

## Agency Guidance Snapshot: Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors

The Yale Human Research Protection Program (HRPP) has launched the “*Agency Guidance Snapshot*” series. The purpose of the Agency Guidance Snapshots is to highlight recent agency guidance from the Food and Drug Administration (FDA)<sup>1</sup>, Office for Human Research Protections (OHRP), and other federal agencies that specifically impacts Yale University and affiliate stakeholders who conduct or oversee *human subjects research*.

**Please Note:** Yale University does not expect any immediate changes to policies due to this guidance; however, this guidance will be taken into consideration as policies and procedures are reviewed and revised in the future. Yale University may have additional requirements related to the topics covered in this guidance. For more information, please refer to the following Yale University Human Research Protection Program (HRPP) documents located on the HRPP website ([Policies, Procedures, Guidance, and Related Documents](#)) and in the Yale HRPP IRES-IRB Library ([IRES IRB LOGIN](#)): **1) Yale HRPP Policy and Standard Operating Procedure Manual**; **2) Yale HRPP Investigator Manual**; **3) Yale IRB Members and Chairs Manual**; and **4) HRPP Supplemental Guidance Manual**. Please also refer to [University Policies & Procedures](#) and policies published by the various Yale University schools and departments.

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### Overview of Guidance Document:

On August 15, 2023, the U.S. Food and Drug Administration (FDA) issued a new guidance document on informed consent (the “Final Guidance”).<sup>2</sup> This guidance finalizes the draft “Informed Consent Information Sheet” from 2014 (the “Draft Guidance”) and supersedes FDA’s guidance from 1998, “A Guide to Informed Consent.”<sup>3</sup> FDA’s issuance of the Final Guidance follows the Agency’s continuing efforts in recent years to modernize and streamline the clinical trial enterprise. The document is structured to first

<sup>1</sup> FDA Guidance documents represent the Agency’s current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

<sup>2</sup> FDA, Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors (Aug. 2023), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent>, [hereinafter Final Guidance].

<sup>3</sup> FDA, Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors (Draft Guidance: July 2014) [hereinafter 2. Draft Guidance].

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present general guidance on FDA’s regulatory requirements for informed consent and a discussion of the roles of IRBs, clinical investigators, sponsors, and FDA related to informed consent, followed by a series of frequently asked questions.

Several of the more substantial changes are discussed in the following comprehensive summary prepared by Ropes & Gray, LLP, and authored by David Peloquin, Gregory H. Levine and Mark Barnes. The [summary](#) is available to the general public. Key areas of focus are:

- ***Streamlining IRB Review of Informed Consent Forms:*** The Final Guidance highlights certain changes to informed consent forms in ongoing studies that do not require IRB review. These include corrections of typographical and spelling errors, changes in contact information, and translations of consent forms into languages other than English.
- ***Communicating New Information to Subjects:*** The Final Guidance highlights several examples of new information concerning a clinical investigation that do not need to be communicated to previously enrolled subjects. These include most instances in which a subject has completed active participation in the study and instances in which the information is unlikely to affect the subject's willingness to continue in the study.
- ***Investigator Conflicts of Interest:*** Like the Draft Guidance, the Final Guidance advises investigators to consider the effects of potential conflicts of interest on clinical investigations. The Final Guidance adds that IRBs have final responsibility for determining whether the informed consent process should include disclosure of investigators' financial conflicts of interest. This suggests that IRBs should maintain processes to require disclosures of financial interests to the IRB.
- ***Template/Model Informed Consent Forms:*** The Final Guidance addresses the reality that template informed consent forms are often provided to study sites by the sponsor. FDA provides recommendations for how changes to the template forms suggested by FDA during the IND or IDE review process should be communicated to investigators and how site-specific, substantive changes to the template informed consent form should be communicated to other study sites in a multisite study.
- ***Sponsor-Subject Interactions:*** In the Final Guidance, FDA addresses a scenario in which sponsor personnel may be present to observe certain study procedures. FDA states that the presence of sponsor personnel should be disclosed to subjects during the informed consent process.
- ***Enrollment in Multiple Investigations:*** As in the Draft Guidance, FDA discourages concurrent enrollment of a subject in more than one clinical investigation. However, in the Final Guidance, FDA recognizes that a subject's enrollment in more than one study at a time could be appropriate in certain circumstances. These include rare disease trials that evaluate different aspects of a condition or a clinical investigation of a novel drug and a companion in vitro diagnostic device.

