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HHS Finalizes Comprehensive Revisions to the Common Rule

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On Jan. 19, 2017, the U.S. Department of Health and Human Services (HHS) and 15 other federal departments and agencies promulgated a final rule (82 Fed. Reg. 7149) to update and strengthen the federal Policy for the Protection of Human Subjects (the Common Rule), the set of federal regulations governing the conduct of research involving human subjects. The final rule, which includes extensive changes to the informed consent process and institutional review board (IRB) oversight, marks the first major reform to the Common Rule since its original issuance in 1991. The revisions to the Common Rule will have implications for a wide range of clinical research stakeholders in the life sciences and health care industries, including drug and device manufacturers, hospitals, academic medical centers, universities and medical schools, institutional review boards (IRBs), contract research organizations, laboratories, and tissue banks. While the final rule does not modify any regulations administered by the Food and Drug Administration (FDA), the final rule's preamble and the recent 21st Century Cures Act (Pub. L. 114-255) will predictably push HHS to revise FDA human subject regulations to be consistent with the final rule, to the extent permitted by law. Specifically, Section 3023 of the 21st Century Cures Act requires the HHS Secretary, to the extent practicable and consistent with other statutory authorities, to harmonize the differences between the Common Rule (45 C.F.R. Part 46, Subpart A) and FDA's human subject regulations.

This article summarizes the key provisions of the final rule, describes the major changes from the Notice of Proposed Rulemaking that was issued on Sept. 8, 2015 (the "NPRM"), and identifies the important new requirements established by the final rule. Although the new administration and Congress could overturn the regulations, the rule's overarching objectives of facilitating clinical research while maintaining critical hu-

man subject protections and reducing administrative and regulatory burdens and delays, as well as the longstanding need to modernize the federal oversight of clinical research, may decrease the likelihood of repeal.

Background

In July 2011, HHS issued an Advance Notice of Proposed Rulemaking (ANPRM) to announce its efforts to revisit the Common Rule and solicit public feedback on how to increase protections for research subjects while facilitating medical research and reducing administrative and resource burdens and delays. HHS released the NPRM in September 2015, and in response, received more than 2,100 public comments from individuals, institutions, and professional organizations and societies. The final rule, in large part, was shaped by public comment to the ANPRM and the NPRM.

The final rule is intended to reflect the shifting landscape of clinical research over the past two decades. Rapidly evolving technologies have accelerated mobile and computer capabilities, allowing researchers to collect and access troves of data, which may be pooled, mined, analyzed, and shared. Breakthroughs in biomedical sciences related to genome sequencing and precision medicine also have altered the paradigm of clinical research. While medical research continues to be conducted at academic medical centers and hospitals, primary care settings are becoming increasingly involved. Moreover, biospecimen repositories and tissue banks are accumulating hundreds of millions of human samples, which if made more widely available, could hold promise for developing critical drugs, biologics and medical devices.

Along with changes to the nature of research have come changes to the risks and benefits introduced by research. Whereas interventional research often presents the risk of physical harm, risks related to information and biospecimen research often implicate subject privacy and confidentiality. With that in mind, HHS has attempted to apply the fundamental principles announced in the *Belmont Report* of respect for persons, beneficence, and justice to the new clinical research landscape.

Key Changes to the Common Rule

For purposes of this article, we are adopting the final rule's terminology of "the pre-2018 rule" to reference

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the iteration of the Common Rule that was changed by the final rule.

I. Scope of the Common Rule (§ __.101)

A. Coverage of ‘clinical trials’

The pre-2018 rule applies to research funded by a federal department or agency that has adopted the Common Rule. The NPRM would have extended the scope of the Common Rule to cover all “clinical trials,” regardless of funding source, that were conducted at a U.S. institution that received federal support and were not subject to regulation by the FDA. In response to negative public comments, the final rule does not implement the NPRM proposal and instead concludes that the proposal for extending the Common Rule to currently unregulated clinical trials “would benefit from further deliberation” (82 Fed. Reg. at 7156).

B. Direct Oversight of IRBs Not Operated by an Institution with an FWA (§ __.101(a)(1))

The pre-2018 rule does not subject IRBs not operated by an institution holding a Federalwide Assurance (FWA) to oversight for compliance with the Common Rule. Where an institution relies on an IRB that it does not itself operate, the Office for Human Research Protections (OHRP) holds the institution accountable for noncompliance, even when the IRB was directly responsible for the violation. The NPRM would have authorized Common Rule departments and agencies to enforce against IRBs not operated by an FWA-holding institution (known as “independent IRBs”).

The final rule codifies the NPRM proposal and authorizes Common Rule departments and agencies to enforce compliance directly against independent IRBs. This enforcement mechanism allows those parties to avoid involving other engaged institutions in enforcement activities related to the responsibilities of the designated IRB. It is expected that this change will ease liability concerns of institutions using independent IRBs because the government can take compliance action directly against the IRB responsible for the regulatory violation, rather than against the institution that relied on the IRB’s review. This may increase the use of central IRBs in multi-site research by eliminating one of the major concerns that institutions have had regarding relying on such IRBs.

