ROPES & GRAY

ALERT ▪ Health Care ▪ Life Sciences ▪ FDA Regulatory

September 30, 2022

Harmonizing the Common Rule and U.S. Food and Drug Administration Human Subjects Research Regulations

Attorneys
David Peloquin
Mark Barnes
Gregory H. Levine
Leslie A. Thornton
Beth P. Weinman

On September 28, 2022, the U.S. Food and Drug Administration ("FDA") issued two Notices of Proposed Rule Making to harmonize FDA's regulations pertaining to human subjects research (the "HSR NPRM")[1] and the review of cooperative research by a single institutional review board ("IRB") (the "CR NPRM")[2] with those of the Federal Policy for the Protection of Human Subjects (the "Common Rule").[3] Earlier in September, FDA also issued a draft guidance entitled "Ethical Considerations for Clinical Investigations of Medical Products Involving Children."[4]

The Common Rule, which was first promulgated in 1991, applies to human subjects research that is conducted, supported or otherwise subject to regulation by a federal department or agency that has, through administrative action, made the policy applicable to such research, including the U.S. Department of Health and Human Services ("HHS"). FDA maintains a separate set of regulations on the protection of human subjects that is codified at 21 C.F.R. Parts 50 and 56 and applies to clinical investigations that are regulated by FDA (the "FDA Regulations").

In 2016, as part of the 21st Century Cures Act, Congress mandated that HHS "revise the HHS Human Subject Regulations, the FDA Human Subject Regulations, and the vulnerable populations rules to (1) reduce regulatory duplication and unnecessary delays; (2) modernize the provisions; and (3) protect vulnerable populations, incorporate local considerations, and support community engagement."[5] The deadline set for harmonization was December 13, 2019.

In January 2017, after a nearly six-year rulemaking process, HHS published a final rule revising the Common Rule (the "Revised Common Rule"), which made substantial revisions seeking to modernize and strengthen human subjects protections. Following the issuance of the Revised Common Rule, FDA published guidance to clarify how researchers and institutions should handle research subject to both the Common Rule and to the FDA Regulations, such as federally funded research involving an investigational drug or medical device.[6] FDA's guidance document offered some clarification regarding informed consent, expedited review procedures, and IRB continuing review of research but did not address all differences between the Common Rule and the FDA Regulations.

Now, nearly three years after the statutory deadline set by Congress for harmonization, FDA has published its proposed revisions in the NPRMs. The HSR NPRM focuses on updating the FDA Regulations, while also proposing to amend certain investigational device exemption ("IDE") reporting requirements (21 C.F.R. Part 812). The CR NPRM focuses on revising the FDA Regulations pertaining to cooperative research to require, in many cases, review of such research by a single IRB. We outline both NPRMs in detail below. The key topics addressed in this alert include the following: (1) informed consent and subject recruitment, (2) IRB continuing review and IDE reporting, (3) *in-vitro* diagnostic studies using left-over samples, (4) broad consent, (5) single IRB review, and (6) FDA draft guidance pertaining to ethical considerations for clinical investigations involving children.

Human Subjects Research and IRB Regulations

Certain key proposed changes put forth in the HSR NPRM are outlined below, with a proposed effective date of 180 days after the date of publication of the final rule.[7] FDA requests comment on this timeframe.

1. Informed Consent

General Requirements of Informed Consent: **FDA proposes to harmonize the general requirements for informed consent with those found in the Common Rule, including that certain key information be presented at the beginning of the consent form.** The HS NPRM would require that the consent form begin with a concise, focused presentation of key information that is likely to assist a prospective subject or legally authorized representative in understanding the reasons why the subject might or might not want to participate in the research, and that the information be organized and presented in a way that facilitates the subject's or legally authorized representative's

comprehension.[8] When using the short-form consent process, this key information must be presented to the subject first, before any other information is provided.[9]

Elements of Informed Consent: **FDA proposes to harmonize, for the most part, the required elements of informed consent.** The HSR NPRM would add three elements of informed consent pertaining to subject samples; these reflect the same elements in the Revised Common Rule, requiring consent statements regarding: (1) whether samples will be used for commercial profit and whether the subject would share in profits, (2) whether individual research results will be disclosed to subjects, and (3) whether the research might include whole genome sequencing.

