Articles

The U.S. Food and Drug Administration (FDA) released a new set of guidelines on August 15, 2023, concerning informed consent (Final Guidance). This new document finalizes the 2014 preliminary version titled "Informed Consent Information Sheet" (Draft Guidance).

This recent update by the FDA is part of their ongoing commitment to updating and enhancing the procedures surrounding clinical trials.

This article highlights the key takeaways from the Final Guidance with a focus on new information. The most substantial changes in the Final Guidance relate to five overarching themes: (1) updating informed consent to modernize administrative processes and improve patient understanding; (2) providing clarity around the roles

each person plays in the informed consent process (3); acknowledging common sponsor practices; (4) accounting for changes in privacy laws and rules relating to researcher financial conflicts of interest; and (5) addressing unique circumstances.

I. Updating Informed Consent To Modernize Administrative Processes and Improve Patient Understanding

The Final Guidance aims to update the informed consent process by incorporating the use of technology and simplifying the consent form approval process. The guidance also addresses the need to improve patient understanding so that patients fully comprehend what it is they are consenting to undergo.

A. Beyond Paper Consent Forms

Citing to its 2016 guidance on Electronic Informed Consent, the FDA recognizes the role of technology in acquiring consent, acknowledging methods beyond traditional paper consent forms. In situations where in-person or electronic consents aren't possible, like during a contagious disease outbreak, a photographed image of the signed consent form can be used as long as it is accompanied by an attestation regarding its authenticity. This flexibility, which likely arose out of the COVID-19 pandemic, may be used, for example, if a quarantined subject signs a paper form and takes a picture of the signed form on their phone and then sends it to the investigator via text or email.

The FDA does note that a solely oral discussion of informed consent through a telephone conversation is insufficient.

B. Simplifying the Consent Form Approval Process

The Final Guidance clarifies that the Institutional Review Board (IRB) does not need to review and approve nonsubstantive changes to consent forms, nor does it need to review versions of the form that are translated into different languages.

The Final Guidance states that nonsubstantive edits, "such as the correction of typographical and spelling errors, and changes in telephone numbers," do not require IRB review and approval. These changes should still be sent to the IRB, but only so that they have current copies of the informed consent form on file.

For translations of consent forms, IRBs can approve "reasonable procedures for ensuring that translations will be prepared by a qualified individual or entity, and that interpretation assistance is available." This is a departure from the Draft Guidance, which recommended that IRBs review and approve "all English and non-English language versions of any consent documents."

C. Communicating With Patients

1. Helping Patients Understand Materials

In the Final Guidance, the FDA emphasizes the importance of using innovative techniques to communicate better with research subjects. For example, tools like pictures, diagrams, videos, and 3D objects can enhance patient understanding. FDA also recommends that investigators provide "reasonable modifications and auxiliary aids and services when necessary to meet the specific needs of the study population," for example, audio recordings of the contents of the consent form or consent forms with enlarged text font.

2. Communicating New Information to Patients

The FDA discusses the need to convey significant new findings to subjects, especially when it affects their participation decision (e.g., protocol changes or new findings related to safety). The responsibility lies with the IRB to decide how and if this new information should be shared. Alternatives like consent addendums or information sheets can be used for communication. Participants should sign these, and a copy should be provided to them. Information that doesn't affect subjects, like the addition of new participants or changes in contact info, does not need to be shared unless it is about risks manifesting after the study. A change in research contact details does not require reconsent, but the new details should be provided to subjects.

II. Increased Clarity Around the Roles Each Person Plays in the Informed Consent Process

The Final Guidance aims to clarify the roles each person plays in the informed consent process by providing instructions relating to (1) the person obtaining the consent, (2) the translator (if applicable), and (3) the witness in cases of a short form consent process.

A. Person Obtaining the Consent

In the Final Guidance, the FDA reminds investigators that, while they can delegate the consent process, the investigator ultimately remains responsible for ensuring valid informed consent has been obtained per 21 CFR part 50. The individual tasked with obtaining consent should be knowledgeable, well trained, and possess relevant credentials. The FDA suggests that person obtaining consent should preferably be a healthcare professional so that they can adequately address questions about study alternatives and other medical questions.

B. Translator

The Final Guidance reemphasizes that if a translator is used, they should be fluent in both English and the subject's language. The FDA notes that a translator might be needed for subsequent study visits to facilitate communication. Acknowledging a common practice that is not permitted, the FDA clarifies that in pediatric research, if the child speaks English but the parent doesn't, the child should not be used as an interpreter for the parent.

