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Common Rule 2.0: HHS Announces Its Intention To Propose an Overhaul of Human Subject Protections



BY JENNIFER S. GEETTER

On July 26, 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), titled “Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, De-

Jennifer S. Geetter is a partner in the Health Advisory Practice Group of McDermott Will & Emery LLP. She is a frequent writer and lecturer on life sciences issues, including human subject protection regulation and best practices. She wishes to thank Elizabeth Isbey for her assistance in reviewing this article.

lay, and Ambiguity for Investigators.”¹ The department’s stated purpose in issuing the ANPRM is to solicit comments on ways to “better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay and ambiguity for investigators.”² The ANPRM would amend 45 C.F.R. Part 46, Subpart A (referred to as the Common Rule). The broad scope of the areas of possible revision and the proposed changes affecting future use of pre-existing data and biospecimens underscore the importance of stakeholders reviewing and providing comments regarding the questions and concerns raised by the agency. Entities not typically regulated by the Common Rule, such as pharmaceutical companies, device manufacturers, and the biotechnology companies, may also wish to give careful consideration to submitting comments because such entities rely on institutions that are typically regulated by the Common Rule to conduct necessary clinical trials. In addition, given the emphasis

¹ 76 Fed. Reg. 44512 (July 26, 2011).

² *Id.* at 44512. Although HHS might be able to proceed directly to issuing a Final Rule under certain circumstances, HHS 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. See <http://www.hhs.gov/ohrp/humansubjects/anprmqanda.html>. In addition, the ANPRM acknowledges that changes to the Common Rule could affect the Food and Drug Administration regulations, Health Insurance Portability and Accountability Act regulations, and Subparts B-E of the HHS Office for Human Research Protection’s own regulations, and they will likely “need to be harmonized, as appropriately, with any proposed regulatory changes made to the Common Rule.” 76 Fed. Reg. at 44514.

placed on regulatory harmonization in the ANPRM, it is very possible that a revised Common Rule could then serve as the basis for conforming changes to related regulations. In light of similar pressures to update research-related regulations to facilitate biomedical innovation on the Food and Drug Administration (FDA) and the HHS Office for Civil Rights (OCR), which administers the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its implementing regulations (the Privacy and Security Rules), this ANPRM is a critical step in the articulation of a new research compliance and human subject protection framework for biomedical innovation in the 21st century.

Comments are due by Sept. 26.

Background

Currently, research studies involving the participation of human subjects that are funded in whole or in part by over a dozen signatory federal agencies must comply with the Common Rule, which is administered by the HHS Office for Human Research Protections (OHRP). The Common Rule has not undergone significant revision since 1991. Although OHRP has issued a series of guidelines over the years to clarify the Common Rule's requirements and to address emerging compliance issues, these efforts have not been sufficient to keep pace with profound changes in the volume and variety of human subjects research and have not provided appropriate regulatory oversight and guidance tailored to studies involving pre-existing biospecimens and data. These studies are particularly critical to advances in personalized medicine. In the ANPRM, HHS acknowledges 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."³ In addition, HHS confirms that outside panels and associations have been calling for the Common Rule to be updated and notes that the recommendations of these outside experts informed many of the agency's proposals.⁴

To respond to these profound changes and the evolving imperatives of the biomedical enterprise, the ANPRM proposes both (1) an expansion of the jurisdiction of the Common Rule to govern human subjects research studies conducted at any domestic institution that receives federal funding from a Common Rule signatory agency to support human subject research, and (2) a wide range of substantive and procedural changes to the Common Rule. One goal of the procedural changes specifically is to identify modifications that are necessary to begin the process of harmonizing inter-agency federal oversight over human subjects research. Currently, overlapping, and oftentimes inconsistent, federal requirements—such as human subject protection regulations issued by FDA and OCR—can lead to conflicting regulations, making it difficult to structure a specific human subjects research study or an overall strategic research initiative (such as a biobank) that simultaneously complies with these regulatory mandates.⁵ If incorporated into a final rule, the types of

changes proposed in the ANPRM could have a profound effect on the ways in which human subjects research is conducted, and likely would require that research institutions make meaningful operational and compliance changes to their research programs.