FDA also proposes a very significant new fourth element: "[a] description of how information or biospecimens may be used for future research or distributed to another investigator for future research."[10] FDA's approach on this fourth element differs from that of the Common Rule, which requires the use of one of the following two statements pertaining to future use of specimens:

a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

b. A statement 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 future research studies.[11]

FDA clarifies that using either of the Common Rule's consent statements regarding future use of specimens would be consistent with the HSR NPRM, but also notes that "when applicable, an investigator would also be required to provide a description that conveys to subjects the possible future use of their identifiable biospecimens or information that may not be stripped of identifiers."[12]

Therefore, FDA's proposed requirement for a description of future research is broader in scope than that of the Common Rule. (The Common Rule provision focuses on informing subjects regarding future use of information and biospecimens shed of identifiers, which falls outside of the definition of research involving a human subject under the Common Rule.) FDA requests comment on whether this proposed new basic element of informed consent would provide adequate notice to potential subjects, as compared to the provisions under the Common Rule quoted above. FDA also requests comments on whether the research community anticipates challenges in implementing FDA's new proposed element and whether an alternative approach could reduce such challenges.

Subject Recruitment Activities: **FDA reiterates its previously expressed position that certain activities that are merely preparatory to clinical research are not a "clinical investigation" and do not require IRB oversight or informed consent.**[13] FDA's approach differs from the Common Rule, which considers the review of identifiable private information or identifiable biospecimens to identify subjects a "research" activity subject to IRB oversight. It also differs from the approach under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), which considers a use or disclosure of protected health information for these activities to be a research activity that requires a basis under HIPAA, such as compliance with the review preparatory to research provision or a waiver of authorization from an IRB or privacy board.[14] Because FDA does not consider these preparatory activities to be a "clinical investigation" under its human subject protection regulations, FDA does not adopt the provisions from the Revised Common Rule that permit such activities to take place absent informed consent if a research proposal describing such activities is approved by an IRB and only involves obtaining information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects. Consistent with existing draft guidance, FDA reiterates in the HSR NPRM that IRB review and informed consent will need to be obtained prior to "the initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for a clinical investigation."[15] Therefore, researchers and institutions conducting activities preparatory to research will need to remain cognizant of the different approach to such activities taken by the Common Rule, the FDA Regulations, and HIPAA. Because many research studies will be subject

to all three regulatory regimes, many researchers conducting FDA regulated research will also need to comply with the Common Rule and HIPAA in their activities preparatory to research.

Waiver of Documentation for Informed Consent: **The HSR NPRM would allow an IRB to grant a waiver of documentation of informed consent if the subject or legally authorized representative is from a cultural group or community in which signing a consent form is not the norm, so long as the study is minimal-risk and there is no alternative mechanism for documentation.**[16] However, FDA stopped short of adopting the Common Rule provisions that permit a waiver of documentation of informed consent if the consent form is the only record linking the subject to the research, or if the study involves no procedures for which written consent is normally required outside of the research context.[17] Notably, the HSR NPRM does not address an IRB's waiver of informed consent more generally, as the revision of the FDA Regulations to add the ability of an IRB to waive informed consent for certain minimal risk research is currently the subject of a separate rulemaking process for which a proposed rule was issued in November 15, 2018,[18] and FDA currently permits waivers of informed consent under the exercise of enforcement discretion.[19] Nonetheless, FDA requests comment on the relevance of a waiver of documentation for informed consent when the only record linking the subject to the research is the consent form. This may have particular relevance to studies in which participation, by virtue of the eligibility criteria, could identify subjects as violating applicable laws (*e.g.*, users of illegal drugs, sex industry workers) or as members of a stigmatized population. In these cases, the "community" may have no standard that eschews consent forms, but consent documentation, if not waived by the IRB, could link subjects to illegal behaviors or stigmatized populations.

