POLICY FORUM

RESEARCH OVERSIGHT

What do revised U.S. rules mean for human research?

The updated Common Rule raises many questions

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Following a contentious 5½-year process, the U.S. Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) released a revised "Common Rule," which governs federally funded research involving human subjects (*1*). The updated rule includes a number of welcome changes for U.S. institutions and researchers, and their scientific collaborators abroad. Annual protocol review by an institutional review board (IRB) is eliminated for many studies that pose minimal risk to participants following initial approval; IRBs no longer need to review and document concordance between grant proposals and study protocols; and, pertinent to research conducted with international collaborators, the rule recognizes that there may be cultural groups or communities for which signing a consent form is not usual. Concerns remain, however, regarding some elements of the revised rule and their implications. With preparations under way in advance of the rule's taking effect on 19 January 2018, and in light of lingering uncertainty, we highlight provisions that will present the greatest challenges to institutions and researchers.

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EXEMPTION AND LIMITED REVIEW

The revised rule retains the previous definition of research, but deems four categories of activities "not research" and thus excluded from oversight. Exclusion of scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship) will reduce administrative work for researchers.

The rule also adds complexity, however, to the process of identifying categories of research that are exempt from oversight (i.e., minimal-risk research that does not require approval by an IRB) by placing restrictions on exemptions and introducing the concept of "limited IRB review" for projects collecting sensitive, identifiable information from subjects. This could lead to error or noncompliance for investigators making these determinations or institutional risk aversion that increases administrative processes (*2*). A proposed decision tool to assist investigators in making these determinations may be provided by OHRP, but IRB information management systems must be reconfigured to accommodate the changes several months before the 2018 effective date, necessitating development of guidance by each institution.

Federally funded U.S. researchers working with human subjects will soon have to follow revised rules regarding identifiable private information or identifiable biospecimens.

Research involving "benign behavioral interventions" (those that are not physically invasive, offensive, or embarrassing), a new exemption category, provides an example of how complex the new exemptions can be and how "exempt" research may still be subject to additional review requirements. Although this category expands the use of exemption to a broader range of research, the exemption only applies if the information collected is from an adult participant who prospectively agrees to the intervention and information collection and when additional criteria are met—e.g., the identity of the subject cannot readily be ascertained. If the project will collect identifiable information, it is subject to "limited IRB review." If the research involves deception, the subject must prospectively authorize it.

Secondary research using identifiable private information or identifiable biospecimens is exempt without any form of review under certain circumstances (e.g., it is publicly available, the participant cannot readily be identified, or it is regulated under the Health Insurance Portability and Accessibility Act for purposes of "health-care operations," "research," or "public health activities"—but not where the investigator plans to return individual research results). The rule allows (but does not require) "broad consent" for storage and secondary research use of identifiable private information or biospecimens that do not meet these criteria. In this context, broad consent means that potential subjects can agree in writing to unspecified future uses of their identifiable biospecimens or data (as distinguished from study-specific consent). This optional broad consent retains selected customary elements of informed consent and adds new elements pertaining to secondary uses.

The inclusion of optional broad consent further adds to the complexity of the rule. Broad consent would require investigators and institutions to implement new systems to track when it was requested, who refused, and what version of the document was used. Broad consent is thus likely to increase the operational challenges of implementing the rule. It also is not clear how a participant's ability to refuse storage and secondary research use of biospecimens and data under the broad consent mechanism will be reconciled with competing policies requiring that data from federally funded research be

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made accessible to the public and scientific community (*3*). The concept of limited IRB review for exempt research, coupled with additional restrictions and diminished IRB engagement in making these determinations, may lead to inadvertent violations of the rule and misunderstandings about how identifiable specimens or data might be used (*4*).

IDENTIFIABILITY

The final rule indicates that the meaning of "identifiable biospecimens" and "identifiable private information" will be reexamined within 1 year and at least every 4 years thereafter in consultation with "appropriate experts" and that interpretations of these terms may be altered. The ability of technologies, such as whole-genome sequencing, to render data and biospecimens identifiable will also be assessed. This ability to redefine what is "identifiable" potentially only defers the controversial proposal to treat nonidentified biospecimens as human subjects if experts conclude that any tissue containing DNA is always identifiable; a move that could negatively affect biomedical research and medical advances (*5*). These decisions would be made outside of the formal regulatory process, leaving less opportunity for stakeholder engagement.