C. Witness to the Short Form Consent Process

For subjects who may not understand English or have low literacy, a short form of informed consent that is presented orally can be used. FDA regulations require a witness during this oral presentation. This witness should:

- Be fluent in the language of the presentation.
- Verify the accuracy of the information presented.
- Be unrelated to the research subject.
- Remain independent from the research team.

Given the requirements of the short form, the FDA suggests that translating the full informed consent form might be more efficient in many cases.

D. Legally Authorized Representatives (LAR)

The Final Guidance stresses the need to involve cognitively impaired subjects in consent discussions whenever possible. On this topic, the FDA states: "[w]hile some prospective subjects, such as those with profound

cognitive impairment, will not be able to contribute to the consent decision, others may be able to appoint an LAR, define the limits of their own research participation, or remain actively involved in the decision to enroll and remain enrolled in the research. As such, individuals with impaired consent capacity should be included in the process of consent to the extent possible and consistent with their desires and abilities." Subjects anticipated to have decreasing consent capacity during the study (e.g., in the case of Alzheimer's long-term trials) should consider designating an LAR from the outset. The FDA clarifies that physically- or sensory-disabled individuals do not need an LAR for the consent process unless mandated by local or state laws.

III. Common Sponsor Practices

In the Final Guidance, the FDA acknowledges the existence of sponsor practices that are common in clinical investigations. Specifically, the FDA addresses the use of template consent forms and the involvement of sponsor personnel in study activities.

A. Template Consent Forms

The FDA recognizes that sponsors often distribute template consent forms to study sites. Although not directly mentioned in FDA regulations, sponsors often submit these template forms when applying for an investigational new drug or device exception. Once approved, these templates are provided to institutions and investigators for IRB review. If the FDA has any feedback, sponsors will likely need to modify and redistribute the updated form.

The FDA also noted that, for multicenter investigations, changes to the template form may need to be made to account for local and institutional requirements. If these changes are significant, affecting subjects' rights, safety, or well-being, they should be communicated with all involved parties, including all investigators and their IRBs. This will become less complex if a proposed rule, suggesting the use of a single central IRB for many multicenter studies, is approved.

B. Involvement of Sponsor Personnel

Acknowledging another common practice among sponsors, the FDA notes that sponsor staff, often field engineers, may be present during some research activities related to medical devices. Their role could be to provide technical assistance or document study-related data. The presence and role of these sponsor personnel must be mentioned in the informed consent form. While the FDA acknowledges some level of sponsor involvement in trials, sponsors should be cautious of potential risks and liabilities when their staff interacts directly with research participants.

IV. Changes in the Legal and Regulatory Landscape

A. Privacy Considerations

In the Final Guidance, the FDA reemphasizes the importance of compliance with applicable privacy laws, particularly the Health Insurance Portability and Accountability Act (HIPAA). FDA regulations require that informed consent forms include "[a] statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records." The FDA reminds researchers and institutions that consent forms must detail who will have access to patient records, which typically includes the research team, ethics committee members, and

regulatory agencies. A preliminary review of patient records for preparation of clinical research does not need informed consent. However, even for this preliminary review, certain privacy safeguards, such as those found in the HIPAA Privacy Rule, may be required as applicable. Researchers are advised to be careful when reviewing records for identifying research subjects and to take measures to ensure that all protected health information is handled in a manner that is compliant with HIPAA and institutional policies.

B. Conflicts of Interest

In the Final Guidance, the FDA stresses that financial conflicts, like an investigator having a stake in the product under study or owning part of the sponsoring company, can compromise the well-being of research participants. To maintain transparency, the Final Guidance recommends including any potential financial conflicts in the informed consent form. The form should also detail how any conflicts are being managed. If there is a potential conflict, it is advisable to have a party without a vested interest handle the consent process or to have a neutral third party oversee the process.

IRBs are tasked with deciding if research subjects should be informed about funding sources and any potential financial interests. To act on this recommendation, IRBs should have policies in place that mandate the disclosure of these financial interests. While the FDA does not require these policies, many institutions and IRBs have already adopted them, following existing guidelines from the U.S. Department of Health and Human Services (HHS) and the Public Health Service.

C. Subject Withdrawal From the Trial

The FDA restates in the Final Guidance that data "collected on subjects up to the time of withdrawal from clinical investigations should be retained." This retention is vital to maintain the scientific and ethical validity of the research. Subjects should know that even if they leave a study, the data collected until their departure will still be used and may not be deleted.

This stance by the FDA aligns with guidelines from HHS under HIPAA. Even if a research participant revokes their consent for the use of their protected health information (PHI), data acquired before this revocation can still be used "as necessary to maintain the integrity of the research study," as necessary to incorporate the information as part of a marketing application to the FDA, or as necessary to conduct investigations of scientific misconduct or report adverse events. Research participants should be made aware of this at the outset and at the time at which they initiate withdrawal from the study.

