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Proposed Changes to the Common Rule: A Standoff Between Patient Rights and Scientific Advances?

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What is the issue? Proposed changes to the Common Rule would expand the scope of human subjects research to include biospecimen collections and uses for research, regardless of their identifiability. The proposed changes also would update the existing regime of exclusions and exemptions, impose new consent requirements and privacy and security safeguards, and mandate the use of a single institutional review board (IRB) for cooperative research.

What is at stake? While the proposed changes appear to be designed to protect individuals against informational harm, achieve some efficiencies, and allow study participants to formally consent to the use of their biospecimens in an informed manner, some are concerned that the proposed changes could impede research, increase administrative burden, and create more uncertainty regarding exclusions and exemptions from Common Rule coverage.

What should attorneys do? If the proposed changes are finalized, attorneys should act quickly to review policies, procedures, and practices relating to acquiring, storing, using, and disclosing information related to biospecimens; evaluate informed consent forms and procedures; and consider process and procedural changes with respect to IRB review and approval.

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Groden, Martin, and Merrill: Changes to the Common Rule

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Introduction

The clinical research industry has long anticipated changes to the Federal Policy for the Protection of Human Subjects, commonly referred to as the "Common Rule." The Common Rule is the foundational rule of ethics and corresponding compliance obligations for clinical research involving human subjects in the United States. It was published in 1991 and codified in various regulations by several federal agencies and departments.[1] In July 2011, several federal agencies and departments came together to publish an Advance Notice of Proposed Rulemaking (ANPRM) in an effort to modernize the Common Rule and make revisions to enhance its effectiveness.[2] Members of the research and health care communities publicly commented on the ANPRM, some positive and others neutral, mixed, or negative. After nearly five years of consideration, multiple federal agencies and departments (collectively, the Common Rule Agencies) came together on September 8, 2015 to publish the Notice of Proposed Rulemaking (NPRM). The NPRM was designed to "modernize, simplify, and enhance the current system of oversight" for clinical research involving human subjects in the United States.[3]

Some industry members, namely organizations with patient and/or privacy-centered missions, breathed a collective sigh of relief and applauded the Common Rule Agencies for their efforts in publishing

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1 *See* Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28003 (June 18, 1991) (to be codified at 7 C.F.R. pt. 1c; 10 C.F.R. pt. 745; 14 C.F.R. pt. 1230; 15 C.F.R. pt. 27; 16 C.F.R. pt. 1028; 22 C.F.R. pt. 225; 24 C.F.R. pt. 60; 28 C.F.R. pt. 46; 32 C.F.R. pt. 219; 34 C.F.R. pt. 97; 38 C.F.R. pt. 16; 40 C.F.R. pt. 26; 45 C.F.R. pt. 46; 45 C.F.R. pt. 690; 49 C.F.R. pt. 11) [hereinafter *Common Rule*].

2 *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512 (July 26, 2011) (to be codified at 45 C.F.R. pts. 46, 160, & 164; 21 C.F.R. pts. 50 & 56).

3 Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53933, 53933 (Sept. 8, 2015) (to be codified at 6 C.F.R. pt. 46; 7 C.F.R. pt. 1c; 10 C.F.R. pt. 745; 14 C.F.R. pt. 1230; 15 C.F.R. pt. 27; 20 C.F.R. pt. 431; 22 C.F.R. pt. 225; 28 C.F.R. pt. 46; 29 C.F.R. pt. 21; 32 C.F.R. pt. 219; 34 C.F.R. pt. 97; 38 C.F.R. pt. 16; 40 C.F.R. pt. 26; 45 C.F.R. pt. 46; 45 C.F.R. pt. 690; 49 C.F.R. pt. 11) [hereinafter *NPRM*].

the NPRM. On the other hand, research institutions and investigators criticized the complexity of the NPRM and the new requirements that would be placed on research. Notably, the Secretary's Advisory Committee on Human Research Protections (SACHRP), a committee that provides expert advice and recommendations to the Secretary of the U.S. Department of Health & Human Services (HHS) on issues pertaining to the protection of human research subjects, is among those critics.[4] However, common concerns in both camps include the expanded scope of human subject research to include biospecimens, the lack of clarity with respect to exclusions and exemptions, and the expanded layer of privacy and security measures.

In this Article, we address several of the proposed changes, including a discussion of the strengths and weaknesses of key changes, and assess the future impact of the changes if enacted as currently drafted. Institutions engaged in clinical research and their advisors should keep these proposed changes in mind, pending finalization of the NPRM, as they review policies, procedures, and practices relating to acquiring, storing, using, and disclosing information related to biospecimens. We further note that the final rule will likely impact the informed consent process as well as institutional review board (IRB) review and approval procedures. We anticipate that issuance of the final rule, as detailed more fully herein, will require responsive measures by sponsors, research sites, IRBs, and other members of the research community.

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4 *See* U.S. Dep't of Health & Human Servs., The Secretary's Advisory Comm. on Human Research Protections, *Attachment A: Recommendations NPRM: Recommendations on the Notice of Proposed Rulemaking entitled "Federal Policy for the Protection of Human Subjects*," www.hhs.gov/ohrp/sachrp-committee/recommendations/2016-january-5-recommendation-nprm-attachment-a/index.html (last visited Apr. 4, 2016).

Expanding the Scope of Human Subject Research

The NPRM would expand the scope of human subject research by extending the application of the Common Rule and expanding the definition of "human subject."

Extending the application of the Common Rule

Currently, the Common Rule applies to "research involving human subjects" that is "conducted, supported or otherwise subject to regulation by any federal department or agency . . . ."[5] Thus, the Common Rule may not apply to all of an institution's human subjects research unless the research is federally funded or the research institution voluntarily "checks the box" on a Federalwide Assurance (FWA) form, thereby opting to apply the Common Rule to all of its research studies.[6]

Under the NPRM, application of the Common Rule would extend to all "clinical trials," regardless of funding source, conducted at a U.S. institution that receives federal funding for human subjects research, with the exception of (i) research excluded or exempt under the Common Rule and (ii) clinical trials subject to U.S. Food and Drug Administration (FDA) regulation.[7] The NPRM defines "clinical trials" broadly to mean "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes."[8]

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5 *Common Rule* § __.101(a).

6 *See* U.S. Dep't of Health & Human Servs., *Federalwide Assurance (FWA) for the Protection of Human Subjects* § 4(b), www.hhs.gov/ohrp/assurances/assurances/filasurt.html (last visited Apr. 4, 2016). Under the NPRM, "institution" is defined to include "any public or private entity, or department or agency (including federal, state, and other agencies)." *NPRM*, at 54047 (proposed § __.102(f)).

7 *NPRM*, at 54045 (proposed § __101(a)(2)). *See also* 21 C.F.R. pts 50 & 56.

8 *NPRM*, at 54047 (proposed § __.102(b)).

Expanding the definition of "human subject"

In recognition of the increasing importance of biospecimens in secondary research (i.e., research involving biospecimens that were collected for another purpose, such as clinical reasons or another research study), the NPRM seeks to clarify when and how biospecimens may be used for future research and increase opportunities for consent.[9] To achieve these goals, the Common Rule Agencies offer three proposals for revising the definition of "human subject," all of which would expand the scope of the Common Rule's application to biospecimens.