MULTISITE RESEARCH REVIEW

The Common Rule requires use of a single IRB (sIRB) to oversee study activities for most domestic federally funded research with more than one participating site (although agencies may determine that use of an sIRB is not appropriate in some contexts) (*6*).

Although the sIRB requirement is intended to alleviate concerns that multiple reviews of the same protocol at different sites can delay clinical trial activation and introduce variability from site to site, the rule reaches beyond large multisite clinical trials, applying the sIRB requirement to all studies with more than one site, including social and behavioral research, and involving studies where different activities will be conducted at each site. Although researchers and disease advocacy groups have supported the change with respect to larger biomedical studies, there will be far less support for smaller, nonbiomedical studies, particularly once the costs, both financial and administrative, are fully understood.

This will be an expensive endeavor, requiring IT infrastructure, staffing, and policy changes. It is unclear whether and how infrastructure costs not directly associated with a research award will be recovered (*7*). The increased costs associated with sIRB review and oversight will be charged, in many instances, directly to awards; further, it is not clear whether there will be any reduction in investigators' or IRBs' administrative workloads over time. Although efficient sIRB review models currently exist, such as the National Cancer Institute (NCI) central IRB (CIRB), the rule will require researchers to rely to a far greater extent on an unpredictable patchwork of institutional and independent IRBs, with different software systems, policies, and processes that study teams will have to learn whenever their institution is not the reviewing IRB. When an institution relies on another IRB for review, the relying institution will still have to deliberate on a number of issues, including state law, local context, conflict of interest, and biosafety. This complex model, broadly applied, is untested, and empirical data on streamlining IRB review for multisite research are limited (*8*). There are no data to suggest that this rule change would enhance protections, and it could increase costs and administrative work.

Many in the research community have suggested that HHS reconsider this rule change or substantially narrow the scope to larger-scale biomedical studies. Beneficial steps the agency could take range from clarifications to better assessment tools. For example, the agency could clarify that the rule applies only to research in which each participating site will conduct the same research protocol. Metrics should be developed to assess the cost and effectiveness of using an sIRB, as well as a timeline for such assessment and reconsideration of the rule. Greater use and expansion of federal central IRBs (e.g., NCI CIRB) would reduce the administrative work and cost for institutions and researchers that are expected to result from this change.

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UNCERTAINTY AND IMPLEMENTATION

Circumstances under which this regulation was reviewed and issued have resulted in an unusual level of uncertainty following a rule. The confluence of the release of the rule on 19 January 2017, the last day of the outgoing Obama Administration, despite a 2016 National Academy of Sciences' recommendation that the proposed rule be withdrawn (*9*); the Trump Administration's commitment to reducing overall regulations (*10*); and statements by OHRP staff at several meetings, including a recent meeting of the HHS Secretary's Advisory Committee on Human Research Protections that the new Administration was reviewing the Final Common Rule (*11*), have fueled curiosity as to whether this rule is truly "final" or may be changed or delayed before the effective date.

Realizing that the Trump Administration has no obligation to either review, approve, or make a public statement about the status of the rule for it to come into effect as finalized, institutions and other stakeholders have had to prepare to implement the rule on 19 January 2018. Higher education associations have, however, requested a 1-year delay in the compliance date, noting uncertainty surrounding the rule. The request also pointed to the atypical challenge of concordant effective and compliance dates, which are typically several months apart, requiring investigators and IRBs to essentially "flip a switch" from the former to the revised final rule (*12*). This delay, if implemented, would maintain the effective date of 19 January 2018 but provide an additional year to be fully compliant.

Institutions that conduct human research will have substantial work ahead in implementing the rule and educating researchers and staff. Some of the required changes will rely upon guidance and updates that OHRP has yet to provide, such as guidance on consent. Irrespective of the outcome of the revised final rule, the protracted rulemaking process would seem to suggest the need for greater stakeholder engagement throughout the process and flexibility to adapt aspects of the rule to a rapidly changing research environment. ■

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10.1126/science.aan5855

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Science **357** (6352), 650-651.
DOI: 10.1126/science.aan5855