Lastly, if a participant opts out of a clinical study, they should be asked if they wish to withdraw only from the trial interventions while continuing to provide follow-up clinical information or if they wish to withdraw from all participation in the study. If the participant only wishes to withdraw from study interventions, the participant should give informed consent for any follow-up not addressed in the original consent form. This consent should be obtained using a new IRB-approved consent form.

D. Undue Influence

In the Final Guidance, the FDA recognizes that any group can be subject to coercion or undue influence, not just traditionally vulnerable groups like employees or students. The FDA stresses that these pressures can be context-specific, like when consent for extra tissue samples for research is sought just before a surgical procedure. Researchers and institutions should implement policies that guard against undue influence and ensure that potential study participants are able to exercise true and complete freedom of choice when deciding whether or not to participate in a study.

E. Circumstances in Which Consent Is Not Required

The FDA's Final Guidance touches on instances in which informed consent may not be necessary, aside from life-threatening or emergency research scenarios as outlined in their regulations. The FDA clarifies that there may be circumstances in which the FDA may not strictly enforce informed consent rules for previously gathered human specimens used in FDA-regulated diagnostic device studies, as long as these specimens cannot be traced back to individuals. Additionally, the FDA indicates that it will not object to IRBs modifying or omitting certain informed consent elements for specific low-risk clinical studies, as detailed in the FDA's 2017 guidelines on altering or waiving informed consent. It is important to note that the FDA's stance on these matters could evolve, especially with future harmonization with the Common Rule or finalization of the FDA's proposed regulations regarding waiving informed consent.[1]

V. Flexibility in Unique Circumstances

The Final Guidance includes new flexibilities for investigators and sponsors in certain scenarios.

A. Multiple Investigations

While the FDA generally discourages people from participating in more than one study at the same time, in the Final Guidance it acknowledges that there are special circumstances where co-enrollment may be acceptable. Examples include rare disease studies that are evaluating different aspects of a condition and will not interfere with each other. The FDA also states that risks of participating in multiple studies should be discussed during the consent process but do not have to be part of the formal consent form.

B. Indirect Costs

In the Final Guidance, the FDA emphasizes that subjects should be informed of costs not directly related to the clinical procedures, like time off work or child care. This aims to help participants understand the full scope of what their participation might entail.

C. Risks and Benefits in Standard of Care

In the Final Guidance, the FDA recommends that, in certain situations, the most common risks and benefits of the standard of care should be mentioned in the consent form. Included in the Final Guidance (but not the 2014 Draft Guidance) is FDA's recommendation that "[f]or clinical investigations involving the comparison of an investigational product to one or more standards of care, it may be acceptable to describe the most common risks and benefits of the standard(s) of care in the consent form and provide additional information that may be relevant to a particular subject as part of the consent discussion, if appropriate." The FDA defines "medically recognized standard of care" as one supported by peer-reviewed publications or recognized by professional medical societies.

D. Unapproved Uses

The Final Guidance states that if an unapproved use of an FDA-approved drug or device is considered standard of care, it can be included in the consent form in the discussion of appropriate alternative procedures or courses of treatment. However, this should be presented in a factual, nonpromotional manner. If new alternative procedures become available during the study, consent forms and discussions may need to be updated.

VI. Conclusion

In summary, the Final Guidance contains updates, clarifications, and additional details aimed at modernizing and streamlining the informed consent process for all parties involved while simultaneously increasing transparency and understanding for study participants. The FDA intends for the guidance to assist IRBs, clinical investigators, and sponsors in complying with FDA's existing informed consent regulations for clinical investigations. Institutions are advised to familiarize themselves with the guidance and review their internal informed consent processes, policies, and forms to ensure alignment with the Final Guidance. For additional information, please see the FAQ section of the Final Guidance Document.

[1] Protection of Human Subjects and Institutional Review Boards, 87 Fed. Reg. 58,733 (Sep. 28, 2022) (to be codified at 21 C.F.R. Parts 50, 56, and 812); Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations, 83 Fed. Reg. 57,378 (Nov. 15, 2018) (to be codified at 21 C.F.R. Parts 50, 312, and 812).

Authors

LaDale K. George

Partner
LGeorge@perkinscoie.com 312.324.8504

Elizabeth Smith

Associate
ElizabethSmith@perkinscoie.com 737.256.6124

Liana Sulaiman

Associate
LSulaiman@perkinscoie.com 415.344.7172

Explore more in

Emerging Companies & Venture Capital Law Ethics & Compliance Technology Transactions & Privacy Law Healthcare Medical Device Biotechnology & Pharmaceutical