Primary proposal regarding the definition of "human subject"

The Common Rule currently defines a "human subject" as a "living individual" about whom an investigator conducting research obtains "data through intervention or interaction with the individual" or "identifiable private information."[10] The Office for Human Research Protections (OHRP), a division of HHS, has interpreted this definition to mean that the Common Rule does not apply to secondary research uses of unidentifiable biospecimens.[11]

Under their primary proposal, the Common Rule Agencies would expand the scope of "human subject" to include a living individual about whom an investigator (whether professional or academic) conducting research "[o]btains, uses, studies, or analyzes biospecimens."[12] Accordingly, the NPRM seeks to extend the application of the Common Rule to *all* biospecimen collections for research and all research uses

9 *Id.* at 53942. The Common Rule Agencies posit that "a growing body of literature shows that in general people prefer to have the opportunity to consent (or refuse to consent) to research involving their own biological materials." *Id.*

10 *Id.* at 54047 (proposed § __.102(e)(1)(i)–(ii)).

11 U.S. Dep't of Health & Human Servs., *Guidance on Research Using Coded Private Information or Specimens* (Oct. 16, 2008), www.hhs.gov/ohrp/policy/cdebiol.html (last visited Apr. 4, 2016).

12 *NPRM*, at 54047 (proposed § __.102(e)(1)(iii)).

of biospecimens, regardless of whether the biospecimens are identifiable.[13] Operationally, this expanded definition of "human subject" would necessitate obtaining informed consent for almost all secondary research uses of biospecimens, even if the biospecimen has been stripped of identifiers such that an investigator cannot readily ascertain a human subject's identity. Informed consent for secondary research use of unidentifiable biospecimens is not currently required by the Common Rule. Further, the proposed broader definition of "clinical trials" would extend this obligation beyond those studies that are funded by federal dollars (or voluntarily opted in, checking the box on the FWA form to expand application) to virtually all clinical trials.

Reactions to these changes are varied, although public comments suggest that a broad cohort of the clinical research community objects to at least one aspect of the changes. Patient-centered organizations on the other hand, argue that ethical principles underlying these revisions are integral to study participant autonomy with respect to privacy, ensuring an opportunity to consent to the use of their biospecimens in an informed manner.[14] Thus, patient-centered organizations like the National Health Council applaud the expanded protection of individual privacy through broad biospecimen consent.[15] This support is balanced, however, with concern that informed consent changes, particularly for de-identified biospecimen information, could impede research. Additionally, there appears to be some concern that the biospecimen changes

13 *Id.* at 53944–45.

14 *See* U.S. Dep't of Health & Human Servs., Office of the Sec'y, The Nat'l Comm'n for the Protection of Human Subjects of Biomedical & Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Apr. 18, 1979), www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html (last visited Apr. 4, 2016).

15 Letter from Marc Boutin, Chief Exec. Officer, Nat'l Health Council, to Jerry Menikoff, Office of Human Research Protections, U.S. Dep't of Health & Human Servs., at 2 (Jan. 6, 2016), *available at* www.nationalhealthcouncil.org/sites/default/files/Common-Rule.pdf.

could present a significant enough administrative burden that non-research oriented health care providers and institutions would opt not to pursue broad consent because it (i) would not be needed for the care to be provided by that provider or institution and (ii) would require the provider or institution to undertake unnecessary additional administrative obligations. For example, the Council on Governmental Relations (COGR), a self-identified "association of 190 research universities and their affiliated academic medical centers that conduct over $60 billion in research and development[,]" argues that the infrastructure required to document and track consent for all biospecimen research could only be afforded by the "largest, wealthiest research hospitals" and that "one would expect such infrastructure costs to be charged as a direct cost to grants, further reducing research funding."[16] Further, the COGR argues that "broad consent for storage and secondary research use of biospecimens regardless of identifiability, would result in a significant loss of research without improving protections for human subjects."[17] Similarly, the American Cancer Society Cancer Action Network (ACS CAN) comments that "requiring written consent from subjects for future research using their biospecimen(s) is an important means of ensuring that they understand and agree with such use[,]" but acknowledges the risk that non-research oriented institutions such as community hospitals, ambulatory surgical centers, and pathology laboratories, will not adopt the new broad consent for biospecimens into existing clinical consent processes, thereby limiting biospecimens available for studies, particularly long term registry studies.[18]

16 Letter from Anthony DeCrappeo, President, Council on Governmental Relations, to Jerry Menikoff, Office for Human Research Protections, Dep't of Health & Human Servs., at 1, 4 (Dec. 8, 2015), *available at* http://cogr.edu/COGR/files/ccLibraryFiles/Filename/000000000257/NPRMCommonRuleCOGRResponse12-8-15%20(2).pdf.

17 *Id. at* 19.

18 Letter from Dr. Otis Brawley, Chief Med. Officer, Am. Cancer Soc'y & Chris Hansen, President, Am. Cancer Soc'y Cancer Action Network, to Jerry Menikoff, Office of Human Research Protections, Dep't of Health & Human Servs., at 2–3 (Jan. 5, 2016), *available at* www.acscan.org/content/wp-content/uploads/2016/01/ACS_ACS_CAN%20NPRM%20Common%20Rule%20Final%20Comment%20Letter.pdf.

Other organizations have taken a harder stance on the expansion of human subject research to include biospecimens. For example, the Association of American Universities and the Association of Public and Land-grant Universities explicitly "oppose the proposed inclusion of biospecimens within the definition of human subject" and criticize what the organizations perceive as the NPRM's indicating "that biospecimens inherently cannot be rendered non-identifiable" without adequate explanation or justification.[19] The Association of American Medical Colleges (AAMC) urges the Common Rule Agencies to revisit or withdraw certain proposals, including the expanded definition of "human subject" research. The AAMC comment letter indicates that the oversimplification of this approach, among other proposed changes, has "confused and frustrated a very engaged and thoughtful community of investigators, institutions, and ethicists."[20] The AAMC argues that the provisions addressing "treatment of research with biospecimens fail to achieve any reasonable balance between informing subjects, reducing potential for harm, increasing justice, and facilitating 'current and evolving types of research'" and concludes that the proposals "would greatly increase institutional cost and burden and impede research without increasing meaningful understanding by or protection of human subjects."[21]

The decision by the Common Rule Agencies to include biospecimens within the scope of human subject research appears from the NPRM to be influenced by ethical principles as well as a concern that technical developments in the future may make biospecimens more

19 Letter from Hunter R. Rawlings III, President, Ass'n of Am. Univs. & Peter McPherson, President, Ass'n of Public & Land-grant Univs., to Jerry Menikoff, Office for Human Research Protections, U.S. Dep't of Health & Human Servs., at 3 (Dec. 22, 2015), *available at* www.aplu.org/members/councils/governmental-affairs/CGA-library/aplu-aau-comments-to-ohrp-on-the-common-rule-nprm/file.

