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Client Alert

FDA & Life Sciences and Healthcare Groups

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HHS Issues Final Rule that Substantially Revises the Federal Policy for the Protection of Human Subjects

On January 19, 2017, the Department of Health and Human Services (HHS) and fifteen other Federal departments and agencies published a final rule[1] that extensively revises and modernizes the Federal Policy for the Protection of Human Subjects, which is also known as The Common Rule (the Policy). The new rule is effective on January 19, 2018, which is also the compliance date.[2] The Common Rule was originally promulgated in 1991 and the new rule, which will amend 45 C.F.R. Part 46, is the first substantive revision in over two decades. Although FDA has not yet issued a notice of proposed rulemaking, the agency is expected to harmonize its human subjects protection regulations with the Common Rule to the extent permitted under their differing statutory authorities and HHS is required to carry out this harmonization of the two policies under Section 3023 of the 21st Century Cures Act.

The preamble clarifies that the rule is intended to address, and in certain ways, facilitate the broader types of clinical research that are now sponsored by HHS and other federal agencies, and to ensure the protection of human subjects in the context of explosive growth of the use of sophisticated techniques to analyze biospecimens, including genomic sequencing, and very large datasets. Major changes include: (1) new requirements regarding the information that must be disclosed to prospective human subjects during the informed consent process; (2) allowance of the use of broad consent for storage, maintenance, and unspecified future research uses of identifiable private information and identifiable biospecimens; (3) new categories of research that are exempt from IRB review or that would require limited IRB review to ensure adequate privacy safeguards; (4) a new requirement for U.S. institutions engaged in cooperative research to use a single IRB; and (5) removal of the requirement for IRBs to conduct continuing review of studies that undergo initial expedited review as well as certain other types of studies.

For more information, contact:

Beverly H. Lorell, MD
+1 202 383 8937
blorell@kslaw.com

Christina Markus
+1 202 626 2926
cmarkus@kslaw.com

Elaine Tseng
+1 415 318 1240
etseng@kslaw.com

Seth Lundy
+1 202 626 2924
slundy@kslaw.com

King & Spalding LLP
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 202 737 0500
Fax: +1 202 626 3737

101 Second Street, Suite 2300
San Francisco, CA 94105-3664
Tel: +1 415 318 1200
Fax: +1 415 318 1300

www.kslaw.com

This client alert focuses on these major revisions that are likely to have the greatest potential impact on U.S. healthcare institutions, as well as pharmaceutical and medical device companies, that conduct clinical research. Be aware, however, that the Final Rule is lengthy and contains additional detail.

KEY PROVISIONS

NEW REQUIRED DISCLOSURES TO PROSPECTIVE SUBJECTS DURING INFORMED CONSENT

Under the general requirements of informed consent, the new rule adds a requirement that the prospective subject or legally authorized representative "*must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.*" The rule does not define the characteristics of a "reasonable person;" thus, it is likely that HHS will issue guidance with hypothetical examples to help clarify the interpretation of this new requirement. Further, except for the new category of broad consent, the informed consent document 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 why one might or might not want to participate in the research.*" In addition, this new component of informed consent "*must be organized and presented in a way that facilitates comprehension.*" Notably, the new rule does not require that the proposed subject be tested or interrogated to demonstrate comprehension of key information about the research.

- **A new "Basic element of informed consent" – Biospecimens.** The Common Rule, as well as FDA regulations pursuant to 21 C.F.R. Part 50, currently require that eight "Basic elements" be disclosed to each human subject or legally authorized representative during informed consent. The new rule adds a ninth "Basic element" for clinical research that involves the collection of identifiable private information or identifiable biospecimens. The new "Basic element" requires that one of the following disclosures must be provided: (1) that identifiers might be removed from the identifiable private information or identifiable biospecimens and that after such removal, the information could be used for future research or distributed to other investigators without further informed consent, if this might be a possibility; or (2) an affirmation that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for any future research studies.

