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FDA Consolidates, Revises Informed Consent Guidance; 2018 Common Rule Not Addressed

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Nearly nine years to the day the Food and Drug Administration (FDA) issued a draft "information sheet" on informed consent, the agency published a 66-page final guidance document on the topic—marking the first time since 1998 FDA has comprehensively addressed this bedrock of human subjects research.[1]

The guidance addresses the basics of informed consent—such as the elements of the process—as well as the responsibilities of institutional review boards (IRBs), investigators and FDA. The guidance also includes 16 FAQs on an array of significant topics; electronic informed consent and the sharing of aggregate study results are among them. Unfortunately, the wait goes on for truly current guidance or regulations—to comport with the 2018 revised Common Rule and to offer more harmonization with other agencies that oversee federally funded research. The guidance also draws attention to a number of other rules FDA has not finalized—some of them equally significant.

As compliance officials know, guidance is not the same as regulations, and it is not legally binding, as FDA points out. Still, the guidance will be useful for those conducting or overseeing FDA-regulated drug and device trials, as it brings previous documents on aspects of informed consent together in one place.

FDA acknowledged in the guidance, published Aug. 16, that the 2018 revisions "include significant changes to the provisions regarding informed consent" and said the agency is "currently engaged in notice and comment rulemaking to harmonize its human subject protection." FDA issued two proposed rules—a general one and another on cooperative research—on Sept. 28, 2022. It has not yet issued final rules.

"This guidance supersedes FDA's guidance entitled '*A Guide to Informed Consent*,' issued in September 1998, and finalizes FDA's draft guidance entitled '*Informed Consent Information Sheet*,' issued in July 2014," FDA explained.

RRC asked FDA to highlight some of the changes from its 2014 informed consent information sheet. An official noted FDA "clarified our guidance regarding financial payments to clinical trial participants and the additional costs they may face due to participation."

FDA: Payments Should Be 'Just, Fair'

Regarding payment to subjects, FDA said, "paying research subjects in exchange for their participation is a common and, in general, acceptable practice," although this is "not specifically addressed by FDA regulations [and] may, in some cases, raise difficult questions that should be addressed by IRBs."

FDA recommended IRBs "address how much money research subjects should receive, and for what subjects should receive payment (e.g., their time, inconvenience, discomfort, or some other consideration)."

Moreover, FDA "does not consider reimbursement for reasonable travel expenses to and from the clinical trial site (e.g., airfare, gas, tolls), and associated costs, such as parking and lodging, to raise issues related to coercion

or undue influence. Reimbursement for other expenses may be considered by an IRB on a case-by-case basis, and IRBs should consider whether the proposed remuneration could be an undue influence. Payment for participation in research should be just and fair."

FDA's statements on payment are generally in line with its 2018 information sheet on payment. The agency also addressed the possibility that research subjects may incur "additional expense" while in a trial. Informed consent documents "must explain the added costs" and whether they will be borne by subjects, their insurance "or other reimbursement mechanism." If subjects are to be charged for the investigational drug or device, this also must be included in the informed consent process, FDA said.

Aggregate Results Should Be 'Clear'

The research community has been grappling with the issue of returning results—both aggregate and individual—to trial participants. The HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) developed recommendations on both in 2015; however, like most of its work, the Office for Human Research Protections (OHRP) has not formally adopted or officially published them. The new guidance tiptoes into this topic with an FAQ that asks, "Should subjects be informed of aggregate study results at the completion of a trial?"

In response, FDA gives a qualified "yes," stating it recognizes participants are interested in aggregate results and that it "supports the return of aggregate research results and recommends that they be returned to subjects in a clear and comprehensible manner."

Pointing out that summary results of some trials must be posted on http://www.ClinicalTrials.gov, FDA added that "nothing would prevent an investigator, sponsor, or IRB from informing prospective subjects of the plan to submit such information in an appropriate manner."

The agency noted that "FDA regulations do not directly address the issue of IRB review of return of aggregated results to subjects; however, when return of aggregated results is planned at the time of initial IRB review of the study, or the decision to share results is made after initial IRB approval but while the study is still open with the IRB, then the plan for communicating this information to subjects should be reviewed by the IRB."

If investigators or sponsors choose to share aggregate results "after the study is closed with the IRB, the IRB does not need to review the sponsor's plan to share the aggregate results," according to the guidance, which makes reference to SACHRP, and largely hews to the committee's recommendation on aggregate results.

SACHRP: Some Results May Pose Risks

However, SACHRP made three arguments for—and an equal number against—requiring the IRB to get a look at such plans. The arguments for review include to assure there are no breaches in confidentiality when the results are disclosed; the need to minimize the possibility that participants will "misunderstand or misinterpret the information they receive, and take an inappropriate action. Finally, it is worth questioning whether an IRB's duties to subjects completely end once the study is closed with the IRB. For instance, if there were a breach of confidentiality or new risk information important to the subjects, it is likely that the IRB would feel that it had the authority and the duty to take appropriate actions to protect and inform subjects," SACHRP said in 2015.[2]

Overall, SACHRP concluded that the arguments for review after closure "are not sufficient to make IRB review of return of results a requirement in all cases if the study is closed with the IRB."

