Grinding to a Halt: The Effects of the Increasing Regulatory Burden on Research and Quality Improvement Efforts

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The Infectious Diseases Society of America is concerned that excessive regulatory oversight is seriously affecting translational research and quality improvement efforts. Careful studies on the subject of research oversight have documented the adverse effects of regulatory burden on clinical, epidemiological, and health systems research. We identified 5 problem areas. First, the application of the Health Insurance Portability and Accountability Act to research has overburdened institutional review boards (IRBs), confused prospective research participants, and slowed research and increased its cost. Second, local review of multicenter studies delays research and does not improve protocols or consent forms. Third, reporting of off-site adverse events to local IRBs is wasteful of the resources of sponsors, investigators, and local IRBs and does not add to participant safety. Fourth, uncertainties about key terms in the regulations governing pediatric research lead to marked differences in the ways that local IRBs review research involving children. Fifth, the lack of consensus on when IRB review is required for quality improvement efforts is slowing progress in this critical area. Relatively simple steps, which do not require legislation or a change in the Common Rule, could improve regulatory oversight in these problem areas.

Epidemiological and clinical research is important in every field of medicine, particularly for infectious diseases. Interactions between humankind and the microbial world are remarkably dynamic; new infections are discovered, and previously-described pathogens spread to new areas and develop enhanced virulence and antimicrobial resistance. There have been tremendous successes in research on infectious diseases. Within 3 years of the first clinical description of AIDS, the pathogen had been identified, and soon thereafter, therapy was developed that has saved hundreds of thousands of lives. Such progress requires a flexible research infrastructure that can assimilate new ideas and respond quickly to urgent research questions.

Six years ago, Califf and Muhlbaier [1] warned that "the system of research could become increasingly paralyzed as most of the transaction costs for research may be exhausted in response to regulations that have no useful purpose" (p. 917). Evidence gathered in the subsequent years has heightened concerns about excessive regulatory burden on translational research and quality improvement efforts. The Infectious Diseases Society of America (IDSA) is concerned that the research infrastructure in the United States is slowly grinding to a halt under this increasing burden of ineffective regulatory oversight (and similar problems have been noted in other countries) [2–5].

Institutional review boards (IRBs) are overwhelmed by the application of the Health Insurance Portability and Accountability Act (HIPAA) to research. Federally sponsored studies are being delayed and becoming

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more expensive as a result of regulatory burden [6–8]. Industry-sponsored clinical trials have largely left academic medical centers and are now moving out of the United States [9]. Quality improvement efforts are held up by uncertainties about when and how IRB review should be done. Finally, increasing regulatory burden is a major disincentive to trainees who are considering a career in research [10–12].

We are concerned about the current oversight system, but we are in complete agreement about the need for independent review of research involving humans. The unfortunate history of abuse of vulnerable subjects in research must not be repeated. To agree on the need for independent oversight, however, is not to defend the redundancies and inefficiencies that consume resources and delay research but do not contribute to the safety and privacy of research participants. The subject of research oversight has itself become the subject of careful quantitative research. We used this literature to identify 5 areas in which pragmatic steps can be taken to improve research oversight (Table 1)—steps that would not require new legislation or a change in the Common Rule [13].

THE EXAMPLE OF HIPAA

HIPAA legislation was enacted to facilitate electronic billing, improve privacy protections, and promote continuity of health insurance coverage [14]. Notably, an advisory committee for the Department of Health and Human Services (DHHS) "identified no instances of breaches of confidentiality resulting from researcher use of records" [15] and noted the confidentiality protections that have long been a part of research oversight. Despite the lack of evidence of a problem and over the strong objections of the research community [16, 17], DHHS included research in HIPAA regulations [18]. As a result, many more forms of investigation and quality improvement require review, and an "authorization form" was added to the consent process [19].

The negative repercussions of HIPAA have echoed throughout the system. The workload of IRBs increased [20] at a time when they were already overloaded [21–23]. HIPAA authorization forms average 2 pages and use complex, legalistic language [19, 24, 25] unlikely to be understood by study participants [26]. In 2 controlled trials, prospective participants randomized to receive a HIPAA authorization form were less likely to enroll in a study than were participants who received only the informed consent document [27, 28].

