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Client Alert

Government Matters

FDA (Finally!) Issues Proposed Rule to Amend FDA Regulations on the Protection of Human Subjects and Institutional Review Boards

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The Food and Drug Administration (FDA) recently issued a proposed rule that would extensively modify and modernize its current regulations governing the protection of human subjects and Institutional Review Boards (IRBs).[1] If finalized, and to the extent consistent with differing statutory authorities, this proposed rule would harmonize FDA regulations for the protection of human subjects (21 C.F.R. Part 50) and IRBs (21 C.F.R. Part 56) with the revised Federal Policy for the Protection of Human Subjects rule at 45 C.F.R. Part 46, Subpart A that came into effect on July 19, 2018 (the revised Common Rule). This FDA proposed rule would also revise the Agency's Investigational Device Exemption (IDE) regulations (21 C.F.R. Part 812). Section 3023 of the 21st Century Cures Act,[2] which was signed into law on December 13, 2016, required FDA to harmonize its regulations with the revised Common Rule "not later than 3 years after the date of enactment of this Act," i.e., by December 13, 2019—a deadline the Agency obviously missed.

The harmonization of FDA's human subject protection and IRB regulations with the revised Common Rule is needed to reduce confusion and the regulatory burden on IRBs that have oversight of clinical studies subject to both FDA regulations and the revised Common Rule. In addition, the proposed rule would add new basic and additional elements of informed consent and modify the presentation of information in the consent form. The proposed rule would also address provisions in the revised Common Rule that are intended to permit IRBs to focus on research that presents a higher risk to human subjects. The proposed rule, however, does not adopt all the provisions in the revised Common Rule.

This Client Alert focuses on the major proposed changes that will impact sponsors of clinical studies of investigational drugs and medical devices and the human subjects that participate in this research.

KEY PROPOSED CHANGES TO FDA REGULATIONS

The proposed rule would make major changes to the informed consent process and IRB oversight of FDA-regulated clinical investigations.

- **New mandatory introductory section of informed consent** – Among the changes to the *general requirements for informed consent*,[3] the proposed rule would require that informed consent "begin with a concise and focused presentation of key information that is most likely to assist a prospective subject or legally authorized representative (LAR) in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension."[4] FDA also proposes that this new section of focused key information must always be presented first when informed consent is obtained by oral presentation to the potential subject using the short form process.[5]

  As an additional provision to bolster the information provided to a potential subject and facilitate the decision whether or not to participate in the research, FDA proposes that the *general requirements for informed consent* contain an additional new section that would clarify that the potential subject or LAR "must be provided with the information that a reasonable person would want to have to make an informed decision about whether to participate and be given an opportunity to discuss that information."[6] It is notable that the proposed rule and the preamble do not attempt to define a "reasonable person" or clarify the potential parameters of "an opportunity to discuss" the information.

- **New focus on identifiable private information and identifiable biospecimens** – Consistent with the revised Common Rule, FDA proposes to add new terms and definitions regarding *identifiable private information* and *identifiable biospecimens*. Importantly, these terms and definitions do not coincide with the definition of Protected Health Information (PHI) under the HIPAA Privacy Rule. *Private information* is defined as including ""information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.,* a medical record*).*"[7]

  – *Identifiable private information* is "private information for which the identity of the subject is or may readily be ascertained by the sponsor or investigator or associated with the information."[8] The proposed text of the definition of *identifiable private information* is more explicit than the revised Common Rule because FDA proposes to include information that is or may be readily ascertained by the sponsor and the research team under the supervision of the investigator, as well as the investigator.

  – *Identifiable biospecimen* is a "biospecimen for which the identity of the subject is or may readily be ascertained by the sponsor or investigator or associated with the biospecimen."[9]

  As context, the preamble to the revised Common Rule extensively discusses the concern that any private information or biospecimen may be identifiable in the current era of advanced genomic and large database analytics. In addition, the revised Common Rule explicitly requires that federal Departments and Agencies reexamine the meaning of "identifiable" private information and biospecimens at least every four years. In the proposed rule, FDA emphasizes that it intends to participate in this effort.

