

## HHS Proposes Overhaul of Human Subject Protections for Domestic Clinical Trials

July 27, 2011

In an advance notice of proposed rulemaking published in the July 26, 2011, *Federal Register*, the U.S. Department of Health and Human Services issued a request for comments on amendments to 45 C.F.R. Part 46, Subpart A (the Common Rule) to improve protections of human subjects in research and to revise the research process to reduce burdens, delays and ambiguities for investigators. The broad scope of the areas of possible revision underscores the importance of stakeholders to review, and provide comments regarding, the questions and concerns raised by the agency in this advance notice of proposed rulemaking.

On July 26, 2011, the Office of the Secretary of the U.S. Department of Health and Human Services (HHS), in coordination with the Office of Science and Technology Policy (OSTP), published an advance notice of proposed rulemaking (ANPRM), entitled "[Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators.](#)" 76 *Fed. Reg.* 44,512 (July 26, 2011). The stated purpose of the ANPRM is to solicit comments in order to identify ways to "better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay and ambiguity for investigators." 76 *Fed. Reg.* 44,512. The ANPRM would amend 45 C.F.R. Part 46, Subpart A (referred to as the Common Rule). Comments are due by September 26, 2011.

The Office for Human Research Protections (OHRP) has issued a statement on its website indicating that it will use public comments received in response to this ANPRM in order to develop any proposed regulations to be issued through a future Notice of Proposed Rulemaking. Although HHS might be able to proceed directly to issuing a Final Rule under certain circumstances, the website announcement indicates that HHS will issue proposed regulatory revisions first in order to provide an additional opportunity for interested stakeholders to comment. Accordingly, this ANPRM presents an invaluable opportunity for institutions, pharmaceutical companies, medical device companies and other interested stakeholders to provide HHS with initial comments and/or suggestions on human research issues that may substantially influence the agency's development of any proposed changes to the Common Rule.

The ANPRM proposes both an expansion of the jurisdiction of the Common Rule to govern human subjects research studies conducted at any domestic entity (institution) that receives federal funding to support human subject research, and a wide-range of significant substantive and procedural changes to the Common Rule. The ANPRM could have a profound effect on the ways in which human subjects research is conducted domestically, and would likely require that research institutions make meaningful operational and compliance changes to their research programs.

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Currently, research studies involving the participation of human subjects that are funded in whole or in part by 15 federal agencies must comply with the Common Rule, which is administered by the OHRP. Although OHRP has issued a series of guidelines over the years to clarify the Common Rule's requirements and address emerging compliance issues, the rule itself has not undergone significant revisions since 1991. HHS acknowledged that the "landscape of research activities has changed dramatically" and that there are "many questions about whether the current regulatory framework is adequate and appropriate for the protection of human subjects in the 21st century." 76 *Fed. Reg.* 44,513.

To respond to these dramatic changes and the evolving imperatives of the biomedical enterprise, the ANPRM proposes a wide range of sweeping and significant changes to the current Common Rule and seeks to identify modifications to better harmonize it with other, overlapping federal requirements, such as human subject protection regulations issued by the Food and Drug Administration (FDA) and the Privacy and Security Rules promulgated pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which is enforced by the Office of Civil Rights (OCR) (for an overview of the regulation of human subjects research by OHRP, FDA and OCR, see J. Geetter, *Another Man's Treasure: The Promise and Pitfalls of Leveraging Existing Biomedical Assets for Future Use*, *Journal of Health and Life Sciences Law*, Vol. 4., No. 3, June 2011).

The ANPRM states that the Common Rule currently raises the following seven overarching concerns:

1. It does not calibrate the review process to the degree of risk posed to participating human subjects.
2. It leads to multiple institutional review boards (IRBs) reviewing multi-site trials, resulting in inconsistencies and inefficiencies.
3. It does not afford necessary and appropriately calibrated requirements and practices for informed consent.
4. It does not adequately address "informational" risks to subjects in light of the increasing deployment of pre-existing data and biospecimens in future research.
5. It does not set forth adequate processes for the ongoing evaluation and monitoring of human subject protections.
6. It does not protect all human subjects.
7. It lacks sufficient coordination and harmonization, where possible, with other federal sources of regulation over research. 76 *Fed. Reg.* 44,513-14.

The ANPRM then sets forth proposed recommendations to address each of these areas. For each concern, the ANPRM sets forth specific questions on which it seeks comments. There are a total of 74 distinct questions (many of

which have subparts) and commenters are instructed to indicate the specific question to which their response is directed. Commenters are also invited to provide general feedback on the current lattice work of protections for human subjects provided by the Common Rule, the Privacy and Security Rules, FDA regulations and any other rules, regulations or guidances. 76 *Fed. Reg.* 44,529. The broad nature of these requests for comments and feedback further reinforces this important opportunity for stakeholders to submit suggestions and guidance to HHS.

The ANPRM proposes a series of changes that seek to expedite the research review and oversight process, such as expanding the categories of human subjects review under 45 C.F.R. § 46.101(b), (currently referred to as Exempt), and eliminating the mandatory continuing review of appropriately characterized minimal risk studies.