20 Letter from Ann Bonham, Chief Scientific Officer, Ass'n of Am. Med. Colls., to Jerry Menikoff, Office for Human Research Protections, Dep't of Health & Human Servs., at 1–2 (Jan. 4, 2016), *available at* www.aamc.org/download/451896/data/aamcsubmitscommentstohhsonthecommonrulenprm.pdf.

21 *Id.* at 3–4.

easily identifiable. The impetus for the proposed expansion is not fully detailed in the NPRM, and members of the clinical research community seem to be frustrated by what appears to them to be a lack of specificity and thoughtful reasoning.

Importantly, the storage, maintenance, and secondary research use of biospecimens would be exempt from Common Rule compliance requirements only if the research qualifies under an exemption, discussed more fully below.[22] Further, if an investigator anticipates that individual biospecimen research results will be returned to a subject (e.g., in instances when investigators incentivize potential participants to give consent by committing in their protocols to return unexpected test results), then the biospecimen research cannot be exempted and must be reviewed by the IRB and the standard informed consent for the research must be obtained.[23]

Alternative proposals regarding the definition of "human subject"

While the primary proposal in the NRPM defines "human subject" as including all biospecimens, the Common Rule Agencies offer two alternative proposals, both of which would provide for a more limited expansion of the Common Rule.

Whole genome sequencing data. Under this first alternative proposal, the NPRM would define "human subject" to include only whole genome sequencing (WGS) data, or any part of the data generated as a consequence of WGS, regardless of the individual identifiability of biospecimens used to generate such data.[24] WGS would be defined as the "sequencing of a human germline or somatic biospecimen with the intent to generate the genome or exome sequence of that biospecimen."[25] Under this alternative, the use of unidentifiable bio-

22 *See NPRM*, at 54049 (proposed § __.104(f)).
23 *Id.* at 53967.
24 *Id.* at 53945.
25 *Id.*

specimens for WGS would constitute human subject research, but other secondary uses of unidentifiable biospecimens would continue to fall outside the scope of the Common Rule. Although this alternative proposal seems narrower than the primary proposal described above, it is possible that this approach would expand application of the Common Rule to certain data not protected under the primary proposal. Specifically, under the primary proposal, data derived from WGS could be used for research without additional consent because HHS currently does not consider WGS data "identifiable private information" (though broad consent would still be required to use biospecimens to generate the original WGS data, and such broad consent likely would contemplate such downstream research uses). Under this alternative proposal, consent would be required to use WGS data for research purposes.[26]

According to the Common Rule Agencies, this alternative proposal may be more protective of information considered to pose the highest information risk in that it would require consent "only for the type of studies that many people seem most concerned about (genomic research, including secondary use of genomic information that was produced for clinical purposes)."[27] In addition, such a proposal may be less administratively burdensome, given that there is arguably less WGS research taking place compared to other types of biospecimen research.[28] As noted in the NPRM, however, the major concern with this alternative proposal is that it would codify only a single technology as producing information that would be subject to the Common Rule, necessitating a re-evaluation of the Rule's scope in light of new technological developments.[29]

The exclusion of research use of WGS data under the primary proposal may be viewed by some as a significant oversight, particularly given

26 *Id.*
27 *Id.*
28 *Id.*
29 *Id.*

that many of the proposed Common Rule changes are aimed at reducing informational risk. It is unclear, however, whether the definition of "human subject" would need to be altered to address this concern. A possible alternative would be for HHS to revise its interpretation of "private identifiable information" under the current "human subject" definition to include WGS data.[30] This would avoid codifying a single technology in the Common Rule, while still addressing the informational risk posed by WGS data.

Information generated by applied technology. Under the second alternative proposal, the NPRM would expand the definition of "human subject" to include the research use of information produced from a biospecimen using a technology that generates information "unique to an individual such that it is foreseeable that, when used in combination with publicly available information, the individual could be identified."[31] Information that meets this standard would be referred to as "bio-unique information."[32] The scope of this second alternative is somewhat broader than the first alternative: Whereas the first alternative requires consent for *whole* genome sequencing, this second alternative would require consent for genomic sequencing of even small portions of a person's genome, and also would require consent for the use of other future technologies that similarly generate information unique to a person.[33] While the Common Rule Agencies do not explain their rationale for this proposal, the second alternative seems to recognize the evolving nature of technology. Under the second alternative, new technologies that would make previously unidentifiable information identifiable would not necessitate changes to the regulatory definition of "human subject"; rather, information generated by such new technologies would be captured within the definition of "bio-unique information."

30 HHS does not currently consider WGS data to meet the definition of "private identifiable information" for purposes of the Common Rule. *Id.*
31 *Id.* at 53945–46.
32 *Id.* at 53946.
33 *Id.*

This second alternative proposal seems to introduce a vagueness into the Common Rule's application, however. The proposal's "uniqueness" and "foreseeability" standards could make the contours of the Common Rule difficult to determine. As a result, efficiencies sought by other proposed changes to the Common Rule might be reduced by an increased burden on institutions required to assess whether different technologies produce information that is "unique" enough such that it is "foreseeable" that the individual could be identified. Institutions may need to stay apprised of technological advances and regularly update their policies and procedures regarding human subjects research determinations. Indeed, the Common Rule Agencies recognize the potential burden, including HHS's obligation to continually evaluate new technologies and the nature and amount of information produced, which would (i) involve resources and expertise that may not be available to federal departments and agencies and (ii) introduce ongoing uncertainty that may increase delays in research.[34]

Understanding the New Regime of Exclusions and Exemptions

The NPRM modifies the Common Rule by specifically excluding certain categories of activities from coverage and adding new categories of exempt research.

Exclusions

The current version of the Common Rule excludes from coverage (i) activities that do not meet the definition of "research," (ii) activities that do not involve a human subject, and (iii) research activities that are not "conducted, supported or otherwise subject to regulation" by a federal department or agency that has adopted the Common Rule.[35] Activities that fall within one or more of these definitional exclusions

34 *Id.* at 53946.
35 *See NPRM*, at 54045, 54047 (proposed §§ __.101(a), __.102(d)–(f)). *See also id.* at 53947.

are not subject to Common Rule requirements, such as IRB review and informed consent, resulting in less administrative burden on the investigator and the institution. Among the bases for exclusion, institutions have particularly struggled with whether certain activities (e.g., quality improvement activities)[36] constitute "research," which, for purposes of the Common Rule, is broadly defined as a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[37]

The NPRM attempts to provide more clarity by specifically listing certain categories of activities as "excluded" from coverage under the Common Rule. Six categories of activities that are not exempt under the current Common Rule would be excluded under the revised rule because they are deemed not to be research:[38]

1. Internal operational monitoring and program improvement[39]
2. Oral history, journalism, biography, and historical scholarship activities[40]
3. Criminal justice or criminal investigative activities[41]
4. Quality assurance or improvement activities[42]
5. Public health surveillance activities[43]
6. National security activities[44]

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36 *See, e.g.*, Letter from Ivor A. Pritchard, Senior Advisor to the Dir. of Office for Human Resources Protections, to Anthony L. Asher, Dir., Nat'l Neurosurgery Quality & Outcomes Database & Dir., Brain Tumor Program, Carolinas Med. Ctr., Carolina Neurosurgery & Spine Assocs. (Aug. 11, 2011), www.hhs.gov/ohrp/regulations-and-policy/guidance/august-11-2011-letter-to-dr-anthony-asher/index.html (last visited Apr. 5, 2016) (addressing whether a certain database is "consistent with a quality improvement activity" and "if so, whether this effort is research that requires IRB review.") [hereinafter *OHRP Response*]. *See also NPRM*, at 53949.