- **New elements of informed consent** – To align with the revised Common Rule, FDA proposes to add four new elements of informed consent. The proposed rule would add a new *basic element of informed consent*[10] that would require a "description of how information or biospecimens may be used for future research or distributed to another investigator for future research."[11] Although the text of this disclosure is

not identical to that of the revised Common Rule, FDA opines in the preamble that it would comply with both regulations.[12] The proposed rule would also add three new *additional elements of informed consent*:[13]

  - 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;
  - A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
  - 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).[14]

- **Legally authorized representative (LAR)** – To harmonize FDA's definition of legally authorized representative (LAR) with the revised Common Rule definition, FDA proposes for situations where there is no State or local law that authorizes a LAR to provide consent on behalf of a research subject the following definition: "an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research."[15] Under the proposed rule, such persons may be considered a LAR for the purpose of consenting to a subject's participation in FDA-regulated clinical research.
- **Written documentation of informed consent** – Consistent with the revised Common Rule, the definition of "in writing" or "written" as it applies to informed consent would, under the proposed rule, include paper and electronic formats. The proposed definition would clarify that consent forms, as well as the documentation of the subject's or LAR's consent, may be in electronic format.[16] Notably, electronic format consent forms and electronic documentation of consent by the subject were widely used during the COVID pandemic despite uncertainty about compliance with FDA's current requirements for provision of consent forms and documentation of consent. This proposed definition of "in writing" or "written" would also apply to IRB processes and documentation.

The proposed rule also would add revisions and additions to the current requirements for IRB review of FDA-regulated clinical research under 21 C.F.R. Part 56. The following are proposed major modifications:

- **Waiver of documentation of informed consent** – FDA proposes that an IRB may waive the use of a form for documentation of informed consent "for a study that presents no more than minimal risk of harm to the subjects, if the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, and there is an appropriate alternative mechanism for documenting that informed consent was obtained."[17] The proposed rule does not discuss potential alternative methods for documenting informed consent.
- **Continuing review of research** – Under the current regulations, an IRB is required to conduct continuing review of FDA-regulated clinical research not less than once per year.[18] The proposed rule would, unless the IRB determines otherwise, eliminate the requirement for continuing review "for research that has progressed to the point that it involves only . . . (1) data analysis, including analysis of identifiable private information or identifiable biospecimens or (2) accessing followup clinical data from procedures that subjects would undergo as part of clinical care."[19]
- **Equitable selection of patients** – The current criteria for IRB approval of research include the determination that the research study's selection of patients is equitable.[20] The proposed rule would substantially modify the description of vulnerable subjects with the new descriptor of "a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or

economically or educationally disadvantaged persons."[21] Notably, this new proposed descriptor of vulnerable subjects omits pregnant women and handicapped persons and replaces the term "mentally disabled" with "impaired decision-making capacity."[22]

For consistency with the proposed revisions to the IRB continuing review process, FDA also proposes to revise 21 C.F.R. Part 812 to modify the timing for submission of investigational device exemption (IDE) progress reports by the investigator to the sponsor, the monitor, and the reviewing IRB, as well as the submission of progress reports by the sponsor to all reviewing IRBs, to the extent that continuing IRB review is required. FDA intends, however, to maintain the current requirement that IDE sponsors must submit progress reports to FDA at least yearly or as may be requested by FDA.

Sponsors should also be aware that FDA currently does not propose to adopt several provisions of the revised Common Rule, including the provisions for broad consent, limited IRB review, exempt research, and public health surveillance.