A wide variety of research has been adversely affected by HIPAA [6, 29, 30], and the cost of doing multicenter studies has increased [7, 31]. Enrollment in epidemiological cohort studies and some clinical trials decreased markedly [7, 31–33],

Table 1. Problems with the Human Subjects Protection System and Suggested Remedies That Do Not Require Legislation or Changes in the Common Rule

Problem	Possible remedy
Negative effects of HIPAA on a wide variety of research	Remove research from the list of activities covered by HIPAA regulations
Duplicative review of multicenter studies by the local IRBs of all participating sites	Expand the availability of central review panels for federally funded research Provide incentives for the use of central review
Redundant review of individual adverse event reports by the IRBs of all participating study sites	Harmonize guidance documents on adverse event review from FDA and OHRP Complete the development of a single electronic adverse event reporting form that would fulfill reporting requirements to all involved federal agencies Refocus the efforts of local IRBs on the evaluation of adverse event reports from single-site studies
Uncertainties about the appropriate level of review for some studies among children	Provide updated guidance for key terms, such as "minimal risk" and "minor increase over minimal risk" Make the national review of selected pediatric studies (the "407 process") much more efficient Make the results of previous national reviews readily available through a searchable Web site
Uncertainties about the role of IRBs in the review of quality improvement efforts	Provide clear guidance of the criteria for IRB review of quality improvement activities
Barriers to medical record research that are a disincentive to research by trainees	Remove research from the list of activities covered by HIPAA regulations
Lack of resources at OHRP to provide timely guidance and review of human subjects protection issues	Increase funding for OHRP Provide OHRP a clear mandate to produce timely updates in guidance and review

NOTE. FDA, US Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act; IRB, institutional review board; OHRP; Office for Human Research Protection.

Table 2. Proposed Benefits of Local Review of Multicenter Protocols and the Evidence Regarding Those Benefits

Aspect of the research oversight system	Proposed benefit	Evidence base	
		For	Against
HIPAA	Improve protection of patient confidentiality	None	Authorization forms have inappropriately complex wording [24–26] Requirement for an authorization form decreases participation in research [27, 28] Decreased enrollment in epidemiological studies in the post-HIPAA era [31–33, 38] Biased enrollment into epidemiological studies in the post-HIPAA era [32, 33] Increased delays in study implementation [7, 20, 35] Increased costs for research [31, 35, 38]
Local review of multicenter studies	Assure appropriateness of the protocol and consent form for the local population	None	Increased workload for local investigators [5, 34, 39] Increased costs of multicenter studies [40, 41] Marked differences in the type of review done at local sites [34, 42–50] Changes in consent forms that make them longer and more difficult to read [39, 51] Errors in locally approved versions of consent forms [39, 42] Substantial delays in the implementation of multicenter research [2, 8, 39, 45, 47, 52]
Adverse event review by the local IRB	Protect the safety of research participants	None	Substantial effort by the local investigator and IRB [53]
Pediatric-specific regulations for research oversight	Provide enhanced oversight for children, as a vulnerable population	None	Marked interinstitutional differences in the review of pediatric research [43, 44, 54] Delays in resolution of pediatric studies requiring national review (the "407 process") [55]

NOTE. HIPAA, Health Insurance Portability and Accountability Act; IRB, institutional review board.

and selection biases were introduced [32, 33]. Health systems research has been particularly compromised [20, 30, 34, 35]. Although HIPAA regulations allow research on de-identified data without patient consent, the removal of HIPAA-defined identifiers from medical records resulted in a 31% reduction in data, including information of vital importance for research and quality improvement [36].

We are particularly concerned about HIPAA's effects on medical record reviews, because such studies are often the initial exposure of trainees to research. Medical record review introduces patient-oriented research, and its retrospective nature often allows completion of a project in the limited time available during training. In the post-HIPAA era, nearly all record reviews are judged to require IRB approval, and an increasing percentage are sent for full-committee review [20]. Even expedited review often requires 1–3 months [37]—a delay that may preclude completion of a project.

The application of HIPAA to research is a lesson in unintended consequences. HIPAA legislation was not directed toward research, and there was no need to augment the existing confidentiality protections. Six years later, prospective participants are confused by authorization forms, IRBs are even more overburdened, research takes longer and costs more, and investigators are discouraged by the resulting "thicket of regulatory ambiguity" [6]. The Secretary of DHHS should remove research from the purview of HIPAA, as part of a "new framework for ensuring privacy" [30].

REDUNDANT REVIEW OF MULTICENTER STUDIES

Many clinical trials and epidemiological studies require multiple sites to accrue participants and produce generalizable results. Traditionally, each study site submits the protocol and informed consent document to its own local IRB. Local review is said to be important to assure that unique aspects of the local study population are dealt with appropriately (Table 2). Thus, a multicenter study may be reviewed by hundreds of IRBs.

Local review of multicenter studies requires substantial effort and expense. Sites in a tuberculosis study estimated that submission required a median of 30 h of staff time [39]. Local IRB review of a multicenter observational study required 15,000 pages of documents and consumed 16.8% of the entire budget

[40]. Local review also delays study implementation; the median times to approval for multicenter protocols ranged from 1.5 to 15 months [2, 8, 34, 39, 45, 52, 56].

