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FDA Final Rule - Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations

Fast Facts

- On December 21, 2023, the Food and Drug Administration (FDA) published a Final Rule "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations" (Federal Register: Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations).
- **Background:** The rule implements changes from Section 3024 of the Cures Act (Pub. L. 114–255) to allow for a waiver or alteration of informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects.
- **Summary:** The rule amends FDA's regulations to allow IRBs to approve an informed consent procedure that does not include or that alters certain informed consent elements, or to waive the requirement to obtain informed consent, for certain minimal risk clinical investigations.
    - The rule harmonizes FDA's requirements for waiver or alteration of informed consent with the revised Common Rule's requirements under 45 CFR 46.116(f)(3).
    - Amendments to FDA's regulations include:
        - Adding a new § 50.22, "Exception from informed consent requirements for minimal risk clinical investigations" to part 50.
        - Making three conforming amendments to §§ 50.20, 312.60, and 812.2 to reflect the exception from informed consent for certain minimal risk clinical investigations.
- **Effective Date**: The rule is effective January 22, 2024.
- **Applicability**: The rule will apply to IRB review at any stage of an FDA-regulated clinical investigation conducted on or after the effective date, including initial IRB approval or review of any changes to a previously approved clinical investigation.
- **Plans for FDA Guidance**: FDA plans on issuing further guidance to assist IRBs in applying these criteria to clinical investigations. Guidance will include additional information on:
    - The types of FDA-regulated clinical investigations that may qualify for a waiver or alteration of consent under § 50.22.
    - The types of research activities that may involve no more than minimal risk to the subjects and therefore might qualify for a waiver or alteration of informed consent.

  In Response 21, FDA notes that clarification of specific terms and phrases are provided "throughout this document". For example, FDA discusses interpretation of "minimal risk" and "practicably" (see below).

Secondary Research Involving Leftover Biospecimens

According to the section titled "Comments on Secondary Research Involving Leftover Biospecimens" *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable* will remain in effect.

- "We believe that most IVD device investigations falling within the scope of the policy described in section IV of the Leftover Specimen Guidance will satisfy the criteria at § 50.22. However, to the extent that there are IVD device investigations that fall within the scope of the Leftover Specimen Guidance but do not satisfy the waiver criteria in § 50.22, FDA is retaining the Leftover Specimen Guidance at this time to help avoid potential disruption to IVD device investigations as IRBs gain experience implementing the new waiver provision in § 50.22 for FDA-regulated clinical investigations."

Considerations for HRPPs and IRBs

- Review existing materials to identify where changes need to be made to reflect the final rule. This may include SOPs, IRB submission forms, reviewer checklists, guidance documents, website content, educational materials, etc.
- For institutions that use electronic IRB management systems: Depending on the system that you use, updates may need to be made to conditioning and actions, instructional text, options that display, etc.

Summary and Interpretation of the Informed Consent Exception Criteria

(Emphasis added by HRP)

(a) The Clinical Investigation Involves No More Than Minimal Risk to the Subjects

"Minimal risk" is defined in § 50.3(k) to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

In Response 10, FDA also notes the following:

- "FDA is not revising the definition of minimal risk in this rule. Retaining the current definition of minimal risk will avoid confusion in the research community and maintain harmonization with the revised Common Rule. The Common Rule and FDA regulations have shared the same definition of minimal risk since 1991, and the definition of minimal risk was not changed in the revised Common Rule. Because of the longstanding consistency in the definitions of minimal risk provided in both FDA regulations and the Common Rule, IRBs have experience in applying the term "minimal risk" to research involving human subjects, including determining when a clinical investigation involves no more than minimal risk."

(b) The Waiver or Alteration Will Not Adversely Affect the Rights and Welfare of the Subjects

"FDA stated in the preamble of the proposed rule that, to make this finding, IRBs may consider, for example, **whether the waiver or alteration has the potential to negatively affect the subjects' well-being or whether the subject population in general would likely object to a waiver or alteration being granted for the research in question** (83 FR 57378 at 57381 to 57382). It would **not be necessary** for an IRB to find that obtaining informed consent would be harmful or contrary to the best interests of subjects in order to satisfy this criterion."

(c) If the Clinical Investigation Involves Using Identifiable Private Information or Identifiable Biospecimens, the Clinical Investigation Could Not Practicably Be Carried Out Without Using Such Information or Biospecimens in an Identifiable Format

"To match the structure of the revised Common Rule's general waiver provision (*i.e.,*45 CFR 46.116(f)), this criterion has been incorporated into the codified text at § 50.22(c)."

