Burdens on Research Imposed by Institutional Review Boards: The State of the Evidence and Its Implications for Regulatory Reform

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Context: Federal regulations mandate independent review and approval by an “institutional review board” (IRB) before studies that involve human research subjects may begin. Although many researchers strongly support the need for IRB review, they also contend that it is burdensome when it imposes costs that do not add to the protections afforded to research participants and that this burden threatens the viability of research. The U.S. Department of Health and Human Services recently announced its intention to reform the regulations governing IRB review.

Methods: We used a search of the PubMed database, supplemented by a bibliographic review, to identify all existing primary data on the costs of IRB review. “Costs” were broadly defined to include both expenditures of time or money and constraints imposed on the scope of the research. Burdensome costs were limited to those that did not contribute to greater protections for the participants.

Findings: Evidence from a total of fifty-two studies shows that IRBs operate at different levels of efficiency; that waiting to obtain IRB approval has, in some instances, delayed project initiation; that IRBs presented with identical protocols sometimes asked for different and even competing revisions; and that some decisions made (and positions held) by IRBs are not in accord with federal policy guidance.

Conclusions: While the evidence is sufficient to conclude that there is burden associated with IRB review, it is too limited to allow for valid estimates of its magnitude or to serve as the basis for formulating policies on IRB reform. The single exception is multicenter research, for which we found that review by

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several local IRBs is likely to be burdensome. No mechanism currently exists at the national level to gather systematic evidence on the intersection between research and IRB review. This gap is of concern in light of the changing nature of research and the increasingly important role that research is envisioned to play in improving the overall quality of health care.

Keywords: Institutional review board, clinical trials, research ethics, government regulations, research costs.

WHEN THE CLINICAL CENTER OF THE NATIONAL INSTITUTES of Health (NIH) opened more than a half a century ago, its director required that independent committees review any research that posed high or unusual risks for its human subjects. In 1966 the requirement for independent review was extended to all human subjects research funded by the NIH, and in 1974, this was codified as federal law by the National Research Act. The law required organizations seeking funding from the U.S. Public Health Service to form committees that would review the adequacy of protections for human subjects. The committees—which came to be known as “institutional review boards,” or IRBs—were specifically charged with assessing the safety of the proposed research and the adequacy of the consent to be obtained from the research participants.

A survey conducted the year after the new law was enacted found overwhelming support for IRBs among researchers, with 91 percent of the respondents agreeing that IRBs protect patients and 70 percent supporting the statement that IRB review improves the overall quality of research (Gray, Cooke, and Tannenbaum 1978). The researchers did have some reservations, however. Approximately half the respondents (43 percent of biomedical and 54 percent of behavioral and social scientists) believed that the need to obtain IRB review impeded their research to some extent, and a small number (8 percent) even concluded that the difficulties associated with IRB review outweighed its benefits.

In the time since that survey, both the volume of research and the number of IRBs have grown. Between 1995 and 2009, the NIH's research budget increased almost fourfold, from \$7.7 billion to almost \$30 billion (US DHHS 2009), while the number of IRBs grew at more than double that rate, from 491 in 1995 to almost 4,000 by 2008 (Catania et al. 2008). During this interval, there also were a number of government-commissioned evaluations of IRBs, as well as the wider

system for protecting human research participants, which largely concluded that reforms were necessary to ensure adequate protections (Bell, Whiton, and Connelly 1998; Federman et al. 2003; NBAC 2001; US DHHS 1998; US GAO 1996). Although there has not been any broad-based effort to examine the corollary impacts that IRB review might have on research, the U.S. Department of Health and Human Services (US DHHS) recently announced its intention to reform the regulations that govern such review (US DHHS 2011).

Editorials and commentaries from a wide range of clinical and research disciplines characterize IRBs as “slow and cumbersome [and] inconsistent” (Straight 2009, 376) and claim that they unduly delay research (Marsh et al. 2008), create disincentives for research participation (Infectious Diseases Society of America 2009), do not have the requisite expertise needed for review (Emanuel et al. 2004), and, more generally, impose a “staggering” cost on the research (Gordon et al. 2003). More pointedly, some people have argued that even though many of the costs and constraints resulting from IRB review are necessary, other costs constitute an unnecessary “burden” because they do not increase the research participants’ protections.

Objectives

Our review focuses on the burdens for research resulting from IRB review. Specifically, we assembled the primary evidence on (1) the burdens that IRB review imposes on health-related research and (2) those aspects of IRB performance—inefficiency, inconsistency, and poor decision making—that would serve as indicators of a burden. Our goals were to describe the evidence on which claims of burden rest and, from that evidence, to suggest changes in regulatory policy or practice that would reduce the burden while retaining the benefits of IRB review. These objectives are particularly timely given the recent announcement by the US DHHS that it is embarking on regulatory reform (US DHHS 2011).