Additional revisions to the Final Guidance may be needed if FDA finalizes its proposed regulations to harmonize the FDA regulations with those of the Federal Policy for the Protection of Human Subjects (i.e., the “Common Rule”) and its proposed regulation to permit a waiver of informed consent by IRBs.<sup>4</sup> (These

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<sup>4</sup> 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);

matters are discussed in greater detail in a previous Ropes & Gray alert.<sup>5)</sup>

## **Key Points for IRB/HRPP Staff, Chairs, Members, and Sponsors:**

### **1. Modernizing Informed Consent**

#### **a. Facilitating subject understanding of the informed consent materials**

In the Final Guidance, FDA encourages researchers to use innovative methods and technologies in informed consent to aid in communicating and educating research subjects. In accordance with 21 CFR Parts 50 and 56, the IRB is responsible for reviewing informed consent materials and ensuring the adequacy and appropriateness of the wording of the consent materials. Acknowledging that a lengthy informed consent form may not always communicate information to subjects effectively, FDA stated in the Draft Guidance that pictures and diagrams “may be used to improve understanding of medical terms or how an investigational product functions.”<sup>6</sup> The Final Guidance adds to this point, noting that there might be “other visual aids” that can be used for this purpose<sup>7</sup>, suggesting that video or three-dimensional objects may be used to facilitate communication during the informed consent process. For subjects with physical or sensory disabilities, FDA 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.<sup>8</sup>

#### **b. Alternatives to paper consent forms**

FDA acknowledges in the Final Guidance that new technologies can be used to obtain consent through mechanisms other than paper consent forms, citing to its guidance from 2016 on Electronic Informed Consent.<sup>9</sup> FDA clarifies that despite the flexibility of investigators to use methods other than paper consent forms, a purely oral discussion of informed consent is not sufficient, explaining that “[w]hen written documentation of informed consent is required, informed consent cannot be obtained and documented by oral communication through the telephone alone.”<sup>10</sup>

Doubtless informed by FDA's experience with the COVID-19 pandemic, the Final Guidance also accounts for situations in which neither in-person nor electronic consent is an option. The Final Guidance states that “[i]n situations in which the signed document cannot be retrieved . . . and electronic consent is not available, it is acceptable to retain for the study records a photographic image of the signed consent form along with an attestation by the person entering the photograph into the study records that states how the photograph was obtained and that it is a photograph of the informed consent form signed by the subject.”<sup>11</sup> This flexibility may be useful, for example, if a subject is isolated with an infectious disease, signs a paper form while in isolation, and takes a picture of the signed form on their smartphone, which is then texted to the

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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).

<sup>5</sup> Ropes & Gray LLP, Harmonizing the Common Rule and U.S. Food and Drug Administration Human Subjects Research Regulations (Sep. 30, 2022),

<https://www.ropesgray.com/en/newsroom/alerts/2022/september/harmonizing-the-common-rule-and-us-food-and-drug-administration-human-subjectsresearch-regulations>).

<sup>6</sup> Draft Guidance at 22.

<sup>7</sup> Final Guidance at 32.

<sup>8</sup> Final Guidance at 51.

<sup>9</sup> Final Guidance at 25; FDA, Use of Electronic Informed Consent Question and Answers: Guidance for Institutional Review Boards, Investigators, and Sponsors (Dec. 2016), <https://www.fda.gov/media/116850/download>.

<sup>10</sup> Final Guidance at 26.

<sup>11</sup> *Id.*

investigator.

**c. Streamlining certain administrative steps in IRB review of consent forms**

FDA regulations are silent regarding the types of changes to an informed consent form that must be reviewed by an IRB.<sup>12</sup> As a result, institutions and IRBs sometimes require that the IRB review and approve all changes made to an informed consent form. FDA clarifies in the Final Guidance that the IRB does not need to review and approve certain administrative changes to consent forms or the translated versions of an informed consent form.

