SOUNDING BOARD

Reforming the Regulations Governing Research with Human Subjects

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In the wake of the scandal surrounding the Tuskegee syphilis study, Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The commission investigated and made recommendations regarding basic ethical principles guiding research with human beings and the special principles relating to research with fetuses, prisoners, and children. In 1981, on the basis of the National Commission's recommendations, the Department of Health and Human Services (DHHS) revised and expanded its regulations regarding the protection of human subjects, which were entered into the Code of Federal Regulations (title 45, part 46). In 1991, subpart A of those regulations, delineating the general rules for informed consent and for the operation of institutional review boards (IRBs), was extended to 14 other federal departments, thus creating what came to be called the Common Rule. (Similar, but not identical regulations, title 21, parts 50 and 56, govern research with human beings regulated by the Food and Drug Administration [FDA].)

Since 1991, there has been almost no change to the Common Rule. Yet research with humans has substantially increased in volume, with more international and multisite studies, more health-services research, and more research with biospecimens.[1,2] Decades of experience have revealed a great deal about the functioning — and limitations — of existing regulations, and have prompted critical evaluations by the Institute of Medicine, the Government Accountability Office, and many scholars.[3,4]

Two themes emerge from these critiques. First, there are complaints that the regulations impose a variety of burdensome bureaucratic procedures that seem to do little to protect research participants, yet consume substantial resources. These impediments are claimed to be particularly vexing for researchers conducting studies that pose few physical or psychological risks. More important, critics have noted that current regulations could be doing a significantly better job in protecting research subjects.

A PROCESS FOR REVISING THE COMMON RULE

Consistent with the President's executive order to critically examine all regulations to minimize burden and increase effectiveness,[5] the Office of Management and Budget convened a working group to consider revisions to the Common Rule. We participated in that working group. The group drafted an Advance Notice of Proposed Rulemaking (ANPRM) that was circulated for comment by all departments and agencies that observe the Common Rule. After considering the critiques and making numerous revisions, the DHHS, in coordination with the Office of Science and Technology Policy (whose efforts led to the 1991 adoption of the Common Rule) issued an ANPRM entitled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators."[6]

The goal of this ANPRM is to delineate options for simultaneously enhancing protections for research subjects and improving the effectiveness of the federal oversight system. A key purpose is to better focus oversight resources on higher-risk research studies.

An ANPRM is the first step in an administrative process; it indicates that the government is considering issuing or revising regulations and is therefore soliciting comments and suggestions from stakeholders and the public. After consideration of comments, there will be a determination of whether and how to move forward with publication of a Notice of Proposed Rulemaking (NPRM) that specifies the proposed wording of the new regulations. Like ANPRMs, NPRMs are subject to public comment, a process that influences further

revisions. The end result might be the issuance of a final rule. This detailed process permits multiple opportunities for public comment on any proposed revision of the regulations.

As two participants in the process, we have summarized some key aspects of the ANPRM "Human Subjects Research Protections" and encourage researchers, other stakeholders, and the public to provide comments. Readers can view the ANPRM and related documents and submit comments at www.hhs.gov/ohrp/humansubjects/anprm2011page.html and are invited to offer their comments at www.regulations.gov.

IMPROVING THE EFFECTIVENESS OF OVERSIGHT

In its 2002 report on research oversight, the Institute of Medicine called for a more risk-based review process so that studies posing "minimal risk" (defined below) "should be handled diligently, but expeditiously, while studies involving high risk should receive the extra time and attention they require."[3] To this end, several changes to the current rules regarding IRB review are being considered (Table 1).

STUDIES POSING GREATER THAN MINIMAL RISK

For studies posing a level of risk that is more than minimal, the current rules would be largely preserved. Such studies would be reviewed by a convened IRB. As other reforms reduce their workload, IRBs should be able to better fulfill their original and central mandate: to carefully review studies that pose risks of serious physical or psychological harm. The ANPRM requests comment on whether these studies should no longer be required to undergo annual continuing review when the remaining activities are limited to the collection of follow-up data in accordance with standard clinical procedures and data analysis.

STUDIES POSING MINIMAL RISK

In the Common Rule, minimal risk means "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."[7] The ANPRM asks whether this definition is appropriate and seeks comment on four reforms proposed for the type of IRB review (expedited review) which is used for most studies that pose minimal risk.

First, comment is requested on whether the list of qualifying research activities, which has not been updated since 1998, should be regularly revised in accordance with accumulating empirical data about risks. Second, the ANPRM asks whether a research study that includes only activities that appear on this list should be deemed to be of minimal risk and thus receive expedited review[8] unless the reviewer provides specific reasons why the study involves more than minimal risk. Such studies might include those in which the cumulative risk of multiple interventions is greater than the risks "ordinarily encountered in daily life."[7]

Third, because these studies involve well-understood research activities that are generally no more risky than the activities ordinarily encountered in daily life, the ANPRM seeks comment on whether the requirement for continuing annual review should be eliminated unless the reviewer explains why continuing review would enhance protections. Finally, to reduce paperwork, the protocol submitted by researchers for studies posing minimal risk could be streamlined, and templates might be created to simplify the process of putting together a protocol and consent form that satisfy regulatory standards.