Overview of the ANPRM

The ANPRM states that the department has identified seven overarching concerns with the Common Rule. These concerns can be summarized and categorized as follows:

- it does not sufficiently calibrate the review process to the degree of risk posed to participating human subjects (discussed in Section II of the ANPRM);
- it leads to multiple institutional review boards (IRBs) reviewing multisite trials, resulting in inconsistencies and inefficiencies (discussed in Section III of the ANPRM);
- it does not afford an adequate "extent and quality" of informed consent protections (discussed in Section IV of the ANPRM);
- it does not adequately address "informational" risks to subjects in light of the increasing deployment of pre-existing data and biospecimens in future research (discussed in Section V of the ANPRM);
- it does not set forth adequate processes for the ongoing evaluation and monitoring of human subject protections (discussed in Section VI of the ANPRM);
- it does not protect all human subjects (discussed in Section VII of the ANPRM); and
- it lacks sufficient coordination and harmonization, where possible, with other federal sources of regulation over research (discussed in Section VIII of the ANPRM).⁶

The ANPRM then sets forth proposed recommendations to address each of these areas. Further, for each area of concern, the ANPRM sets forth specific questions for which it seeks comments. There are 74 distinct questions (many of which have subparts), and commenters are instructed to indicate the specific question to which their response is directed.⁷ Commenters are also invited to provide general feedback on the current latticework of protections for human subjects provided by the Common Rule, the Privacy and Security Rules, FDA regulations, and any other rules, regulations, or guidances.⁸ The broad nature of these requests for comments and feedback further reinforces this important opportunity for stakeholders to submit suggestions and guidance to HHS.

A Closer Look at the Proposed Changes

1. Calibrating Review Burdens with Risk

The ANPRM seeks to address criticisms that the current system does not adequately balance the burdens and requirements of the review process with the actual degree of risk posed to participating human subjects. This criticism has two parts—one focuses on the requirements of the Common Rule itself and the other fo-

³ 76 Fed. Reg. at 44513.

⁴ Id.

⁵ 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 Exist-

ing Biomedical Assets for Future Use," *Journal of Health and Life Sciences Law*, Vol. 4., No. 3 (June 2011).

⁶ 76 Fed. Reg. at 44513-44514.

⁷ Id. at 44529.

⁸ Id.

cuses on how IRBs and other research oversight mechanisms have sought to comply with the Common Rule.⁹

The current Common Rule does have essentially three tiers relating to risks to subjects, but the ANPRM states that this may not offer sufficient flexibility for IRBs. The Common Rule classifies human subjects research as either exempt, minimal risk, or non-minimal risk. Exempt studies are those that fall within one of six enumerated categories exempting the study from further IRB review and from the standard informed consent requirements.¹⁰ OHRP, however, has issued guidance recommending that exempt studies still undergo some sort of review by the research site.¹¹ Minimal risk studies are those that only involve research activities itemized in a published list by HHS¹² and are found by reviewers to pose no more than minimal risk to participating subjects. Such studies are eligible, at the research site's discretion, to undergo expedited IRB review if such a process is set forth in the site's IRB policies and procedures.¹³ This typically involves review by the IRB chair or other IRB members. Non-minimal risk studies are those that pose more than minimal risk to participating subjects and must undergo review by a fully convened IRB. Although these three current categories do adjust the review process and the protections afforded to human subjects based upon the likely involved risks, the department states that it is concerned that these calibrations may not be sufficient.¹⁴

The department cites as an example of the potential shortcomings of the current structure the concern that these risk stratifications are not appropriate for the review process for social and behavioral research. As the department notes, the types of risks posed to subjects are "often significantly different in many social and behavioral research studies as compared to biomedical research, and critics contend that the difference is not adequately reflected in the current rules."¹⁵ In particular, the department notes that in a standard, interventional study, the main risks are physical risks (e.g., side effects from the medications). In social and behavioral studies, the most serious risks are likely to be psychological (e.g., learning something they were not prepared to know) or informational (e.g., the inadvertent disclosure of sensitive, personal information).¹⁶

To demonstrate further the insufficiency of the current framework, the ANPRM notes concerns that IRBs do not always avail themselves of the expedited review

process available for minimal risk studies. This may result in a convened IRB expending scarce time and effort resources on studies posing very low risks to subjects. Further, the ANPRM notes concerns that IRBs have a "tendency to overestimate the magnitude and probability of reasonably foreseeable risks."¹⁷ Although not stated in the ANPRM, it is also possible that IRBs are spending considerable time on minimal risk studies because these studies are often those that involve only the use of pre-existing biospecimens and data. Although not discussed in the ANPRM, it is also possible that IRBs are doing that because IRBs may be struggling to determine how best to apply the Common Rule to studies where a subject's "participation" is limited to the deployment of these biospecimens and data and are not the type of interventional, experimental test article studies that formed the basis for the Common Rule and other types of human subject protections.