Background

History of Independent Ethics Review

The first federal policy requiring an independent review of the risks and benefits of research for human participants was enacted in 1953

when the NIH director created the Clinical Research Committee of the Medical Board to review any studies at the newly opened clinical center that investigators thought might involve unusual risks (NIH 1953).

In 1966, the U.S. Surgeon General directed that all institutions receiving research funds from the U.S. Public Health Service ensure that all studies with human subjects be reviewed by an independent group, which was to determine the appropriateness of the methods used to obtain informed consent and also to consider the risks and potential benefits of the research (Bureau of Medical Services 1966). This internal policy was incorporated into federal regulations in May 1974, shortly before Congress passed the National Research Act of 1974. This act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. As part of its charge, the commission produced a report on IRB review that served as the basis for the 1981 extension of the regulatory requirement for review to all federally funded research, as well as research conducted at institutions that received federal funding (U.S. National Commission 1978). Although the regulations have been revised since then, the basic roles and responsibilities of investigators, IRBs, and research institutions have remained largely unchanged.

Current Regulations

Two regulatory sources in the U.S. Code of Federal Regulations (CFR) are relevant to today's requirement that research be reviewed by an IRB before it is begun. Title 45 CFR, part 46, establishes the requirement for all federally funded research or research conducted at institutions that receive federal funds, and title 21 CFR, part 56, does the same for research conducted in order to obtain approval from the Food and Drug Administration (FDA) to market a new drug or biological. The Office of Human Research Protections (OHRP) in the U.S. Department of Health and Human Services has oversight authority for studies covered by title 45, and the FDA is the regulatory authority for studies covered by title 21 (US DHHS 2005).

The two sets of regulations impose similar, though not identical, requirements. Specifically with respect to IRBs, they establish requirements for the number and types of members and for various operations (frequency of review, documentation requirements). The regulations also

list the specific criteria that must be met for the IRBs to approve research. Of the seven criteria, two are related to risk (that it is minimized and reasonable in light of the expected benefits), and two concern informed consent (that it is sought and properly documented). The remaining criteria are that participants be selected in an equitable manner; that provisions are made to protect privacy and confidentiality; and that suitable plans exist for monitoring the participants' safety once the research begins.

Institutions that support human subjects research must give the OHRP their written assurance that they will comply with all federal regulations directed at protecting human research participants (CFR 45, part 46, section 103) (US DHHS 2009). This commitment means that institutions can be held accountable by the OHRP for any noncompliance with the regulations governing IRB operations.

Methods

As does all summative research, our study faced the challenge of designing a search strategy that identifies all relevant studies without selecting substantial numbers of irrelevant studies. In addition, the substantive focus on "burden" presented us with the subject-specific challenge of distinguishing necessary from unnecessary costs.

Search Strategy

Our search for information on the costs to research of IRB review or the factors that contributed to such costs involved multiple modalities to ensure that we obtained a comprehensive list of relevant studies. Our initial search of the PubMed database looked for studies at the intersection defined by the (MESH) terms "institutional review board" (as a major topic heading) and "cost" or "economics" in any study field. Additional searches used IRB and "efficiency" or "consistency." We reviewed abstracts of potentially relevant studies (or full articles when abstracts were not available) to determine their relevance: that is, whether they contained primary data on IRB-research interaction, the efficiency of IRBs, or IRB positions or decisions. We also looked at the reference lists of all the selected studies to identify other candidate studies. We

then reentered into the PubMed subject line the citation for any study with information on “costs to research” and asked for all “related citations.” These searches took place between September and December 2009. Weekly updates from PubMed were tracked through the end of August 2010 to ensure inclusion of newly published relevant studies.

As part of our search for information, we searched the websites of all regulatory agencies that were responsible for human research protections, as well as those of organizations that had produced reports on either IRBs or human subjects protection, to find any original studies that our PubMed search might have missed.¹

We also monitored the IRB Forum (<http://www.irbforum.org/>), a list-serve and news service on human research ethics, for any newly published studies that had not been entered into PubMed. Finally, we reviewed the tables of contents for all issues of the journal *IRB: Ethics & Human Research* (formerly *IRB: A Review of Human Subjects Research*) from 2002 through 2010. These combined activities identified a total of 311 potentially relevant studies, of which 52 contained primary evidence on costs, burden, efficiency, consistency, or quality of decisions.

Cost and Burden

The need to obtain IRB approval necessarily adds costs to research, including the costs of preparing the submission; the costs associated with additions, deletions, or modifications to the research made in response to the IRB review; the costs of resubmission when necessary; and, if the project’s initiation is delayed waiting for IRB approval, the costs of such a delay. Our search selected those studies that included evidence on any of these costs, as well as on such nonmonetary “costs” as the IRB’s constraints on the scope or methodology of the research, or any decrease in the likelihood of the investigators’ or subjects’ participation as a consequence of the IRB’s decisions. Although we present the evidence from all the identified studies, we restricted our characterization of costs as burdensome to those instances in which (1) the costs were attributed to some aspect of IRB review *and* (2) the authors stated that the expenditure did not increase (or impact) the protections afforded to research participants.

