Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations

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Guidance for Sponsors, Investigators, and Institutional Review Boards

Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number FDA-2018-D-3551.

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations

Guidance for Sponsors, Investigators, and IRBs

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I. INTRODUCTION

FDA's regulations on human subject protection (21 CFR part 50) and Institutional Review Boards (IRBs; 21 CFR part 56) help to ensure that the rights, safety, and welfare of human subjects participating in FDA-regulated clinical investigations are protected. These regulations generally conform to the Department of Health and Human Services' (HHS') Federal Policy for Protection of Human Research Subjects (45 CFR 46, Subpart A; "the Common Rule"), which sets forth requirements for the protection of human subjects involved in research that is conducted or supported by HHS.

In a final rule published on January 19, 2017, HHS and a number of federal departments and agencies made revisions to the Common Rule.[1] The general compliance date for the revised Common Rule is January 21, 2019.[2]

FDA intends to undertake notice and comment rulemaking to harmonize, to the extent applicable, FDA's regulations with the revised Common Rule. Because FDA has not revised its regulations, FDA is issuing this guidance to reduce confusion and burden associated with complying with two different sets of human subject protection regulations. This guidance is intended to address questions from stakeholders regarding the impact of certain provisions of the revised Common Rule on FDA-regulated clinical investigations during FDA's rulemaking process.[3]

If a clinical investigation is conducted or supported by HHS and involves an FDA-regulated product, then the study is subject to both 45 CFR part 46 and 21 CFR parts 50 and 56. As FDA has

[1] 82 FR 7149, January 19, 2017; https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf.

[2] 83 FR 28497, June 19, 2018; https://www.gpo.gov/fdsys/pkg/FR-2018-06-19/pdf/2018-13187.pdf.

[3] For more information on related guidances, see FDA's Web page "Clinical Trials Guidance Documents," available at https://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm.

previously described in guidance concerning the protection of human subjects, where the regulations differ, the regulations that offer the greater protection to human subjects should be followed.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA's regulations on human subject protection (21 CFR part 50) and Institutional Review Boards (IRBs; 21 CFR part 56) help to ensure that the rights, safety, and welfare of human subjects participating in FDA-regulated clinical investigations are protected. HHS, through its application of the Common Rule, regulates human subject research that is conducted or supported by HHS. The purposes of the Common Rule are to promote uniformity, understanding, and compliance with human subject protections and to create a uniform body of regulations across the federal departments and agencies. The Common Rule has been adopted by 16 other federal departments and agencies, and, in 1991, FDA amended its regulations in 21 CFR parts 50 and 56 to conform to the Common Rule,[5] with a few exceptions because of differences in FDA's mission or statute.

On December 13, 2016, the 21st Century Cures Act (Cures Act) was signed into law.[6] Section 3023 directs the Secretary of HHS, to the extent practicable and consistent with other statutory provisions, to harmonize differences between the HHS' human subject regulations and FDA's human subject regulations. The Cures Act supports HHS' and FDA's longstanding efforts to harmonize the human subject protection regulations to reduce burdens on sponsors, investigators, and IRBs while protecting research subjects.

As previously mentioned, on January 19, 2017, HHS published a final rule, which revised the Common Rule.[7] The revisions to the Common Rule ("2018 Requirements") have created certain differences between FDA's human subject regulations and HHS' human subject regulations. Many sponsors, investigators, and IRBs are involved in both HHS-regulated research and FDA-regulated clinical investigations. Some FDA-regulated clinical investigations may also be

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[4] See, e.g., "Use of Electronic Informed Consent Questions and Answers: Guidance for Institutional Review Boards, Investigators, and Sponsors," (December 2016), https://www.fda.gov/downloads/drugs/guidances/ucm436811.pdf.

[5] 56 FR 28025, June 18, 1991.

[6] Public Law 114-255, enacted December 13, 2016; https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf.

[7] The January 19, 2017 final rule that revised the Common Rule had an effective and general compliance date of January 19, 2018 (82 FR 7149). By an interim final rule published on January 22, 2018, the effective and general compliance dates were delayed for a 6-month period, until July 19, 2018 (83 FR 2885). On June 19, 2018, a final rule was published to delay the general compliance date until January 21, 2019 (83 FR 28497). The revised Common Rule, including technical amendments made by the January 22, 2018 interim final rule and the June 19, 2018 final rule, is referred to as the "2018 Requirements."

conducted or supported by HHS, and would therefore be subject to both sets of regulations. As a result, many sponsors, investigators, and IRBs would need to be familiar and comply with both HHS' and FDA's regulations. While FDA intends to undertake rulemaking to harmonize, to the extent practicable and consistent with other statutory provisions, its regulations with the 2018 Requirements consistent with Section 3023 of the Cures Act, we recognize the potential for confusion in the interim. This guidance is intended to clarify the impact of certain provisions of the 2018 Requirements on FDA-regulated clinical investigations.