In many respects, the ANPRM relaxes provisions of the current Common Rule to improve efficiency and remove burdens on investigators that do not, in the agency's view, meaningfully add to human subject protections. However, a few of its proposed changes add or strengthen aspects of the current Common Rule. For example, the ANPRM would require compliance with the Common Rule for all studies by any institution that receives federal funding from a Common Rule-participating human subjects research agency, even if the *particular study* in question is not supported with federal funds. 76 *Fed. Reg.* 44528. This would significantly expand the reach of OHRP's jurisdiction with regard to a given institution, although clinical research conducted at other institutions or by biomedical companies (such as pharmaceutical or medical device manufacturers) that do not receive any federal funds would still remain outside of the Common Rule. In addition, the proposed changes would require written consent for future research use of any biospecimens (tissue samples), whether identifiable or de-identified, or initially obtained for medical purposes. 76 *Fed. Reg.* 44525. In addition, the ANPRM proposes that the Common Rule could impose "mandatory standards for data security and information" rather than allowing investigators and research sites to decide for themselves the necessary data security and stewardship protections. 76 *Fed. Reg.* 44516.

Finally, certain of the proposed changes are intended to harmonize the Common Rule with other federal regulations. The ANPRM indicates the agency is considering adopting the HIPAA Privacy Rule definitions of identifiable, limited data set and de-identified data as the guiding principles in determining which "mandatory standards" for data protection would be required for a given research study. 76 *Fed. Reg.* 44525. As noted in a recent article by two members of the working group tasked with proposing potential revisions to the Common Rule, data security and informed consent revisions should be designed to balance the need to clarify and enhance protections related to research with biospecimens with the agency's recognition of the "huge benefits" to be gained from future use of these biomaterials. See E.J. Emanuel and J. Menikoff. Reforming the Regulations Governing Research with Human Subjects, *New England Journal of Medicine* (July 25, 2011).

Despite this emphasis on harmonization, significant differences would persist. For example, the ANPRM indicates that the agency is considering adopting the position that all biospecimens are identifiable given advances in genetics.

76 *Fed. Reg.* 44,525. In addition, there are certain inconsistencies that would need to be addressed by sister agencies in order to bring harmonization. For example, the FDA requires convened IRB review and approval for any investigation of a clinical medical device. 21 U.S.C. § 360j(g)(3)(A) and (B). Therefore, although the ANPRM proposes that covered studies involving biospecimens be eligible for a new Excused category (currently referred to as Exempt), clinical trials involving biospecimens that are also considered FDA-regulated medical device clinical trials would not be eligible for the expedited process for Excused clinical trials. 76 *Fed. Reg.* 44,518. To the extent that there are research institutions that receive federal funds to support research but are not Covered Entities (as defined in the Privacy Rule), incorporation of Privacy and Security Rule standards into the Common Rule in furtherance of harmonization could lead to confusion and uncertainty for institutions that would not otherwise be covered by the Privacy and Security Rules.

Although the ANPRM covers a wide range of concerns posed by the research community, it does not address a number of other contested issues. For example, the ANPRM does not revisit the ban on exculpatory language in informed consents, which has been a source of confusion, ambiguity and controversy for many years. The ANPRM also does not address how the “research development” component of the definition of research squares with the “preparatory to research” pathway under the HIPAA Privacy Rule. The ANPRM does not tackle related human subject protection considerations like conflicts of interest or the functioning of data safety monitoring boards. Further, HHS declines in the ANPRM to make all of the changes necessary to bring the Common Rule into alignment with either FDA clinical research regulations or the Privacy and Security Rules. With the publication of this ANPRM, it is possible that the FDA will propose changes to, or additional guidance for, its own human subject protection regulations under its current Human Subject Protection/Bioresearch Monitoring Initiative. Because some inconsistencies would persist and because of the sheer volume of the proposed changes, a careful review of the ANPRM is warranted to identify potential unintended consequences or ambiguities of the proposed changes, instances of persistent inconsistency between the Common Rule and other federal regulations that might undermine the goals of improving efficiency, barriers to enhancing subject protections, and ambiguities or gaps in understanding the agency’s expectation for ongoing compliance.

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In recent years, the rise of personalized medicine, the increasing importance of and role for pre-existing biospecimens and data in clinical research, the significant uptick in the volume of research requiring IRB review, and the myriad overlapping and oftentimes inconsistent federal regulations touching upon human subjects research, have resulted in significant uncertainty over how to interpret and apply the Common Rule in this new research environment. The ANPRM is an attempt to respond to these developments and situations by proposing far-reaching changes to how certain human subjects research is regulated domestically. Even for those entities not receiving any

federal funds, the ANPRM is important as the Common Rule has come to be a basic standard against which human subject protection programs are judged. The ANPRM, along with proposed changes to the HIPAA Privacy Rule's regulation of future research (see *Modifications to the HIPAA Privacy, Security, and Enforcement Rules Under the Health Information Technology for Economic and Clinical Health Act*, 75 *Fed. Reg.* 40,868, July 14, 2010), suggests a renewed effort on the part of HHS to update and harmonize research protections across agencies. Given the long list of questions presented for comment, research institutions, hospitals and health systems, sponsors, investigators, institutional review boards, contract research organizations and the biomedical industry should consider commenting on the ANPRM to ensure the agency hears from all affected participants as part of this major overhaul effort.

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