committees, with ERBs making the final decisions, could create additional delays in the research review process without necessarily enhancing human subject protections.

Overall Assessment and Future Directions

In the last 3 decades, clinical research has changed dramatically from primarily investigator-designed and -implemented to more sponsor-initiated and -supervised studies that require multiple sites and many more participants. Sponsorship of research is increasingly commercial, and studies are frequently conducted in sites outside the United States. Yet the basic oversight system has changed little. Problems of the oversight system are now widely recognized and go well beyond IRB operations that are the primary focus of current reform efforts. Indeed, as this review suggests, few of the currently proposed reforms address the most important problems that are structural, evolving from an institution-based system of review with little accountability and virtually no central coordination, data collection, standard setting, and performance assessment.

Effective solutions to the delineated problems will require 5 fundamental reforms to the oversight system:

1. Establish a single federal office with regulatory authority over all human participants research conducted in the United States or by investigators based in the United States.
2. Establish a permanent advisory committee to systematically examine ethical issues related to human participants research and recommend authoritative policies.
3. Mandate single IRB review of all multisite research proposals with liability protection for local institutions.
4. Increase funding for oversight of human participants research by both the federal government and commercial sponsors of research.
5. Develop standards to assess the performance of the oversight system, and systematically collect and disseminate data on adverse events and the functioning of the human participants research oversight system.

To remedy the major structural problems with the system, lack of federal oversight of all—commercial, foundation-funded, and government-funded—human participant research and inconsistent federal regulations, requires the creation of a single federal office with the authority to regulate and monitor all research involving human participants. This office could also be the home of a permanent advisory committee to address ongoing ethical issues in oversight of research. Experience reveals that temporary federal commissions and ad hoc committees created to review occasional research proposals of national significance lack continuity and ability to see their proposals implemented and revised when necessary. A standing advisory committee could recommend policies such as uniform and mandatory conflict-of-interest rules for investigators and institutions that would be implemented through the new federal office for research as well as policies on issues such as payment to research participants, use of stored biological samples, and placebos.

The solution to the problem of repetitive and time-consuming review of multisite proposals, whether funded by corporations, foundations, or the government and whether conducted internationally or just within the United States, is the establishment of a system of single review of multisite research with liability protection for local institutions. To prevent additional layers of review, participation in this process by institutions wishing to be part of such national or international multisite studies would need to be mandatory rather than voluntary. Previous approaches to having a single review have been largely unsuccessful because institutions are reluctant to voluntarily forgo their own comprehensive review of multisite studies without liability waivers. A process that was federally monitored and mandatory for institutional participation would be far more likely to result in compliance and reduce the burden on local IRBs. This, along with additional financial support for IRBs, through both federal and commercial recognition of the resources required for adequate review and monitoring of human subject research, should result in a stronger local IRB system.

In addition, guidelines on operations and standards for accountability enforced through federal review can create increased uniformity of practice. This should include a standardized system for collecting, assessing, and disseminating data on adverse events with standards for interaction between IRBs and Data Safety and Monitoring Boards and federal authorities. Critical to the future of research oversight is the creation of systemic performance standards and a data collection mechanism to evaluate the overall performance of the system, including how well IRBs are functioning and how research participants are being protected.

To many, these proposed solutions may seem too comprehensive, overly burdensome, and intrusive, with the potential to obstruct important clinical research. Ironically, the same warnings arose in the 1960s and 1970s before codification of the current system. The U.S. government ignored these dire warnings and took bold steps to establish a system of protections for human research participants. For years this oversight system performed well, although not perfectly. However, it has not evolved with changes in the research environment, especially greater use of multicenter trials with more commercial sponsorship, and with the identification of deficiencies through experience. Indeed, many commentators think its deficiencies are now themselves the source of burdensome requirements that obstruct clinical research without protecting research participants. It is time to update and reinvigorate the system for current realities to enhance clinical research productivity while ensuring the protection of future research participants.

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