FDA REQUEST FOR PUBLIC COMMENTS

FDA requests public comment on several issues including:

- The proposed new basic elements of informed consent and whether they provide adequate notice to potential subjects about the possible future research uses of their information and biospecimens.
- The Agency's current policy is that IRB review or informed consent is not required for sponsors to survey a site's medical records to determine if the site has sufficient patients with the condition of interest for the clinical investigation. As context, FDA does not propose to add to Agency regulations a revised Common Rule provision that requires an IRB to approve a proposal under which investigators obtain information or biospecimens without informed consent of the individual or LAR for the purpose of screening, recruiting, or determining eligibility of the individual for a clinical investigation. FDA requests public comment on whether FDA's current policy adequately addresses screening, recruiting, or determining eligibility for an FDA-regulated clinical investigation.
- FDA's intent not to adopt a revised Common Rule provision that allows an exception to the documentation of informed consent if the only record linking the subject and the research would be the informed consent form.
- The proposed effective date of any final rule issued by FDA would be 180 days after the date of publication in the Federal Register. The FDA requests public comment on this time frame.

SUMMARY

The proposed rule to amend FDA regulations for the protection of human subjects and IRBs is likely to simplify IRB review of clinical investigations that are subject to both the revised Common Rule and FDA regulations. Sponsors should know, however, that the proposed harmonization of FDA regulations with the revise Common Rule will include major changes to the informed consent process. Among the modifications, the proposed rule would require new sections of information in the consent form, including an introductory section with concise and focused "key information" to assist prospective subjects in understanding why they may or may not want to participate in the research. The proposed rule heightens attention on the uses of a subject's biospecimens and adds new disclosures to potential subjects regarding possible future uses of their information and biospecimens outside of the clinical investigation; whether 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; and whether research involving biospecimens may involve whole genome sequencing. In addition, the proposed rule would result in multiple changes in IRB oversight of FDA-regulated clinical research, including the addition of a new exception for the documentation of informed consent; elimination of the requirement for continuing review of clinical studies under certain conditions; and changes to the way subjects vulnerable to coercion or undue influence are considered.

Sponsors of FDA-regulated clinical investigations should carefully review the proposed rule and consider submitting comments no later than **December 28, 2022**.[23]

If you have questions regarding the proposed rule or would like assistance in preparing comments, please contact Beverly Lorell, Chris Markus, Gary Messplay, Kyle Sampson, or Elaine Tseng for more information.

[1] *See* FDA, Proposed Rule, "Protection of Human Subjects and Institutional Review Boards," 87 Fed. Reg. 58,733 (Sept. 28, 2022), https://www.federalregister.gov/documents/2022/09/28/2022-21088/protection-of-human-subjects-and-institutional-review-boards.
[2] *See* The 21st Century Cures Act, Pub. L. 114-115, § 3023 (enacted Dec. 12, 2016) (codified at 42 U.S.C. § 289 note), https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.
[3] *See* 21 C.F.R. § 50.20.
[4] Proposed Rule, 87 Fed. Reg. at 58,736.
[5] *Id.* at 58,738-39.
[6] *Id.* at 58,737.
[7] *Id.*
[8] *Id.*
[9] *Id.*
[10] *See* 21 CFR § 50.25(a).
[11] Proposed Rule, 87 Fed. Reg. at 58,738.
[12] *See id.*
[13] *See* 21 C.F.R. § 50.25(b).
[14] *See* Proposed Rule, 87 Fed. Reg. at 58,738.
[15] *Id.* at 58,736.
[16] *Id.* at 58,736-37.
[17] *Id.* at 58,740.
[18] *See* 21 C.F.R. § 56.109(f).
[19] Proposed Rule, 87 Fed. Reg. at 58,746.
[20] *See* 21 C.F.R. § 56.111(a)(3).
[21] Proposed Rule, 87 Fed. Reg. at 58,742.
[22] *Id.*
[23] FDA, Proposed Rule, "Protection of Human Subjects and Institutional Review Boards, and Institutional Review Boards; Cooperative Research; Extension of Comment Period," 87 Fed. Reg. 68,118 (Nov. 14, 2022), https://www.federalregister.gov/documents/2022/11/14/2022-24689/protection-of-human-subjects-and-institutional-review-boards-and-institutional-review-boards.