To respond to these concerns, the department proposes that the current risk-based framework be adjusted and refined, and announces five specific proposals:

a. *Establishment of mandatory data security and information protection requirements for studies involving identifiable information and protections against the re-identification of information previously de-identified.*¹⁸ The ANPRM states that the majority of risks to human subjects can be categorized as physical risks, psychological risks, and informational risks.¹⁹ Informational risks are those posed by the "inappropriate use or disclosure of information, which could be harmful to the study subjects or groups."²⁰ The degree of informational risk is associated with the level of identifiability of the data and also with the sensitivity of the information itself.

IRBs are tasked with reviewing all three types of risks, but the ANPRM expresses concerns that IRBs may not be best equipped to evaluate informational risks.²¹ IRB members may not be sufficiently knowledgeable about available data protection strategies and may have historically inconsistently required and applied these strategies.²² The ANPRM also states that evaluating informational risks and ways to minimize them may not be an appropriate use of IRB time but could be better addressed with standardized requirements.²³

Accordingly, the ANPRM states that HHS is considering imposing mandatory standards for data security and information protection "whenever data are collected, generated, stored, or used."²⁴ The ANPRM proposes to "model" these mandatory standards on the HIPAA Security Rule. It is not clear, however, whether in "modeling" Common Rule data security and information standards on the HIPAA Security Rule, the department is proposing to adopt the Security Rule standards wholesale or issue new standards that use the Security Rule as a guide. The ANPRM also proposes to adopt the HIPAA standards for identifiability including

⁹ The discussion of these concerns and the proposed solutions set forth in Section II of the ANPRM are the most extensive. In addition, many of the proposed changes to better calibrate risk-based protections touch on proposals in Sections III-VIII. For example, the ANPRM proposes revisions to better structure the review process for studies that may not have significant risks to the health and safety of subjects, but instead principally pose so-called informational risks. Accordingly, the ANPRM proposes to develop safeguards that protect the security and confidentiality of personal information shared by and learned about participating human subjects. These safeguards are also discussed in Section V, which addresses mandatory data security and information protection standards.

¹⁰ 45 C.F.R. § 46.101(b).

¹¹ <http://answers.hhs.gov/ohrp/categories/1564>.

¹² <http://www.hhs.gov/ohrp/policy/expedited98.html>.

¹³ 45 C.F.R. § 46.110(a).

¹⁴ 76 Fed. Reg. at 44514.

¹⁵ Id. at 44513.

¹⁶ Id.

¹⁷ Id.

¹⁸ Id. at 44515.

¹⁹ Id.

²⁰ Id. at 44516.

²¹ Id.

²² Id.

²³ Id.

²⁴ Id.

HIPAA's standards for Protected Health Information, what constitutes a Limited Data Set and De-Identified Information.²⁵ The mandatory data protections then would be specified for each of these levels of identifiability.²⁶ These recommendations also are discussed further in the ANPRM's proposal to respond to concern No. 4 (informational risks) described below and in the ANPRM in Section V. This proposal might simplify the research approval process for research sites that are covered entities or business associates as they already must comply with HIPAA; however, for research sites that have not operated under HIPAA previously, the impact of the incorporation of HIPAA standards should be carefully considered. Because this proposal would affect some studies currently classified as exempt in the Common Rule, the ANPRM also recommends that the exempt category be renamed as "Excused" to underscore that while such studies may be excused from IRB oversight or other requirements specifically, they are still required to comply with the Common Rule, for example, with respect to these new informational risk standards.

b. *Revise continuing review requirements.* Currently, non-exempt studies must be reviewed by an IRB or by an expedited review process at least annually. The ANPRM proposes to eliminate completely continuing review for minimal risk studies that underwent expedited review unless the expedited reviewer (1) specifically requires that continuing review occur, and (2) states the rationale for this requirement.²⁷ For non-minimal risk studies, continuing review would occur at least annually until the study reaches the stage where either it only analyzes data (even if identifiable) or it only reviews follow-up clinical care data from procedures that are part of the standard of care and otherwise would have occurred notwithstanding the research.²⁸ At this stage, the "default" would be that continuing review would no longer be required, but the IRB could override the default.²⁹ The ANPRM does not specify who would be responsible for determining which follow-up services are standard of care and which are research-related, and it is not clear whether research sites could rely on the personnel typically tasked with making these distinctions for clinical trial billing compliance (as opposed to human subject protections).

c. *Revise the Common Rule governing expedited review.* The ANPRM proposes three changes with regard to the expedited review process: (1) revise the criteria for eligibility for expedited review; (2) eliminate routine, annual continuing review; and (3) streamline how such studies are submitted for oversight. First, the ANPRM states that the agency is considering an update to the list of qualifying research activities, which was last updated in 1998. It also proposes establishing a panel that would periodically, but more predictably, review the list (for example, every two years).³⁰ The ANPRM proposes to establish a presumption that any study that involves only activities included on the list is a minimal risk study and qualifies for expedited re-

view.³¹ The reviewer would not have to make a secondary finding that the study posed only minimal risk. The reviewer could still refer the study for a fully convened IRB if he or she thought it was necessary.

