COMMENTARY

Pruning the regulatory tree

For human-subjects research, maximum regulation does not mean maximum protection. Stop regulating minimal risk research, say **Scott Kim**, **Peter Ubel** and **Raymond De Vries**.

The rapid improvement of the US system to protect research subjects is an important human-rights achievement, but it has grown in ways that require careful cultivation and, at times, cutting back.

Consider a much-discussed study in which Peter Pronovost, a critical-care researcher at the Johns Hopkins University in Baltimore, Maryland, tested how using a simple checklist of scientifically proven steps, such as hand washing, might reduce catheter-induced infections. The study enlisted 108 intensive-care units in Michigan and over the course of 18 months it saved an estimated 1,500 lives and US$175 million through shorter hospital stays. But not long after the results were published, the Office for Human Research Protections (OHRP) at the US Department of Health and Human Services ordered the hospitals to halt data collection on the study.

> "At least half of institutional-review-board costs are devoted to evaluating minimal-risk research."

Although the OHRP agreed that the study was minimal risk and did not need informed consent, it concluded[1] that Johns Hopkins University had incorrectly deemed the study exempt from review by institutional review boards (IRBs). Without this exemption, the study would have taken longer, cost more and resulted in greater variation between procedures at different study sites (given the involvement of dozens of IRBs). This is not a case of abuse or even misinterpretation of current regulations. Rather, it illustrates a serious flaw in the regulations: the requirement of extensive and expensive protocol reviews that yield no ethical benefit.

Many are frustrated with the current system for protecting research subjects: some find it too flimsy, others see it as too overbearing[2]. This tension paralyses reform efforts. We propose a way around the stalemate through a simple regulatory change that is far-reaching, equitable and yet low risk: exempt minimal-risk research from IRB review.

Low-risk research protocols are common in several disciplines including health-services research, education research, history and the social sciences.The US Federal regulations define minimal-risk research as that in which "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[3] Review boards routinely use the concept in making decisions, but current oversight is complex and extensive (see table).

We propose that institutions streamline oversight of minimal-risk research by requiring investigators to complete a brief application describing research procedures, risks, burdens and the potential loss of otherwise expected benefits to the subjects. An institution-designated person reviews the application, and exempted protocols would not be subject to further IRB review. The application becomes the project's registration and serves as an accountability document. Note that our proposal is not meant to apply to minimal-risk research involving direct interactions with people who are incapable of informed consent, because research with such people raises special ethical concerns.

How would our proposal affect subject safety? Since only those studies with minimal chance of minimal harm are exempted, the effect on subject welfare would be minimal. What about the effect on informed consent and subject autonomy? Consider studies that require direct interaction with subjects. Informal voluntary consent should still be given by subjects. This is the prevailing practice for low-risk interpersonal interactions of everyday life in a liberal democratic society, and should suffice for minimal-risk research interactions too. Indeed, formal consent is contrary to the implicit, intuitive norms of communication and can even cause mistrust[4].

Current regulations justify exceptions to formal informed consent mainly by appealing to minimal risk. They allow verbal consent rather than the usual written consent largely based on minimal-risk considerations[3]. Informed consent itself can be waived if the study is minimal risk and other conditions are met[3]. We believe that the minimal-risk criterion serves as the sole ethical justification of these waivers; other regulatory conditions (such as the requirement that the research would not be 'practicable' without the waiver) provide no additional ethical justification.

The burdens of oversight

Although the ethical benefits of regulating minimal-risk research are negligible, the costs are not. The IRB system is widely recognized as being underfunded[2] yet a 2005 study[5] found that 41% of all new protocols reviewed by US academic medical centre IRBs are expedited (and thus minimal risk). The median annual cost for a medical-centre IRB was $750,000. Because expedited reviews cost about the same as full reviews[5], the median cost of expedited reviews is approximately $300,000 per year. And because 43% of IRBs surveyed do not pay their review-board members (who are generally highly remunerated professionals), these costs represent an underestimate of true costs. Moreover, minimal-risk-research reviews are likely to be more common at non-medical centre IRBs. At our institution (a major research university with a medical centre),

