

RESEARCH ETHICS

Aligning Regulations and Ethics in Human Research

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Government officials are revising the 1991 Common Rule regulations that govern most human research in the United States. They have already received public comments on a 2011 Advance Notice of Proposed Rulemaking (ANPRM) (1). The public will have another chance to comment when officials publish specific proposals. The revision effort's overall goal is to remove unwarranted regulatory impediments to research while strengthening essential human subject protections. I offer three ideas for additions to the oversight system, each tied to one of the 1979 Belmont Report's (2) three ethical principles governing human research.

Although prepared by a U.S. advisory group, the Belmont Report expresses values embodied in historic documents like the Nuremberg Code, international statements like the Helsinki Declaration, and domestic oversight systems in countries around the world. The report emphasizes three ethical concepts (see the table). Although these concepts underlie many Common Rule provisions, insights gained since 1991 and unaddressed problems in the current oversight system point to new measures that could enhance the rule's ethical legitimacy.

Teaching about research participation

One of the Common Rule's major objectives is to promote informed decisions about research participation. To this end, the Common Rule requires researchers to disclose certain facts about a study, such as its purpose and the risks and discomforts it could impose. The Common Rule lists eight basic elements of informed consent and six additional elements to be disclosed when they are relevant. Institutions often add even more material to consent forms, a practice critics say is motivated by liability fears rather than a desire to inform subjects.

The combined government and institutional demands produce long and detailed consent forms that can be hard for prospective subjects to understand. Indeed, empirical evidence indicates that many subjects are

unaware of essential facts about the studies they join (3). Moreover, as the ANPRM complained, "Instead of presenting the information in a way that is most helpful to prospective subjects—such as explaining why someone might want to choose not to enroll—the forms often function as sales documents."

Responding to widespread dissatisfaction with research consent forms, the ANPRM requested comments on potential changes to the current regulatory requirements. Several of the modifications, such as limiting the length of some consent form sections, reflect the popular view that a brief, plain-language description of essential facts about a study, together with optional access to more detailed material, would be superior to the current approach. Regulatory requirements for simplified consent forms could promote more informed choices about research participation (4, 5). But achieving this objective will require another measure described in the ANPRM: assessment of "how well potential research subjects comprehend the information provided to them."

As every teacher knows, well-crafted lectures and readings do not necessarily lead to learning, nor do careful study discussions and well-written consent forms. To discover whether the message has gotten through, research team members must evaluate whether potential participants have absorbed what they have heard and read.

The idea of evaluating subject understanding is not new. Experts have developed assessment tools (6), including model assessment forms researchers can adapt for use in individual studies (7). During my many years as an Institutional Review Board (IRB) member, however, I have rarely seen

New U.S. rules should ensure assessment of subjects' understanding, compensation for injury, and standards of study quality.

the forms used. Few studies appear to incorporate evaluation procedures, although there are exceptions. For example, a high-profile randomized trial comparing arthroscopic knee surgery to placebo required participants to write in their charts: "On entering this study, I realize that I may receive only placebo surgery. I further realize that this means that I will not have surgery on my knee joint. This placebo surgery will not benefit my knee arthritis" (8).

Why haven't procedures like this become standard in research decision-making? Part of the reason is surely the extra effort, time, and cost involved in developing assessment measures. But a reluctance to discourage participation might also account for this situation. A collaborator in the knee surgery study reported "a significant refusal rate" among subjects, which he described as "the price you may have to pay if you increase potential subjects' understanding" (9).

It is possible that genuinely informed individuals will be more likely to decline research participation (10). At the same time, efforts to ensure understanding might promote the research effort, for informed subjects may be less likely to drop out once they decide to enroll (11). But the main reason to require evaluation is to promote autonomous choice. If we believe that research participation is a matter of individual choice, we should be willing to live with the consequences of genuinely informed decision-making.

When research harms subjects

Because risks are unavoidable in research, some subjects will inevitably be harmed as a result of their participation. In a just research system, the burdens and benefits of research are equitably distributed. Some subjects personally benefit from study participation, but subjects are not the primary beneficiaries of research. Instead, research is done for the benefit of the wider community. Because subjects accept research burdens so that others may benefit, it seems only fair that the community offer assistance when subjects end up worse off than they would have been if they had refused to enroll (12).

The U.S. regulatory system fails to incorporate this straightforward moral judgment.

BELMONT REPORT'S THREE ETHICAL CONCEPTS

Respect for persons, requiring researchers to obtain subjects' informed consent to study participation.

Justice, requiring equitable distribution of research burdens and benefits.