- **New "Additional elements of informed consent" – More disclosures about biospecimens.** The Common Rule, as well as FDA regulations, also require the disclosure of six "Additional elements," when appropriate. The new Rule adds three "Additional elements" that must be provided during informed consent, if applicable:

- A disclosure 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 the commercial profit;*"
- A statement as to whether clinically relevant research results, including individual results, will be disclosed to subjects, and if so, under what conditions; and
- A statement regarding biospecimen research as to whether the research will or might include whole genome sequencing.

- **New definition of human subjects.** To implement these and other new requirements, the rule also provides multiple new definitions. Among these is a modified definition of "*human subject*" that now addresses biospecimens. "Human subject" is redefined to mean "*a living individual*" about whom an investigator conducting research:
  - "*Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or*
  - *Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.*"

The new rule does not address head on whether all biospecimens are inherently "identifiable" in the context of current genomic analytic technology when interfaced with large publicly available databases. However, it requires Common Rule agencies and departments to assess every four years whether new scientific and technology developments should trigger reconsideration of how identifiability of biospecimens or information should be interpreted for purposes of human research.

BROAD CONSENT FOR STORAGE, MAINTENANCE, AND UNSPECIFIED FUTURE RESEARCH USES OF IDENTIFIABLE PRIVATE INFORMATION OR IDENTIFIABLE BIOSPECIMENS

The new rule provides for an entirely new category of informed consent that is applicable for storage, maintenance, and secondary future research uses of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes). As an alternative to obtaining new IRB review and informed consent in the future for such research, a subject or legally authorized representative may be asked to provide broad consent if specified requirements are met, including the provision of:

- Certain specific "Basic" and "Additional" elements of consent;
- A general description of the types of future research that may be conducted such that "*a reasonable person would expect that the broad consent would permit the types of research conducted;*"

- A description of the identifiable private information or identifiable biospecimens that might be used and whether sharing with others might occur, and "*the types of institutions or researchers*" that might conduct the research;

- The time period that such materials may be stored and maintained, and a description of the time period in which these materials may be used for research purposes (which could be indefinite);

- A statement that the subject will not be informed of the details of any future research studies that might be conducted, including the disclosure the subject might have chosen not to consent to some of those specific research studies;

- Unless it is known that clinically relevant research results, including individual research results, will be provided, a statement that results may not be disclosed to the subject; and

- An explanation of whom to contact for answers about the subject's rights and the storage and future uses of identifiable private information or identifiable biospecimens, including "whom to contact in the event of a research-related harm."

The rule does not explicitly state whether the subject may later revoke permission for storage and future uses of biospecimens after the subject is no longer enrolled in the initial research project.

NEW CATEGORIES OF RESEARCH OUTSIDE OF THE POLICY'S SCOPE OR EXEMPT FROM IRB REVIEW

The new rule clarifies that there are four types of human research that are outside the scope of the Policy. Examples include (1) scholarly and journalistic activities (e.g., oral history, biographies, and legal research); (2) public health surveillance activities: (3) collection and analysis of information, biospecimens or records solely for criminal justice or investigative purposes; and (4) authorized activities in support of national security and defense.

Separately, the new rule adds categories of clinical research that are within the scope of the Policy but are exempt from IRB review or exempt from some of the Policy's requirements. As an example, the new rule identifies that research involving certain types of "*benign behavioral interventions*" in adults is exempt from IRB review. Some of the exempt types of research will be required to undergo limited IRB review to ensure that there are adequate privacy safeguards for the human subjects. Taken together, these modifications are aimed at making very low risk research involving humans less burdensome, allowing the resources of institutions and IRBs to focus on oversight of higher risk human research.

NEW REQUIREMENT FOR USE OF A SINGLE IRB IN COOPERATIVE MULTI-SITE RESEARCH

The new rule defines cooperative research as research covered by the Policy that involves more than one institution. Each institution remains responsible for safeguarding the rights and welfare of human subjects

at the institution, and complying with the Policy. However, the new rule requires, with few exceptions, that any institution located in the U.S. that is engaged in federally funded cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the U.S. For federally supported or conducted cooperative research, the Federal department or agency will identify the single reviewing IRB. Among the few exceptions to this provision is cooperative research for which more than single IRB review is required by law or research for which the Federal agency or department determines that use of a single IRB is not appropriate.

