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New Developments in Human Subjects Protections: Proposed Updates to the Common Rule

Richard Weinmeyer, JD, MPhil, MA

The history of human subjects research in the United States is checkered with horrifying examples of exploitation that demonstrate the need for overarching protections for research participants. From the US Public Health Service Syphilis Study at Tuskegee, in which poor African American men in rural Alabama were denied treatment for their syphilis so that federal researchers could study its natural progression [1], to Willowbrook, where institutionalized mentally disabled children were deliberately infected with hepatitis in order to develop treatments for the disease [2], researchers have time and again trampled upon the legal and ethical rights of vulnerable populations in the name of science. To address these egregious violations, scientists, ethicists, academics, and politicians in the 1970s and 1980s developed a body of regulations to oversee biomedical and behavioral research involving human subjects in the US, known today as the Common Rule.

Based on the ethical principles elucidated in the Belmont Report and the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the Common Rule was published by the Department of Health and Human Services (HHS) in 1991 and codified by fifteen other federal departments and agencies engaged in human subject research [3]. The Common Rule is the part of the Code of Federal Regulations (45 CFR 46) that codifies special recognition and protection for certain vulnerable populations, who are discussed below. For over two decades, the Common Rule has remained largely unchanged while the pace and capabilities of scientific research have greatly altered. This year, the Office of Human Research Protections (OHRP) within HHS has begun the legal procedure for changing the content of the Common Rule to better address modern research environments. This article discusses those changes.

The Structure and Content of the Common Rule

The Common Rule for protection of human research subjects is divided into four main subparts. Subpart A establishes the "Basic HHS Policy for Protection of Human Research Subjects" [4], discussing the jurisdictional power of the regulations and defining the types of research controlled by the Common Rule, including "research that is conducted or supported by a federal department or agency" [5], "research that...must be reviewed and approved...by an institutional review board (IRB])" [6], and "research, involving the

collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded…in such a manner that subjects cannot be identified" [7]. This subpart also defines the composition, operation, and oversight of IRBs at research institutions [8]; the requirements for obtaining informed consent [9]; and the documentation requirements of informed consent [10].

The next three subparts provide regulatory guidance for research on populations considered vulnerable within the research setting. Subpart B provides additional protections for pregnant women, fetuses, and newborns [11]. Subpart C pertains to prisoners, whose capacity to participate voluntarily in research can be restricted or undermined because they are incarcerated [12]. Subpart D considers research involving children, with special attention to risks and benefits. Specifically, this section distinguishes two important sets of conditions: (1) when there is more than minimal risk to the child [13] and the possibility of direct benefit to the child [14], and (2) when there is no direct benefit to the child but the research is "likely to yield generalizable knowledge about the subject's disorder or condition" [15] or "present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children" [16].

Changes to the Common Rule

Reasoning. Since the Common Rule was published and codified in 1991, the human subject research landscape has changed dramatically, growing in both scale and diversity [17]. Study designs have changed in their complexity and variety; sophisticated and detailed inquiries are being conducted in biomedical, behavioral, and social sciences; and large quantities of electronic health and behavioral data are being collected, analyzed, and studied in new ways. HHS acknowledges that "these developments have not been accompanied by major change in the human subjects research oversight system" [18]. So, on September 8, 2015, OHRP published a notice in the *Federal Register* outlining proposed changes to the federal Common Rule [17].

Proposed changes in the 2015 notice of proposed rulemaking [17] incorporate public comments submitted in response to a previous (2011) advanced notice of changes to the *Federal Register* [19] and promulgate eight potential changes to the Common Rule, which can be organized into three categories.

Consent. The current Common Rule specifies elements of and documentation requirements for informed consent [3]. The proposed revisions seek to more precisely clarify what information must be given to prospective subjects and to improve the clarity and usefulness of consent forms as a way to try to more effectively ensure that subjects and their guardians are appropriately informed about the risks and benefits of protocols in which they or their wards are enrolled [20]. Similarly, proposed changes also seek to limit informed consent guidelines regarding researchers' uses of biospecimens,

particularly in secondary research, in which the use of the specimens for research purposes "may be unforeseen at the time in which consent is being sought" [21]. While the Common Rule allows for use of biospecimens without consent from the donor if the specimens are de-identified, the new rule would require broad consent for both the storage and future research use of these materials [20] and make waivers of consent much rarer [22].

Exemptions. The second category of changes addresses research thought to be exempt from IRB review or not subject to the Common Rule. These changes propose designation of new categories of research that could be exempt from IRB review because they pose no risk [20]. They also propose that activities deemed by IRBs not to constitute research or to pose less than minimal risk to subjects be excluded from the Common Rule [20]. Proposed changes also would eliminate the need for IRBs to renew approval of expedited-review studies, that is, studies involving de-identified data analysis or observational follow-up in the clinical care contexts [22].

Efficiency. Proposed changes to the Common Rule suggest mandating use of a single IRB for review of collaborative, multi-institutional research in the US, rather than relying upon review and approval from multiple institutions' IRBs [22]. Proposed revisions to the Common Rule also seek to make it more responsive to the needs of researchers conducting cross-national clinical trials at institutions in the US that receive federal funding for non-exempt human subjects research [22].

Conclusion

With the publication of the notice of proposed rulemaking for the Common Rule revisions, HHS has begun an extensive conversation with the American scientific community and the public about how best to make human subject protection guidelines more responsive to changes in research design and conduct. Greater congruence between research activity and research regulations is one goal of these proposed changes.

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Richard Weinmeyer, JD, MA, MPhil, is a senior research associate for the American Medical Association Council on Ethical and Judicial Affairs in Chicago. Mr. Weinmeyer received his master's degree in bioethics and his law degree with a concentration in health law and bioethics from the University of Minnesota, where he served as editor in chief for volume 31 of *Law and Inequality: A Journal of Theory and Practice*. He obtained his first master's degree in sociology from Cambridge University. Previously, Mr. Weinmeyer served as a project coordinator at the University of Minnesota Division of Epidemiology and Community Health. His research interests are in public health law, bioethics, and biomedical research regulation.

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