In addition, minimal risk studies must currently comply with all of the criteria for IRB approval.³² The ANPRM states that HHS is considering whether all or only a specified subset of these criteria should be required for minimal risk studies.³³ Second, as noted above, the ANPRM proposes that minimal risk studies that initially underwent expedited review no longer would be required to undergo continuing review unless the initial reviewer determined that continuing review was warranted and provided a justification for this determination. The ANPRM does not specify whether minimal risk studies that nonetheless were referred by the expedited reviewer to a fully convened IRB for initial review also would be exempt from continuing review. Third, the ANPRM proposes that minimal risk studies could benefit from a streamlined review process. The agency discusses whether "templates" and "sample versions" for some forms (e.g., informed consent documents) might facilitate the process and also raises the possibility that all of the documentation required for non-minimal risk studies (for example, a detailed protocol, informed consent documents, and other related materials) may not be required for minimal risk studies.³⁴

d. *Revise the standards for exempt studies.* As discussed above, the current Common Rule exempts six types of studies involving human subjects from the Common Rule's requirements. The ANPRM states that HHS is considering "moving away from the [c]oncept of Exempt"³⁵ and proposes renaming the currently exempt studies as excused studies. Excused studies would not require IRB review, but would be subject to the proposed new data security and information protection standards discussed elsewhere in the ANPRM and would, in some cases, require informed consent.³⁶

The ANPRM proposes to maintain the current six categories of exempt studies in the new excused category. The ANPRM proposes to expand the studies eligible for the current second category of exempt studies and to add a new category for certain behavioral or social science studies that are more intensive than a survey but nonetheless involve only the specified minimal risk categories, provided that, for both categories, the subjects are competent adults and the new mandatory data protections are deployed.³⁷

The ANPRM also proposes to expand the current exempt category 4 (research involving the use of existing data or biospecimens). Exempt category 4 has a series of limitations that the ANPRM proposes to eliminate. In addition, the ANPRM proposes to clarify that the word "existing" in this category would mean "collected for purposes other than the proposed research and would not mean that all of the data or biospecimens to be used in the study need to exist at the time the study is com-

²⁵ Id. at 44515.

²⁶ Id. at 44516.

²⁷ Id. at 44515.

²⁸ Id.

²⁹ Id. at 44516.

³⁰ Id.

³¹ Id. at 44515 and 44516.

³² 45 C.F.R. § 46.111.

³³ 76 Fed. Reg. at 44517.

³⁴ Id.

³⁵ Id. at 44518.

³⁶ Id.

³⁷ Id. at 44518-44519.

menced.”³⁸ This change would permit institutions to obtain informed consent (if required to do so) prior to the data or biospecimens coming into existence. The newly expanded category would then encompass all future research involving pre-existing identifiable data and biospecimens, provided that the new informed consent proposals are followed and the individualized results from any testing performed during the study were not provided back to the subjects.³⁹

The ANPRM also would require random retrospective audits to confirm that the studies were indeed exempt.⁴⁰ To enable this audit process, investigators would be required to “register” an excused study by filing a form with the institution. This would put the institution on notice that the study was occurring and the institution could elect to review some of the registrations at the time of submission and redirect any submissions, as necessary, for expedited or fully convened IRB review.⁴¹ Such a requirement might be consistent with other institutional practices requiring institutional notice and oversight over research to ensure compliance with contractual, budgeting, intellectual property, and other considerations. While clarifying that extensive review of these exempt studies is not required is likely to be welcome news to research institutions, the ANPRM states that more thorough review may “not even [be] recommended.”⁴² Discouraging more robust IRB review could have unintended consequences as institutions seek to implement a research oversight program that they feel is best tailored to that specific research institution.