In addition, the new rule explicitly gives Common Rule agencies and departments the authority to directly enforce compliance against an IRB that does not hold a Federalwide Assurance (FWA) (i.e., an independent central IRB) rather than the institution where the research is being conducted.

REMOVAL OF THE REQUIREMENT FOR CONTINUING IRB REVIEW OF CERTAIN STUDIES

Following initial IRB review and approval, the new rule identifies three categories of studies for which subsequent periodic, continuing IRB review is no longer required. These categories include (1) research that was initially approved under the expedited IRB review process; (2) certain types of research that were initially reviewed and approved under "*limited IRB review*" (e.g., some types of research eligible for the new process of broad consent); and (3) research that has progressed to a stage where only data analysis is being done or where observational follow-up is being done using procedures that subjects would undergo as part of standard clinical care.

Regarding continuing IRB review, the new rule also explicitly states that an IRB shall have authority to observe or have a third party observe the consent process and the research.

THE PRESIDENT'S FREEZE MEMORANDUM

Importantly, the new rule is, as of the date of this writing, currently suspended due to the White House's January 20, 2017 "Regulatory Freeze Pending Review" memorandum. Under that memorandum, the President ordered enforcement or implementation of all published regulations that had not yet taken effect to be postponed for at least 60 days, and allowed agencies to publish notices of delays beyond 60 days so that the incoming Administration could review the policies in the Final regulation. It may be that following a policy review by the new Administration the rule is re-proposed for notice and comment to amend certain provisions in the "final" rule, or to withdraw the rule altogether. Similarly, the new Administration may choose to allow the final rule to proceed, keeping the January 2018 effective date intact. We urge stakeholders to watch for announcements in or around March 2017 addressing the fate of this final rule.

IMPLICATIONS OF THE FINAL RULE FOR HEALTHCARE INSTITUTIONS, AND DRUG AND MEDICAL DEVICE COMPANIES

Healthcare institutions that conduct federally-sponsored or supported research, and their IRBs, will need to thoroughly review the extensive changes in the new rule and implement changes in written procedures and training of personnel involved in clinical research to ensure readiness for compliance in less than one year (January 19, 2018). In particular, although biospecimens are not even cited in the current Policy, the extensive new provisions related to clinical research that includes storage, maintenance or future uses of identifiable biospecimens merit particular attention, including the implementation of the new category of broad consent.

Drug and medical device companies that sponsor clinical research should be prepared for harmonization of the FDA regulations for protection of human subjects with the new rule in the near future. In addition, currently many institutions submit a Federalwide Assurance (FWA) to HHS that asserts that all human research at the institution will be reviewed in accordance with the Policy (even if not federally funded). The preamble states that the long-standing option of using the FWA process to assert voluntary compliance with the Common Rule for all research at an institution will be eliminated by non-regulatory means. However, the final rule explicitly clarifies that any institution may voluntarily mandate via its policies that all clinical research, whether or not federally funded, is overseen in compliance with the Common Rule. Thus, drug and device manufacturers may wish to consider that many IRBs will apply the criteria in the new rule to industry-sponsored clinical research, including the inclusion of the new informed consent requirements applicable to future research uses of biospecimens.

King & Spalding will continue to monitor developments related to the new final rule, and would be pleased to assist in helping healthcare institutions, as well as pharmaceutical and medical device companies, understand and navigate the rule, update internal procedures and personnel training, and prepare short briefing materials for corporate leadership regarding major changes in the requirements.

[1] 82 Fed. Reg. 7149 (January 19, 2017).
[2] The exception to the compliance date is the provision for cooperative research for which the compliance date is January 20, 2020.