REVISIONS TO THE EXEMPT CATEGORY

Many studies pose risks that are largely informational: harms result primarily from the inappropriate release of information and not from the research interventions themselves. Accordingly, the ANPRM presents for consideration a requirement that research studies adhere to standards for data security and confidentiality modeled on those for health information in the Health Insurance Portability and Accountability Act (HIPAA), thereby permitting expansion of the current category of "exempt" studies. Studies posing risks that are largely informational and not physical could be excused from IRB review if they adhere to these standards for data security. Studies now referred to as exempt would instead be referred to as "excused," since they would not be exempt from federal oversight and all regulatory requirements: they would have to adhere to the new standards for data security and information protection.

In particular, the ANPRM asks whether all surveys, focus groups, and research with similar methods, when conducted with competent adults,

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Table 1. Proposed Changes to the Current Rules Regarding IRB Review.*

Goal	Area of Change	Details
Improving effectiveness	Distinction between types of risk	For most studies in which risks are primarily informational, research could commence immediately after the study is registered through submittal of a one-page form, accompanied by a commitment to observe data-security protections.
	Annual reviews	For research posing more than a minimal level of risk, an annual review would be conducted except when the activities performed involve only standard clinical follow-up data collection or data analysis.
		For research posing minimal risk, no annual review would be required unless a reviewer explicitly justified the request for such a review.
	Research activities posing minimal risk	The list of research activities qualifying for expedited review would be regularly updated as empirical data are accumulated.
	Review of multisite studies	Only a single IRB of record would be allowed for the oversight of all domestic sites.
	Guidance	The need for a mechanism intended to harmonize guidance across federal agencies would be evaluated.
Enhancing protections	Federal oversight	If a U.S. institution receives some Common Rule agency funding for human-subjects research, all research conducted at the institution would be subject to federal oversight.
	Data concerning adverse events	Records of all adverse events or unanticipated problems would be submitted to and stored in a central database.
	Informed consent	The goals of change in the treatment of informed consent would be to specify more explicitly the content of consent documents, limit the length of documents, simplify and streamline institutional boilerplate, promulgate the use of standardized consent documents, and permit the use of oral consent for surveys, focus groups, and interviews conducted with competent adults, even if identifiers are retained.
	Use of biospecimens	Written consent would be required (even if no information identifying the source was retained) but could be obtained with the use of a standardized form allowing open-ended use in future research. This change would be applied only prospectively — that is, to specimens collected after the revised regulations become effective.
	Confidentiality protections	Institutions would be required to implement confidentiality and data-security protections modeled on those used in HIPAA (e.g., the use of encryption and audit trails).

* HIPAA denotes Health Insurance Portability and Accountability Act, and IRB institutional review board.

should be excused from IRB review regardless of whether the information is collected with identifiers and regardless of the sensitive nature of the questions as long as the researchers are bound by strict standards of data security and information protection. Similarly, studies involving the secondary use of data or biospecimens, which would also have to comply with the data-security measures, could also generally qualify for excused status, whether or not the data are considered identifiable.

In seeking to further rationalize the review process, comment is sought on allowing researchers to register their excused studies with a brief information sheet (approximately one page) and to receive authorization to begin conducting the study immediately after the filing. Consequently, current federal guidance recommending that all research that might qualify for exempt status should undergo some type of explicit institutional review to determine whether it really should be classified as exempt would be revoked. In this model, compliance with these proposed rules would remain the responsibility of the institution and could be accomplished in a number of ways, such as by conducting random audits of these filings.

Comments are requested on two additional changes designed to improve the effectiveness of the oversight system. First, comment is sought on whether there should be only one IRB of record for all domestic sites in multisite studies. Evidence suggests that multiple IRB reviews lead to unjustified variation in assessments without enhancing protections for research subjects.[9-11] Furthermore, it has been argued that for the great majority of multisite studies, critical IRB functions, including those ensuring that risks are minimized and balanced by benefits and that research is scientifically valid, are not dependent on local factors that only a local IRB can assess. Using a single IRB of record should result in a substantial reduction of IRB

workloads, allowing allocation of those resources to studies posing higher levels of risk. It would still be acceptable to designate the local IRB as the IRB of record for international sites.

The ANPRM also addresses the problem of multiple federal agencies issuing conflicting guidance, requesting comment on the extent of a need for a mechanism that would ensure consistency in guidance concerning protections for human subjects across the federal government.

ENHANCING PROTECTIONS FOR RESEARCH PARTICIPANTS

The ANPRM seeks comment on five specific reforms designed to enhance the protection of research participants (Table 1). Both the National Bioethics Advisory Commission and the Institute of Medicine objected to the fact that some clinical research occurs without any federal oversight and argued that federal oversight should be extended to all research involving human beings.[3,12] Legislation would be required to extend federal protections to all studies. The ANPRM presents the suggestion that much of that goal could be accomplished by extending the streamlined federal research protections to all studies conducted at U.S. institutions receiving some federal funding from a Common Rule agency for human subjects research.