As a general matter, the ANPRM proposes to maintain the current informed consent practices for currently exempt studies as applied to the new excused studies.⁴³ The ANPRM, however, does propose changes. First, “written, general consent” would be required for the use of biospecimens in future research in all circumstances going forward.⁴⁴ This proposal is addressed below. Second, with respect to pre-existing data (redefined under the proposed changes as data that were collected for some prior purpose other than the extant study), if the data were collected for non-research purposes (e.g., treatment), written consent for future use would not be required unless the downstream investigator intends to obtain identifiable information. This is consistent with HHS’s interpretation of the current Common Rule. With respect to data originally collected for a research purpose, however, consent would be required for future use research regardless of whether the downstream investigator intends to obtain identifiable information. This is a change from the current Common Rule.⁴⁵ In addition, the ANPRM’s

proposed approach would be a meaningful departure from current practice, which pivots on identifiability. The ANPRM does not address how this broad upfront consent should best be structured to obtain consent for identifiable information to be shared for future research. Obtaining upfront consent for the use of identifiable information in future unspecified research could introduce inconsistencies with HIPAA and it may be challenging to structure a broad upfront consent document for future use of identifiable information that meaningfully informs potential participants of what they can expect may happen in the future. Further, the ANPRM does not address why it recommends different consent approaches depending on the origin of the data.

e. *Written informed consent for studies involving biospecimens.*⁴⁶ The ANPRM proposes to require written informed consent for any research that would involve biospecimens collected for clinical purposes after the effective date of the new rule, even if such biospecimens were de-identified in accordance with HIPAA.⁴⁷ The ANPRM states that written consent is necessary for all biospecimens because advances in genetics may undermine the entire concept of “de-identification” as it relates to biospecimens.⁴⁸ Currently, consent is not required when the researcher does not possess, and does not have access to, information that would enable him or her to identify the individual from whom the biospecimens were collected. This newly required consent could be obtained as part of a general consenting process when the individual first interacts with the institution for treatment or research, and would require the institution to describe biospecimens generally to the patient. The written informed consent could involve a brief form that was broad enough to govern any future use of such biospecimens or even to include any biospecimens to be collected at any time by the institution.⁴⁹

Some IRBs, however, may have concerns about presenting such an open-ended future consent encompassing, potentially, a wide range of health conditions and different degrees of downstream data identifiability. The ANPRM does state that this broad consent also could allow a patient to decline to participate in all future research or to indicate “yes” and “no” to different check boxes describing categories of research.⁵⁰ Although the ANPRM makes a series of proposals to harmonize the Common Rule with HIPAA, this broad, upfront approach to future unspecified research and the reliance on check boxes may introduce potential inconsistencies with corresponding HIPAA requirements.⁵¹

³⁸ Id. at 44519.

³⁹ Id. Studies that intend to “provide to subjects individual results from the analysis of their biospecimens or data” would not be able to avail themselves of this category. This presumably would apply regardless of whether the results were provided to the subject directly, to the subject’s treating provider, or to the subject indirectly through a right to inspect research records in which those results are maintained. The ANPRM, however, does not state this directly.

⁴⁰ Id. at 44515 and 44519.

⁴¹ Id. at 44519.

⁴² Id. at 44515.

⁴³ Id. at 44519.

⁴⁴ Id.

⁴⁵ Id.

⁴⁶ Id. at 44515.

⁴⁷ Such studies would fall under the newly expanded category 4 excused studies.

⁴⁸ 76 Fed. Reg. at 44525.

⁴⁹ Id. at 44515.

⁵⁰ Id. at 44519-44520.

⁵¹ The ANPRM appears to take notice of potential inconsistencies. For example, the ANPRM notes that the HIPAA Privacy Rule generally has “not been interpreted to permit general authorizations for future, unspecified research” use of Protected Health Information. Id. at 44523. The ANPRM also notes that OCR is reviewing comments received in response to its notice of proposed rulemaking from July 14, 2010, as to whether a single, broad, upfront authorization may be appropriate (see “Modifications to the HIPAA Privacy, Security, and Enforcement Rules Under the Health Information Technology

2. Redundant IRB Review

The department's second principal concern pertains to multisite trials. Frequently, research studies are open at multiple institutions to assist with subject recruitment, enlist the participation of multiple investigators with necessary expertise, and minimize statistical bias. Although the current Common Rule sets forth a procedure by which each institution can elect to rely on a single, centralized IRB, few IRBs elect to do so, perhaps stemming from concerns that institutions would continue to face enforcement risks even if the compliance concerns stemmed from the actions of an outside, independent IRB.⁵² Rather, multisite trials typically result in multiple IRBs reviewing the study. According to the department, this often results in inconsistencies in the review process, with different IRBs imposing different requirements.⁵³ In addition, the department contends that this added level of review is inefficient and may not advance human subject protections. In those cases where local conditions may need to be taken into account, the ANPRM states that mechanisms other than fully convened IRB review could be deployed, or local IRBs could be limited to those specific local issues.⁵⁴

To respond to these concerns, the department proposes to mandate that there be a single IRB of record for all domestic sites engaged in a multisite trial.⁵⁵ Such a requirement would "not relieve any site of its other obligations under the regulations to protect human subjects."⁵⁶ In addition, such a proposed requirement would not prevent an institution from requiring other types of internal, ethical reviews, but such reviews "would no longer have any regulatory status in terms of compliance with the Common Rule (and could be discouraged)."⁵⁷ As noted above, commenters may wish to consider the impact that any final rule or guidance discouraging IRB involvement may have on the operation of a research program.