II. Definitions (§ __.102)

A. ‘Human subject’ (§ __.102(e))

The most significant change from the NPRM to the final rule is the decision not to include non-identifiable biospecimens in the definition of “human subject.” The NPRM would have required that research involving non-identified biospecimens be subject to the Common Rule, and that consent be obtained to conduct such research. Now, with respect to biospecimens, the final rule is aligned with the pre-2018 rule by applying only to research that involves the use, study, or analysis of *identifiable* biospecimens.

The NPRM would have expanded the pre-2018 rule’s definition of “human subject” to cover all research uses of biospecimens, regardless of whether the biospecimens were identifiable. Consent for the secondary re-

search use of biospecimens could have been waived in extremely limited circumstances, but otherwise would have had to be study-specific or broadly applicable to future, unspecified research (“broad consent”). Public opposition to this proposal was vigorous and sustained, and appears ultimately to have persuaded HHS to drop the provision.

The final rule adds a definition of “identifiable biospecimen,” defining it as a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. The pre-2018 rule’s definition of “identifiable private information” had encompassed identifiable biospecimens. Further, the final rule adds a new process by which Common Rule departments and agencies can regularly assess, in consultation with data matching and re-identification experts, whether new technological developments merit reconsideration of how identifiability of information or biospecimens should be interpreted in the context of research. This process is to occur within one year and at least once every four years thereafter. If this process results in a determination that particular technologies and techniques, when applied to nonidentifiable biospecimens, could generate identifiable private information or identifiable biospecimens, those technologies will be placed on a list, and recommendations may be made as to how to manage privacy and security protections, such as informed consent requirements for using these technologies. The Common Rule departments and agencies would provide notice and opportunity for comment before placing a technology on this list, which will be published in the Federal Register and maintained on a publicly accessible website. Notably, the preamble states that “the expectation is that whole genome sequencing will be one of the first technologies to be evaluated to determine whether it should be placed on the list” (82 Fed. Reg. at 7169). In addition to creating a list of technologies and techniques, the final rule provides that the Common Rule departments and agencies will reexamine the meaning of the terms “identifiable private information” and “identifiable biospecimen” within one year and at least once every four years thereafter, and may alter the interpretation of these terms, including through the issuance of guidance.

B. ‘Legally authorized representative’ (§ __.102(i))

The pre-2018 rule defines a legally authorized representative to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research. “Applicable law” referred to state or local law in the jurisdiction where the research was being conducted. However, in those jurisdictions that have not enacted relevant laws to designate a legally authorized representative to provide consent on behalf of a prospective research participant, the final rule permits an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context to be a legally authorized representative for the purposes of the Common Rule.

C. ‘Research’ (§ __.102(l))

As described below, certain activities proposed under the NPRM to be “excluded” from the scope of the Common Rule are either expressly carved out from the defi-

inition of “research” or incorporated into the exempt category. Specifically, the definition of “research” is revised to exclude public health surveillance (§ __.102(l)(2)). The NPRM proposed this exclusion category to include the collection and testing of information or biospecimens necessary to allow public health authorities to identify, monitor, assess, or investigate potential public health signals. The preamble to the final rule notes that FDA’s adverse event reporting systems would fall outside the definition of “research” (82 Fed. Reg. at 7176).

The NPRM also proposed exclusion categories for certain scholarly and journalistic activities, criminal justice activities, and authorized operational activities for national security missions. In the final rule, these activities are codified out of the definition of “research” (§ __.102(l)(1), __.102(l)(3), __.102(l)(4)). In discussing scholarly and journalistic activities that are not research, the final rule at § __.102(l)(1) includes additional fields and methodologies that fall outside the definition of “research,” including literary criticism and legal research. The final rule preamble notes that these fields are cited solely as examples “in order to clarify that the focus of the excluded activities is on the specific activities that collect and use information about specific individuals themselves, and not generalizing to other individuals, and that such activities occur in various fields of inquiry and methodological traditions” (82 Fed. Reg. at 7174). The final rule preamble contrasts these activities to “studies using methods such as participant observation and ethnographic studies, in which investigators gather information from individuals in order to understand their beliefs, customs, and practices, and the findings apply to the studied community or group, and not just the individuals from whom the information was obtained” (82 Fed. Reg. at 7175). The final rule preamble clarifies that the latter types of studies fall within the definition of “research.”

D. ‘Written’ or ‘in writing’ (§ __.102(m))

The final rule adopts a definition of “written” or “in writing” to mean writing on a tangible medium (e.g., paper) or in an electronic format. Although not proposed in the NPRM, the definition includes the option of an “electronic format” to denote the legal effectiveness of electronic consent forms.

III. Exempt Activities (§ __.104)

The NPRM would have created a new section of research “excluded” from the scope of the Common Rule. Unlike exempt research, “excluded” activities would not have been subject to any institutional, administrative or IRB review to determine whether the activity is in fact excluded. Rather, investigators would have been responsible for self-determining whether their research is excluded. Even though a research activity may have been excluded, the NPRM recommended that such research still be conducted consistent with the principles outlined in the *Belmont Report*.

