IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

Guidance for Sponsors, Investigators, and Institutional Review Boards

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(3) without initially seeking prior comment. The Agency has determined that prior public participation is not feasible or appropriate because this guidance presents a less burdensome policy that is consistent with the public health. Although this guidance document is immediately in effect, it remains subject to public comment in accordance with the Agency's good guidance practices regulation (21 CFR 10.115).

You may submit comments or suggestions 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. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Janet Norden, 301-796-1127; Carol Drew, 301-796-8510; (CDER) Ebla Ali Ibrahim, Office of Medical Policy, 301-796-3691; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Office of Device Evaluation, Clinical Trials Program, 301-796-5640.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice (OGCP)
Center for Drug Evaluation and Research (CDER)
Center of Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2017

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

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IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects

Guidance for Sponsors, Investigators, and IRBs[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document provides guidance to sponsors, investigators, and institutional review boards (IRBs) on enforcement of FDA regulations governing informed consent requirements for clinical investigations that involve no more than minimal risk[2] to human subjects. This guidance informs sponsors, investigators, IRBs and other interested parties that the FDA does not intend to object to an IRB waiving or altering informed consent requirements for certain minimal risk clinical investigations as described in Section IV of this guidance. In addition, FDA does not intend to object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described in Section IV of this guidance.

Over the years, FDA has received numerous inquiries from sponsors and investigators about conducting important minimal risk clinical investigations for which obtaining informed consent was not practicable. Many of these minimal risk clinical investigations did not proceed because FDA did not have the statutory authority to permit a waiver of informed consent for such investigations. As described in Section II of this document, an amendment to the Federal Food, Drug and Cosmetic Act (FD&C Act) has provided FDA with authority to permit an exception from informed consent for minimal risk clinical investigations when specific criteria are met. Since this amendment passed, FDA has received additional questions regarding requirements for informed consent in minimal risk clinical investigations. FDA believes this guidance will facilitate the conduct of certain minimal risk clinical investigations that are important to addressing significant public health needs without compromising the rights, safety, or welfare of

[1] This guidance has been prepared by the Office of Good Clinical Practice, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] Minimal risk is defined in applicable FDA regulations as "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." (21 CFR 50.3(k), 56.102(i)).

human subjects. Although this guidance is immediately in effect, FDA will consider all comments received and will revise this guidance when appropriate.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency'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 Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On December 13, 2016, the 21st Century Cures Act (Cures Act) (P.L. 114-255) was signed into law. Title III, section 3024 of the Cures Act amended sections 520(g)(3) and 505(i)(4) of the FD&C Act to provide FDA with the authority to permit an exception from informed consent requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject. This statutory amendment became effective on December 13, 2016. FDA intends to promulgate regulations to reflect this statutory change, including appropriate human subject protection safeguards.

Currently, FDA's regulations governing the protection of human subjects (21 CFR parts 50 and 56) allow exception from the general requirements for informed consent only in life-threatening situations when certain conditions are met (21 CFR 50.23) or when the requirements for emergency research are met (21 CFR 50.24). This limitation in FDA's regulations stemmed from section 520(g)(3)(D) of the FD&C Act, relating to the investigational use of devices. Before the Cures Act amendments, this provision in the FD&C Act directed that FDA regulations require informed consent be obtained except where the investigator "determines in writing that there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device" and it is not feasible to get the consent of the subject or the subject's representative.

The requirement in section 505(i) of the FD&C Act for informed consent for investigational use of drugs (including biologics) provided that FDA regulations must ensure informed consent is obtained "except where it is not feasible or it is contrary to the best interest of such human beings." In order to promote consistency across medical products, FDA adopted regulations reflecting the device standard for all medical product research.