3. Informed Consent

The department notes that there have been a variety of criticisms of the current informed consent process. For example, some critics contend that the informed consent forms have become more focused on shielding the research sites from liability than on informing subjects about the study⁵⁸ or on serving as "sales documents."⁵⁹ The forms are long and often require a high reading level.⁶⁰ The department is concerned that current forms may not contain all of the necessary information such as information on financial relationships

between the study sponsor or funder, and that they may be organized in a such a way that important information is missed by potential subjects.⁶¹ Further, some critics feel that the informed consent requirements are reflexively applied to types of research (e.g., studies involving surveys), when informed consent may be unnecessary.⁶²

To respond to these concerns, the department proposes to improve the consent process, and proposes templates and standard language for informed consent forms. In particular, the ANPRM proposes six specific recommendations: (1) prescribe content that must be included in all informed consent forms; (2) specify content that should not be included in informed consent forms; (3) limit the length of specific informed consent form sections; (4) specify how certain types of information need to be presented in informed consent forms; (5) reduce "institutional boilerplate" language that the agency feels is "primarily intended to protect institutions from lawsuits"; and (6) provide standardized forms.⁶³ The impact of these proposed categories of changes will vary dramatically based on the specific proposals that may be developed, and whether the subsequent proposals address informed consent content difficulties with which institutions have struggled. For example, these informed consent forms may need to explain the availability of financial assistance for subject injuries or for services provided pursuant to a research protocol that are not covered by insurance in light of the so-called Medicare Secondary Payer Rule, or how to explain to subjects that they may not share in any downstream commercialization profits in light of the exculpatory language ban.

The ANPRM also notes that there have been criticisms of the current Common Rule's approach to granting waivers of the informed consent process. The current process may not be sufficiently flexible for dealing with all of the situations in which waiver of all or part of the written informed consent process may be appropriate. Although the ANPRM does not list specific proposed changes, it does request comments on how the waiver process might be reformed. The different proposed consent rules are summarized in a table.⁶⁴

4. Informational Risks

The department notes that in recent years future use has accelerated. Future use (or "future research" or "secondary research") is the use of pre-existing biospecimens and data that were collected for some other primary purpose than research. These biomedical assets, perhaps originally collected for treatment, payment, regulatory, or research purposes, can be repurposed to support research studies. Future use is particularly important for certain types of studies that depend on knowing the long-term health outcomes of the people who provided the biospecimens to search for patterns and correlations. A particular risk for these types of studies is an informational risk.

Current informed consent, authorization, and information security requirements turn, in part, on definitions of identifiability. The ANPRM notes that it believes that such standards are "fluid" and that "rapidly

for Economic and Clinical Health Act," 75 Fed. Reg. 40868, July 14, 2010). Id.

⁵² Id. at 44522. For a discussion of OHRP's recent changes to the Federalwide Assurance process of designating multiple IRBs, see J. Geetter and J. Kim, "OHRP Revises Federalwide Assurance," *On the Subject*, July 7, 2011, <http://www.mwe.com/info/news/ots0711j.htm>. The ANPRM does not address how the proposed revisions would affect these recent changes.

⁵³ Id. at 44522.

⁵⁴ Id.

⁵⁵ Id. at 44521. Note, this proposed change would not apply to FDA-regulated device studies. Id.

⁵⁶ Id. at 44522.

⁵⁷ Id.

⁵⁸ Id. at 44513.

⁵⁹ Id. at 44522.

⁶⁰ Id.

⁶¹ Id. at 44513.

⁶² Id.

⁶³ Id. at 44523.