37 *NPRM*, at 54047 (proposed § __.102(l)).

38 *Id.* at 54045 (proposed § __101(b)(1)). *See also id.* at 53946–50.

39 *Id.* (proposed § __.101(b)(1)(i)).

40 *Id.* (proposed § __.101(b)(1)(ii)).

41 *Id.* (proposed § __.101(b)(1)(iii)).

42 *Id.* (proposed § __.101(b)(1)(iv)).

43 *Id.* (proposed § __.101(b)(1)(v)).

44 *Id.* (proposed § __.101(b)(1)(vi)).

An additional four categories of activities (two of which currently appear as exemptions under the existing Common Rule) would be excluded because, despite being research, they are considered low-risk and already subject to independent controls separate from Common Rule requirements:[45]

1. Educational tests, survey procedures, interview procedures, or observation of public behavior[46] (exempt under current Common Rule[47])
2. Research involving collection or study of information that has been or will be acquired solely for non-research activities or were acquired for research studies other than the proposed research study[48] (exempt under current Common Rule[49])
3. Research conducted by a federal department or agency using government-generated or government-collected information obtained for non-research purposes[50]
4. Research that involves only data collection and analysis of HIPAA-regulated identifiable health information[51]

A final category of activities—secondary research use of non-identified biospecimen designed only to generate information about an individual who is already known—would be excluded because it is considered low-risk and does not meaningfully diminish subject autonomy.[52]

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45 *Id.* at 54045–46 (proposed § __.101(b)(2)). *See also id.* at 53950–54.
46 *Id.* at 54045–46 (proposed § __.101(b)(2)(i)).
47 This proposed exclusion is a modified version of the exemption currently found at *Common Rule* § __.101(b)(2).
48 *NPRM*, at 54046 (proposed § __.101(b)(2)(ii)).
49 This proposed exclusion is a modified version of the exemption currently found at *Common Rule* § __.101(b)(4)).
50 *NPRM*, at 54046 (proposed § __.101(b)(2)(iii)).
51 *Id.* (proposed § __.101(b)(2)(iv)).
52 *Id.* (proposed § __.101(b)(3)).

Notably, investigators would self-determine whether their research falls within an excluded category.[53] While allowing researchers to self-determine would reduce the administrative burden on institutions to review every study for coverage under the Common Rule, this proposal may be problematic from a conflict of interest standpoint, particularly given that the NPRM (i) does not outline how exclusion determinations should be made, (ii) does not require the creation of a decision tool that can be used by researchers (akin to the NPRM's proposed decision tool for exemption determinations), and (iii) does not require exclusion determination to be documented and tracked such that institutions could conduct periodic reviews or audits.[54] It is relatively common for institutions to maintain internal policies and procedures requiring investigators to assess definitional determinations through the institution's research program and/or the applicable IRB (or privacy board). We suspect that institutions will continue to maintain such policies and procedures, despite the proposal that investigators self-determine whether their research falls within an excluded category, because institutions are incentivized from a risk aversion perspective to address the conflict of interest issues and minimize risk of Common Rule enforcement if the determination is wrong. Thus, the real issue is whether there will be sufficient clarity in the final rule with respect to these categories to make an accurate assessment about whether a particular study falls into an exclusion category, both for the investigator and the institution.

Of the proposed exclusion categories, two categories are particularly notable for research institutions: (i) quality assurance and quality improvement activities, which are excluded because they are deemed

53 *Id.* at 53947, 53950. In comparison, while the current Common Rule does not specify who should determine whether research is exempt, the OHRP has recommended that investigators not be given the authority to make an independent determination that research is exempt. *See* U.S. Dep't of Health & Human Servs., Exempt Research Determination FAQs, www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/exempt-research-determination/index.html (last visited Apr. 11, 2016). *See also id*. at 53955.

54 *See NPRM,* at 53950, 54045 (proposed § __.101(b)).

not research, and (ii) certain activities covered by the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations (collectively, HIPAA), which are excluded as low-risk research.[55]

The quality assurance and quality improvement exclusion would exclude from Common Rule coverage activities "involving the implementation of an accepted practice to improve the delivery or quality of care or services," but not "evaluation of an accepted practice."[56] Given industry confusion about whether quality assurance activities constitute "research,"[57] the explicit exclusion of quality assurance and quality improvement activities provides the research community greater clarity. Unfortunately, the NPRM does not define what constitutes an accepted practice and what types of activities are considered to have the goal of improving the delivery or quality of care of services. Similarly, while the NPRM provides some examples of what the exclusion would and would not cover,[58] it does not explain how to distinguish between the *implementation* of an accepted practice and the *evaluation* of such a practice.

The HIPAA exclusion would remove "data collection and analysis" involving the use of protected health information (PHI) for "health care operations," "public health activities," or "research" from Common Rule coverage if the use is by a HIPAA-covered entity or if an investigator is a HIPAA-covered health care provider,[59] the rationale being that such use of PHI is already subject to independent protections through

55 *Id.* at 54045–46 (proposed § __.101(b)(1)(iv) and proposed § __.101(b)(2)(iv)).
56 *Id.* at 54045 (proposed § __.101(b)(1)(iv)). *See also id.* at 53948–49.
57 *See, e.g., OHRP Response* (addressing whether a certain database is "consistent with a quality improvement activity" and "if so, whether this effort is research that requires IRB review"). *See also NPRM*, at 53949.
58 According to the NPRM, a randomized study in which half of participating institutions would undergo educational intervention about the need to use an accepted practice and the other half would not undergo that intervention would satisfy the exclusion, "since it would only be intended to see if the intervention resulted in greater use of the accepted practice." *NPRM*, at 53948. In contrast, a study designed to determine how well the accepted practice works would not satisfy the exclusion, "since it would be studying the effectiveness of the practice itself, in contrast to studying an effort to increase use of the practice." *Id.* at 53949.
59 *Id*. at 54046 (proposed § __.101(b)(2)(iv)). *See also id.* at 53953–54.

HIPAA. Given this rationale, the exclusion does not apply if the investigator is not covered by HIPAA, even if the entity disclosing the PHI is a covered entity.[60] The exclusion may remove from Common Rule coverage research studies involving more than the informational risk addressed by HIPAA, however. For example, to the extent that research involves data collection through interactions with human subjects (e.g., interviews), physical, emotional, or social risks may exist independent from the risks associated with inappropriate use or disclosure of PHI (e.g., inappropriate interview techniques). HIPAA was not designed to address such risks.[61]

Exemptions

Six categories of research are fully exempt from current Common Rule requirements.[62] As noted above, the NPRM changes two of these exemptions to exclusions, retains the remaining four exemptions in modified form, and expands the number of exempt categories. The NPRM also imposes requirements on certain exempt categories calibrated to the level of informational risk involved. Such requirements would include documenting that a study was determined to be exempt, meeting the NPRM's proposed safeguards to protect biospecimens and identifiable private information, broad consent, and limited IRB review.