In addition to selecting studies with information on costs, we also chose all studies containing evidence on three factors that, if present,

would increase the likelihood of burden: (1) inefficiency in IRB operations (including lengthy review times), (2) inconsistent IRB policies or inconsistent decisions made by IRBs participating in the same multi-site research study, and (3) decisions made (or positions held) by IRB members that either were contrary to regulatory policy or reduced the protections afforded to research participants.

Limitations

The need for IRB review is generally accepted in clinical research. Accordingly, given our interest in the more inclusive category of health-related research, our examination of the burden imposed by IRB review assumed that such review was indeed needed. This assumption is not universally shared, however, especially by researchers in fields in which physical interactions with human subjects are typically more limited (Gunsalus et al. 2007; Thomson et al 2006). Their position is that whenever the risks to human participants are negligible, any resources expended to obtain IRB approval constitute a burden. Additional criticisms have come from some legal scholars who argue that IRBs inappropriately censor research. Our study did not examine the merits of these positions, and therefore, our results are not intended to inform the ongoing debate about what has often been referred to as "IRB creep."

Findings

We found a total of fifty-two studies that contained primary evidence on either the costs associated with an IRB review or the factors contributing to those costs. These studies were from throughout the period of interest, although most were after the 1998 publication of two evaluations of IRB performance conducted (or sponsored) by the government (Bell, Whiton, and Connelly 1998; US DHHS 1998). Twenty-three of the studies were included because they had evidence on one of the dimensions of interest: six had data on review time; one enumerated review decisions made by an IRB over time; five examined the efficiency of review; nine provided data on IRB policies or positions in specific substantive areas; and two used simulations to measure the consistency of review. The remaining twenty-nine studies contained information from more than one dimension of

interest. These latter studies also were similar in that they all focused on situations in which multiple IRBs reviewed the same research protocol (or the same small number of research protocols).

The principal limitation of the studies was their lack of generalizability. Only those surveys of IRB policies and the studies of IRB efficiency drew their samples from specified populations to which their conclusions could be extended. The other studies presented evidence that came either from a single IRB or, more typically, from multiple IRBs reviewing a single study (or a small number of similar studies).

We organized the evidence from all the studies into sections for each of the three indicators of burden: efficiency (which includes review times), consistency of decisions, and quality of decisions. The section presenting the evidence on impacts on research—including those judged as burdensome—concludes this section on findings.

Efficiency of IRB Review

Case reports from researchers cited specific instances in which IRBs exhibited inefficient behaviors, such as lost paperwork (Green et al. 2006), multiple iterations to resolve issues (Greene et al. 2006), and expedited reviews that took longer to complete than full reviews did (Larson et al. 2004). The broadest evidence of inefficiencies, however, came from studies of IRBs' operating costs and from reports of the time needed to obtain an IRB's approval. These first studies are now somewhat dated (having been published between 2003 and 2005 and reporting data from two to four years earlier), but they consistently show that lower-volume IRBs are less efficient than their higher-volume counterparts. The magnitude of some of the reported differences is considerable. One study's relative costs for initial and subsequent reviews (including reviews of adverse event reports) were estimated to be \$799 and \$277 for low- and high-volume IRBs, respectively (Wagner et al. 2003), and a companion study of Veterans' Administration IRBs estimated an even greater difference of \$2,781 versus \$187 (Wagner, Cruz, and Chadwick 2004). A third study surveyed medical school IRBs and reported a more modest ratio of \$644 to \$431 (for initial reviews; see Sugarman et al. 2005). Added support for very different cost profiles across IRBs came from a recent evaluation comparing average costs for research reviewed by the National Cancer Institute's adult central IRB (\$91 for initial and \$106 for later reviews),

with the average costs for reviews at other IRBs (\$389 initial, \$254 later) (Wagner et al. 2003).

Subsequent analyses of the operating cost data led Byrne and colleagues to conclude that inefficiencies in IRB operations extended beyond those attributable to economies of scale (Byrne et al. 2006). Their conclusion was based on the considerable variation observed among IRBs in the same volume strata. One measure of that variation is the ratio of staff resources to IRB board resources expended on protocol review. Byrne and colleagues argued that the range of 0.33 to 11.3 indicates very different models of how review proceeds at different IRBs. When combined with the variation in costs per review, the different approaches to reviewing suggest that relative efficiencies depend on factors other than just volume.

