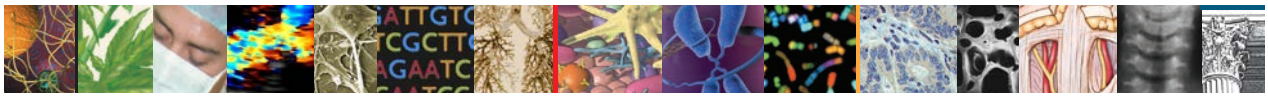

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Perspective

Reform of Clinical Research Regulations, Finally

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In 1972, Jean Heller of the Associated Press reported on a 40-year-old research study that had followed black Alabama sharecroppers, some of whom had syphilis. The revelation of deception, withholding of appropriate treatment, and other unethical practices exploded into the Tuskegee scandal. Tuskegee led to the National Research Act of 1974, which authorized the Department of Health, Education, and Welfare (now the Department of Health and Human Services [HHS]) to augment government policies for protecting human research subjects.[1] The protections, ultimately codified as 45 Code of Federal Regulations 46 (45 CFR 46), specify requirements for valid institutional review board (IRB) assessment of most human-subjects research and informed consent by research participants.[2]

In the decade after 1974, specific safeguards were added for pregnant women, fetuses, neonates, children, and prisoners. For instance, research involving prisoners, such as commonly conducted early-phase drug studies, was severely restricted; only research on "possible causes, effects, and processes of incarceration, and of criminal behavior, prisoners as incarcerated persons, [and] . . . conditions particularly affecting prisoners as a class" was permitted. In 1991, many other (though not all) federal departments and agencies adopted the main part of 45 CFR 46 for their human-subjects research, which became known as the Common Rule.

Despite deaths of research participants (including well-publicized cases such as Jesse Gelsinger's death in a University of Pennsylvania gene-therapy trial), the changing nature of research (e.g., more multisite trials, genetic research, research involving biospecimens), and problems with the regulations and their application, the rules have changed little since 1991.[3] Informed-consent documents grow ever longer and consistently exceed the eighth-grade reading level, with wide variation in participants' comprehension. Researchers have documented unjustified variation in assessments of studies' risks and benefits. And the review system is inefficient, with numerous IRB reviews for multicenter studies delaying initiation of research for months or years, despite little evidence that multiple reviews enhance protections.

Simply documenting problems,

Classification of Research Activities under Proposed Changes to the Common Rule.

Classification	Application of Common Rule Protections	Examples
Excluded	"Outside the scope of the regulations." The Common Rule regulatory requirements (e.g., IRB review) do not apply to these research activities.	Oral histories and interviews for biographies. Data collection for an institution's operational monitoring and quality-improvement activities. Operations-improvement activities to evaluate the effects of programs to change use of an accepted practice such as hand washing but not evaluate the practice itself. Research that carries no physical risks and is nonintrusive, such as surveys of adults and observations of public behavior, when information is recorded without linked identifiers and disclosure would not harm the finances or other interests of the person. Research involving collection or analysis of existing data, records, or specimens if the source is publicly available or if information cannot be linked to individuals (e.g., census data).
Exempt	Low-risk research or research involving information that needs privacy protections. Because they are unlikely "to result in harm to the subject and the subject must prospectively agree to intervention or data collection" these studies do not require IRB review or informed consent.	Social and behavioral research with adults involving brief, "harmless, painless, not physically invasive" interventions, such as reactions to watching a video, playing games, or solving puzzles. Secondary analysis of large databases including identifiable information when "prior notice has been given and privacy safeguards" (e.g., Health Insurance Portability and Accountability Act) exist. Research involving educational practices, public benefit programs, or taste and food quality.
Expedited	Research involving minimal-risk procedures ("risks are no greater than those of everyday life") according to an HHS-approved list. Existing procedures for review by one IRB member. Two changes: if the procedures are on the HHS list, they are to be expedited unless the reviewer explicitly states that they are greater than minimal risk; and the list of accepted procedures will be updated at least every 8 years.	Studies involving only blood draws (less than 500 ml per 8-week period) or biospecimens collected in a noninvasive manner (e.g., placenta, hair clippings, or cells from a mucosal swab).
Full panel	Research that involves greater-than-minimal-risk interventions. No changes in requiring review by full IRB panel and written informed consent.	Phase 1 study of experimental drug or vaccine.

however, is insufficient to catalyze changes in laws or regulations. Concrete solutions must be developed, and then an event such as a scandal or an election can force political action. As health care reform attests, this combination rarely coalesces to generate actual reform.[4] Fortunately, in November 2009, while working at the White House Office of Management and Budget, I was able to convene representatives of HHS and other departments to develop reforms to enhance participant protections and make the oversight process more efficient. Those meetings led to an Advance Notice of Proposed Rulemaking in 2011 and release of a Notice of Proposed Rulemaking (NPRM) this September.[5] The end of this long process is now in sight.