The final rule does not adopt the proposed new concept of “excluded” activities. Instead, many of the NPRM’s excluded activities are either carved out from the definition of “research” (as described above) or classified as exempt under § __.104. The final rule makes additional revisions to the pre-2018 rule exemptions, as described below.

A. NPRM-Excluded Activities Implemented in the Final Rule (§ __.104(d)(4))

The pre-2018 rule contains an exemption for research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. The NPRM contained an exclusion category that would have expanded the exemption to include not only research involving the collection or study of information that had already been collected, but also information that would be collected in the future. The exclusion further would have required that (i) the sources of information be publicly available; or (ii) the information be recorded by the investigator in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator does not re-identify subjects or otherwise conduct an analysis that could lead to creating individually identifiable private information. This exclusion category would have been confined to information and would not have included the secondary research use of biospecimens.

The NPRM also contained an additional exclusion for secondary research activities that are conducted by an investigator who is subject to the requirements of the Health Insurance Portability and Accountability Act (HIPAA) rules.

The final rule creates a new exemption category, “Secondary Research for which Consent is Not Required” (§ .104(d)(4)). The preamble explains that the term “secondary research” refers to “re-using identifiable information and identifiable biospecimens that are collected for some other ‘primary’ or ‘initial’ activity” (82 Fed. Reg. at 7191). Under this exemption, secondary research use of identifiable private information or identifiable biospecimens would not require consent if any of the following apply:

(i) The research involves the secondary use of publicly available identifiable biospecimens or publicly available identifiable private information.

(ii) The research involves the use of identifiable private information and identifiable biospecimens that have been or will be collected so long as the information is recorded by the investigator in such a manner that the identity of human subjects cannot be ascertained readily or through identifiers linked to subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.

(iii) The research use of identifiable private information and identifiable biospecimens when the research involves only information collection and analysis and the use of such information is subject to the protections of HIPAA. The final rule preamble states an expectation that these protections will include, where appropriate, the individual’s authorization for future, secondary research uses of protected health information, or waiver of the authorization requirement by an IRB or Privacy Board. Notably, this exemption does not apply where the information originates at an entity subject to HIPAA but is disclosed to an investigator who is not subject to HIPAA for use in the research.

(iv) The research involves the use of identifiable private information or identifiable biospecimens for secondary research conducted by, or on behalf of, a federal

department or agency using government-generated or government-collected information obtained for nonresearch activities, if both the original collection of the information and the secondary research use of the information are subject to certain federal statutory privacy safeguards.

B. NPRM-Excluded Activities Not Implemented in the Final Rule

Certain exclusions were not adopted in the final rule. Notably, the following categories of activities would have been considered “excluded” under the NPRM, but were not implemented by the final rule.

1. Program improvement activities

The NPRM would have created this exclusion category, which would have included data collection and analysis, including the use of biospecimens, for an institution’s own internal operational monitoring and program improvement purposes, if the data collection and analysis were limited to the use of data or biospecimens originally collected for any purpose other than the proposed activity, or were obtained through oral or written communications with individuals (e.g., surveys or interviews). In omitting this category of activities, the preamble to the final rule notes that “some program improvement activities involve research and deserve the protections of the rule, while others are not research and are not under the rule. We believe that this topic would be better addressed through other means” (82 Fed. Reg. at 7179).

2. Quality assurance and quality improvement (QA/QI) programs

The NPRM would have created this exclusion category to cover QA and QI activities involving the implementation of an accepted practice to improve the delivery or quality of care or services, if the purposes were limited to altering the utilization of the accepted practice and collecting data or biospecimens to evaluate the effects on the utilization of the practice. This proposal was not intended to cover the evaluation of the accepted practice itself. The final rule did not implement this proposal, citing, in part, the fact that certain QA/QI activities are already considered not to meet the definition of “research” under the pre-2018 rule.

3. Non-identified biospecimen designed to generate information about the person that is already known

The NPRM would have excluded secondary research use of a non-identified biospecimen designed only to generate information about the person that is already known. This exclusion would have encompassed the development and validation of certain diagnostic tests and assays (such as research to develop an *in vitro* diagnostic test for a condition using specimens from individuals known to have the condition and those known not to have the condition) and quality assurance and control activities. The final rule omits this exclusion, explaining that it is no longer necessary, given that the final rule does not adopt the NPRM proposal to modify the definition of human subject to include all biospecimens, regardless of identifiability.

C. Revised Exemptions

Only one exemption proposed in the NPRM—exempting secondary research use of identifiable pri-

vate information when notice was given—was not included in the final rule. In addition, notably, the NPRM proposed the development by federal departments and agencies of a voluntary “exemption determination tool” to assist investigators in determining whether their study is exempt. The final rule does not include the NPRM’s proposed tool, declining to specify a particular way in which investigators and institutions might make exemption determinations. However, the final rule suggests that the federal agencies will continue to explore development of such a tool and could issue a subsequent notice seeking public comment on this topic.