The principal mechanism through which efficiency of review is seen to affect research is that it contributes to what are regarded as inordinately long review times. The most comprehensive data on review times come from an evaluation of IRBs reviewing NIH-funded research (conducted in 1995 and reported three years later) (Bell, Whiton, and Connelly 1998). This survey found a relatively modest median review time of twenty-seven days between submission and IRB approval. As table 1 shows, in subsequent studies, the review times are almost uniformly higher.

The longer review times compared with those reported by Bell and colleagues (Bell, Whiton, and Connelly 1998) may be the result of numerous factors, including increasing IRB workloads over time, changes in the complexity of research, or even more poorly prepared submissions. But the considerable variation in review times for IRBs looking at identical protocols—the average range for the fifteen studies that allow this computation is 220 days—suggests that some reviews take longer than needed or that some IRBs did not devote sufficient time to review, or some combination of the two.

Consistency of IRB Decisions

Studies of IRB decision making initially relied on simulations to explore whether IRBs presented with identical research would reach similar or different conclusions. One study submitted three mock protocols with problematic ethical components to twenty-two reviewing IRBs

TABLE 1
Studies Reporting IRB Review Times

Source	Condition or Issue	Study Type	Number of IRBs	Number of Protocols	Type of Review	Number of Days ^a	Range (days) ^b
Hirshon et al. 2002	Domestic abuse	Survey	3	1		108*	91
Burman et al. 2003	Tuberculosis	Clinical trials	25	2		104.5	305
Mosesso et al. 2004	Defibrillation	Clinical trial	101	1		108	153
McWilliams et al. 2003	Cystic fibrosis	Genetic epidemiology	31	1	Expedited Full	32.3 81.9	
Larson et al. 2004	Nosocomial infections	Observational	68	1		45.2*	300
Dziak et al. 2005	Quality of care	Phone survey	15	1			167
Camacho et al. 2007	Cancer	Clinical trials	1	31		107	107
Clark et al. 2006	Asthma	Registry construction	4	1			51
Dilts and Sandler 2006	Cancer	Clinical trials	1	13		111	274
Greene et al. 2006	Prophylactic mastectomy	Survey	6	1		28 to 56	28
Jester et al. 2006	West Nile virus	Observational	28	1		48	452
		Clinical trial	27	1		74	335
Sherwood et al. 2006	Recurrent respiratory papillomatosis	Observational	14	1		93*	280
Dyrbye et al. 2007	Medical education	Survey	6	1		13	114

Continued

TABLE 1—Continued

Source	Condition or Issue	Study Type	Number of IRBs	Number of Protocols	Type of Review	Number of Days ^a	Range (days) ^b
Govindarajan et al. 2007	Cancer	Clinical trials	1	175	Cooperative group trials Industry-sponsored trials	19 48	266 185
Mansbach et al. 2007	Pediatric emergency admissions	Observational	37	1		42	34
Chaney et al. 2008	Depression	Implementation research	13	4	Expedited Full Exempt		70 75 64
Dilts et al. 2008	Cancer	Clinical trials	1	28		116	692
Helfand et al. 2009	BPH ^c	Clinical trial	6	1		35.8*	54
Finch et al. 2009	Child abuse	Clinical trial	75	1		109	
	Child safety	Observational	75	1		81	
Wagner et al. 2010	Cancer	Clinical trials	1	38	CIRB ^d	13.1	
			N/A	28	non-CIRB	35.5	193
Pogorzelska et al. 2010	Nosocomial infections	Observational	50	1		35*	
Ravina et al. 2010	Parkinson's disease	Clinical trial	42	1		61.4	

Notes: ^aMean number of days are labeled with an asterisk; median days do not have an asterisk.
^bRange (days) is defined as the (maximum days / minimum days).
^cbenign prostatic hypertrophy.
^dcentral IRB.

(Goldman and Katz 1982). The IRBs were consistent in not approving the protocols, but they gave different reasons for their decisions and for the revisions they requested in order to obtain approval. A second study presented actual research protocols—ones that had already been approved by other IRBs—to simulated IRBs created at a conference on medical ethics (Harding and Ummel 1989). Of the eight protocols reviewed, only one was considered acceptable as written; five others were determined to require revisions; and two were deemed unacceptable. Critics of the first study (Caplan 1984; Levine 1984) argued that the participating IRBs had not taken the hypothetical studies seriously, but they did acknowledge that inconsistent decisions could be problematic. The authors of the second study also were limited by the artificiality of their experiment but concluded that the different decisions regarding approval or rejection raised concerns about the validity of IRB reviews.