The ANPRM also presents the idea of establishing an electronic reporting system for adverse events in which the data collected would be used to develop a comprehensive database. This would facilitate the identification of "hotspots" of research risk — or safety — and allow the targeting of resources for oversight and risk reduction. Seven federal agencies — the National Institutes of Health (NIH), the Centers for Disease Control and Prevention, the FDA, the Agency for Healthcare Research and Quality, the Department of Defense, the Department of Veterans Affairs, and the Office for Human Research Protections — have developed a harmonized data set for reporting adverse events and unanticipated problems. Recently, the NIH and FDA have pioneered a reporting system that uses this harmonized data set for gene-transfer studies. In the ANPRM, comment is sought about the value of expanding this system to include other types of research. Such a system would replace the complicated array of definitions and reporting requirements for adverse events and unanticipated problems with harmonized rules, together with a single Web site where researchers can input data and instantly fulfill multiple federal reporting requirements.

Another focus of concern is improving informed-consent documents. A growing body of research shows that these documents are often too lengthy, written at too high a reading level, filled with legal boilerplate, and frequently lacking the vital information needed for informed decision making.[13-15] In the ANPRM, consideration is given to the value of more explicitly specifying the information that must be provided in consent documents, appropriately organizing the presentation of that information, and making similar changes that could better help prospective subjects to make informed decisions about study participation. The ANPRM also asks for comment on whether it would be acceptable to allow competent adults to provide oral rather than written consent to participation in surveys, interviews, focus groups, and similar types of research, even for instances in which the information collected may be sensitive and the identity of the subjects is obtained.

Many commentators have argued that uncertainty about the regulations on biospecimens has impeded research. Yet research with biospecimens is becoming increasingly important. Although such research often entails no or minimal physical risk — the specimens already exist or are obtained during procedures associated with minimal risk (e.g., with the use of buccal swabs) — there are unresolved issues about the extent to which someone should be able to control the use of their biospecimens for purposes of research. The current rules allow researchers unlimited use of leftover clinical specimens (for purposes of research) without having to obtain consent from the person who is the source of the specimen, as long as the researchers never learn the identity of that person. Although the public strongly supports research with biospecimens, some commentators have suggested that greater controls are desirable when research entails the use of clinical specimens.

The ANPRM asks for comment on a proposal to clarify procedures and enhance protections related to research with biospecimens. In almost all cases, persons would have the right to allow or disallow the use of their biospecimens for research, regardless of whether the specimens were initially collected for research purposes or as part of clinical care. Recognizing the huge benefits to be

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gained from such research, the ANPRM includes a suggestion that a standard, brief, and general form be used to obtain consent for the future open-ended use of biospecimens in research. Further, such a form need not be signed each and every time a specimen is collected. Rather, researchers or hospitals might ask participants to sign one form in which they agree to such future use of all specimens (existing or to be collected in the future). It is also suggested that these rules be applied only to biospecimens collected after the effective date of new regulations. The millions of existing biospecimens might continue to be governed by the current rules.

Finally, the ANPRM includes a response to weaknesses in the current system with regard to protecting subjects from breaches of confidentiality and other informational risks. The existing level of protection from informational risks is variable. There are no uniform security standards for research data, and IRB members are seldom selected for their expertise in information technology and data security. The ANPRM suggests the establishment of uniform data-security standards modeled on the protections provided by HIPAA. IRBs would no longer be tasked with the responsibility of evaluating and minimizing informational risks. The new standards could be calibrated to the level of identifiability of the data and include encryption, limited-access specifications, and audit trails. Institutions could ensure that researchers adhere to these protections through periodic audits.

AN OPEN AND VIGOROUS DEBATE

It is no accident that the ANPRM devotes nearly as much space to posing questions (more than 70) as it does to delineating the reforms that are being considered. For many of the issues discussed in the ANPRM, there may be arguments for and against the need for specific reforms. For example, with regard to giving researchers permission to commence certain studies without first presenting them for review by an IRB member or administrator, the ANPRM asks whether protections for some subjects will be inappropriately weakened. The ANPRM also asks whether using data-security and information-protection standards modeled on those described in HIPAA might be too burdensome, especially for many social and behavioral studies. The purpose of the public comments on the ANPRM are to guide future decision making regarding possible reforms. The process of reforming the regulations will present multiple opportunities for stakeholders to raise or rebut these and other concerns.

CONCLUSIONS

After 20 years, and the introduction of significant changes to the research landscape, many believe that the Common Rule needs revision. The ANPRM offers a rare opportunity for needed modernization that is consistent with the President's mandate to enhance protections while simultaneously eliminating unreasonable burdens. Not everyone will agree with every proposed change. But the ideal should not be the enemy of substantial progress in achieving these two important goals. If this reform effort fails, 20 years from now, someone might write an article for the *Journal* to bemoan the fact that the Common Rule has undergone essentially no change in 40 years.

The views expressed in this article are those of the authors and are not necessarily those of the Department of Health and Human Services or its divisions, the National Institutes of Health, or the Office of the Assistant Secretary for Health.

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