The following exemptions were proposed in the NPRM and are included in the final rule:

1. Benign behavioral interventions involving adult subjects (§ __.104(d)(3))

The NPRM proposed a new class of exempt research involving benign interventions in conjunction with the collection of data from an adult subject. “Benign interventions” would be brief in duration, harmless, painless, not physically invasive, and not likely to have a significant adverse lasting impact on the subjects. In addition, the investigator would have to believe that the subjects would not find the interventions offensive or embarrassing. As examples, the NPRM mentioned research activities in which a subject is asked to read materials, review pictures or videos, play online games, solve puzzles, or perform cognitive tasks. The subject would have to agree prospectively to the intervention and data collection, and (i) the information obtained would have to be recorded in such a manner that the subjects could not be identified directly or through identifiers, or (ii) any disclosure of the human subjects’ responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, educational advancement, or reputation.

The final rule adopts this exemption with modifications. First, the final rule adds “behavioral” to modify the type of intervention that is covered by this exemption, which the preamble explains was for the purpose of excluding medical interventions. Second, the final rule broadens the type of research that may meet this exemption by allowing investigators to satisfy the provision’s requirements if they obtain and record information in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subject, and an IRB conducts a limited review to make the determination required under __ § .111(a)(7), namely, that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

2. Storage or maintenance for secondary use of identifiable biospecimens or identifiable private information for which broad consent is required (§ __.104(d)(7))

The NPRM proposed an exemption for storage or maintenance for secondary use of identifiable biospecimens or identifiable private information if certain conditions were met. Specifically, this exemption would have covered the storage and maintenance for secondary research use of biospecimens or identifiable private information that had been or will be acquired for research studies other than for the proposed research

study, or for nonresearch purposes, if (i) written consent for the storage, maintenance, and secondary research use of the information or biospecimens were obtained using a broad consent template that the Secretary of HHS would develop; and (ii) the reviewing IRB were to conduct a limited review of the process through which broad consent would be sought, and, in some cases, whether the standards for data security would be met.

The final rule adopts this exemption with modifications. Because the final rule does not incorporate the NPRM proposal to alter the definition of “human subject” to extend to research involving non-identifiable biospecimens, the final rule modifies the exemption to apply only to storage or maintenance for secondary research use of identifiable private information or *identifiable* biospecimens. Further, the much-touted HHS-created broad consent template is not being finalized at this time; instead, institutions will have flexibility to create their own broad consent forms.

For the exemption to apply, the IRB must determine that broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained, including through reviewing the process through which broad consent will be obtained. Because issuance of the HHS broad consent template was not included in the final rule, IRBs must also determine that the broad consent used contains the required elements of consent and that broad consent be appropriately documented or documentation waived. In addition, if changes are made to the ways in which the identifiable information or identifiable biospecimens are stored or maintained, the IRB must determine, when appropriate, that adequate provisions are in place to protect the privacy of subjects and to maintain the confidentiality of data, consistent with the requirements found at § __.111(a)(7) for non-exempt research involving human subjects.

3. Research involving the use of identifiable biospecimens or identifiable private information for which broad consent is required (§ __.104(d)(8))

The NPRM introduced an exemption to permit the research use of identifiable biospecimens and information stored pursuant to the exemption discussed immediately above. This exemption would have addressed research involving the use of biospecimens or identifiable private information that had been stored or maintained for secondary research use, if broad consent for the storage, maintenance, and secondary research use of the information and biospecimens had been obtained. If the investigator anticipated that individual research results would be provided to a research subject, then the research would not be eligible for exemption and instead would need to be reviewed by an IRB and study-specific consent would have to be obtained.

The final rule modified this exemption by restricting its application to *identifiable* biospecimens. The final rule also requires that limited IRB review include an IRB determination that, when appropriate, adequate provisions are in place to protect the privacy of subjects and the confidentiality of data. Because the final rule does not include issuance of an HHS-developed broad consent template, each time a specific study is proposed, the final rule requires that an IRB review the study to determine whether the proposed secondary analysis is permissible under the broad consent that

was obtained for secondary research use. Consistent with the NPRM, the exemption does not apply if the investigator includes returning individual research results to subjects as part of the study plan. The preamble states that when secondary studies include a plan to return research results, it would almost always be appropriate for the study to be reviewed by an IRB to ensure that research results are returned to the subject in an appropriate manner.

IV. Informed Consent (§ __.116)

As the NPRM and final rule express, consent forms have increased in length and complexity, which adversely affects prospective subjects’ ability to understand the information and make an informed choice about participation. The NPRM proposed a number of changes to facilitate shorter and more understandable consent forms. The NPRM aimed to address unduly long documents in which important information could be buried at the end and difficult for a potential research subject to find. The final rule implements many of the concepts proposed in the NPRM.

A. Facilitating Subject Understanding (§ __.116(a)(5))

The NPRM emphasized the importance of a consent form’s providing first the essential information that a reasonable person would want to know to make an informed decision about whether to participate in research. The NPRM would have required informed consent forms to present information in a way that would facilitate the prospective subject’s understanding of why one might or might not want to participate, rather than merely providing a list of isolated facts.