Enforcement Discretion for Studies Commenced before Effective Date: **For studies that were initially approved by an IRB before the proposed effective date, FDA states that it would not enforce compliance with several informed consent provisions.** These include the requirement that informed consent begin with a concise, focused presentation of key information and other requirements regarding organization and presentation, the requirement that key information is presented first when informed consent is administered orally and documented using a short form consent, and the four new elements of informed consent. FDA requests comment regarding this approach.[20]

2. <u>Continuing Review & IDE Reporting</u>

Continuing Review: **The HSR NPRM would adopt one of the three scenarios in the Common Rule in which continuing review of ongoing research by an IRB is not required.** Continuing review will no longer be required (unless the IRB determines otherwise) if the study has progressed to involve only (1) analysis of identifiable private information or identifiable biospecimens, and/or (2) accessing follow-up clinical data from routine clinical care.[21] However, FDA does not adopt the other two Common Rule scenarios in which continuing review is not required, namely, (a) studies eligible for expedited review and (b) exempt studies reviewed in accordance with the limited IRB review procedures.[22] Therefore, FDA-regulated research eligible for expedited review would still need to undergo annual review by the IRB. FDA notes that it would continue to require IRB review in such cases because analysis of risks to subjects receiving an FDA-regulated product may change based on adverse events that occur during the course of the study but that do not rise to the level of unanticipated problems involving risks to human subjects or otherwise require reporting to the IRB. FDA-regulated research would not be eligible for limited IRB review because the Common Rule's concept of exempt research, to which the limited IRB review concept applies in some instances, does not exist under FDA regulations.

IDE Reporting Requirements: **The HSR NPRM proposes to revise certain IDE reporting timelines to match the proposed revisions to the continuing review requirements.**[23] Currently, under 21 C.F.R. Sections 812.150(a)(3) and -(b)(5), an investigator in a study under an IDE must submit reports to the sponsor, monitor, and the reviewing IRB at least once per year, and a sponsor must submit progress reports to all reviewing IRBs at least once per year. The HSR NPRM proposes to revise both requirements such that progress reports would be required only to the extent that IRB continuing review is required. However, study sponsors still would be required to submit progress reports to FDA at least once per year or as requested (per 21 C.F.R. Section 812.150(b)(5)). Further, treatment IDE progress reports still would have to be submitted to the IRB and FDA at semi-annual intervals until a marketing application is filed (21 C.F.R. Section 812.36(f)).

3. Other Revisions

Definitions: FDA proposes to revise or add several definitions to harmonize with the Common Rule (*i.e.*, "legally authorized representative," "written or in writing," "private information," "identifiable private information," and "identifiable biospecimen").[24] However, FDA's definitions of "identifiable private information" and "identifiable biospecimen" would capture scenarios in which the identity of the individual may be readily ascertained by either the sponsor or investigator, as opposed to the investigator only.

Disqualification: The HSR NPRM proposes revisions to 21 C.F.R. Section 56.121, which pertains to disqualification of an IRB or institution, so that FDA would not be limited to publishing disqualification notices in the Federal Register, but also could publish such notices via other available and appropriate outlets, such as on the FDA website. FDA notes that it routinely posts disqualifications on its website.[25]

IRB Membership: FDA is proposing to harmonize the language regarding diversity in IRB membership set forth in 21 C.F.R. Section 50.107 with the corresponding language in the Common Rule. Specifically, it would replace the requirement that the IRB should not consist entirely of members of one gender or one profession, with requirements that the IRB membership reflect a diversity of professional qualifications and other factors (*e.g.*, race, gender, cultural backgrounds).[26]