⁶⁴ Id. at 44527.

evolving advances in technology coupled with the increasing volume of data readily available may soon allow identification of an individual from data that [are] currently considered de-identified.”⁶⁵ The department’s apparent concern about the reliability of the principle of de-identification raises more general questions about the direction regulators may take with respect to reviewing approaches to de-identification. Furthermore, the ANPRM states that existing protections under the Common Rule, HIPAA, and other federal provisions “are limited in scope.”⁶⁶ The ANPRM notes that the “majority of unauthorized disclosures of identifiable health information from investigators occur due to inadequate data security.”⁶⁷ For example, the ANPRM notes that HIPAA only governs covered entities, and more recently, business associates. However, it will not necessarily govern free-standing research institutes or cooperative groups receiving federal funds for research.⁶⁸

To respond to these concerns, the ANPRM proposes to mandate data security and information protection standards using three specific requirements. First, research that involves the collection or use of identifiable data (including “limited data set” data) would have to comply with data security standards that would mirror those set forth in the HIPAA Security Rule. As discussed above, this approach, according to the ANPRM, would both promote stratification among standards of identifiability (and according risks and protections), and would resolve inconsistencies between information that would not be considered identifiable under the Common Rule (like dates of service) but would be considered identifiable under HIPAA.⁶⁹ The ANPRM provides as an example that these standards could require the use of encryption for data maintained or transmitted in electronic form.⁷⁰ By modeling Common Rule requirements on the HIPAA Security Rule, the ANPRM also proposes that investigators be required to comply with the breach notification standards that were promulgated under the HITECH Act.⁷¹ As the Common Rule generally is interpreted to require IRB determinations on when subjects need to be informed of information that might affect their willingness to participate (presumably including information about the risks to the confidentiality of their information) and to require IRB approval of all communications with potential or enrolled subjects, incorporation of the HITECH Act breach notification provisions could re-involve IRBs in assessing the magnitude of harm involved with certain informational risks and how best to communicate this information back to subjects.

Despite efforts at improving harmonization, gaps and ambiguities would persist. For example, as noted above, the ANPRM proposes a significant departure from HIPAA standards in concluding that biospecimens always would be considered identifiable under the Common Rule even if the biospecimens were not associated with any data considered identifiable under HIPAA. In addition, the ANPRM does not discuss whether the

Common Rule also would incorporate the “preparatory to research pathway” set forth under the Privacy Rule that allows for the use and disclosure of Protected Health Information in connection with research development activities. Currently, “research development” is a subset of the definition of “research” under the Common Rule, and IRBs historically have struggled with how best to apply the Common Rule to preliminary uses of identifiable information for activities such as developing a protocol or determining whether a given research site could meet recruitment goals.⁷² Second, the ANPRM proposes that data could qualify as de-identified or a limited data set if the investigators can see fully identifiable information but do not record this information in the “permanent research file.”⁷³ The ANPRM does not discuss what would constitute such a file or whether the information could be temporarily recorded for preliminary data analysis and later destroyed or returned. Third, the ANPRM proposes to strengthen enforcement mechanisms, including periodic, random audits.⁷⁴

These new standards would apply, however, only to “prospective collections of data and biospecimens after the implementation of any changes to the Common Rule and not retrospectively to research involving existing data.”⁷⁵ Thus, institutions may need sophisticated systems to keep track of the regulatory requirements applicable to different subsets of biospecimens and data. This may be particularly challenging for data included in medical records because it may be extremely difficult to differentiate data subject to the new informed consent rules since they are commingled and integrated into a single medical record with data not subject to these new requirements.

5. Ongoing Monitoring and Evaluation

The department notes that critics have voiced concerns that the current requirements do not result in sufficient mechanisms for the ongoing oversight of research nor for gathering the information necessary to evaluate the effectiveness of the research oversight procedures in place. In addition, different oversight agencies have different requirements for the circumstances under which compliance-related information must be self-reported.⁷⁶

To respond to these concerns, the ANPRM proposes upgrades to the collection and analysis of data on unanticipated problems and adverse events. The ANPRM states that the proposed changes are “intended to simplify and consolidate the reporting of information that is *already required* to be promptly reported by an investigator, and *not* to expand the information to be reported.”⁷⁷ These proposed changes are, therefore, not only important for commenters but are also instructive as to OHRP’s current understanding of reporting requirements. First, the department proposes adopting a standardized set of data elements that must be reported

⁶⁵ Id. at 44524.

⁶⁶ Id.

⁶⁷ Id. at 44526.

⁶⁸ Id. at 44514.

⁶⁹ Id. at 44525.

⁷⁰ Id. at 44526.

⁷¹ Id.

⁷² 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).

⁷³ Id. at 44526.

⁷⁴ Id.

⁷⁵ Id. at 44525.

⁷⁶ Id. at 44527.