In Responses 15 & 16, FDA also notes the following:

- "Definitions of "identifiable private information" and "identifiable biospecimen" are included in FDA's proposed rule to amend part 50, Protection of Human Subjects, and part 56, Institutional Review Boards (87 FR 58733, September 28, 2022)."
- "Additionally, the revised Common Rule includes provisions at 45 CFR 46.102(e)(7)(i) and 46.102(e)(7)(ii) that require Federal departments and Agencies implementing the revised Common Rule, regularly and upon consultation with appropriate experts, to (i) reexamine the meaning of "identifiable private information" and "identifiable biospecimen" and (ii) assess whether there are analytic technologies or techniques that should be considered to generate identifiable private information or identifiable biospecimens. FDA intends to participate in these efforts with HHS and the other Federal departments and Agencies, providing input on FDA-regulated research and promoting consistent and appropriate interpretation of these terms across HHS and FDA human subject research regulations. Including a new requirement in FDA's regulations for FDA to consider issues relating to the meaning of "identifiable," on a periodic basis and in light of evolving technology, is thus unnecessary and could result in duplicative efforts and additional burden on the Agency without added benefit."

(d) The Clinical Investigation Could Not Practicably Be Carried Out Without the Waiver or Alteration

"In the preamble to the proposed rule, FDA stated that, if scientifically sound research can practicably be carried out using only consenting subjects, FDA believes it should be carried out without involving nonconsenting subjects. **FDA also provided an example of what practicable means (*i.e.,* (1) that recruitment of consenting subjects does not bias the science and the science is no less rigorous as a result of restricting it to consenting subjects or (2) that the research is not unduly delayed by restricting it to consenting subjects)** (83 FR 57378 at 57382). As noted in our response to comment 7, **the emphasis is on situations where it is impracticable to carry out the clinical investigation, as designed, without the waiver or alteration, rather than on situations where it is not feasible to obtain informed consent from subjects**."

Further discussion on FDA interpretation of the term "practicably" can be found in Response 13 .

- "With respect to the interpretation of the term "practicably," we reiterate that the emphasis is on situations where it is impracticable—**not necessarily impossible**—to carry out the clinical investigation, as designed, without the waiver or alteration."
- "Practicability should be assessed on a case-by-case basis considering the **unique factors** associated with the clinical investigation, **such as its aims, its population(s), and the impact on its scientific validity if informed consent were required** (*e.g.,* introduction of bias)."
- "The relevant considerations, and the weight given to each consideration, should reflect the unique circumstances of the clinical investigation for which a waiver or alteration of informed consent is being sought."
- **"If an IRB finds that a clinical investigation can be practicably carried out using only consenting subjects, then FDA believes it should be carried out without involving nonconsenting subjects.**

However, we agree that, under this final rule, an IRB **can** approve a clinical investigation falling within the scope of part 50 in which investigators will have access to and utilize data and/or biospecimens that **have already been collected** without having to obtain informed consent, provided the IRB finds and documents that the criteria under § 50.22 are met."

- "In addition, we agree that IRBs may find under § 50.22(b) (§ 50.22(c) in the proposed rule) that a clinical investigation could not practicably be carried out without a waiver or alteration of informed consent **based on the unavailability of certain subjects** in an investigation to give consent for a new investigation (*e.g.,* subjects lost to follow up), when restricting the research to the subjects available to provide consent **would compromise the scientific or ethical integrity**, or **cause undue delay** of, the investigation."
- "As some comments point out, SACHRP made recommendations in 2008 related to waivers of informed consent and the interpretation of minimal risk under the Common Rule, including the Common Rule waiver criterion that corresponds to § 50.22(b). In its recommendations, SACHRP emphasized that the criterion "states that the research could not practicably be carried out without the waiver or alteration. Put another way, it would not be practicable to perform the research (as it has been defined in the protocol by its specific aims and objectives) if consent was required" (Ref. 2). SACHRP also offered the following concepts to help an IRB determine whether the research could not be practicably carried out without the waiver or alteration of consent: **(1) the scientific validity of the research would be compromised if consent were required; (2) ethical concerns would be raised if consent were required; (3) there is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained; and (4) practicability should not be determined solely by considerations of convenience, cost, or speed.**