References to Tribal Law: In line with the Common Rule, FDA also proposes revisions to clarify that federal, state and local laws (referenced under 21 C.F.R Section 50.25 (d) and (e), and Section 56.103(c)) to include tribal laws of American Indian or Alaska Native tribes.[27]

Vulnerable Subjects: Mirroring the Common Rule, FDA proposes to add language in 21 C.F.R. Section 56.111(a)(3) and -(b) regarding equitable selection of subjects and safeguards for vulnerable subjects, to clarify that "children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons" should be considered vulnerable to coercion or undue influence.[28] Accordingly, an IRB that regularly reviews FDA-regulated research involving subjects vulnerable to coercion or undue influence should give consideration to include IRB members who are knowledgeable and experienced in working with that particular category of subject. Further, in reviewing research, the IRB would need to account for such categories of vulnerable subjects when ensuring that subject selection is equitable.

4. Key Changes Not Made

In-vitro Diagnostics: **FDA did not propose alterations to IRB review requirements for *in vitro* diagnostic studies using leftover, de-identified specimens (*e.g.*, by amending the definition of "subject" under the IDE regulations).** FDA's IDE regulations define a "subject" to include individuals "on whom or on whose specimen an investigational device is used or as a control."[29] Accordingly, even if the HSR NPRM is enacted in its current form, **IRB review still will be required for *in-vitro* diagnostic studies involving remnant, de-identified human specimens if the results of such studies are submitted to, or held for inspection by, FDA** in support of an application for a research or marketing permit.[30] This is a key divergence from the Common Rule, which would consider research involving leftover de-identified specimens as not involving a human subject and, therefore, not requiring IRB review.

Broad Consent: **FDA does not propose to adopt any of the Common Rule provisions pertaining to "broad consent."** Under the Common Rule, broad consent is a type of informed consent that can be used to obtain permission for secondary research involving identifiable private information or identifiable biospecimens.[31] The Common Rule's version of broad consent has not been adopted by many institutions given the difficulties created by the need to track subjects who are offered and refuse to provide such broad consent, to ensure that their information and specimens are never the subject of an IRB waiver of informed consent. This may be the reason for FDA's determination not to adopt this provision of the Common Rule in the HSR NPRM.

Single IRB Review

Current FDA regulations permit, but do not require, multi-site FDA-regulated research to be reviewed by a single IRB. Acknowledging the growth in multi-site and collaborative trials, FDA issued a 2006 guidance favoring the use of single IRBs to reduce duplicative review.[32] On June 21, 2016, NIH issued a policy requiring single IRB review for multi-site research funded by NIH to streamline the IRB review processes.[33] The NIH policy became effective on January 25, 2018. The revised Common Rule also included a requirement of single IRB review for all U.S. sites engaged in cooperative research subject to the Common Rule (set forth in 45 C.F.R. Section 46.114). The compliance date for this Common Rule requirement was January 20, 2020. Relatedly, the 21st Cures Act removed the requirement that the IRB supervising the clinical testing of an investigational or humanitarian medical device must be local, thus removing a statutory impediment to single IRB review for medical device research.[34]

In the CR NPRM, FDA proposes requiring single IRB review for all U.S. sites in FDA-regulated cooperative research. In line with the Common Rule, FDA proposes revising 21 C.F.R Section 56.115 to require documenting the reliance on a single IRB and each entity's compliance responsibilities. **However, there are also some notable differences from the Common Rule's single IRB requirement.**

First, the CR NPRM does not require any individual or entity to identify the single IRB.[35] This departs from the Common Rule, which states that either the IRB is to be identified by the federal agency funding or supporting the research or the lead institution should propose the single IRB for acceptance by the federal agency.