In general, FDA's regulations governing the protection of human subjects conform to the requirements in the "Federal Policy for the Protection of Human Subjects" (the Common Rule), with a few exceptions because of differences in FDA's mission or statutory authority. The Common Rule, originally promulgated in 1991[3], sets forth requirements for the protection of

[3] The Common Rule was recently revised to better protect human subjects involved in research, facilitate valuable research, and reduce burden, delay and ambiguity for investigators (82 FR 7149, January 19, 2017). The final rule that revised the Common Rule adopts an effective and general compliance date of January 19, 2018. References to the Common Rule in this document are to the pre-2018 requirements that are in effect at the time of issuance of this guidance.

human subjects involved in research that is conducted or supported by the Department of Health and Human Services (HHS) (see 45 CFR 46, Subpart A) and 15 other Federal departments and agencies. The purpose of the Common Rule is to promote uniformity, understanding, and compliance with human subject protections as well as to create a uniform body of regulations across the Federal departments and agencies.[4] FDA regulations and the Common Rule share the same definition for "minimal risk," but the Common Rule allows a waiver of informed consent for minimal risk research if specific criteria are met. As stated above, FDA's regulations currently do not include an exception from informed consent for minimal risk clinical investigations.[5]

III. DISCUSSION

The Common Rule standard has been adopted and successfully employed for decades by numerous other Federal agencies. The Common Rule permits an IRB to waive the requirements to obtain informed consent, or to allow changes to, or omission of, some or all elements of informed consent if the IRB finds and documents that: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. (45 CFR 46.116(d)).[6]

The Secretary's Advisory Committee on Human Research Protections (SACHRP) provided input on the issue of whether waiver of informed consent provisions for certain minimal risk clinical investigations would be appropriate and helpful to FDA-regulated research. On March 13, 2014, SACHRP considered this issue. Recognizing that harmonization with the Common Rule would promote consistency and help to reduce confusion in the research community about when a waiver of informed consent may be permitted, while also facilitating certain FDA-regulated research, SACHRP recommended to the Secretary of HHS that FDA adopt the provisions for waiver of informed consent that exist under the Common Rule at 45 CRF 46.116(d). On October 26, 2016, SACHRP reiterated that recommendation to the Secretary.[7]

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[4] 80 FR 53931 at 53935, September 8, 2015.

[5] Note that this exception from the requirement to obtain informed consent differs from the waiver from the requirement for documentation of informed consent permitted under both the Common Rule and FDA regulations (45 CFR 46.117(c); 21 CFR 56.109(c)).

[6] The final rule that recently revised the Common Rule (82 FR 7149, January 19, 2017) adds a fifth criterion (i.e., "if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format" (new 2018 requirement at 45 CFR 46.116(f)(3)(iii)). As FDA revises its regulations to harmonize to the extent appropriate and permissible with the Common Rule, we will consider including this new criterion in any waiver provision.

[7] SACHRP's recommendations are available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2014-july-3-letter-attachment-c/index.html and https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-november-2-2016-letter/index.html.

IV. IRB WAIVER OR ALTERATION OF INFORMED CONSENT

Waiver of informed consent for certain FDA-regulated minimal risk clinical investigations will facilitate investigators' ability to conduct studies that may contribute substantially to the development of products to diagnose or treat diseases or conditions, or address unmet medical needs. In light of the Cures Act amendment to the FD&C Act described above, FDA intends to revise its informed consent regulations to add this waiver or alteration under appropriate human subject protection safeguards to the two existing exceptions from informed consent (i.e., in life-threatening situations and for emergency research). However, until FDA promulgates these regulations, we do not intend to object to an IRB[8] approving a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 21 CFR 50.25, or waiving the requirements to obtain informed consent when the IRB finds and documents[9] that:

1. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA does not intend to object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described above. FDA intends to withdraw this guidance after we promulgate regulations to permit a waiver or alteration of informed consent under appropriate human subject protection safeguards consistent with section 3024 of the Cures Act.

V. INQUIRIES ABOUT SPECIFIC CLINICAL INVESTIGATIONS

Sponsors, investigators and IRBs may contact FDA for questions about implementing the recommendations in this guidance for a specific clinical investigation. Questions should be directed to the appropriate Center contact listed below.

Center for Drug Evaluation and Research
Ebla Ali Ibrahim
Office of Medical Policy Initiatives, Office of Medical Policy
301-796-2500 or 301-796-3691
Email: Ebla.Ali-Ibrahim@fda.hhs.gov

[8] An institutional review board (IRB) is defined in 21 CFR 56.102(g) and is subject to the requirements of 21 CFR part 56.

[9] An IRB is required to prepare and maintain adequate documentation of its activities, including actions taken by the IRB, under 21 CFR 56.115.

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