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60 *Id.* at 53953–54.

61 This issue is highlighted by the Common Rule Agencies in their NPRM inquiry: "Public comment is sought regarding to what extent the HIPAA Rules and HITECH adequately address the beneficence, autonomy, and justice aspects for the collection of new information (versus information collected or generated in the course of clinical practice, e.g., examination, treatment, and prevention)." *See NPRM*, at 53954 (Question #23). Given the NPRM's ambiguity, however, it is possible that the Common Rule Agencies meant for the HIPAA exclusion to apply only to research data collected using a data set with PHI in it, not collection through interactions with human subjects.

62 *NPRM*, at 54045 (proposed § __.101(b).

The following table summarizes the NPRM's proposed exemption categories:

NPRM Proposed Exemption Categories

Exemption Category	Requirements	Exempt under Current Common Rule?
Research conducted in established and commonly accepted educational settings involving normal educational practices[63]	Document exemption determination	Yes[64]
Research or demonstration projects conducted by a federal department or agency[65]	Document exemption determination	Yes[66]
Research involving benign interventions in conjunction with the collection of data from an adult subject through verbal or written responses or video recording[67]	Document exemption determination	No

Table continues

63 *Id.* at 54048 (proposed § __.104 (d)(1)).
64 This proposed exemption is a modified version of the exemption found at *Common Rule* § __.101(b)(1).
65 *NPRM,* at 54048 (proposed § __.104 (d)(2)).
66 This proposed exemption is a modified version of the exemption found at *Common Rule* § __.101(b)(5).
67 *NPRM*, at 54048–49 (proposed § __.104 (d)(3)).

Exemption Category	Requirements	Exempt under Current Common Rule?
Taste and food quality evaluation and consumer acceptance studies[68]	Document exemption determination	Yes[69]
Educational tests, survey procedures, interview procedures, or observation of public behavior where information recorded is identifiable[70]	Document exemption determination Privacy and security safeguards	Yes, subject to limitations[71]
Secondary research use of identifiable private information that has been or will be acquired for non-research purposes[72]	Document exemption determination Privacy and security safeguards	No
Storage or maintenance of biospecimens or identifiable private information for secondary research use, where the biospecimens have been or will be acquired for research studies other than for the proposed research study or for non-research purposes[73]	Document exemption determination Privacy and security safeguards Broad consent Limited IRB review	No

Table continues

68 *Id.* at 54049 (proposed § __.104 (d)(4)).
69 This proposed exemption is identified to the current exemption found at *Common Rule* § __.101(b)(6).
70 *NPRM*, at 54049 (proposed § __.104 (e)(1)).
71 This proposed exemption is a modified version of the exemption found at Common Rule § __.101(b)(3). The current exemption would apply only if the human subjects are elected or appointed public officials or candidates for public office or if federal statute(s) require(s) that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
72 *NPRM,* at 54049 (proposed § __.104 (e)(2)).
73 *Id.* (proposed § __.104 (f)(1)).

Exemption Category	Requirements	Exempt under Current Common Rule?
Research involving the use of biospecimens or private identifiable information that has been stored or maintained for secondary research[74]	Document exemption determination Privacy and security safeguards Broad consent already obtained for storage, maintenance, and secondary research use	No

One of the NPRM's most significant changes is the expansion of "human subject" to include biospecimens (including data generated therefrom), regardless of identifiability. The two biospecimen exemptions may reduce the potential cost and burden of that change by allowing for the storage, maintenance, and secondary research use of biospecimens and identifiable private information without having to comply with all Common Rule requirements for human subjects research, such as traditional informed consent and full IRB review. These exemptions would require not only documentation and privacy safeguards, however, but also "broad consent" for storage, maintenance, and secondary research use and "limited IRB review" of the procedures for obtaining broad consent.[75] The rationale for these requirements is the increased risk that biospecimens may be re-identified (hence the need for privacy and security safeguards) and that many prospective research participants would want to be asked for their consent before

74 *Id.* (proposed § __.104 (f)(2)).
75 *See id.* at 54049–51 (proposed § __.105 and proposed § __.111(a)(9)). *See also id.* at 53965–68.

their biospecimens are used in research (hence the need for broad consent and limited IRB review).[76]

In assessing the potential burden of these exemption requirements, it is important to recall that under the current version of the Common Rule storage and maintenance of identifiable biospecimens and private identifiable information, as well as secondary research use thereof, would be considered human subjects research and thus subject to informed consent requirements and full IRB review (which may result in the imposition of privacy and security safeguards).[77] Thus, these exemption requirements would create new burdens only for secondary research involving unidentifiable biospecimens, currently not subject to Common Rule requirements.

In regard to "limited IRB review," the IRB would be required to review only an "overall general institutional protocol" for the manner in which people can provide broad consent (as opposed to reviewing specific studies).[78] According to the NPRM, for many institutions, limited IRB review would "be essentially a one-time event."[79] The "broad consent" requirement would appear to be more burdensome. On the one hand, institutions and investigators would not be required to develop their own broad consent forms; rather, HHS would develop a broad consent template that must be used for this exemption to be met.[80] On the other hand, and as discussed later in this article, the broad consent, may not be all that different from traditional informed consent.

The exemption regarding maintenance and storage of biospecimens or identifiable private information for secondary research use only applies where biospecimens or private identifiable information are initially collected for a different research study or for non-research (e.g., clinical) purposes. This exemption does not apply to the creation of any

76 *Id*. at 53938.
77 *See id.* at 54050–55 (proposed §§ __.109, __.111, __.116).
78 *Id.* at 53966.
79 *Id.* at 53966 (internal quotations omitted).
80 In some instances (never involving biospecimens), oral consent is permissible. *Id.* at 54049 (proposed § __.104(f)). *See also id*. at 53966.

data or the actual new collection of any biospecimens from a person through a research interaction or intervention (e.g., creating a research repository of DNA samples obtained by taking cheek swabs).[81] While the NPRM does not explain the reason for this limitation, presumably the rationale is that interaction or intervention with human subjects should be properly evaluated through, for example, IRB review of the initial study (in the case of research interventions) or informed consent and standard of care requirements for clinical interventions.

Although the distinction in the proposed exemption would be easy to follow and is consistent with the current Common Rule, some may argue that it presents an unnecessary burden to biobanking efforts that pose little or no risk of physical harm and that would be exempt if samples were obtained for a separate study or clinical purposes.