The advent of multicenter trials provided a real-world test of how different IRBs would respond to identical research protocols. A 2006 review identified twenty U.S. studies that examined IRB decisions when reviews of identical proposals were conducted by multiple IRBs (Greene and Geigen 2006). All the reviewing IRBs were reported to have inconsistencies. The areas of divergence included determinations of risks (and related decisions about the type of review required) (Green et al. 2006; Hirshon et al. 2002; Larson et al. 2004), recruitment procedures (whether payments could be made to participants) (Greene et al. 2006), consent requirements (whether consent was needed or could be waived) (Dziak et al. 2005), and assessments of the adequacy of consent forms (Schneider et al. 2004; Stair et al. 2001). Our search identified eleven additional studies that documented decisions made by multiple IRBs reviewing identical protocols. With one exception, all reported inconsistencies in the IRBs' decisions. Specifically,

- Of the eleven IRBs reviewing a study that planned to track disease progression among adolescents with HIV/AIDS, four decided that it posed “no more than minimal risk,” and one stated that the risk was greater than minimal. A sixth IRB concluded that the risk was more than minimal for the healthy controls enrolled in the study but not for the HIV/AIDS participants. Two IRBs required changes to reduce the risk: one asked that enrollees be screened for anemia, and the other asked that a planned wrist X-ray of controls not be carried out. Finally, three IRBs did not mention risk in their

communications with the investigators, even though one of the IRBs had requested a waiver of parental permission (Rogers et al. 1999).

- Four of the twenty-four IRBs reviewing a prospective, randomized trial of the effects of making automated external defibrillators publicly accessible did not ask for any revisions, whereas ten of the IRBs asked for multiple revisions (Mosesso et al. 2004).
- Of the thirty-four IRB reviews of a protocol to study the management of pediatric bronchiolitis in emergency departments, thirteen approved the protocol without change, eighteen offered conditional approval, and three deferred on the submission (Mansbach et al. 2007).
- Twenty-one IRBs reviewing a study of the natural history of West Nile virus and twenty-two IRBs reviewing a trial of a vaccine for that condition requested from 0 to 172 changes for the former study and from 0 to 268 changes for the latter (Jester et al. 2006).
- Sequential submissions of a protocol for a minimal-risk genetic study to eight IRBs did not reduce the number of revisions requested by the later-reviewing IRBs (Sherwood et al. 2006).
- A research team creating a registry for instances of fatal asthma submitted its procedures to IRBs in four states. All the reviewing IRBs required the consent of the surviving family members, but two allowed the consent to be tacit (through an opt-out mechanism), and the other two required that entry into the registry be allowed only if a family member opted in (Clark et al. 2006).
- Of the six IRBs reviewing a survey of medical students, the median number of change requests for five of the IRBs was thirteen, while the sixth IRB approved the study with no changes (Dyrbye et al. 2007).
- Nine IRBs reviewing a protocol to study the implementation of collaborative care for depression reached different conclusions about the type of review required, with two requiring full review, five granting an expedited review, and two exempting the research from IRB review. For a related study (reviewed by four of the same IRBs and four different IRBs), one IRB required a full review, two IRBs gave it an expedited review, two more exempted it from review, and the last one determined that the study did not involve human subjects (Chaney et al. 2008).

- The fifty-five IRBs reviewing three pediatric protocols differed in whether the participants could be compensated, what they could be compensated for, and the amount they could be compensated. For the study perceived to be the most demanding—a hypertension study—all the IRBs allowed compensation but with an eightfold difference in the allowable maximum (Kimberly et al. 2006).
- Nine IRBs reviewing a study of vitamin supplements for low birth-weight neonates initially withheld approval because of concerns about risk, whereas seven other IRBs approved the study with no concerns (Stark, Tyson, and Hibberd 2010).
- In a trial of a surgical versus a medical intervention reviewed by six IRBs, 95 percent of the 259 revisions requested in either the first or second review were unique. Inconsistencies were observed both across IRBs and within IRBs over time (between first and second review) (Helfand et al. 2009).
- A 2004 study of sixty-eight IRBs reviewing research that relied on publicly available data and survey responses to examine the relationship between working conditions for nurses and outcomes in the ICU found that the IRBs' procedures were "nonstandardized" (Larson et al. 2004). A recently published follow-up reported on experiences with review by fifty IRBs of a similar observational protocol (focused on nosocomial infections as the outcomes of interest) (Pogorzelska et al. 2010). The earlier study had found considerable variation in the type of review: forty-two IRBs decided on expedited review, and the remaining twenty-six split almost evenly between those that selected a full review (12) and those that exempted the protocol from review (14). The more recent publication, however, reported that the type of review selected by the participating IRBs was more consistent, with forty-two of the fifty IRBs opting for an expedited review.

Supplementing the evidence on the degree of consistency in IRB decisions are surveys that explore the extent to which opinions and policies vary across IRB members (or across the guidance offered on IRB websites). Table 2 lists the studies that we identified through our search.