The Final Guidance provides that administrative changes “such as the correction of typographical and spelling errors, and changes in telephone numbers....do not require formal review and approval.”<sup>13</sup> Such changes “should be sent to the IRB so that they have current copies of the informed consent form on file.”<sup>14</sup>

With respect to translated versions of informed consent forms, the Final Guidance provides that IRBs can approve “reasonable procedures for ensuring that translations will be prepared by a qualified individual or entity, and that interpretation assistance is available.”<sup>15</sup> This differs from the approach articulated in the Draft Guidance, which recommended that IRBs review and approve “all English and non-English language versions of any consent documents.”<sup>16</sup> FDA's Final Guidance appears to acknowledge that IRBs in the United States often have limited capabilities to review consent forms in languages other than English and thus frequently ask investigators to submit documentation indicating that the consent forms are accurately translated.

**d. Streamlining communication of new information with subjects**

In the Final Guidance, FDA provides an in-depth discussion regarding communicating to subjects “significant new information (e.g., protocol changes, new findings related to safety) . . . that could affect a subject's willingness to continue their participation in the clinical trial.”<sup>17</sup> In such situations, the IRB is responsible for determining (1) “whether currently enrolled subjects should be provided with the new information and given an opportunity to affirm their willingness to continue in the research”; and (2) “whether the investigator should provide currently enrolled subjects with the new information either with the revised informed consent document or an alternative method . . . .”<sup>18</sup>

FDA also provides certain clarifications about the means of communicating new information to subjects and accounting for subject withdrawal.

- **Consent Addendums and Information Sheets:** Alternative methods of communication “such as a consent addendum or information sheet” can be used to communicate significant new information to subjects. In such cases “the enrolled subject should be asked to sign and date the consent addendum or information sheet” and “a copy of the signed and dated consent addendum or information sheet [should] be provided to the subject.”<sup>19</sup>
- **Subjects Unaffected by the Information:** Researchers do not need to share significant new information with (1) “subjects who have completed their active participation in the study . . . unless

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<sup>12</sup> See generally, 21 CFR Parts 50, 56.

<sup>13</sup> Final Guidance at 33.

<sup>14</sup> Final Guidance at 34.

<sup>15</sup> Final Guidance at 46.

<sup>16</sup> Draft Guidance at 31.

<sup>17</sup> Final Guidance at 60.

<sup>18</sup> *Id.*

<sup>19</sup> Final Guidance at 60-61.

the new information relates to risks that may manifest after such participation” and (2) “subjects who are still actively participating . . . when the change will not likely affect their decision to continue in the study (e.g., an increase in the number of study subjects).”<sup>20</sup>

- **Change in Contact Information:** Reconsent of subjects is not required upon a change of contact information for the individual(s) whom the subject may contact for questions about research subject rights or to report a research-related injury. New contact information “may be given to the subject during a visit or mailed to the subject in an envelope to protect the subject’s privacy.”<sup>21</sup>

These points of clarification will likely aid investigators, institutions, and IRBs to streamline their processes for communicating with study subjects.

## 2. Acknowledging the Broader Legal and Regulatory Environment

FDA's Final Guidance acknowledges two key areas: the *evolving complexities in privacy laws* and the *changing rules related to researcher financial conflict of interests*.

### a. Privacy considerations

As with the Draft Guidance, in the Final Guidance, FDA continues to emphasize the role of privacy laws such as HIPAA, stating that “sponsors and investigators will need to comply with all applicable requirements under HIPAA and other applicable laws . . . .”<sup>22</sup> 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.”<sup>23</sup>

Researchers often need access to subject protected health information (“PHI”) throughout the course of the clinical trial, which generally requires authorization from subjects as set forth in the HIPAA Privacy Rule.<sup>24</sup> For researchers and institutions, it is crucial that the consent forms and HIPAA authorization forms comprehensively specify the parties that might later have access to the records.

In the Final Guidance, FDA emphasizes that there might be several parties who require access to the patient records, such as “the study sponsor, the research team, regulatory agencies, and/or ethics committee members,” and that this information should be communicated to subjects during the informed consent process.<sup>25</sup>

In the Final Guidance, FDA also restates its position from the Draft Guidance that a “preliminary review of the patient's record and recording of limited information is considered preparation for a clinical investigation, does not fall within the definition of a clinical investigation, and, therefore, does not require informed consent.” However, FDA also notes that “other steps necessary to safeguard the privacy and confidentiality of the patient's information in these records may be required (e.g., under the HIPAA Privacy and Security Rules and/or institutional policies).”<sup>26</sup> This portion of the guidance illustrates the importance of taking a holistic approach to evaluating study subject recruitment activities, as under HIPAA the review

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<sup>20</sup> Final Guidance at 61.