The final rule adopts, except with respect to broad consent under § __.116(d), the NPRM concept that consent forms should be reorganized and should more actively promote understandability of the salient aspects of the research. Specifically, the final rule requires that informed consent must begin with “a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.” The final rule requires that this presentation be organized and communicated to the prospective subject in such a manner that facilitates comprehension. In codifying the NPRM, the final rule provides that “[i]nformed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts.”

The final rule does not codify the NPRM proposal that the investigator present first the Common Rule-required information, before providing other information, if any, to the subject, nor the NPRM proposal that the consent document include only the elements of consent required by the Common Rule, with any other information included in appendices. The changes were in response to commenters who worried that such an approach would lead to a “dual document” system. Instead, the final rule replaces references to the Common Rule requirements that must be included in the “body” of the form as opposed to in an appendix with references to the “beginning” section of the form. Addition-

ally, the information provided in the beginning section is not limited to solely Common Rule requirements.

B. New Basic Element (§ _____.116(b)(9))

Under the NPRM, research with non-identifiable data would not have met the definition of “human subject,” with only non-identifiable biospecimens proposed to be added to that definition. The NPRM proposed a new basic element of informed consent to inform prospective subjects either that (1) identifiers might be removed from the data and that the non-identified data could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject; or (2) the subject’s data collected as part of the research would not be used or distributed for future research studies, even in a non-identified form.

The final rule adopts the NPRM proposal but expands it to include identifiable biospecimens, consistent with the change to the definition of “human subject.” Under the final rule, the definition of “human subject” includes research in which an investigator obtains, uses, studies, analyzes, or generates *identifiable* biospecimens or identifiable private information. Thus, the new element of consent has been clarified to apply to any research that involves the collection of identifiable biospecimens or identifiable private information.

The NPRM acknowledged that the investigators generally will not select the second option, which hamstring institutions and researchers from de-identifying the data and biospecimens and using for future research purposes. In fact, the NPRM preamble states that:

It is anticipated that very few investigators will elect to offer the option to restrict the future research use of non-identified data, in part because of the challenges of marking and tracking such decisions. However, should they offer this option, then institutions and investigators will have to develop a system for tracking impermissible uses of non-identified information. Since most investigators will likely elect to inform subjects that identifiers might be removed from the data and distributed for future research without additional informed consent, it would be reasonable for investigators and institutions to generally assume that the secondary research use of non-identified information would be permissible unless marked otherwise. 80 Fed. Reg. 53933, 53971 (Sept. 8, 2015).

Notably, the prohibition does not extend to the non-research uses of the leftover data and biospecimens, such as for education, training, quality improvement, and quality assurance.

C. New Additional Elements (§ _____.116(c))

The NPRM proposed three additional elements be added to § _____.116(c), which contain additional elements that must be provided to each subject or legally authorized representative, when appropriate. The additional elements proposed by the NPRM were:

- (i) a statement that the subject’s biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- (ii) a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

- (iii) an option for the subject to consent, or refuse to consent, to investigators recontacting the subject to seek additional information or biospecimens or to discuss participation in another research study.

The final rule adopts the first two additional elements: (i) and (ii). The final rule fails to implement the third additional element—(iii)—though such information may be included in the consent form at the investigator’s discretion. Instead, the final rule includes a further additional element: “For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).” The final rule preamble explains that this requirement was added because of the unique implications of the information that can be developed through whole genome sequencing, such as important insights into the health of individuals as well as their biological families.

D. Broad Consent for the Storage, Maintenance, and Secondary Research Use of Identifiable Private Information or Identifiable Biospecimens (§ _____.116(d))

The NPRM proposed to allow broad consent to cover the storage or maintenance for secondary research use of all biospecimens (regardless of identifiability) and identifiable private information. Because the NPRM proposed to expand the definition of “human subject” to include all biospecimens, it also proposed to facilitate research using biospecimens by permitting broad consent to be obtained for the storage or maintenance for secondary research use of biospecimens.

The final rule includes an option to obtain broad consent for the storage, maintenance, and secondary research use of identifiable private information and identifiable biospecimens. The broad consent is available only for secondary research use (collected for either research studies other than the proposed research or non-research purposes). The option to obtain a broad consent for future use of identifiable biospecimens and identifiable private information provides a new alternative for investigators, in addition to the options available under the pre-2018 rule: obtaining an IRB waiver of consent or obtaining study-specific consent for each protocol. Below we describe in more detail the final rule’s requirements for broad consent.

1. General elements of broad consent

The NPRM proposed requiring that broad consent include a general description of the types of research that may be conducted with information and biospecimens, the types of information or biospecimens that might be used in research, and the types of institutions that might conduct research with the biospecimens or information.