As the table shows, there were differences between IRBs in five policy areas: (1) whether study results should be released to the individuals who consented to participate in the research (Kozanczyn, Collins, and Fernandez 2007), (2) review of research located at community-based sites

TABLE 2
Studies of IRB Policies and Positions

Source	Sample	Focus	Findings
Kozancyn, Collins, and Fernandez 2007	207 medical school and commercial IRB websites	Policies on return of research results to participants	More than half had no policy, and another third had vague policies. One-quarter had policies specifically referring to genetic results. Half had formal policy for review.
Silverstein et al. 2008	196 academic IRB directors	Policies for review of community-based research	One-third do not require disclosures.
Vogeli, Koski, and Campbell 2009	211 medical school IRB chairs	Policy on conflict of interest for IRB members	Variation found, with higher-volume IRBs displaying greater compliance with federal regulations.
White and Gamm 2002	427 chairs of OHRP-registered IRBs	Required elements of consent for use of stored blood	Half of respondents have a policy and half do not.
Whittle et al. 2004	188 chairs of pediatric, commercial, and general IRBs	Policies on pediatric assent	More than half the respondents did not consider OHRP-recommended mechanisms for resolving ethical concerns (de-identification or waiver of consent), but the remainder did.
Wolf et al. 2008	55 chairs of OHRP-registered IRBs	Ethical concerns with genomic research	Inconsistencies were observed in the understanding of COI policies at the seven institutions that did not have written policies for COI.
Dinan et al. 2006	9 medical schools	Policies on conflict of interest (COI) in research and coordination between IRB and COI committee	

(Silverstein et al. 2008), (3) conflict of interest for IRB members (Vogeli, Koski, and Campbell 2009), (4) elements of consent for use of stored blood (White and Gamm 2002), and (5) requirements for obtaining assent in pediatric research studies (Whittle et al. 2004). The IRB chairs in one study differed in their willingness to rely on (or in their awareness of) federally accepted mechanisms for allowing researchers access to genomic data (Wolf et al. 2008). These observed differences complement the inconsistencies observed in the IRB decisions that we described earlier.

We found only one study (Pogorzelska et al. 2010) that concluded that IRB decisions or IRB policies were generally consistent.

Quality of IRB Decisions

The inconsistencies among IRBs reviewing identical protocols raise questions about the validity of those decisions and suggest that at least some IRB decisions do not increase the research participants' protections. More definitive evidence comes from specific examples cited in those studies, including the following:

- In their initial review of an interventional trial examining a vitamin supplement for low birth-weight neonates, one IRB initially withheld approval because there was insufficient evidence that the intervention had any benefit, and another questioned whether randomization was ethical, given the established benefits of the intervention (Stark, Tyson, and Hibberd 2010).
- Changes in consent forms requested by local IRBs for two studies of tuberculosis were evaluated by independent reviewers who concluded that the changes lengthened the forms and decreased their readability by almost a full grade level. In addition, errors were introduced as a result of the changes, and 66 percent of the forms eventually approved by local IRBs were found to contain errors (Burman et al. 2003).

The broadest evidence that IRB decisions may not be related to protections comes from studies of IRB policies and positions taken on specific substantive issues. A 2003 examination compared the readability of language for consent forms suggested by medical school IRBs with the standards that those IRBs established for readability and found that the

suggestions made the forms less, rather than more, readable (Paasche-Orlow, Taylor, and Brancati 2003). Another cross-IRB comparison asked IRB chairs to assess the risk of various research procedures for a pediatric population and found considerable inconsistencies in the assessments of risk as well as divergence from the federally established standard for defining minimal risk (Shah et al. 2004). Among the findings were that (1) more than 70 percent of respondents concluded that allergy skin testing posed more than minimal risk—a position at odds with data on skin testing—and (2) 59 percent of respondents indicated that they would prohibit a pharmacokinetic study that had a 1-in-100,000 chance of death because it was too risky, but 37 percent of respondents considered the same study to pose no more than minimal risk.

Impact on Research and Burden

The only study we found that estimated the unnecessary costs associated with less efficient IRB review did so for total expenditures (rather than solely research costs) and also derived its estimate by combining the savings expected from using more efficient IRBs with those from relying on a single IRB for multicenter studies (Sobolski, Flores, and Emmanuel 2007). Nonetheless, the idea that between 10 and 35 percent of costs devoted to IRB review could be saved by relying on a central review for multicenter research does show that some current costs are unnecessary.

The more immediate consequences of inefficient review are those resulting from slower-than-necessary review times. In one study, the long review times caused four prospective sites to withdraw from participation (Mansbach et al. 2007), and in another, the delays prevented two sites from using the survey vendor retained by the other participating sites (Greene et al. 2006).

Two condition-specific points are worth noting. The relatively long time required to obtain IRB approval was reported as a reason for not being able to recruit patients with West Nile virus for a vaccine trial because the height of the season had passed by the time that recruitment could begin (Jester et al. 2006). Nonetheless, the only study explicitly examining delays in cancer trials found that IRB review—despite requiring an average of 111 days—did not delay the trial because processes other than the IRB review took longer to complete (Dilts and Sandler

2006). In neither instance was the review time necessarily burdensome, according to our definition, because the delays in the first study may have been necessary to ensure adequate protections and those in the cancer study did not delay the project's initiation.