<sup>21</sup> Final Guidance at 18.

<sup>22</sup> Final Guidance at 58.

<sup>23</sup> 21 CFR § 50.25(a)(5).

<sup>24</sup> See 45 CFR § 164.508.

<sup>25</sup> Final Guidance at 16.

<sup>26</sup> Final Guidance at 58-59.

of study records to identify research subjects would need to fit within one of HIPAA's pathways for the use and disclosure of PHI for research purposes, such as a review preparatory to research or an IRB waiver of authorization.

#### **b. Financial conflicts of interest**

FDA maintains regulations and guidance pertaining to disclosure to FDA of investigator financial interests.<sup>27</sup> In the Final Guidance, FDA further comments on conflicts of interest from an informed consent perspective, noting that financial conflicts of interests (such as a researcher's proprietary interest in the investigational product being studied or ownership interest in the sponsor) can negatively impact the rights and welfare of research subjects.

The Final Guidance advises that investigators should consider including information in the informed consent form regarding any investigator financial interests that could affect the research as well as details of any associated conflict management plan.<sup>28</sup> It also notes that investigator conflicts of interest may militate in favor of having an individual without a conflict perform the consent process or using independent monitoring of the consent process. The Final Guidance elaborates that “IRBs have the final responsibility of determining whether subjects should be provided with information regarding the source of funding, funding arrangements, or financial interests of parties involved in the clinical investigation as part of the informed consent process.”<sup>29</sup> While not stated expressly in the Final Guidance, in order for IRBs to follow this recommendation, they would need to establish policies requiring disclosure of investigator financial interests to the IRB. Such policies are not a requirement set forth in FDA regulations; however, many institutions and central IRBs already have such policies in place to follow U.S. Department of Health and Human Services (“HHS”) 2004 guidance on financial conflicts of interest and to facilitate compliance with the Public Health Service regulations on conflicts of interest.<sup>30</sup>

#### **c. Withdrawal of subjects**

In the Final Guidance, FDA maintains its position that subject data “collected on subjects up to the time of withdrawal from clinical investigations” should be retained.<sup>31</sup> FDA emphasizes that removal of records upon a subject's withdrawal “would undermine the scientific validity, and therefore the ethical integrity” of a study.<sup>32</sup> FDA notes that subjects should be advised in the consent document that the data collected up until the point of their withdrawal will remain part of the study database and may not be removed.

FDA's position here is consistent with that taken in guidance issued by HHS under HIPAA, which provides that upon a research subject's revocation of their authorization for use and disclosure of PHI, a covered entity may continue to use and disclose PHI obtained prior to the time of revocation “as necessary to maintain the integrity of the research study,” including to account for the subject's withdrawal from a research study, as necessary to incorporate the information as part of a marketing application submitted to FDA, or as necessary to conduct investigations of scientific misconduct or report adverse events.<sup>33</sup>

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<sup>27</sup> 21 C.F.R. Part 54; FDA, Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators (Feb. 2013),

<https://www.fda.gov/media/85293/download>.

<sup>28</sup> Final Guidance at 29, 31.

<sup>29</sup> Final Guidance at 37 (citing 21 CFR §§ 56.109, 56.111(a)(4)-(5)).

<sup>30</sup> See HHS, Financial Conflict of Interest: HHS Guidance (2004), <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest>

</index.html>; 42 C.F.R. Part 50, Subpart F – Promoting Objectivity in Research.

<sup>31</sup> Final Guidance at 55.

<sup>32</sup> *Id.*

<sup>33</sup> See HHS, HIPAA FAQ# 316, available at <https://www.hhs.gov/hipaa/for-professionals/faq/316/if-a-research-subject-revokes-authorization-can-a-researcher-continue-using-information-obtained/index.html>.



FDA further clarifies that if subjects withdraw from a clinical investigation, they should be asked if they wish to withdraw only from investigational interventions while continuing to provide follow-up clinical information. If the withdrawal is limited to study interventions, the subject should be asked to provide informed consent for any follow-up not addressed in the original consent document using a new IRB-approved consent document.<sup>34</sup>

#### **d. Vulnerability to coercion or undue influence**

FDA acknowledges in the Final Guidance that coercion and undue influence can affect any population and not only certain subject populations, such as employees or students, that have traditionally been seen as vulnerable to coercion or undue influence.<sup>35</sup> FDA emphasizes that coercion and undue influence may be situational, such as if informed consent for collection for research purposes of additional tissue samples during surgery is obtained immediately before the surgery.