The outcomes of local review of multicenter studies have not been reported in detail for a large number of studies, but the available data are quite consistent. Study protocols are seldom changed, but local IRBs often have markedly different interpretations about review of multicenter studies of a wide variety of types: pediatric [43, 44, 54], epidemiological [45, 57], health services [3, 34, 46, 47, 58], and minimal risk research [48, 49].

Changes in consent forms are usually required during local review [39, 42, 45]. In studies that have carefully evaluated these changes, consent forms became longer [51] and more complex [39]. Indeed, local IRBs often require complex language to be used in consent forms [59]. Finally, errors in the study description or in the description of possible adverse effects have been made and approved during local review [39, 42].

In summary, local review of multicenter protocols delays study implementation and consumes valuable resources of local IRBs and investigators. That neither protocols nor consent forms are improved in the process (Table 2) strongly suggests that local review of multicenter studies is another unnecessarily redundant part of the system.

STEPS TO INCREASE USE OF CENTRAL REVIEW

Federal regulations allow one IRB to rely on the review of another IRB [60], allowing central or cooperative review of multicenter studies. Since being introduced by the National Cancer Institute (NCI) [61], the idea of central IRB review has slowly gained ground. The 2 NCI central IRBs have now been accepted by 600 local IRBs [62], and other federal agencies have begun to use the model [63, 64]. We recommend that all major institutes and centers at the National Institutes of Health (NIH) develop a central IRB for multicenter studies.

Despite encouragement from the Office for Human Research Protection (OHRP) and the US Food and Drug Administration (FDA), cooperative review is underused [65]. Local institutions continue to have concerns or lack of familiarity with central review [66, 67]. NIH and other federal agencies that fund research should develop incentives for central IRB review; applicants who use a central IRB could receive points toward the peer-reviewed score of a grant application.

ADVERSE EVENT REPORTING

Careful monitoring of adverse events is critical in interventional studies; despite extensive preclinical testing, there may be serious unanticipated side effects from new treatments [68, 69]. Data centers for multicenter trials have sophisticated systems for reporting and analysis of adverse events. Reports are completed over the internet and analyzed using software packages and professional review. The data center can review real-time data, by assigned treatment arm. If concerns are identified, they can be reviewed with the Data Monitoring Committee, an independent committee of subject experts and biostatisticians. This 21st century system is the way that human subjects are and should be protected in interventional biomedical research.

Despite this robust method for monitoring patient safety in multicenter trials, there is a parallel system of adverse event reporting (Figure 1). Reports of serious adverse events (often as paper documents) are sent to all other investigators using the same study medication or device. Investigators review these reports and forward copies to their IRB. The local IRB reviews and stores these reports, consuming 9% of its resources in the process [53]. Importantly, neither the investigator nor the IRB have access to data elements—study assignment and denominators—that would make adverse event reports meaningful. OHRP and FDA agreed that this parallel system is not required by the Common Rule [70] and that it has the effect of "in-

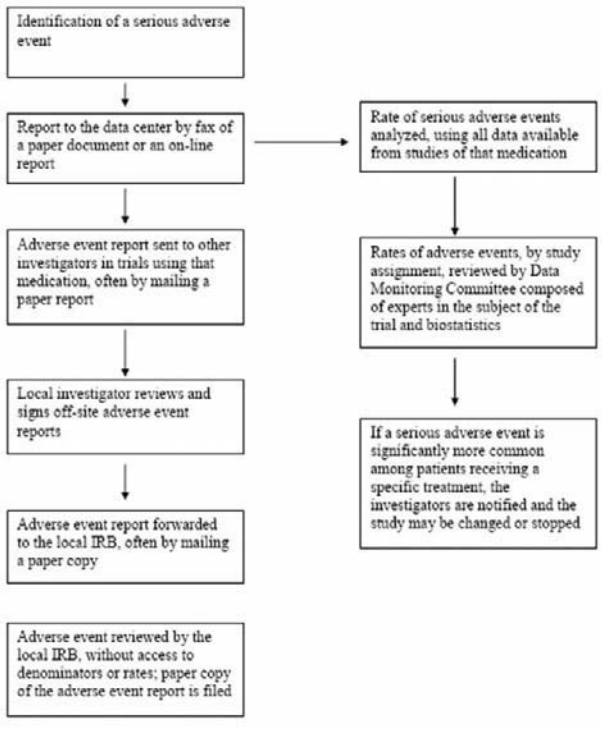

Figure 1. Data flow in the current system for reporting and analyzing serious adverse event reports.

hibiting rather than enhancing IRBs' ability to adequately protect human subjects" [71]

Thus, there is general agreement that the system of adverse event reporting includes a redundant and expensive process that does nothing to improve patient safety. OHRP and FDA have responded to this situation with updated guidance documents [70, 72]. Unfortunately, these 2 documents differ in several important ways, leading to continued uncertainties about adverse event review.