Web-based tools for exemption determinations

The NPRM indicates that one or more web-based decision tools will be created to facilitate exemption determinations.[82] Such decision tool(s) would provide the user with a determination whether a particular study qualifies as exempt and institutions would be able to rely on a tool's outcome as a safe harbor for exemption determinations, even if the tool was used by an investigator.[83] As long as the tool was properly used and accurate and correct information was supplied by the user, the determination would result in a presumption by the Common Rule Agencies that the determination of exempt status is appropriate.[84]

Multiple web-based decision tools

The NPRM indicates that "federal departments or agencies will develop one or more exemption determination tools."[85] It is not yet

81 *Id.* at 53966.
82 *Id.* at 53936.
83 *Id.*
84 *Id.*
85 *Id.* at 53956.

known whether a single web-based decision tool will be developed for all studies or if several decision tools will be established by some or all funding agencies. If the latter, it is unclear whether use of any established tool will suffice or, for example, an investigator must use the tool(s) established by agencies from which the sponsor receives funding for that particular study (if any). An additional level of ambiguity may exist for studies that fall under the expanded scope of the Common Rule but receive no federal funding. Because these studies have no federal funding, the question arises whether any of the federal agency decision tool determinations will suffice. Should this lack of clarity carry forward in the final rule, it is feasible that impacted sponsors and investigators could selectively utilize the most preferable web-based tool.

Institutional burden

Institutions may not have blind faith in the accuracy and completeness of information independently submitted by investigators via web-based decision tools. To counterbalance the risk of "bad" information and resulting faulty determinations, institutions should consider establishing processes, procedures, and other specific requirements to promote accuracy and integrity of data input—as well as some degree of oversight. Institutions should consider including a warranty in applicable agreements to contractually obligate researchers to input information into web-based decision tools in good faith and in compliance with institutional policies, procedures, and other requirements, particularly when contracting with non-employee researchers. Additionally, institutions should consider updating indemnification provisions to protect against a researcher's failure to enter complete, accurate, and correct information. Institutions also should consider developing meaningful policies, procedures, and oversight mechanisms regarding use of and reliance on web-based exemption determinations. Thus, despite the efficiencies sought by the Common Rule Agencies in developing the web-based tool approach, it is possible this approach will ultimately increase an institution's administrative burden.

Reliability of determinations

Institutional utilization of, and reliance upon, the web-based decision tool(s) will likely depend, at least in part, on the reliability of exemption determinations. Put another way, institutional confidence in tool determinations may hinge on whether an exemption determination would remain consistent regardless of who submits the information (e.g., the principal investigator, a research coordinator, or an institution representative) and their variation in perspective, communication styles, and volume of information submitted, assuming that any such individual is submitting truthful information in good faith and in compliance with institutional policies and procedures.

The New "Broad Consent"

At present, the application of Common Rule requirements to the secondary research use of biospecimens is limited to only those specimens that are identifiable.[86] Historically, some institutions and investigators maintained a practice of obtaining consent for use of de-identified biospecimens for research by including a broad consent statement within the larger, more specific informed consent form. The Common Rule Agencies sought in the ANPRM,[87] and now seek in the NPRM,[88] to require a more formal and separate "broad consent" under the exemptions for storage, maintenance, and secondary research use of biospecimens. As evidenced in public comments to the NPRM, many organizations and institutions view this new consent requirement to be an unnecessary obstacle to research consent and a disincentive for many providers due to the added form and administrative burden.

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86 *See id.* at 54045, 54047 (proposed §§ __.101(a), __.102(f)). *See also,* U.S. Dep't of Health & Human Servs., *Guidance on Research Using Coded Private Information or Specimens* (Oct. 16, 2008), www.hhs.gov/ohrp/policy/cdebiol.html (last visited Apr. 10, 2016).

87 Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44519 (July 26, 2011) (to be codified at 45 C.F.R. pts. 46, 160, & 164; 21 C.F.R. pts. 50 & 56).

88 *NPRM,* at 53965–69.

As currently conceived in the NPRM, the broad consent for the storage, maintenance, and secondary research use of biospecimens must provide (i) a "general description of the types of research that may be conducted . . . and the information that is expected to be generated from the research," (ii) the "types of information or biospecimens that might be used in research[,]" and (iii) the types of institutions that might conduct the research.[89] Additionally, the broad consent must include clear descriptions of "the types of biospecimens or information that were or will be collected and the period of time during which biospecimen or information collection will occur"[90] and "the period of time during which an investigator can continue to conduct research using the subject's biospecimens and information" (e.g., "indefinitely" or "x number of years").[91]

Consistent with current informed consent requirements under the Common Rule, the broad consent also should include statements acknowledging that "participation is voluntary," "refusal to participate will involve no penalty or loss of benefits[,]" "the subject may withdraw consent, if feasible, . . . without penalty or loss of benefits[,]" and "information or biospecimens that already have been distributed for research use may not be retrieved[.]"[92] The NPRM requires additional information to the extent applicable and/or available.[93]

The adoption of these broad consent requirements faced opposition when initially proposed in the ANPRM. For example, the American Society for Investigative Pathology (ASIP) commented that the existing Common Rule approach to consent for archival biospecimens

89 *Id.* at 54053 (proposed § __.116(c)(1)(i)).
90 *Id.* (proposed § __.116(c)(1)(ii)(A)).
91 *Id.* (proposed § __.116(c)(1)(iii)).
92 *Id.* (proposed § __.116(c)(1)(iv)).
93 *See id.* at 54053–54 (proposed § __.116(c)(1)(v)–(viii)). Information may include notice of the expectation that the subject's information and biospecimens are likely to be shared broadly for many types of future research studies, notice that the subject will not be informed of the details of any specific research studies that might be, and notice of an option for an adult subject to refuse consent to the inclusion of the subject's data in an openly accessible database.

"recognizes the value of the archival material and the complexities and impracticability of obtaining consent[.]"[94] ASIP indicates based on its "extensive . . . experience working with biospecimens on a daily basis, the current system[,]" which allows for "research on biospecimens that were collected outside of a research study without obtaining informed consent, as long as the subject's identity is never disclosed to the investigator[,]" has "greatly enriched the opportunity for discoveries that were unknown at the time of collection[.]"[95] ASIP asserts that "[l]oss of ability to use certain types of archived tissues without obtaining consent may be the death knell of live-saving translational research."[96]

Similarly, the AAMC commented that the broad consent requirement as proposed in the NPRM has "the greatest impact to institutions with the least benefit to individuals whose biospecimens may be used" and argues that the change "fails to promote individual autonomy in a meaningful way."[97] The AAMC further argues that the proposed broad consent requirement presupposes that "biospecimens will in fact be collected from each individual and used for research" when, in reality, the clinical care provider typically has not "made a determination in advance whether a particular individual's biospecimens might be collected and stored for future research use."[98] This issue is compounded by the fact that the institutional caregiver may have little to no knowledge of potential future clinical research applications and, as a result, may be unable to provide meaningful assistance to a patient with questions or concerns regarding the broad consent.

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94 Letter from Mark E. Sobel, Exec. Officer, Am. Soc'y for Investigative Pathology, to Jerry Menikoff, Office of Human Research Protections, Dep't of Health & Human Servs., at 2–3 (Oct. 20, 2012), *available at* www.regulations.gov/contentStreamer?documentId=HHS-OPHS-2011-0005-1114&attachmentNumber=1&disposition=attachment&contentType=pdf.

95 *Id.* at 2.