#### **e. Instances in which consent is not required**

FDA discusses in the Final Guidance circumstances in which informed consent is not required beyond the circumstances of life-threatening situations and emergency research that are contemplated expressly in FDA regulations.<sup>36</sup> The Final Guidance notes that FDA continues to exercise enforcement discretion regarding informed consent when human specimens that were previously collected and are not individually identifiable are used for FDA-regulated in vitro diagnostic device investigations.<sup>37</sup> FDA also reiterates that it does not intend to object to IRBs approving consent procedures that do not include some, or that alter, some or all of the elements of informed consent set forth in 21 CFR Section 50.25 for certain minimal risk clinical investigations under the circumstances described in FDA's 2017 guidance on waiver or alteration of informed consent.<sup>38</sup> This guidance is discussed in more detail in an earlier Ropes & Gray alert.<sup>39</sup> As noted earlier, FDA's position in these areas might be subject to further changes upon FDA issuing a final rule on harmonization with the Common Rule or finalization of FDA's proposed rule on waiver of informed consent.<sup>40</sup>

### **3. Distinct Roles in Clinical Trials**

FDA highlights throughout the Final Guidance the roles played by different types of individuals in the informed consent process. Specifically:

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<sup>34</sup> Final Guidance at 55.

<sup>35</sup> Final Guidance at 7.

<sup>36</sup> 21 C.F.R. § 50.23; 21 C.F.R. § 50.24.

<sup>37</sup> Final Guidance at 4, n.12; *see also* FDA, Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable: Guidance for Sponsors, Institutional Review Boards, and Food and Drug Administration Staff (Apr. 2006), <https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/guidance-informed-consent-in-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not>.

<sup>38</sup> Final Guidance at 6; *see also* FDA, 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 (Jul. 2017), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-waiver-or-alteration-informed-consent-clinical-investigations-involving-no-more-minimal-risk>.

<sup>39</sup> Ropes & Gray, FDA Issues Immediately Effective Guidance Allowing Waiver of Informed Consent for Minimal Risk Research, <https://www.ropesgray.com/en/newsroom/alerts/2017/07/fda-issues-immediately-effective-guidance-allowing-waiver-of-informed-consent>.

<sup>40</sup> 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).

- **Individual Obtaining Consent:** FDA provides in the Final Guidance that the consent process may be delegated by the investigator to another party. FDA reiterates, however, its long-standing position that even if the task of obtaining consent is delegated, “the investigator remains responsible for ensuring that legally effective informed consent is obtained for all subjects in accordance with 21 CFR part 50” and the individual obtaining consent must be “knowledgeable” and “have the appropriate training and credentials.”<sup>41</sup> In the Final Guidance, FDA adds that this individual must also “be able to address any questions or concerns the subject may have about the study and/or alternative procedures or courses of treatment, if any, that might be advantageous to the subject.”<sup>42</sup> FDA’s reference to “credentials” and the ability to discuss “alternative procedures or courses of treatment” suggests that FDA might expect that depending on the nature of the study and likely questions from subjects, the individual obtaining consent should be a health care professional, as opposed to a research coordinator who lacks training as a health care professional.
- **Translator:** FDA provides that when a translator is used during the consent process, “[t]he translator should be fluent in both English and in the subject’s language” and that “[i]t may be appropriate to have a translator available for all subsequent study visits to relay information between the subject and study personnel.”<sup>43</sup> FDA also emphasizes that in the case of pediatric research where the research subject speaks English but the parent providing parental permission does not, “[t]he child who will be participating in the research should not be used as an interpreter for the parent, even if the child is fluent in English and may be able to assent.”<sup>44</sup>
- **Witness to the Short Form Consent Process:** A short form informed consent document stating that the elements of informed consent have been presented orally to the subject is often used for subjects who do not understand English or who have low literacy. FDA regulations require that when such a short form is used, a witness must be present for the oral presentation and sign both the short form and a written summary of what is said to the subject.<sup>45</sup> The Final Guidance provides several recommendations for witnesses, including that the witness (1) be “fluent in the language of the oral presentation”; (2) “have sufficient proficiency in the language of the oral presentation to be able to attest to the information that was . . . presented orally to the prospective participant”; (3) not be related to the research subject; and (4) be independent from the research team (such as “clinical staff not involved in the research,” a “patient advocate,” or “independent interpreter”).<sup>46</sup> Given these requirements, FDA notes that “[d]ue to the additional requirements of having a witness and providing a written summary of the consent discussion, use of the short form may not ease or expedite the consent process.”<sup>47</sup> This suggests that FDA believes that in many cases, translation of the full informed consent form may be more efficient than relying on the short form consent process.
- **Legally Authorized Representatives:** FDA also emphasizes the importance of including cognitively impaired individuals in the informed consent discussions to the extent possible and giving them the opportunity to designate a legally authorized representative (“LAR”). FDA states: “While 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