Second, the CR NPRM proposes to adopt only one of the two Common Rule exceptions to the single IRB review requirement (*see* a. below) and proposes three new exceptions (*see* b., c., and d. below):

a. Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe);

b. Cooperative research involving a highly specialized FDA-regulated medical product for which unique, localized expertise is required;

c. Cooperative research on drugs that meets the exemptions from an investigational new drug application ("IND") under 21 C.F.R. Section 312.2(b); or

d. Cooperative research on medical devices that meets the abbreviated requirements under 21 C.F.R. Section 812.2(b) or the requirements for exempted investigations under 21 C.F.R. Section 812.2(c).[36]

FDA declined to adopt an exception analogous to the exception in the Common Rule at 45 C.F.R. Section 46.114(b)(2), which provides that a Federal department or agency can determine and document that use of a single IRB is not appropriate for the particular context. FDA reasons that such an approach would be impractical under the FDA Regulations because there are many FDA-regulated studies for which there is no interaction with or submission to FDA prior to the study beginning. Adding an exception that requires documentation/determination from FDA would likely increase administrative burden and delay the initiation of research.[37] Similarly, FDA's rationale for exceptions (c) and (d) above is that IND exempt studies, device studies that meet the abbreviated requirements, and IDE exempt studies do not require a submission to FDA. FDA further reasons that in the case of IND-exempt research, a single IRB process is not likely to bring new drugs or new uses of drugs to patients sooner, and thus for such research the burden of establishing a cooperative review agreement may be greater than any efficiencies gained through single IRB review.[38]

The single IRB requirement will become effective one year after the final rule is published and will apply only to FDA-regulated cooperative research initially approved by an IRB on or after the proposed effective date.[39] Therefore, it would not apply, for example, to IND studies or IDE studies that are already approved by an IRB.

Because FDA's single IRB review requirement will not apply to IND-exempt studies, non-significant risk device studies, or IDE-exempt device studies, there will continue to be a significant amount of FDA-regulated research that is exempt from these single IRB requirements. FDA notes that FDA's proposed rule allows for permissive use of the single IRB process (*e.g.*, if single IRB is required by the Common Rule but not by the proposed FDA regulations).

FDA requests comment in multiple areas such as whether there should be (a) an exception to the single IRB requirement based on the single IRB's inability to meet the needs of specific populations, (b) an exception based on a small number of investigational sites, (c) a provision that provides for FDA to determine and document that a single IRB review is not appropriate for a particular context, and (d) any other criteria that should be considered when assessing an exception to the single IRB process. FDA also requests comment on (1) whether a single IRB can supplement its members' knowledge and experience with additional information or expertise to account for the specific needs of special populations, (2) whether there are unique challenges of the single IRB model that could not be addressed by FDA's proposed exceptions, (3) the impact on stakeholders due to the differences in FDA's and the Common Rule's single IRB exceptions, and (4) possible approaches to avoid or minimize such potential negative effects.

FDA Draft Guidance

The key provisions pertaining to safeguards for children are set forth in FDA regulations at 21 C.F.R. Part 50, Subpart D and in the Common Rule at 45 C.F.R. Part 46, Subpart D. Although the two NPRMs did not propose any regulatory changes specific to children, on September 23, 2022, FDA issued a draft guidance describing the ethical framework for protecting children in clinical trials.[40] This guidance outlines considerations associated with risks, benefits, parental permission and child assent, and design considerations for clinical investigations, among others.

Key Takeaways

FDA's two NPRMs propose to harmonize the FDA Regulations with the Common Rule. However, the NPRMs would not adopt the Common Rule framework in certain respects, including with respect to research on de-identified specimens and the concept of broad consent, which would result in some significant continued divergences between the two regulatory regimes. FDA also is proposing to introduce some provisions that will be unique to its regulations, such as certain exceptions to the single IRB requirement. Sponsors, institutions, IRBs, and investigators wishing to comment on the two NPRMs have until November 28, 2022 to do so. Similarly, those wishing to comment on the FDA draft guidance pertaining to ethical considerations for clinical investigations involving children have until December 27, 2022 to do so.