As these studies examining the local review of multicenter research show, the best evidence regarding the impact of inconsistent IRB decisions on research comes from multicenter research. A number of studies provide dollar estimates for the incremental costs of having to obtain approval from multiple IRBs, but the extent to which these costs are solely because of inconsistency or redundancy is not clear. In the first two studies, the study authors explicitly characterized the changes as not affecting the level of protections afforded to research participants.

- A 2003 study estimated that it cost researchers studying the treatment of substance abuse at eight sites more than \$56,000 (almost 17 percent of their total project budget) to respond to the revisions requested by the participating IRBs after the host IRB had already approved the research (Humphreys, Trafton, and Wagner 2003).
- A fifty-two-site study of Parkinson's disease spent more than \$102,000 to obtain approval from forty-two reviewing IRBs, with approximately three-quarters going to cover the IRBs' review fees (Ravina et al. 2010).
- A Veterans' Administration-based study of outcomes of repairing ventral hernia estimated that \$53,000 (almost 14 percent of the total project budget) was for staff costs required to obtain approval from the participating IRBs (Vick et al. 2005). This cost may be an underestimate since the study was published before all IRB approvals were secured.

Other reports describe the impacts of IRB review that are likely to include additional costs for research but do not provide a dollar estimate of those costs. An effort to measure the quality of cancer care by reviewing medical records and surveying patients was delayed by more than a year because of inconsistent IRB responses (Schneider et al. 2004). A multisite study that used interviews, surveys, and pharmacy-dispensing data to examine the relationship between how guidelines on treating hypertension were disseminated and adherence to those guidelines spent 4,680 staff hours interacting with the participating IRBs (Green et al.

2006). A randomized trial of treatment for postpartum depression was stopped at various sites for between two and thirteen weeks because of the participating IRBs' inconsistent policies regarding the date stamping of consent forms and the calendar period for staff training (Yawn et al. 2009). Finally, several studies reported that addressing inconsistent and slow IRB responses forced some prospective sites to withdraw from participation (Dyrbye et al. 2007; Mansbach et al. 2007). The impacts of IRB review were described as burdensome only in the hypertension and depression studies.

Conclusions

The assembled evidence on the costs to research of IRB review includes a relatively small number of studies that explicitly identify some of those costs as unnecessary. Although we found these case reports to be credible, they are not enough by themselves to allow us to estimate the frequency of such occurrences, the magnitude of the burden imposed, or its impact on the conduct of health-related research. There is a more substantial body of evidence on what might be considered the "risk factors" for burden. The studies we reviewed demonstrate that

- IRBs operate at different levels of efficiency,
- decisions made (and positions held) by IRBs and their members are not always in accord with regulatory guidance,
- waiting times for approval for the same study protocol are sometimes lengthy and highly varied,
- IRBs presented with identical protocols will sometimes ask for different and even competing revisions, and
- decisions made (and positions held) by IRBs are not always in accord with policy guidance from OHRP.

Again, the evidence is not sufficient to estimate the frequency with which the IRBs' inefficiency, inconsistency, and poor decision making was encountered or the magnitude of burden that such behaviors impose on research. What is clear, however, is that the interplay of these factors is particularly important to multisite studies in which local IRBs review the same protocol at each participating site. In those instances, the inherent redundancies of duplicative review and the multiplicative

consequences of any inconsistent decisions by participating IRBs make it more likely that costs are unnecessarily imposed on research.

The greater likelihood of burden for multisite studies may explain why the disproportionate share of the evidence on costs and burdens comes from examinations of such studies. At least part of that explanation is also methodological, however. The quasi-experimental nature of multisite studies (i.e., many units performing an identical task) makes it easier to detect any burden that does exist because it allows for comparative assessment. The ability to state conclusions based on “more” (or “less”), “longer” (or “shorter”), and “different from” is essential because the evidence needed for empirically based, normative conclusions about IRB performance or IRB impact on research does not exist.

Implications

In late July 2011—after we had completed a draft of this article—the U.S. Department of Health and Human Services issued an advanced notice of proposed rule making (“Notice”) announcing that it was considering reforming the regulations governing the protection of human subjects (US DHHS 2011). The proposed reforms are directed at both enhancing the protections of research subjects and reducing the regulations’ burden on research, goals that closely parallel those of our study. The scope of the reforms extends beyond IRB review, but with respect to review, the department’s position is consistent with our conclusions. As we do, the department concluded that IRB review may impose a burden and that the burden is likely to be greatest when several local IRBs review a single multicenter study. Based on this position, the department is requesting public input “on the feasibility, advantages, and disadvantages of mandating that all domestic sites in a multi-site study rely upon a single IRB of record for that study.” That reliance “would not prohibit individual institutions from conducting ‘additional internal ethics reviews’ for their own purposes, although such reviews ‘could be discouraged.’”