But "institutions and sponsors can require IRB review based on internal policies if desired. Furthermore, IRBs can serve as a resource when there are questions about returning results, and in this circumstance can provide

consultation or an opinion without having to reopen the study," SACHRP wrote. As noted, the new guidance makes no mention of the return of individual results. For more of SACHRP's thoughts on this, see https://bit.ly/3OLhy18.

One FAQ addresses how "informed consent [can] be obtained through electronic methods." The agency noted that it "supports the use of electronic processes to obtain informed consent," which can include "use [of] an interactive interface for the informed consent process, which may facilitate the subject's ability to retain and comprehend the information. Furthermore, these electronic processes may also promote timely entry of any electronic informed consent into a study database and facilitate collection of the subject's informed consent from remote locations." In 2016, FDA issued a separate set of FAQs on electronic informed consent. It is available at https://bit.ly/47DNxcw.

Multiple Trials Could Be 'Confusing'

A more unusual FAQ recognizes that there are individuals who enroll in more than one trial at a time and asks if this is allowed.

"FDA generally discourages enrollment in multiple investigations, although there are some circumstances in which co-enrollment may be appropriate (e.g., rare disease studies that are evaluating different aspects of the condition and involvement in one study does not affect the other study)," according to the guidance. "In addition, this recommendation does not apply to certain appropriately designed studies, such as a clinical investigation of a novel drug and a companion in vitro diagnostic device that is essential for the safe and effective use of the drug."

"When appropriate, the risks of participating simultaneously in more than one clinical investigation should be discussed with subjects during the consent process but do not necessarily need to be included in the informed consent form," the guidance states.

Simultaneous enrollment "could increase risks to subjects, particularly because they may be exposed to more than one investigational product for which the safety profile may not be well understood, and there may be potential drug or device interactions. Also, subjects may find it difficult to understand the risks and potential benefits or meet the demands of multiple protocols," FDA said.

Language Issues, Impairment Addressed

The other FAQs ask:

- What are some considerations for enrolling a child into a clinical investigation?
- Are there any additional protections required when enrolling children who are wards of the state?
- What are some considerations for enrolling non-English speaking subjects?
- What process should be followed when it is expected that subjects who do not understand English will be enrolled?
- What process should be followed when the enrollment of subjects who do not understand English is not expected?
- What should be considered when enrolling subjects with low literacy and numeracy?
- What should be considered when enrolling subjects with physical or sensory disabilities?

- What should be considered when enrolling adult subjects with impaired consent capacity?
- Who can serve as a legally authorized representative, and what is their role?
- How should data be handled when an enrolled subject decides to withdraw from a trial?
- What steps should be taken to inform subjects when a study is suspended or terminated?
- Is informed consent required to review patient records?
- How should subjects be informed of new information that may affect their willingness to continue participation in the research?

Rules, Guidance Still to Come

It will be more than a year and perhaps longer before FDA completes rules affecting informed consent.

Before the Common Rule revisions were finalized, Congress passed the 21st Century Cures Act, which amended FDA's legislation to broaden the kinds of minimal risk research that is exempt from IRB review. The 2016 law gave FDA "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," the agency explained in July 2017 guidance.[3]

According to its regulations, however, exemptions for informed consent apply "only in life-threatening situations when certain conditions are met…or when the requirements for emergency research are met."

To implement the law, FDA needs to issue regulations; it issued a proposed rule on this topic in November 2018. The spring regulatory update lists November of this year for publication of the final rule, but such dates are only estimates and are often missed. However, the 2017 guidance was issued in final form.

FDA's two final regulations implementing the 2018 Common Rule requirements and for the use of a single IRB for cooperative research are both estimated to be published in December 2024.

Additionally, neither OHRP nor FDA has finalized the 2011 joint draft guidance on exculpatory language in informed consent; this guidance does not appear on the regulatory update and the new guidance provides no estimate of publication.

1 U. S. Department of Health & Human Services, Food and Drug Administration, Office of Clinical Policy,*Informed Consent, Guidance for IRBs, Clinical Investigators, and Sponsors,* August 2023, https://bit.ly/3sluCmz.
2 U.S. Department of Health & Human Services, Office for Human Research Protections, "Attachment D: Recommendations Regarding Return of General Research Results," last reviewed April 25, 2015, https://bit.ly/3QLE4d0.
3 U. S. Department of Health & Human Services, Food and Drug Administration, Office of Good Clinical Policy,*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*, July 2017, https://bit.ly/3qGEUNG.