96 *Id*. at 2.

97 Letter from Ann Bonham, Chief Sci. Officer, Ass'n of Am. Med. Colls., to Jerry Menikoff, Office for Human Research Protections, Dep't of Health & Human Servs., at 5–6, (Jan. 4, 2016), *available at* www.aamc.org/download/451896/data/aamcsubmitscommentstohhsonthecommonrulenprm.pdf.

98 Id. at 6.

Under the NPRM's broad consent requirements, "the period of time during which biospecimen or information collection will occur cannot exceed 10 years from the date of consent."[99] When the research involves children, the time period cannot exceed the shorter of "10 years after parental permission is obtained or until the child reaches the legal age for consent to the treatments or procedures involved in the research[.]"[100] These time restrictions do not apply to biospecimens or information initially collected for research purposes.[101]

Although the language specifically refers to "collection" activity, the proposed time limitation could be read to extend to use of the biospecimen. On the one hand, the proposed regulation provides that "the period of time during which biospecimen or information collection will occur cannot exceed 10 years from the date of consent."[102] On the other hand, when explaining that, for children, broad consent would expire after 10 years or when the child reaches the age of majority, whichever comes first, the NPRM states that, "[a]t the time the child became an adult, the broad consent or permission would no longer be valid and either broad consent would need to be sought from the child-turned adult, or the investigator would need to seek a waiver of informed consent in order to use the individual's biospecimens or identifiable private information for research, unless one of the exclusions or exemptions were applicable."[103] Thus, it may be the case that if a biospecimen was collected over 10 years ago (pursuant to a valid broad consent), the broad consent expires, and a new broad consent is not obtained, then the biospecimen may no longer be usable for research.

With no cited objective reasoning to support the duration, the 10-year time limitation appears to be arbitrarily chosen. Retrospective

99 *NPRM*, at 54053 (proposed § __.116(c)(1)(ii)(B)).
100 *Id.*
101 *See id.*
102 *Id.* (proposed § __.116(c)(1)(ii)(B)).
103 *Id.* at 53973–74.

studies using registry and other forms of historic de-identified biospecimen data have proven incredibly valuable over the last few decades. A recent article published by *Modern Healthcare*, "War on Cancer, Take Two," applauds the work of the National Cancer Institute in launching a database that "contains information about genetic mutations and cancer treatments" for "as many as 50,000 patients and clinical trial participants[.]"[104] Similarly, in the comments submitted by ACS CAN, the organization notes that "[c]ancer-related research often involves analyzing biospecimens collected decades earlier."[105] ACS CAN provided a tangible example from a study that began in 1992, the "CPS-II Nutrition Cohort." The organization provides:

> [I]n the CPS-II Nutrition Cohort, which began in 1992, blood or buccal cell samples were collected from over 110,000 study participants between 1998 and 2002. A broad consent was obtained for the indefinite, long-term storage of the samples, and for the testing of the samples for future research analyses. As the biospecimen sub-cohort has matured, some participants developed certain types of cancer such as breast, colorectal or prostate cancer. Their samples, analyzed along with their matched controls that did not develop cancer, have been used in large international research consortia to identify genetic factors that increase risk for these cancers.[106]

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104 Maria Castellucci & Sabriya Rice, *War on Cancer, Take Two*, Modern Healthcare, Jan. 16, 2016, at 8–9, *available at* www.modernhealthcare.com/article/20160116/MAGAZINE/301169920.

105 Letter from Dr. Otis Brawley, Chief Med. Officer, Am. Cancer Soc'y & Chris Hansen, President, Am. Cancer Soc'y Cancer Action Network, to Jerry Menikoff, Office of Human Research Protections, Dep't of Health & Human Servs., at 5 (Jan. 5, 2016), *available at* www.acscan.org/content/wp-content/uploads/2016/01/ACS_ACS_CAN%20NPRM%20Common%20Rule%20Final%20Comment%20Letter.pdf.

106 *Id.*

Retrospective studies often rely heavily on registries and other forms of storage that contain previously donated biospecimens and corresponding information collected far beyond the proposed 10-year time frame. Placing an arbitrary time limit on broad consents could result in the unintended consequence of precluding collection, and possibly use, of a vast amount of information currently used to advance science and treatment, particularly with regard to cancer and chronic disease. The ability of donors to opt out of their prior consent at any time is arguably sufficient to protect the subject's individual interest in privacy and his/her right to make an autonomous decision. These interests are bolstered by provider reminders that patients may opt out of prior consent at any time—subject to prior reliance on donated biospecimens and/or corresponding information—through, for example, subsequent, and possibly unrelated, consent forms. ACS CAN recommends that "once a subject offers broad consent to use their biospecimens in future research, the consent associated with a biospecimen should remain valid indefinitely unless the subject actively withdraws that consent . . . to ensure medical research can continue to make scientific advances to prevent cancer[.]"[107]

Single IRB for Cooperative Research

The NPRM seeks to change the way cooperative research studies conducted across multiple institutions are approved by IRBs. Currently, the Common Rule requires each institution engaged in cooperative research to obtain IRB approval of the study, but permits such institutions to rely on the review of a central IRB or the IRB of another institution.[108] Institutions have been reluctant to rely on these options

107 *Id.*
108 *NPRM*, at 54052–55 (proposed § __.114). *See also id*. at 53982.

due to various concerns, which might include enforcement. OHRP's current practice is to enforce Common Rule requirements against the institutions engaged in the research, even in circumstances where the regulatory violation was directly related to the responsibilities of an external IRB. As a result, institutions engaged in cooperative research often require local IRB independent review of the research protocol, resulting in multiple reviews of the same study.[109]

To reduce these inefficiencies, the NPRM would alter the Common Rule to require (rather than merely permit) institutions engaged in cooperative research to rely on the approval of a single IRB for the portion of the research conducted in the United States. The reviewing IRB would be selected by the federal department or agency supporting or conducting the research or, if there is no funding agency, by the lead institution conducting the research.[110] This single IRB requirement would not apply to cooperative research for which more than single IRB review is required by law (e.g., FDA-regulated research involving a device [111]) or where the federal department or agency supporting or conducting the research determines that the use of a single IRB is not appropriate for the particular study.[112] To address concerns about enforcement, the NPRM would give Common Rule departments and agencies the authority to enforce compliance directly against external IRBs.[113]

The required use of a single IRB has the potential to make the clinical research process more efficient. Currently, the practice of having multiple IRBs review the same study can cause significant delays in research

109 *Id.* at 53982. *See also* Nat'l Insts. of Health, *Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research* (Dec. 3, 2014), *available at* https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html [hereinafter *Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research*].

110 *NPRM*, at 54052 (proposed § __.114). S*ee also id*. at 53980–84.

111 A person applying for the investigational device exemption must submit an investigational plan to the local IRB. 21 U.S.C. § 360j(g)(3)(A).

112 *NPRM*, at 54052 (proposed § __.114). *See also id*. at 53983.