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<sup>41</sup> Final Guidance at 36.

<sup>42</sup> *Id.*

<sup>43</sup> Final Guidance at 49.

<sup>44</sup> Final Guidance at 42.

<sup>45</sup> 21 C.F.R. § 50.27(b)(2).

<sup>46</sup> Final Guidance at 29, 49.

<sup>47</sup> Final Guidance at 29.



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.”<sup>48</sup> For potential subjects who have capacity to provide consent at the beginning of the study but are “expected to become less capable of providing continued consent as the research progresses (e.g., a long-term clinical trial for Alzheimer’s), consideration should be given at the start of the trial to having subjects designate an individual to serve as their LAR.”<sup>49</sup> FDA clarifies in the Final Guidance that the enrollment of individuals with “physical or sensory disabilities . . . does not require a LAR to be involved with the informed consent process or to sign the consent document unless required by State or local law.”<sup>50</sup>

#### 4. Sponsor Practices

Notable in the FDA Final Guidance is FDA’s acknowledgement of certain sponsor practices that are common in clinical investigations – specifically, the use of template consent forms prepared by the sponsor and the involvement of sponsor personnel in certain study activities.

- **Template/Model Informed Consent Forms:** FDA’s Final Guidance acknowledges the sponsor practice of distributing template consent forms to study sites, a practice that is not expressly contemplated by FDA regulations. The model consent form is often submitted to FDA with an investigational new drug or investigational device exception application. This template model consent form is then distributed to the institution/investigators for submission to and review by the applicable IRB. The Final Guidance states that if FDA has comments directed to the sponsor, then “[a] modified model consent form reflecting the changes may be used to convey the necessary edits.”<sup>51</sup> FDA also notes that in the case of multicenter studies “it may be more efficient to share the changes with the sites using a modified model consent form, when appropriate.”<sup>52</sup>

Additionally, FDA notes that for multicenter investigations, modifications may need to be made to the consent form to reflect local and institutional requirements. FDA states that when local IRBs require substantive modifications to consent forms, such as changes that affect the rights, safety, or welfare of the subjects, the sponsor should share the revisions with all investigators and their IRBs.<sup>53</sup> The potential for such changes will be minimized if the FDA’s proposed rule requiring that a single, central IRB be used for much multicenter research is finalized in its current form.<sup>54</sup>

- **Involvement of Sponsor Personnel:** The Final Guidance also addresses the presence of sponsor personnel during certain research activities, requiring that this practice be disclosed in the informed consent form. It states that “Sponsor personnel (usually a field engineer) may be present during the procedure and/or follow-up visits for some medical device studies. These individuals may provide technical support and/or record study-related information for the test article. If sponsor personnel will be present during the procedure or follow-up, or if the activities of the sponsor personnel directly affect the subject, those activities should also be described in the informed consent form.”<sup>55</sup>

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<sup>48</sup> Final Guidance at 53.

<sup>49</sup> Final Guidance at 54.

<sup>50</sup> Final Guidance at 51.

<sup>51</sup> *Id.*

<sup>52</sup> *Id.*

<sup>53</sup> *Id.*

<sup>54</sup> Institutional Review Boards; Cooperative Research, 87 Fed. Reg. 58,752 (Sep. 28, 2022) (to be codified at 21 C.F.R. Part 56).

<sup>55</sup> Final Guidance at 39.

