

February 8, 2019

Via Electronic Submission

Ms. Leslie Kux
Associate Commissioner for Policy
Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: ACRO Comment on:
FDA Proposed Rule on Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations (21 CFR Parts 50, 312, and 812)
Docket No. FDA-2018-N-2727

Dear Ms. Kux,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all FDA-regulated clinical investigations worldwide. With more than 130,000 employees engaged in research activities in 114 countries, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO appreciates the FDA's move to implement Sections 3023 and 3024 of the 21st Century Cures Act via this proposed rule. We also welcome this proposed rule as a key step in progress towards harmonization of the differences between the HHS human subject regulations and FDA's human subject regulations. ACRO is providing feedback on the two specific requests from the Federal Register notice: (1) the possible future 5th criterion on biospecimens and (2) the types of FDA-regulated, minimal-risk clinical investigations for which sponsors would anticipate requesting a waiver or alteration of informed consent.

Future harmonization with the 5th criterion of Common Rule is unnecessary, but may be helpful

The Federal Register notice from Thursday, November 15, 2018 notes:

The Common Rule was recently revised (82 FR 7149, January 19, 2017), introducing new terminology and regulatory provisions. Although it retains the same criteria for IRB waiver or alteration of informed consent as were included in the 1991 version of the Common Rule, it 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 requirement at 45 CFR 46.116(f)(3)(iii)). We are proposing to adopt the four criteria from the 1991 version of the Common Rule. At this time, we are not proposing to adopt the new fifth criterion in the revised Common Rule, which has a general compliance date of January 21, 2019; however, we invite comments on this issue.

ACRO does not believe that adoption of this 5th criterion (as a 5th prerequisite) to IRB waiver or alteration of informed consent in minimal-risk FDA-regulated clinical investigations is necessary because such biospecimen research does not meet the FDA definitions of “clinical investigation,” which requires a “human subject” (which must be a human individual).

The FDA defines “clinical investigation” as:

any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. (21CFR50.3(c))

And, FDA defines “human subject” as:

an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. (21CFR50.3(g))

We believe that adoption of the 5th criterion is unnecessary. However, ACRO does recognize that biospecimen research is an area of confusion and controversy, which can be an impediment to research utilizing identifiable personal information or biospecimens. So, inclusion of this criterion as a reason for an IRB waiver may be helpful. Typically, if a sponsor wishes to perform a new clinical investigation to support a drug application on existing data or bio-specimens from a prior clinical investigation -- but did not previously obtain appropriate informed consent from research subjects for the proposed clinical investigation -- this proposed research would not be possible. With this 5th criterion provision, there could be a pathway to conduct the clinical investigation through an IRB waiver.

Instances where sponsors would anticipate requesting a waiver or alteration of informed consent from the IRB for FDA-regulated minimal risk clinical investigations seem rare

ACRO appreciates the FDA’s move to implement Sections 3023 and 3024 of the 21st Century Cures Act via this proposed rule. We also welcome the Agency’s further movement towards harmonization of the differences between the HHS human subject regulations and FDA’s human subject regulations via this proposed rule.

However, it is unclear to us why the current provisions for exception from the general requirements of informed consent are inadequate – namely, (1) in life-threatening situations when certain conditions are met (50.23) or (2) when the requirements for emergency research are met (50.24). We believe the situations in which informed consent is difficult or impossible to obtain in minimal-risk clinical investigations would be



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rare. Many common examples used to illustrate minimal risk research are unlikely to qualify as clinical investigations (e.g., observational studies or post-hoc studies). We do recognize that there may be some that qualify for reduced or waived informed consent, such as the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) to determine the safest dose of oxygen for premature infants. We are unfamiliar with the issues relating to minimal risk device studies and so will defer to others with more expertise in this area.

ACRO thanks the Agency for the opportunity to provide comment on this proposed rule. Please do not hesitate to contact ACRO if we can answer any questions or provide additional details.

Respectfully submitted,

Karen A. Noonan

A handwritten signature in blue ink that reads "Karen A. Noonan".

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