Like the NPRM, the final rule requires broad consent to include:

- (i) a description of any reasonably foreseeable risks or discomforts to the subject;
- (ii) a description of any benefits to the subject or to others that may reasonably be expected from the research;
- (iii) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(iv) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;

(v) when appropriate, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(vi) when appropriate, for research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen);

(vii) a general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens (This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted. Regarding this requirement, the final rule preamble states that where there is reason to believe that some subjects would find the research controversial or objectionable, a more robust description of the research is required to meet the "reasonable person" standard (82 Fed. Reg. at 7221));

(viii) a description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;

(ix) a description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);

(x) unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;

(xi) unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

(xii) an explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

2. Ability to withdraw consent

The final rule codifies the NPRM proposal that broad consent include an element that informs subjects that, at any time and without penalty or loss of benefits to which the subject is otherwise entitled, the subject

could withdraw consent, if feasible, for research use or distribution of the subject's information or biospecimens. Broad consent must contain the same basic element as specific consent related to the voluntariness of enrolling and withdrawing from the study, at any time, without the loss of benefits to which the subject is otherwise entitled. However, both the final rule and the NPRM recognize that information that has been stripped of identifiers might not be traceable. Thus, it might not be feasible to withdraw consent for future use or distribution. Whereas the NPRM required a specific statement in the consent form to that effect, the final rule does not, but the intent appears to be the same and the final rule preamble attaches no significance to the change. The final rule preamble further states that if an investigator commits to permitting a subject to discontinue use of the subject's identifiable private information or identifiable biospecimens, the final rule expects that the investigator would honor this commitment and not remove identifiers (82 Fed. Reg. at 7221). Investigators would be incentivized to inform the subject that his/her biospecimens and information will be de-identified, and, once the identifiers are stripped, the further distribution or research use could not be discontinued based on inability to trace. Otherwise, researchers and institutions may be expected, and in fact required, to maintain identifiers with biospecimens and information if the consent form promises that subjects could discontinue, at any time, the future research use of all biospecimens and information.

3. Public posting of non-identifiable data

The NPRM proposed an element of broad consent related to the public posting of non-identifiable data about a subject. This proposed element of broad consent would have included an option, if relevant, for an adult subject to consent or refuse to consent to the inclusion of the subject's data, with removal of the identifiers listed in the HIPAA Privacy Rule, in a database that would be publicly available and openly accessible to anyone.

This NPRM proposal appeared fundamentally inconsistent with countervailing pressures and requirements, including with ongoing developments in European Union (EU) and European Medicines Agency (EMA) law and policy that would require de-identified, subject-level clinical trials data to be made widely available for review. In other words, in light of EU and EMA policy developments requiring public posting of de-identified subject-level data, and given an increasing set of journal and professional society expectations that de-identified, subject-level data be made available to other researchers, the NPRM proposal to allow subjects to "opt out" of public availability of their de-identified data was infeasible. The final rule, indeed, does not include this NPRM proposal. The final rule commentary regards this proposal as unnecessary and as overlapping with the broad consent elements that require (i) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and (ii) a description of any reasonably foreseeable risks or discomforts to the subject.

4. Broad consent template

As noted in Section III.C.2 above, to facilitate the use of broad consent, the NPRM proposed that the HHS Secretary would publish in the Federal Register broad

consent templates that would contain all of the required elements of consent. The NPRM noted that at least two broad consent templates would be developed: one for information and biospecimens originally collected in the research context, and another for information and biospecimens originally collected in the nonresearch context. The final rule does not include the issuance of these broad consent templates by the HHS Secretary. HHS agreed with public comments that favored allowing institutions to create their own broad consent forms that can be tailored to a variety of circumstances. However, the preamble notes that the HHS Secretary expects to develop broad consent guidance in the future, which may include broad consent templates. Whether this will in fact occur is, of course, unclear, as the Presidential administration, and its HHS Secretary, changed within hours of the issuance of the final rule.

E. Waiver of Consent (§ _____.116(f))

The pre-2018 rule permits an IRB to waive the requirements for obtaining informed consent, or to alter such requirements, if certain criteria are met: (i) the research must involve no more than minimal risk to subjects; (ii) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (iii) the research could not practicably be carried out without the waiver or alteration; and (iv) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

1. New waiver criterion (§ _____.116(f)(3))

The NPRM proposed to add a new waiver criterion, which would require that, for research involving access to or use of identifiable biospecimens or identifiable information, the research could not practicably be carried out without accessing or using identifiers. The NPRM modeled this on the similar criterion in the HIPAA Privacy Rule's requirements for a waiver of HIPAA authorization, which requires that the research could not practicably be conducted without access to and use of the protected health information (PHI).

The final rule adopts a similar waiver criterion that mandates that for research involving the use of identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format. According to the final rule preamble, the purpose underlying the new criterion is that "nonidentified information should be used whenever possible in order to respect subjects' interests in protecting the confidentiality of their data and biospecimens" (82 Fed. Reg. at 7224). The new standard will require that investigators accurately predict whether proposed biospecimen research will require identifiers at any point during the conduct of the study. Researchers will be encouraged to use de-identified biospecimens for proposed research to be eligible for waiver. This incentive structure will push more research, even when obtaining consent would be impracticable and the study involves no more than minimal risk, to use de-identified information and biospecimens based on the likelihood of obtaining a waiver, despite the fact that a proposed research project with identifiable biospecimens may be more clinically important but the researchers could not meet the new criterion. This heightened standard for waiver likely will decrease the volume of research conducted on large swaths of identifiable biospecimens. Moreover,

IRBs will be asked to make determinations regarding whether a proposed biospecimen study requires the use of identifiers, which may be beyond the current expertise and qualifications of many IRB members.