113 *Id.* at 54045 (proposed § __.101(a)). *See also id*. at 53983.

initiation and recruitment.[114] Moreover, as the National Institutes of Health (NIH) has noted, the premise that multiple IRB reviews enhance protections for human subjects is not supported by evidence. Rather, the use of a single IRB may lead to enhanced protections for research participants by "eliminating the problem of distributed accountability, minimizing institutional conflicts of interest, and refocusing IRB time and resources toward review of other studies."[115]

The NPRM does not provide guidance on how the funding agency/department or lead institution should choose the single IRB. In its recommendations on the NPRM, the SACHRP illustrates the myriad issues that may need to be considered to determine whether a single IRB is qualified, including:

- adequacy of record keeping systems and written standard operating procedures (SOPs) for tracking each site independently,
- whether a process is in place to adequately obtain knowledge of state laws where the single IRB reviews sites in other states,
- whether written SOPs are maintained describing how local cultural and resource context information will be gathered, both at initial and continuing review,
- capacity to conduct site visits as necessary,
- whether written SOPs describe how the single IRB and institutions will coordinate issues such as review by other committees and unique institutional policies,

114 *Id*. at 53982–83. *See also Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research.*

115 *Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research.*

- accreditation of the institution's human research protection program, and
- appropriate oversight by OHRP and FDA.[116]

The NRPM also does not clarify what, if any, role local IRBs should have if they are not designated as the IRB of record and does not provide criteria for how the funding department/agency should determine when the use of a single IRB is not appropriate. Such guidance would help to make a single IRB system more efficient and uniform across institutions and agencies/departments.

It appears that, under the NPRM, institutions do not have the ability to determine whether use of a single IRB is appropriate for a particular study, even in instances where there is no federal funding department/agency. Even though multi-site studies generally would not require local IRB review for each study location to protect human subjects, it seems problematic that a sponsor or participating site does not have the authority to require local IRB or Privacy Board review, regardless of whether the study benefits from federal funding. While the NPRM does not explain why lead institutions were not given the option to assess whether local IRB review is appropriate (where there is no funding agency), presumably the concern was that such an option would lead to institutions unnecessarily electing not to use a single IRB, thereby increasing cost and administrative burden. While this concern is valid, particularly given the current trend of institutions not electing to use a single IRB,[117] providing criteria to make such a determination would reduce the likelihood that institutions could rely on this exception to circumvent the proposed single IRB requirement.

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116 *See* U.S. Dep't of Health & Human Servs., *Attachment A: Recommendations NPRM: The Secretary's Advisory Committee on Human Research: Recommendations on the Notice of Proposed Rulemaking entitled "Federal Policy for the Protection of Human Subjects,"* www.hhs.gov/ohrp/sachrp-committee/recommendations/2016-january-5-recommendation-nprm-attachment-a/index.html (last visited Apr. 14, 2016).

117 *NPRM*, at 53982.

Privacy and Security Safeguards

Many studies do not involve interactions with research subjects but instead involve analyzing data records or biospecimens. For these studies, the main risk to human subjects is not physical but informational should unauthorized access to or release of information occur. The Common Rule Agencies speculate that this risk is compounded due to evolving technology and the rise of "big data,"—the collection of massive amounts of information and analysis of information across multiple sources resulting in greater potential for re-identification—which may allow information previously considered non-identifiable to be re-identified.[118]

Currently, the Common Rule requires that IRBs determine on a study-by-study basis whether adequate provisions are in place to protect the privacy of subjects and maintain data confidentiality.[119] The NPRM seeks to remove this assessment from IRB responsibility and instead impose (arguably) uniform privacy and security requirements for institutions and investigators conducting research subject to the Common Rule or operating under an exemption involving the use of private identifiable information or biospecimens.[120]

Specifically, all such institutions and investigators would be required to implement and maintain "reasonable and appropriate safeguards" to protect biospecimens and private identifiable information that they collect, obtain, receive, maintain, or transmit for research.[121] Institutions and investigators could meet this requirement by either implementing measures to be published by HHS or applying safeguards that meet certain standards derived from the HIPAA Privacy and Security Rules.[122]

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118 *Id.* at 53938, 53978.
119 *Id.* at 54051 (proposed § __.111(a)(7)).
120 *Id.* at 54049–50 (proposed § __.105). *See also id*. at 53978–80.
121 *Id*. at 54049 (proposed § __.105(a)).
122 In regard to the HIPAA option, institutions and investigators would be required to apply safeguards that meet the standards in 45 C.F.R. §§ 164.308, .310, .312, and .530(c) (i.e., HIPAA's administrative, physical, and technical safeguards). *NPRM*, at 54049 (proposed § __.105(b)). *See also id*. at 53979. As currently proposed, federal departments and agencies would have an additional option for meeting the safeguard requirement. *Id.*

According to the Common Rule Agencies, uniform privacy and security standards could provide much needed protection for research subjects' private information, thereby reducing the risk of harm.[123] IRBs often have little expertise in evaluating privacy and confidentiality risks, and given the increasing harm that can result from data breaches, a more formal minimum threshold for privacy protection in the research context could prove useful. While a risk exists that uniform standards could unnecessarily overburden certain lower-risk studies, this risk may be outweighed by the administrative efficiencies achieved by eliminating IRB privacy assessments.

As for the second compliance option, applying safeguards that meet certain standards derived from the HIPAA Privacy and Security Rules, it is unclear whether the NPRM's proposed safeguards would address the privacy concerns of the Common Rule Agencies. Many of the NPRM's key changes are motivated by concerns regarding the informational risk posed by biospecimens, even if de-identified.[124] However, as the NPRM explicitly acknowledges, HIPAA does not apply to biospecimens in and of themselves.[125] Allowing institutions and investigators that have implemented HIPAA safeguards (either voluntarily or because they are, at least in some capacity, covered entities or business associates) to meet the NPRM's proposed safeguard requirements could ease the administrative burden caused by multiple privacy and security standards. That said, compliance with an additional set of privacy protections might not be overly burdensome, as many institutions currently meet the requirements of multiple privacy and security standards (e.g., HIPAA and state laws) and thus may be equipped to implement additional privacy and security protections in the research context with minimal burden.

123 *See NPRM*, at 53941.

124 *See, e.g., id*. at 53940 ("Of particular interest for this proposal is addressing risks from inappropriate disclosure of information generated from biospecimens . . . there is a possibility that it will be increasingly difficult, if not impossible, to make biospecimens fully non-identified.")

125 *Id.* at 53978.

Conclusion

The Common Rule Agencies appear in the NPRM to balance important, but often conflicting, ethical principles. Many of the NPRM's key proposals, such as the expansion of "human subject" to include all biospecimens and the imposition of privacy and security safeguards reflect a heightened concern regarding informational harm. On the other hand, the proposals aimed at achieving efficiencies, such as the use of a single IRB and the addition of numerous exclusions and exemptions appear aimed at reducing burdens on research, thereby enabling scientific advances in research and their attendant societal benefits to occur faster. Whether the NPRM achieves the right balance is a matter of debate, as evidenced by the disparate reactions among different members of the research community. Regardless of the balance, the proposed changes to the Common Rule, if finalized, will require a significant re-evaluation of institutional policies, procedures, and processes. Relevant stakeholders should be ready to act once the final rule is published.