  Although SACHRP's recommendations regarding the "practicably" waiver criterion were developed for research that is regulated under the Common Rule, they are consistent with FDA's interpretation of the corresponding waiver criterion in this rule (*i.e.,* § 50.22(b)). It thus may be appropriate for an IRB to find that a clinical investigation could not practicably be carried out without a waiver or alteration of informed consent on the grounds that ethical concerns would be raised if consent were required (*e.g.,* an investigation using previously collected biospecimens where obtaining subjects' consent for secondary research use of the biospecimens may expose individuals to new privacy risks by linking the biospecimens with nominal identifiers in order to contact the individuals to seek consent). In some cases, these ethical concerns could justify a finding of impracticability under § 50.22(b) even if the scientific validity of the clinical investigation would not be compromised by asking the individuals to provide informed consent."
- "In addition, as stated in the preamble to the proposed rule, FDA interprets the term "practicably" in § 50.22(b) to mean, for example, that the research is not unduly delayed by restricting it to consenting subjects (83 FR 57378 at 57382). The phrase "unduly delayed" refers to more than just considerations of speed. **By "unduly delayed," we mean a delay in the initiation of a clinical investigation that is so lengthy as to raise ethical or scientific concerns given the benefit, or value, potentially gained by the research** (*e.g.,* delaying the initiation of an investigation of a rare disease treatment by several years in order to allow for collection of new biospecimens from consenting subjects with the rare disease, when biospecimens from individuals with the disease are available from a repository but the biospecimens have no accompanying current contact information).

Accordingly, an IRB may make a finding that the research could not practicably be carried out without the requested waiver or alteration because requiring consent would unduly delay the research."

- "We note that **it would be inappropriate for an IRB to find that a clinical investigation could not practicably be carried out without a waiver or alteration of informed consent based solely on a clinical investigator being resistant to obtaining informed consent**. We do not consider investigator resistance to obtaining informed consent to be a scientifically or ethically valid reason for finding under § 50.22(b) that a clinical investigation could not practicably be carried out without a requested waiver or alteration of informed consent."

(e) Whenever Appropriate, the Subjects Will Be Provided With Additional Pertinent Information After Participation

"FDA proposed that, whenever appropriate, the subjects will be provided with additional pertinent information after participation. For example, an IRB may find that information that had been previously withheld about the clinical investigation to prevent bias must be provided to subjects following their participation."

Revisions to Part 50 – Protection of Human Subjects

PART 50—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for part 50 is revised to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262~~, 263b–263n~~.

2. In § 50.20 revise the first sentence to read as follows:

§ 50.20

General requirements for informed consent.

Except as provided in §§ 50.22, 50.23, and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. * * *

3. Add § 50.22 to subpart B to read as follows:

§ 50.22

Exception from informed consent requirements for minimal risk clinical investigations.

The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve an informed consent procedure that does not include or that alters some or all of the elements of informed consent set forth in § 50.25(a) and (b), or may waive the requirement to obtain informed consent, provided the IRB finds and documents the following:

(a) The clinical investigation involves no more than minimal risk to the subjects;

(b) The clinical investigation could not practicably be carried out without the requested waiver or alteration;

(c) If the clinical investigation involves using identifiable private information or identifiable biospecimens, the clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format;

(d) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

(e) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

Revisions to Part 312 – Investigational New Drug Application

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

4. The authority citation for part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

5. Revise § 312.60 to read as follows:

§ 312.60

General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall ~~in accordance with the provisions of part 50 of this chapter,~~ obtain the informed consent of each human subject to whom the drug is administered, in accordance with part 50 of this chapter ~~except as provided in §§ 50.23 or 50.24 of this chapter~~. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

Revisions to Part 812 – Investigational Device Exemptions

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

6. The authority citation for part 812 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 360hh–360pp, 360rr–360ss, 360bbb–8b, 371, 372, 374, 379e, 381, 382; 42 U.S.C. 216, 241, 262~~, 263b–263n~~.

21 U.S.C. 331, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 360bbb–8b, 371, 372, 374, 379e, 379k–1, 381, 382, 383; 42 U.S.C. 216, 241, 262,.

7. Revise § 812.2 (b)(1)(iii) to read as follows:

§ 812.2

Applicability.

* * * * *

(b) * * *

(1) * * *

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent in accordance with part 50 of this chapter ~~and documents it, unless documentation is waived by an IRB under § 56.109(c)~~.