In addition, the final rule does not adopt the NPRM's proposal for additional, more stringent waiver conditions applicable to research involving biospecimens (such as that there be "compelling scientific reasons" for the biospecimen research).

2. Waiver of broad consent by individuals who refused to provide consent (§ _____.116(f)(1))

The NPRM prohibited waiver of informed consent by an IRB if a person has been asked for broad consent and refused to provide it. The final rule adopts the proposal providing that, if an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the broad consent requirements, and the individual refused to provide such consent, then the IRB would be prohibited from waiving consent for the storage, maintenance, or secondary research use of the identifiable biospecimens or information. The final rule preamble notes that a person's refusal to sign a broad consent may be for a variety of reasons, and the policy may ultimately have an adverse impact on the biospecimen research enterprise, but the autonomy of individuals and respecting persons weigh in favor of not overriding an individual's refusal to consent. As a practical matter, refusal to consent will be determined solely on the absence of the individual's signature on the broad consent form.

F. Screening, Recruiting, or Determining Eligibility (§ _____.116(g))

Under the pre-2018 rule, IRBs could waive the requirement for informed consent to permit researchers to access and use identifiable private information to contact prospective study subjects. The NPRM characterized this practice as burdensome and unnecessary to protect subjects, and noted that it is not consistent with FDA's regulations, which do not require informed consent or a waiver of informed consent for such activities. The NPRM proposed to allow an IRB to approve a research proposal in which investigators, for eligibility screening and recruitment, obtain identifiable private information about prospective human subjects of research without informed consent either through oral or written communication with the prospective subjects or through accessing pre-existing records containing identifiable private information, provided that the research proposal includes an assurance that the investigator will implement standards for protecting the obtained information, to the extent required by the proposed rule.

The final rule adopts this proposal with minor changes for clarity and without the requirement that investigators adhere to the proposed standards for protecting obtained information set by the NPRM, as these provisions were not included in the final rule (as discussed above). The final rule preamble clarifies that this provision is not a waiver of the consent requirement; rather, it is an exception to the requirement. The preamble further clarifies that, in approving this exception to informed consent for the purpose of screening, recruiting, or determining the eligibility of prospective subjects, the IRB will be reviewing and approving the

entire research proposal, and thus all IRB approval criteria set forth at § __.111 must be satisfied.

G. Public Posting of Consent Forms (§ __.116(h))

The pre-2018 rule contains no requirement to post publicly consent forms from clinical trials. As an additional means of increasing transparency and facilitating the development of more informative informed consent forms, the NPRM proposed that a copy of the final version of the consent form for clinical trials conducted or supported by a Common Rule department or agency would need to be posted on a publicly available federal website. The final rule preamble explains that “[t]he primary purpose of this provision is to improve the quality of consent forms in federally funded research by assuring that—contrary to current practices, under which it is often very difficult to ever obtain a copy of these documents—they eventually would become subject to public scrutiny” (82 Fed. Reg. at 7228).

The final rule adopts the proposal with modifications and clarification, despite the fact that many commenters expressed concern that the proposal introduced an administrative burden without a corresponding increase in protections to human subjects. Consistent with the NPRM, the final rule defines “clinical trial” as 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 effect of the interventions on biomedical or behavioral health-related outcomes. The final rule does not require that the “final version” of the consent form be posted. Rather, investigators are only required to post an IRB-approved consent form that was used for enrollment purposes, even if the form underwent modifications at a later time. The final rule also provides greater flexibility in regard to when the consent form must be posted, which can take place any time after the trial is closed to recruitment, limited to no later than 60 days after the last study visit by any subject. If the federal department or agency supporting or conducting the clinical trial determines that certain information should not be made public, the department or agency may permit redactions to the information posted. The final rule preamble explains that HHS will create a website for the posting of these consent forms, and the other Common Rule agencies may either use the HHS website or develop their own. The preamble further notes that the existing clinical trial registration website, www.ClinicalTrials.gov, may be used for this purpose.

V. Documentation of Informed Consent (§ __.117)

As described above, the final rule includes a definition of “written,” in part, to allow for the use of electronic consent forms. The final rule provides that informed consent must be documented by the use of a written consent form approved by the IRB and “signed (including in an electronic format) by the subject or the subject’s legally authorized representative.” The addition of the phrase “including in an electronic format” clarifies HHS expectations that electronic consent is legally effective.

Further, the NPRM added a new provision to this regulation providing that an IRB may waive the require-

ment for the investigator to obtain a signed informed consent form for some or all of the subjects if the IRB finds that (i) subjects are members of a distinct cultural group or community for whom signing documents is not the norm, (ii) the research presents no more than minimal risk of harm to subjects, and (iii) there is an appropriate alternative mechanism for documenting that informed consent was obtained. The final rule adopts this provision, but omits the requirement that documentation must include a description as to why signing the consent form is not the norm.