The studies we reviewed did not allow us to estimate the magnitude of the burden or the possible benefits of continued reliance on local review. Consequently, we could not construct an evidence-based ratio of the two dimensions of burden and benefit for local versus central review. Without having some idea of what that ratio would look like, we

limited our recommendation to removing an existing regulatory barrier to reliance on a central IRB review in multicenter studies. Our more conservative approach does not reflect a difference in perspective from that adopted in the department's Notice, so much as an unwillingness to go beyond the primary evidence.

Beyond the issue of burden associated with IRB review, we call attention to how little we know about the critically important intersection between research aimed at improving personal and public health and the regulation of that research. While there is both a general acceptance of the need for policy to be informed by evidence and the technology available to make the acquisition of evidence practical, there still are no mechanisms in place to systematically track the interactions between research and IRBs. Data on the number and type of studies being reviewed by IRBs, the adherence of those studies to the principles contained in federal regulations, the decisions made by IRBs, the efficiency of their operations, and the outcomes of those decisions are not readily available to inform policy decisions. Observers have identified this gap as one of the principal threats to the system for protecting human research participants in this country (Catania et al. 2008; Federman et al. 2003; Gunsalus et al. 2007), and recommendations to establish a data system that measures the IRBs' performance and effectiveness have been made for more than a decade (US DHHS 1998).

The Notice acknowledges the absence of any mechanisms to routinely gather the evidence needed to evaluate the system for human subjects protection and recommends collecting data to enhance oversight of the system. However, that recommendation is restricted to data concerning adverse events experienced by research subjects and does not include any data needed to assess the efficiency of the system or its impact on research. In essence, then, the Notice sees the enhancement of protections and the reduction of burdens as two goals of its reforms but then proposes routinely evaluating success for only the first.

A mechanism to monitor IRB decisions would be particularly helpful during periods of rapid change in the conduct of research or in the understanding of the risks and benefits of that research. At such times, data on IRB decisions (and deliberations) would make it possible for (1) IRBs to learn from one another's experiences; (2) researchers to better and more quickly understand IRBs' positions and their implications for how research should be designed; and (3) there to be open discourse on whether the boundaries for research being established by IRBs in

response to the technological changes are in line with those desired by the public.

IRBs have always been confronted with difficult decisions that need to be made under conditions of uncertainty, and they have made those decisions without the benefit of data on what their peers are doing or the consequences of their decisions for research. As proponents of evidence-based decision making, we believe that such data would be of considerable benefit.

As health policy researchers, we see the current understanding of IRB review as somewhat analogous to the understanding of physicians' practice patterns at the time when evidence first emerged of the variation among geographic areas (Wennberg and Gittelsohn 1973). Those differences were initially discounted as reflecting differences in local needs and preferences but were later shown to result from other factors. The process of trying to understand why physicians practiced differently was an important motivator for an evidence-based health care system. Some people see the variations in IRBs' decision making as reflecting differences in local values and preferences. Others contend that the variation is indicative of problems and poor decisions. Although experiences with health care policy do not prove which position is more valid, they do suggest that it might be advantageous to adopt an evidence-based approach to regulating research.

Endnote

1. We searched the following sites:

- The Office for Human Research Protections (<http://www.hhs.gov/ohrp/>).
- The National Bioethics Advisory Commission (<http://www.bioethics.gov/>).
- The Clinical Research Policy Analysis and Coordination Program in NIH (http://oba.od.nih.gov/policy/program_overview.html).
- The Secretary's Advisory Committee on Human Research Protections (<http://www.hhs.gov/ohrp/sachrp/>), U.S. Department of Health and Human Services.
- The Food and Drug Administration, Information Sheet Guidance(s) for Institutional Review Boards, Clinical Investigators, and Sponsors (<http://www.fda.gov/ScienceResearch/Special-Topics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm>).
- The Institute of Medicine of the National Academy of Sciences (www.iom.edu).
- The U.S. Government Accountability Office (www.gao.gov).
- The Office of Inspector General of the U.S. Department of Health and Human Services (<http://oig.hhs.gov/>).
- The archived reports of the Advisory Committee on Human Radiation Experiments (<http://www.gwu.edu/~nsarchiv/radiation/>).

- The Clinical Trials Transformation Initiative established by the FDA and Duke University to increase the quality and efficiency of clinical trials (<https://www.trialstransformation.org/>).
- The Clinical Research Ethics Committee of the Clinical and Translational Science Awards Consortium (http://www.ctsaweb.org/index.cfm?fuseaction=committee.viewCommittee&com_ID=15).
- The NIH Initiative to Reduce Regulatory Burden (<http://grants.nih.gov/grants/policy/regulatoryburden/index.htm>).

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