If you have any questions, please contact David Peloquin, Mark Barnes, Greg Levine, Leslie Thornton, Beth Weinman, or your usual Ropes & Gray advisor.

1. Protection of Human Subjects and Institutional Review Boards, 87 Fed. Reg. 58,733 (Sep. 28, 2022) (to be codified at 21 C.F.R. Parts 50, 56, and 812).
2. Institutional Review Boards; Cooperative Research, 87 Fed. Reg. 58,752 (Sep. 28, 2022) (to be codified at 21 C.F.R. Part 56).
3. 45 C.F.R. Part 46, Subpart A.
4. U.S. Food and Drug Administration, Ethical Considerations for Clinical Investigations of Medical Products Involving Children: Draft Guidance (2022), *available at*: https://www.fda.gov/media/161740/download.
5. 21st Century Cures Act, § 3023.
6. *See* U.S. Food and Drug Administration, Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations (2018), *available at*: https://www.fda.gov/media/117042/download.
7. 87 Fed. Reg. 58,743.
8. 87 Fed. Reg. 58,737.
9. 87 Fed. Reg. 58,750.
10. 87 Fed. Reg. 58,749.
11. 45 C.F.R. § 46.116(b)(9).
12. 87 Fed. Reg. 58,738.
13. *See e.g.*, U.S. Food and Drug Administration, Informed Consent Information Sheet: Draft Guidance (2014), *available at*: https://www.fda.gov/files/about%20fda/published/Informed-Consent-Information-Sheet-%28Printer-Friendly%29.pdf; *see also* U.S. Food and Drug Administration, Screening Tests Prior to Study Enrollment (1998), *available at*: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment.
14. 45 C.F.R. § 164.512(i).
15. 87 Fed. Reg. 58,739; *see also* U.S. Food and Drug Administration, Screening Tests Prior to Study Enrollment (1998), *available at*: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment.
16. 87 Fed. Reg. 58,740.
17. 45 C.F.R. § 46.117(c).
18. Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations, 83 Fed. Reg. 57,378 (to be codified at 21 C.F.R. Parts 50, 312, and 812).
19. U.S. Food and Drug Administration, IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects (2017), *available at*: https://www.fda.gov/media/106587/download.
20. 87 Fed. Reg. 58,743.
21. 87 Fed. Reg. 58,741.
22. 45 C.F.R § 109(f).
23. 87 Fed. Reg. 58,743.
24. 87 Fed. Reg. 58,736; *id.* at 58,740.
25. 87 Fed. Reg. 58,743; s*ee also*, U.S. Food and Drug Administration, Clinical Investigations Compliance & Enforcement, https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm.
26. 87 Fed. Reg. 58,740.
27. 87 Fed. Reg. 58,738; *id.* at 58,740.
28. 87 Fed. Reg. 58,742.
29. 21 C.F.R. § 812.3(p).
30. *See, e.g.*, U.S. Food and Drug Administration, Studies Using Leftover, Deidentified Human Specimens Require IRB Review – Letter to Industry (Oct. 18, 2021), *available at*: https://www.fda.gov/medical-devices/industry-medical-devices/studies-using-leftover-deidentified-human-specimens-require-irb-review-letter-industry.
31. 45 C.F.R. § 46.116(d).
32. U.S. Food and Drug Administration, Using a Centralized IRB Review Process in Multicenter Clinical Trials (2006), *available at*: https://www.fda.gov/media/75329/download.
33. *See* National Institutes of Health, Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research (2016), *available at*: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html.
34. 21st Century Cures Act, § 3056.
35. 87 Fed. Reg. 58,757.
36. 87 Fed. Reg. 58,758.
37. *Id*.
38. 87 Fed. Reg. 58,759.
39. 87 Fed. Reg. 58,760.
40. U.S. Food and Drug Administration, Ethical Considerations for Clinical Investigations of Medical Products Involving Children: Draft Guidance (2022), *available at*: https://www.fda.gov/media/161740/download.