VI. Cooperative Research (§ __.114)

The pre-2018 rule required that each institution engaged in cooperative research obtain IRB approval of the study, though local IRB review was not mandated. However, standard practice has been that local IRBs at each institution independently review the research protocol and consent materials, unless the IRB enters into a reliance agreement with another IRB, such as the central IRB in a multi-site study. The NPRM would have mandated that all institutions in the United States engaged in cooperative research rely on a single IRB, selected by the federal department or agency conducting the research, as the reviewing IRB for that study. This requirement would not have applied to research in which local IRB review is required by law, or when the federal department or agency conducting the research has determined that the use of a single IRB would be inappropriate.

The final rule adopts the NPRM proposal in large measure, but modifies it to allow the lead institution to propose the reviewing IRB, rather than requiring that it be selected by the federal department or agency supporting or conducting the research. However, the federal department or agency must approve the proposed IRB selection. The final rule also clarifies that if an American Indian or Alaska Native group passes a tribal law requiring more than single IRB review, the requirement in the final rule does not apply to such research.

VII. Data Security Standards (§ __.111(a)(7)(i))

Despite the informational risks to subjects posed by research on identifiable data, the pre-2018 rule did not prescribe a standard for privacy and confidentiality safeguards. The NPRM would have set uniform standards to help assure privacy and confidentiality protections for all research subjects by requiring appropriate safeguards against risks to the security and integrity of biospecimens and identifiable private information. The NPRM would have allowed for compliance by either implementing specific measures from a list that would have been published by the HHS Secretary or by implementing safeguards that would comply with HIPAA rules.

Largely in response to public comments expressing concern over the difficulty of adhering to standards that had not yet been issued, the final rule does not adopt the NPRM proposal. Instead, the final rule incorporates data security standards into the criteria for IRB approval, and specifically the data security standard is now an integral part of the “limited IRB review” required for certain exempt research activities. The final

rule requires that in order for an IRB to approve research, the IRB must find that, where appropriate, there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The final rule requires the HHS Secretary to issue guidance to assist IRBs in assessing what provisions would be adequate to protect privacy and confidentiality.

VIII. Expedited Review (§ __.110)

The pre-2018 rule allows an IRB to conduct an expedited review of a study if the research consists only of activities on a list published by the HHS Secretary and is found by the IRB to involve no more than minimal risk. The expedited review process can be conducted by the IRB chairperson or a reviewer the IRB chairperson designates. The NPRM would have allowed a study to undergo expedited review if the study consisted of activities on the HHS Secretary's list, unless the reviewer determined the study involved more than minimal risk. This would have represented a rebuttable presumption that research on the list presents no more than minimal risk unless determined otherwise by the IRB reviewer.

The final rule adopts the NPRM proposal that studies are deemed to be minimal risk if they only involve activities on the HHS Secretary's list, unless the reviewer determines, and documents its rationale for concluding, that the study involves more than minimal risk. The final rule also adopts the NPRM proposal that an IRB may use the expedited review process when conducting limited IRB review. The final rule includes a requirement that the list of expedited review categories be evaluated every eight years and published in the Federal Register.

IX. Continuing Review (§ __.109)

The pre-2018 rule required that IRBs conduct continuing review of research at appropriate intervals, but not less than once per year. Continuing review requires a convened IRB meeting in which the majority of the members are present, except if the research is eligible for expedited review. The final rule adopts the approach proposed in the NPRM, namely, to eliminate continuing review for studies that (i) qualify for expedited review, unless the IRB reviewer documents why

continuing review should occur; or (ii) have since reached the stage where they involved only analyzing data or accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care; or (iii) undergo limited IRB review.

X. Harmonization Among Common Rule Agencies and Departments (§ __.101(j))

The NPRM would have required consultation among Common Rule departments and agencies to harmonize guidance, where appropriate and feasible, before such guidance would be issued. The final rule adopts the NPRM proposal, creating a requirement that Common Rule departments and agencies consult each other before issuing guidance relating to the Common Rule, for the purpose of harmonization, unless consultation is not feasible.

XI. Effective and Compliance Dates, and Transition Provisions

The effective and compliance date for the final rule is Jan. 19, 2018, except for cooperative research (§ __.114(b)), for which the compliance date is three years after publication, i.e., Jan. 19, 2020. Research initially approved by an IRB before Jan. 19, 2018, must comply with the pre-2018 rule, except that an institution engaged in research that continues beyond that time may decide to comply with the final rule, provided that the IRB documents such a determination. Research initially approved by an IRB after Jan. 19, 2018, must comply with the final rule.

Next Steps

The final rule includes extensive and substantive revisions to the Common Rule. The changes, if left in place by the next administration and Congress, will require modifications to how sponsors and researchers conduct clinical investigations, as well as to how IRBs exercise oversight of clinical research. Clinical research stakeholders must carefully review the final rule, consider its implications, and then identify the steps needed to bring their policies, standard operating procedures, forms, and trainings into compliance by the effective dates listed above.