III. INFORMED CONSENT

The 2018 Requirements contain several new informed consent requirements, including changes relating to the content, organization, and presentation of information included in the consent form and process to facilitate a prospective subject's decision about whether to participate in research as well as changes to the basic and additional elements of consent. FDA has received questions from stakeholders as to whether these provisions could be incorporated into consent forms and the consent process for FDA-regulated clinical investigations or if it would be necessary to develop two separate informed consent forms, one for federally-conducted/-supported research and another for research regulated by FDA.

In response to stakeholder inquiries, we are clarifying that the provisions of the 2018 Requirements related to the content, organization, and presentation of information included in the consent form and process as well as the basic and additional elements of informed consent are not inconsistent with FDA's current policies and guidances. This may avoid the need for sponsors or investigators to develop, and IRBs to review, two separate informed consent forms. See Appendix for a subset of the new informed consent provisions from the 2018 Requirements.

IV. EXPEDITED REVIEW PROCEDURES AND LIST

FDA's regulation at 21 CFR 56.110 sets forth expedited IRB review procedures for certain kinds of research involving no more than minimal risk. Section 56.110(a) describes a list of categories of research that may be reviewed by an IRB through an expedited review procedure that may be established through a Federal Register Notice. FDA established and published this list in the Federal Register on November 9, 1998 (the 1998 list).[8] Section 56.110(b) makes clear that, as appropriate, IRB "reviewer(s)" must find that the research on the list involves no more than minimal risk in order for the IRB to use the expedited review procedure.

FDA recognizes that under the 2018 Requirements at 45 CFR 46.110(b), an IRB may use the expedited procedures for research appearing on the expedited review list, unless the IRB reviewer determines that the study involves more than minimal risk. Because FDA has not revised its regulations, IRBs must continue to comply with FDA's regulation at 21 CFR 56.110(b) and use the 1998 list for FDA-regulated clinical investigations, including those that are subject to both HHS and FDA regulations.

[8] 63 FR 60353, November 9, 1998; https://www.gpo.gov/fdsys/pkg/FR-1998-11-09/pdf/98-29748.pdf.

V. IRB CONTINUING REVIEW

The 2018 Requirements eliminated the requirement to conduct continuing review in certain circumstances (see 45 CFR 46.109(f)(1)). Under 45 CFR 46.109(f)(1)(i) and (iii), continuing review will not be required for research that is either eligible for expedited review in accordance with 45 CFR 46.110, or for research that has progressed to the point that the only remaining activities are data analysis, and/or accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care, unless the IRB determines otherwise.

Because FDA has not revised its regulations, IRBs must continue to comply with our current requirements for IRB continuing review at 21 CFR 56.109(f), including for clinical investigations that are subject to both HHS and FDA jurisdiction. IRBs are required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (21 CFR 56.109(f)).[9]

VI. FURTHER CLARIFICATION

FDA is actively working to harmonize its human subject protection regulations consistent with the Cures Act. We recognize there may be questions regarding the application of other provisions of the 2018 Requirements to FDA-regulated clinical investigations during this interim period. Questions and/or comments requesting further clarification may be submitted at any time to the public docket for this guidance, and FDA will consider issuing additional guidance, if necessary, to address other provisions.

[9] For further information, see FDA's "Guidance for IRBs, Clinical Investigators, and Sponsors; IRB Continuing Review after Clinical Investigation Approval," (February 2012), (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm294558.pdf).

APPENDIX: SELECTED INFORMED CONSENT PROVISIONS FROM THE 2018 REQUIREMENTS

A. General Requirements for Informed Consent

The 2018 Requirements contain new general requirements for informed consent related to the content, organization, and presentation of information in the consent form and process to facilitate a prospective subject's decision about whether to participate in the research.

The provisions which are new or include new information are as follows:

> **46.116(a)(4)** The prospective subject or the 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.
>
> **46.116(a)(5)(i)** 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. This part of the informed consent must be organized and presented in a way that facilitates comprehension.
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> **46.116(a)(5)(ii)** Informed 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, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.
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> **46.117(b)(2)** A short form written informed consent form stating that the required elements of informed consent required by 45 CFR 46.116 have been presented orally to the subject or the subject's legally authorized representative and that the key information required by 45 CFR 46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided.

B. Basic and Additional Elements of Informed Consent

The 2018 Requirements contain a new basic element and three additional elements of informed consent, as follows:

New Basic Element at 45 CFR 46.116(b)(9)

One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:[10]

(i) 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

(ii) 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.

New Additional Elements at 45 CFR 46.116(c)(7) - (9)

46.116(c)(7) 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;

46.116(c)(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

46.116(c)(9) 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).

[10] *Private information* includes 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). (45 CFR 46.102(e)(4)).

Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (45 CFR 46.102(e)(5)).

An *identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. (45 CFR 46.102(e)(6)).