The responsibility for adverse event analysis from multicenter studies lies with data centers and data monitoring committees; IRBs and site investigators should have no role, other than responding to a finding by a data monitoring committee. OHRP and FDA should develop consensus guidance on adverse event reporting. It is notable that most highly publicized cases of serious injury to research subjects have been in single-site studies [73, 74]. Freed of the wasteful effort of reviewing adverse events from multicenter studies, local IRBs can focus on reviewing reports from single-site studies.

BARRIERS TO THE INVOLVEMENT OF CHILDREN IN RESEARCH

Children are unable to provide fully informed consent for participation in research and, therefore, have an enhanced level of regulatory protection. However, children have frequently been excluded from research. In the absence of data on pediatric-specific side effects or pharmacokinetics, new treatments have been used off-label for children [75]. Thus, an overzealous effort to protect children can have the paradoxical effect of harming children when lack of inclusion in research leads to use of inappropriate medications or inappropriate doses in children [76].

The Common Rule contains sections on oversight of pediatric research [77]. However, uncertainties about the interpretation of regulatory terms used to classify pediatric research ("minimal risk") and institutional risk aversion has led to markedly different decisions about pediatric trials by local IRBs [54]. The Common Rule allows national-level review by a panel of pediatricians and bioethicists to provide guidance on studies which raise concerns at the local level (the "407 process"). Although well-intentioned, the "407 process" has been so slow as to be a major impediment to research, requiring a median of 27 months for decisions about proposed pediatric trials [55].

We recommend that OHRP work with pediatric researchers, the IRB community and bioethicists to provide clarity about key definitions for pediatric research. Furthermore, OHRP should continue its efforts to streamline the "407 process."

REVIEW OF QUALITY IMPROVEMENT PROJECTS

In recent years, quality improvement projects have been emphasized and required as a means of improving the health care system. At the same time, IRBs have become increasingly involved in review of quality improvement efforts. However, the lack of consensus [78] regarding when and how IRBs should review quality improvement activities was highlighted by a recent high-profile case. The Michigan Hospital Association evaluated the effect of a simple checklist on catheter-related bacteremia. The project was reviewed by the IRB of one of the consulting quality improvement experts and was judged to not be research, because all items on the checklist were part of national standards. The project was strikingly successful in decreasing rates of catheter-related bacteremia [79], and plans were made to disseminate it to other hospitals. OHRP reviewed the project after its publication and determined that the project was research and had not been adequately reviewed [80]. In the ensuing outcry from hospital administrators and quality improvement officers [81], OHRP eventually reversed its decision [82], but the chilling effects of OHRP's handling of this case are likely to affect review of quality improvement activities for some time.

HIPAA regulations led to the perception that review of patient records by someone other than a direct care provider requires IRB review, particularly if there is intent to publish. However, a recent multidisciplinary panel of bioethicists, quality improvement officers, and regulatory officials reached very different conclusions [50]. The panel noted that both patients and providers have an ethical obligation to participate in quality improvement efforts, a fundamental distinction from research. The panel proposed that most quality improvement efforts should *not* be reviewed by an IRB, even when there is an intention to publish the outcomes. The panel's deliberations provide a fresh perspective that is needed to move the field beyond post-HIPAA hyper-expansiveness.

FUND OHRP AT A LEVEL CONSISTENT WITH ITS BROAD MISSION

Several of the recommendations above call for actions from OHRP, but this agency remains critically underfunded. Despite being responsible for a broad range of policy issues and oversight of thousands of IRBs, OHRP is a small agency, with a budget that has not kept pace with inflation (2008 budget of $4.7 million) [83]. Congress should increase funding for OHRP, coupled with a mandate to provide policy guidance on the subjects outlined above.

SUMMARY: RESTORING THE BALANCE IN RESEARCH OVERSIGHT

As an organization devoted to the prevention and care of infectious diseases, the IDSA reiterates its commitment to responsible research oversight. Both for the protection of research participants and to foster public trust in the process, research oversight is critical. However, time and resources are finite, and there are urgent needs for research on many illnesses. The evidence from careful studies provides compelling evidence that the current system includes practices that delay research and increase its costs while failing to contribute to the safety or privacy of research participants.

It will be critical that the much-needed public discourse on appropriate regulatory oversight for research and quality improvement be framed in a broader context than has been true in recent years, a perspective that acknowledges the rare and reprehensible instances of investigator fraud or inattention to participant safety, but one that also provides data on how inefficiencies and redundancies in the current system unduly delay vital research. Patients and disease advocacy groups, as well as researchers and regulators, need to be a part of this discussion. The need for research and the need for oversight are not competing agendas; they are 2 pillars that support the research enterprise. It is time to restore the balance.

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