EXISTING REVIEW PROCESSES FOR MINIMAL-RISK RESEARCH

Current exemption process[3]	Current expedited review process[3]
Researcher submits application — type varies by institution.	Researcher submits a full IRB application.
Institution-designated person determines study is minimal risk according to de facto standard[12].	IRB designee determines whether the study is minimal risk.
The protocol must also meet one of six criteria for exemption.	The protocol must also meet one of nine criteria for expedited review. The IRB designee reviews protocol.
Some IRBs do not allow exemptions, regardless of federal criteria.	If informed consent is required, review board and investigator will exchange drafts of the consent form.
	If waiver/alteration of informed consent, or its documentation, is requested, further review is needed.
	Changes to the protocol require amendment applications to the IRB. Annual review is required.

IRB = institutional review board

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56% of new IRB approvals are expedited, with additional 23% that are exempted[6]. Non-medical centre, low-volume IRBs (which review a disproportionate number of minimal-risk-research protocols) do not enjoy economies of scale[7]. Thus, at least half (and probably much more) of all direct IRB costs are devoted to expensive reviews of minimal-risk studies — resources that could be used to improve the oversight of riskier studies.

There are also significant financial and scientific costs to researchers and sponsors. Even expedited reviews can take several weeks for approval, and those few weeks in the brief life of a single sponsored project add up to a substantial amount when extrapolated to the thousands of such projects. Minor revisions to protocol can add weeks of delay and, when pressed for time, researchers sometimes accept sub-optimal science in order to comply with the rules.

Patients are affected because of lack of quality-improvement research. A report[8] by an interdisciplinary study group notes that the current system has "generated disincentives to engage in quality improvement" and produces "inconsistent decisions, increases costs, retards improvement, and undermines respect for research review". Quality-improvement research has tremendous implications for public health. Provonost's study, for example, addresses a problem responsible for 28,000 deaths and billions of dollars per year in the United States[1]. There is considerable concern that the OHRP actions in this case will have a chilling effect on quality-improvement research.

Unnecessary oversight also generates other costs. Some researchers, when asked to conform to a system they believe is ethically unnecessary, may decide to violate the procedures[9]. Such behaviour can become culturally entrenched and passed on from mentor to trainee. We do not condone such behaviour, but it is counterproductive to knowingly support a regulatory system that undermines the very intent of those regulations. Researchers are also increasingly concerned that some types of human-subject regulation are a form of censorship and an infringement of academic freedom[10].

Institutions have a tendency to impose on themselves requirements that are even more stringent than those required by law. But a new regulation that exempts minimal-risk research from IRB review would send a clear and unambiguous message that the government's priority is not on intense oversight of low-risk research.

Can minimal-risk research determinations be made reliably and validly? Some may point to the debates over minimal risk in the paediatric literature as evidence that 'minimal risk' is a contested concept[11]. But that literature is constrained by the special situation in paediatric research — whether a study is minimal risk can determine whether it is allowed at all. The situation is very different in our proposal, in which a determination of greater than minimal risk simply means that a protocol is non-exempt and in need of the usual institutional review.

Who would make the judgement that a protocol is minimal risk? The system already determines, routinely, which protocols are minimal risk. Although no policy is self-interpreting, most disagreements that arise will be about fuzzy boundaries rather than about the large domain of protocols that are clearly minimal risk. Such boundary disagreements can be conservatively handled without the danger of riskier research falling through the gaps. Even if the new line were drawn so conservatively (which we do not recommend) that only 50% of currently expedited protocols were made exempt, substantial resources would be freed for better uses. There will no doubt be an evolution in the interpretation of the concept when it is used to exempt rather than expedite a protocol review.

It is unethical to support a system that creates a significant financial, scientific, clinical and ethical burden with virtually no counterbalancing good. The maturation of any system involves trimming unnecessary parts, and redoubling the focus on areas that need further attention. Minimal-risk-research oversight should be pruned from the federal regulations and made exempt. Such pruning is necessary for the long-term health of the whole by freeing up scarce resources to where they are most needed. ■

Scott Kim and **Raymond De Vries** are at the Bioethics Program and **Peter Ubel** is at the Center for Behavioral and Decision Sciences in Medicine at the University of Michigan, 300 North Ingalls Street, Ann Arbor, MI 48109, USA.
e-mail: scottkim@med.umich.edu

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