The proposed changes, though imperfect, are a significant step forward. Six aspects deserve special attention; some would enhance protections, while others would improve efficiency — and in turn enhance protections by focusing resources and attention on studies posing the most serious risks and ethical challenges.

First, the proposal applies protections to all clinical trials conducted at U.S. institutions receiving federal funding for human-subjects research. Currently, protections apply only to research funded by departments and agencies that have adopted the Common Rule. Institutions have frequently signed agreements with the government subjecting all their research to the Common Rule, but recently some have balked at doing so, viewing the

regulations as unnecessarily onerous and bureaucratic. There has been persistent concern that participants might unwittingly enroll in research lacking protections such as IRB review, favorable risk–benefit ratio, and valid informed consent.

Unfortunately, the new regulations still wouldn't apply to all U.S. human-subjects research — only to federally funded clinical trials except those regulated by the Food and Drug Administration (FDA). They wouldn't apply to research conducted at institutions receiving no human-subjects research funding from a Common Rule agency — for example, those funded only by the Department of Interior or private sources — or to studies other than clinical trials.

Second, the regulations aim to enhance and streamline the informed-consent process, in part by shortening and focusing informed-consent documents on "essential information that a reasonable person would want to know," with additional details provided in an appendix. Working against such streamlining, however, the reforms would require researchers to inform participants that their biospecimens might be used for commercial profit, tell them whether they would be informed of clinically relevant findings, and ask them whether they could be recontacted for additional research. All final informed-consent documents would be posted on a federal website 60 days after completion of recruitment. The reforms don't include a requirement, advocated by some commentators, for routine formal assessment of participants' mental competency to consent and comprehension of disclosed information.

Third, secondary research on biospecimens and identifiable private information originally collected for research, clinical, or other purposes would require informed consent. In keeping with extensive empirical research, one-time, general, open-ended consent could be obtained at the time of collection. This approach allows people to decide whether they want their specimens and data used for research but obviates the need for subsequent consent for each project. HHS will provide templates for broad consent. Broad consent would be valid for specimens or information to be collected for the subsequent 10 years (less for minors).

This rule would apply only to future research — not existing biospecimens — and would go into effect 3 years after the final rule was enacted. Previously collected biospecimens would be governed by existing consent procedures, which have been confusing and contentious. The informed-consent requirement wouldn't apply to research that merely confirms information about individuals, such as studies validating diagnostic tests and quality-assurance studies.

Fourth, the proposal defines four types of regulatory oversight — delineating the types of research that are excluded (a new category) or exempt, types qualifying for expedited review by a single IRB member because they pose minimal risk, and types requiring full-IRB review (see table).

Fifth, continuing-review requirements would change. Excluded and exempt research would still require no continuing review. The default for expedited research would be no continuing review — a change — but a study's reviewer could make a case for continuing review. For greater-than-minimal-risk research, a change would mean continuing review could cease once recruitment and experimental interventions were completed and only clinical monitoring of participants and analysis and reporting of research results remained.

Finally, instead of protocols for multicenter projects being reviewed by each institution's IRB, all participating U.S. sites would rely on a single IRB review. The only exceptions would be for multicenter projects that require multiple IRB reviews by law (e.g., for FDA-regulated device research), research at non-U.S. sites, and cases in which a funding agency chooses to require multiple reviews.

The NPRM contains many other changes. It proposes several different privacy-protection standards, for instance, and tries to harmonize interpretations and guidance among the Common Rule agencies. The proposals could result in significant improvements, especially in facilitating social and behavioral science, health services, multicenter, and other types of research. They also clarify and specify procedures for research using biospecimens and existing data.

Nevertheless, no one will consider this NPRM perfect. It manifests a near-obsession with the rules governing biospecimens, resulting in what some critics call biospecimen exceptionalism. A proposed centralized database for adverse events that would have streamlined reporting and provided a comprehensive picture of research risks was unfortunately dropped. Some experts doubt that the reforms will truly streamline informed-consent documents, since additional information will

also be required. IRB members strongly object to lack of appreciation for local factors and flexibility in mandatory single-IRB review for multisite studies. Others may object to the broad consent for future use of biospecimens — some objecting to its breadth and some to requiring consent at all. Still others worry that the proposals include promises — for informed-consent templates, an exemption-determination tool, updates on minimal-risk interventions — on which the government might not deliver in a way that appropriately protects research participants.

Inherently, this reform is a compromise. But we cannot let our ideal undermine the only substantive effort since 1991 to reform human-subjects protections. If reforms are spurned because people are holding out for a better deal, the status quo will be maintained. And who knows when the requisite ingredients will come together to generate change? We desperately need reform to better protect research participants, improve the efficiency of the review process, and facilitate more research.

Once the NPRM comment period ends on December 7, I urge the government to issue final regulations expeditiously. Dragging out the process longer won't make the reforms better.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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