Beneficence, requiring that risks to human subjects be justified by the value of the knowledge the study is expected to generate.

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The existing Common Rule lets research sponsors and institutions decide whether to cover the costs of research-related injuries. Even in studies presenting relatively high risk, investigators meet their Common Rule duties simply by warning prospective subjects that they could end up bearing the costs of any injury they suffer as a result of research participation. Although institutions and sponsors do provide care and compensation to some injured subjects, the quality and scope of these efforts are unclear (13, 14).

Although the ANPRM does not address injury compensation, several national advisory groups have recommended adoption of compensation programs that do not require proof that an injury was the result of negligent or other blameworthy conduct (14–16). A 2011 report by the Presidential Commission for the Study of Bioethical Issues expressed strong support for a compensation program (13). Other countries, and some U.S. research institutions, have compensation programs. For example, Germany requires research sponsors to buy insurance to cover injured subjects' economic losses (14). The University of Washington operates a self-insurance program to cover medical care and up to \$10,000 of a subject's out-of-pocket costs (13). Despite decades of ethical support, and evidence that compensation programs are practically feasible, U.S. officials have been unwilling to mandate such programs.

Few data exist on the costs associated with compensation programs (14), but cost concerns are one reason research institutions have failed to adopt such programs (15). Opponents also argue that moral obligations to subjects are met by the risk disclosure element of informed consent, which enables people worried about research injuries to refuse participation. Opponents contend as well that the tort system gives injured subjects adequate opportunities to pursue compensation.

But the ethical considerations supporting compensation outweigh the objections. Although soldiers and police officers accept risks inherent in their work, we nevertheless believe they are owed assistance when they are injured on the job. The same judgment applies to people serving society as research subjects. Barriers to tort recovery are so high that many injured subjects will never obtain compensation through this legal mechanism (15). The success of existing injury compensation programs, which include a process for determining whether injuries resulted from research participation, should allay con-

cerns about costs and feasibility.

Compensation programs can make research participation a more attractive option to prospective subjects and allow institutions and injured subjects to avoid litigation costs. More study and planning will be necessary to determine the details, such as what costs should be covered and the proper standard for determining causation, but U.S. officials should act to ensure that research subjects receive help when they are injured on our behalf (16).

Screening studies for quality

The third way officials could make research more ethical would be to require that all human studies undergo rigorous review of their methodology and significance. Applying the beneficence principle, the Common Rule limits research risks to those that are "reasonable in relation to ... the importance of the knowledge that may reasonably be expected to result." Studies that are poorly designed or conducted cannot produce important knowledge, nor can studies with low social value (17).

Although the Common Rule directs IRBs to consider study value in the review process, this directive is unrealistic. Given their limited membership and time constraints, IRBs cannot rigorously assess the value of the studies they review. The Common Rule authorizes IRBs to enlist scientific experts to assist with specific protocol reviews, but IRBs typically lack the resources to thoroughly assess research quality.

Peer review is imperfect, but it is one of the best ways to evaluate research merit. Many human studies undergo rigorous peer review as part of the National Institutes of Health (NIH) funding process, but many others do not. Nonprofit funding organizations do not always have stringent merit review mechanisms in place, nor do industry research sponsors or institutions dispensing internal funds for research.

Poorly designed and conducted trials do not just waste resources, they also expose subjects to unjustified risk and threaten public trust in the research endeavor (18). Independent merit review can be performed by institutional, professional, or government bodies. Medical product regulators, scientific journals, and clinical trials registries can all play a role in evaluating study quality (19). Developing a comprehensive and rigorous approach to merit review will be challenging, of course. But until such a system is in place, human subjects will be exposed to harm in studies that make no contribution to scientific and medical progress.

A fundamental moral judgment

Underlying the research oversight system is a fundamental moral judgment: Human subjects have interests that should not be subordinated to the interests of the patients, researchers, industry stakeholders, and others who gain health and monetary benefits from the research enterprise. In the United States and elsewhere, allegiance to this moral judgment demands robust efforts to educate prospective research subjects, help subjects who are harmed in research, and evaluate the quality of human research proposals.

References and Notes

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16. It is not clear why this issue was not addressed in the ANPRM. Officials may have wanted to wait for the Presidential Commission Report (13), which was issued several months after the ANPRM. It is possible that compensation will be considered in the next set of Common Rule proposals, or officials could address the issue separately, e.g., by setting up a project to collect necessary data. Noting the persistent lack of a government response to previous advisory group recommendations, the Presidential Commission called on officials to "publicly release reasons for changing or maintaining the status quo."
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