⁷⁷ Id. (emphasis in original).

but that are still sufficiently flexible to allow for customized safety and compliance reporting consistent with most federal requirements. Second, the department proposes implementing a web-based reporting portal that would be consistent with those adopted by FDA and several other federal agencies. This portal would incorporate the standardized data elements and would have the capability of automatically sharing the submitted data with other agencies and oversight bodies as appropriate. Third, the department proposes to harmonize the safety reporting guidelines across “all Federal agencies” and to develop a repository to house much of the data submitted through the portal.⁷⁸

6. Protecting All Subjects

The ANPRM expresses concern that the current Common Rule does not provide adequate protection to all subjects participating in research.⁷⁹ For example, the ANPRM notes that studies that are not funded in whole or in part by a Common Rule signatory agency are not necessarily protected by the regulation. Although institutions can elect to extend the applicability of the Common Rule to all of the human subjects research conducted at their institution, this is not required.⁸⁰ Further, some studies would not be subject to FDA regulations, HIPAA, or the Common Rule and therefore would not be subject to any federal research regulation at all. To respond to this concern, the department proposes to extend the Common Rule protections to all studies conducted at domestic institutions that receive any funding from a Common Rule signatory agency for research involving human subjects, even if the study in question is not federally funded.⁸¹ The department’s proposals, however, for how the Common Rule should apply to studies conducted internationally or to multisite studies where one or more sites are abroad merits further consideration. In addition, the ANPRM does not specify what would constitute “Federal funding from a Common Rule agency for research with human subjects.” For example, the ANPRM does not specify whether the extension of the Common Rule would apply only to institutions that receive federal funding for *specific* human subjects studies or would apply to institutions that receive federal funding that support human subject research programs generally.

7. Harmonization

While some studies may not be subject to any federal oversight, the ANPRM also notes that some studies are subject to multiple regulatory schemes that may be inconsistent and unnecessarily complex. This has led to IRB and investigator frustration as well as variability between multiple IRBs in how they approach overseeing the same study. For example, the Common Rule, HIPAA, and FDA regulations have meaningfully different approaches to (1) determining when information is identifiable and what that determination means for the review process, and (2) regulating the creation of, maintenance of, and withdrawal from biospecimen and data repositories. The ANPRM notes that there are a number of initiatives underway to try and address these incon-

sistencies.⁸² The department notes, however, that there also may be instances when distinct agency approaches and requirements are warranted because of the precise oversight mission of the agency.⁸³ In light of the need to balance harmonization with appropriate distinction, the ANPRM requests comments on how best to approach revisiting federal oversight of research in addition to any of the specific proposals set forth previously in the ANPRM.⁸⁴

The landscape of biomedical innovation has undergone significant transformation since 1991. In recent years, the ascent of personalized medicine, the increasing importance of and role for pre-existing biospecimens and data in research, the significant increase in review demands placed on IRBs, the focus on the importance of data in solving a range of public health dilemmas, and the myriad overlapping and oftentimes inconsistent federal and state regulations touching upon research collectively have resulted in significant uncertainty over how to interpret and apply the Common Rule to this new research topography.

The ANPRM attempts to respond to these developments by proposing far-reaching changes to how human subjects research is conducted, monitored, and regulated domestically. Even for entities that historically have not accepted federal funds for human subjects research, the ANPRM is important because the Common Rule has come to be a standard against which human subject protection programs generally are judged. Thus, a restated Common Rule could have far-reaching effects for entities across the biomedical spectrum. Further, the ANPRM, along with proposed changes to the HIPAA Privacy Rule’s regulation of future research in July 2010, suggests a renewed effort on the part of HHS to update and harmonize research protections across agencies, and it is possible that updates to the Privacy Rule and/or FDA regulations will be modeled on the final rule issued at the end of this process.

However, although the ANPRM covers a wide range of concerns posed by the research community, it does not address a number of other contested issues that stakeholders may wish to address in comments. These omitted areas could, in some cases, be as important as the topics that are the focus of the ANPRM. 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. Although the ANPRM devotes considerable attention to the future use of pre-existing biospecimens and data, it does not revisit its existing published guidance on repository creation and “coded” biospecimens and what constitutes the “engagement” in research, nor does it address enforcement risk for downstream researchers who receive biospecimens from Common Rule-regulated institutions but who are not, themselves, subject to the Common Rule. The ANPRM places considerable emphasis

⁷⁸ Id.

⁷⁹ Id. at 44528.

⁸⁰ Interestingly, the ANPRM states that “[m]ost institutions” have made this election. Id. at 44528.

⁸¹ Id.

⁸² Id.

⁸³ Id.

⁸⁴ Id.

on standardized forms and templates and, in several instances, appears to discourage additional oversight. This approach may, however, introduce new ambiguities as institutions also seek to comply with conflicting state law and implement research programs appropriate to their unique environments and patient populations. The ANPRM does not tackle related human subject protection considerations such as 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 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 inconsis-

tency 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.

Given the extensive list of questions presented for comment and the number of preliminary proposals, 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. 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 and the ripple effect such changes may have on related regulations.