While the Final Guidance notes that FDA accepts certain sponsor involvement in clinical trials, we note that sponsors should be cognizant of the potential risks and liabilities associated with sponsor personnel interacting with research subjects directly. These considerations are discussed in greater detail by Ropes & Gray LLP in a 2021 alert addressing the HHS Secretary's Advisory Committee on Human Research Protections recommendations on interactions between clinical trial sponsors and clinical trial subjects.<sup>56</sup>

## 5. Increasing Flexibility for Unique Circumstances

FDA also addresses new flexibilities for sponsors and investigators in certain areas.

- ***Enrollment in Multiple Investigations:*** In the Final Guidance, FDA restates its position that “FDA generally discourages enrollment in multiple investigations” but adds that “there are some circumstances in which co-enrollment may be appropriate.” These situations include studies involving “rare disease studies that are evaluating different aspects of the condition and involvement in one study does not affect the other study” or “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.”<sup>57</sup> FDA also clarifies that “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.”<sup>58</sup>
- ***Indirect Costs Related to Study Participation:*** FDA provides that subjects should be made aware of costs and risks of trial participation that are not directly related to procedures performed in the clinical trial. The Final Guidance emphasizes the importance of communicating indirect costs such as “time off from work, child or elder care, or transportation costs...to enable subjects to appreciate how much time they may need to take away from work, child care, or elder care.”<sup>59</sup>
- ***Risks in and Benefits in Standard of Care:*** While standard of care procedures are often not considered risks of a study and thus the risks of such procedures are not discussed in the informed consent process, the Final Guidance recognizes that it could be appropriate in certain circumstances to describe the most common risks and benefits related to standard of care. 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.”<sup>60</sup> In footnotes, FDA elaborates that it would consider “medically recognized standard of care to be one evidenced by publication in a peer reviewed journal as a generally recognized standard of care or recognition by a professional medical society (e.g., in a clinical guideline).”<sup>61</sup>

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<sup>56</sup> Ropes & Gray LLP, New SACHRP Recommendations on Interactions among Sponsors, Clinical Trial Sites, and Study Subjects (May 5, 2021), <https://www.ropesgray.com/en/newsroom/alerts/2021/may/new-sachrp-recommendations-on-interactions-among-sponsors-clinical-trial-sites-and-studysubjects>.

<sup>57</sup> Final Guidance at 54.

<sup>58</sup> Final Guidance at 56.

<sup>59</sup> Final Guidance at 21.

<sup>60</sup> Final Guidance at 11, 13.

<sup>61</sup> Final Guidance at 11, n.25.

- ***Unapproved Uses Consistent with Standard of Care:*** The Final Guidance recognizes that use of a drug or device in a manner that deviates from its approved use can in certain cases be represented in consent forms as consistent with standard of care in the discussion of appropriate alternative procedures or courses of treatment.<sup>62</sup> Specifically, FDA states: “When describing in the consent form an unapproved use or treatment regimen of an approved or cleared drug or device that the sponsor markets, and such use or treatment regimen is a part of the medically recognized standard of care, the consent form can provide factual information concerning the unapproved use or treatment regimen of the drug or device.”<sup>63</sup> FDA continues to emphasize in the Final Guidance that “information should not be presented in a promotional manner..” and that “[i]f additional alternative procedures or courses of treatment become available during the course of the clinical investigation, the informed consent discussion and documents may need to be updated.”<sup>64</sup>

## 6. Take-Away Points

The Final Guidance illustrates a continuing trend toward modernization of clinical research through adoption of risk-based positions that attempt to reduce administrative burden while maintaining protections for human subjects. FDA also provides increased guidance on how new technologies can be incorporated into the informed consent process and the interaction between FDA regulations and other bodies of law, including HIPAA and standards for financial conflicts of interest.

Sponsors, institutions, IRBs, and investigators can expect additional changes to FDA's informed consent regulations and guidance upon FDA issuing the final rule on harmonization with the Common Rule and the final rule on waiver of informed consent.

**For more related information, please see the following links to additional resources:**

- [FDA Guidance Documents](#)
- [WCG Regulatory Compliance: What You Should Know About FDA Final Informed Consent Guidance](#)
- [PRIM&R Ampersand: Guidance Document Summary: Unpacking FDA’s Guidance Document on Informed Consent](#)

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<sup>62</sup> Final Guidance at 14.

<sup>63</sup> *Id.*

<sup>64</sup> *Id.*