Informed Consent

Guidance for IRBs, Clinical Investigators, and Sponsors

U.S. Department of Health and Human Services

Food and Drug Administration

Office of Clinical Policy

Center for Drug Evaluation and Research

Center for Biologics Evaluation and Research

Center for Devices and Radiological Health

August 2023

Good Clinical Practice

Contains Nonbinding Recommendations

Informed Consent

Guidance for IRBs, Clinical Investigators, and Sponsors

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create 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 guidance is intended to assist institutional review boards (IRBs), clinical investigators, and sponsors in complying with FDA's informed consent regulations for clinical investigations. 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supersedes FDA's guidance entitled "*A Guide to Informed Consent,*" issued in September 1998, and finalizes FDA's draft guidance entitled "*Informed Consent Information Sheet*," issued in July 2014. This document is structured to first 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.

In a final rule published on January 19, 2017, the Department of Health and Human Services (HHS) and other federal departments and agencies revised the Federal Policy for Protection of Human Subjects. The final rule became effective in 2018 (codified for HHS at 45 CFR 46, subpart A; "the 2018 Common Rule").[2, 3] The 2018 Common Rule sets forth requirements for the protection of human subjects involved in research that is conducted or supported by federal departments or agencies that have adopted the Common Rule. The revisions include significant changes to the provisions regarding informed consent. FDA is currently engaged in notice and comment rulemaking to harmonize its human subject protection

[1] This guidance document was developed by the Office of Clinical Policy (OCLiP), in coordination with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Drug Evaluation and Research (CDER).

[2] 82 FR 7149, January 19, 2017; https://www.govinfo.gov/content/pkg/FR-2017-01-19/pdf/2017-01058.pdf. In this guidance, this final rule will be referred to as the "2018 Common Rule"

[3] All references to the Code of Federal Regulations (CFR) throughout this document can be found at www.ecfr.gov.

regulations and the 2018 Common Rule to the extent practicable and consistent with other statutory provisions.[4] This guidance does not address possible future changes to the FDA's informed consent regulations that may be developed as part of our harmonization efforts. FDA may revise this guidance document in the future to reflect any such changes and/or to address questions the Agency receives regarding informed consent.

FDA's informed consent requirements are set forth in FDA's regulations on Protection of Human Subjects (21 CFR part 50). These regulations apply to clinical investigations regulated by FDA.[5, 6] Throughout this document we primarily provide guidance related to the requirements described in 21 CFR part 50; however, where appropriate we will describe additional regulations pertaining to informed consent found in FDA's regulations on Investigational New Drug Applications (21 CFR part 312) and Investigational Device Exemptions (21 CFR part 812). The informed consent requirements in FDA regulations are not intended to preempt any applicable Federal, State, or local laws that require additional information to be disclosed for informed consent to be legally effective (21 CFR 50.25(d)). If a clinical investigation[7] as defined at 21 CFR 50.3(c) is conducted or supported by HHS then the study may additionally be subject to 45 CFR part 46. Where the regulations differ, the regulations that offer the greater protection to human subjects should be followed.[8]

In general, 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

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[4] On September 28, 2022, FDA issued proposed rules to harmonize certain provisions of 21 CFR parts 50 and 56 with the 2018 Common Rule to the extent practicable and consistent with other statutory provisions (see 87 FR 58733 at https://www.federalregister.gov/documents/2022/09/28/2022-21088/protection-of-human-subjects-and-institutional-review-boards, and 87 FR 58752 at https://www.federalregister.gov/documents/2022/09/28/2022-21089/institutional-review-boards-cooperative-research).

[5] 21 CFR part 50 "applies to all clinical investigations regulated by the [FDA] under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the [FDA], including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products." (21 CFR 50.1)

[6] IRB authority and responsibilities for reviewing informed consent forms are set forth in 21 CFR part 56.

[7] In this guidance document, the terms clinical investigation, study, research, and trial are used interchangeably

[8] See FDA "Guidance for Sponsors, Investigators, and Institutional Review Board; Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations" at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/impact-certain-provisions-revised-common-rule-fda-regulated-clinical-investigations.

of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. SUMMARY OF THE CONSENT PROCESS

To many, the term *informed consent* is mistakenly viewed as synonymous with obtaining a subject's signature on the consent form;[9] however, obtaining documentation of a subject's informed consent is only part of the consent process. Informed consent involves providing a prospective subject, or their legally authorized representative (LAR), with adequate information to allow for an informed decision about participation in the clinical investigation prior to enrollment. Informed consent also involves facilitating the prospective subject's understanding of the information, providing adequate opportunity for the prospective subject to ask questions and to consider whether to participate, obtaining the prospective subject's voluntary agreement to participate prior to enrollment, and continuing to provide information as the clinical investigation progresses or as the enrolled subject or situation requires.[10]

Except as provided in 21 CFR 50.23 and 50.24,[11] (see section III.A.1, "Exceptions to Informed Consent"), no investigator may involve a human being as a subject in FDA-regulated research unless the investigator has obtained the legally effective informed consent of the subject or the subject's LAR (21

[9] In this guidance document, the terms informed consent form and informed consent document are used interchangeably.

[10] See 21 CFR 50.20.

[11] FDA has issued a proposed rule that, if finalized, would allow an exception from the requirement to obtain informed consent when a clinical investigation poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of human subjects. 83 FR 57378, November 15, 2018. This proposed rule would implement new authorities provided in the 21st Century Cures Act. In the interim, FDA has issued guidance regarding IRB waiver or alteration of informed consent for certain clinical investigations involving no more than minimal risk. See FDA "Guidance for Sponsors, Investigators, and Institutional Review Boards; IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-waiver-or-alteration-informed-consent-clinical-investigations-involving-no-more-minimal-risk.

CFR 50.20).[12] To be legally effective, the informed consent process must satisfy the general requirements under 21 CFR 50.20 and include the relevant elements of informed consent described at 21 CFR 50.25 (see section III, "FDA Informed Consent Requirements and Discussion").

FDA considers advertising used to recruit subjects into the clinical trial to be the start of the ongoing consent process, and the information provided in any online or hard copy recruitment materials should be consistent with the informed consent document. Generally, FDA recommends that any advertisement to recruit subjects be limited to the information the prospective subjects need to determine their interest and potential eligibility. The FDA information sheet "Recruiting Study Subjects" includes information regarding scripts for those who will interface with subjects to determine basic eligibility.[13]

Once a prospective subject is identified, and before research activities requiring prior consent occur, a person knowledgeable about the clinical investigation and capable of answering questions raised by the prospective subject should conduct a consent discussion. The consent discussion and the consent form must contain information to allow prospective subjects to make an informed decision about participation in a clinical investigation and provide an opportunity for prospective subjects to ask questions about the clinical investigation and the information in the consent document (see section III, "FDA Informed Consent Requirements and Discussion") (21 CFR 50.20 and 21 CFR 50.25).[14] The consent form serves several purposes, including helping to ensure that prospective subjects receive the required information, providing a "take home" reminder of the elements of the clinical investigation, providing contact information in case additional questions or concerns arise, and documenting prospective subjects' voluntary agreement to participate as well as the date of their agreement.

The informed consent process is an ongoing exchange of information throughout a subject's participation in a clinical trial and does not end after the consent form is signed. For example, if new safety

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[12] As described in guidance, FDA intends to exercise enforcement discretion, under certain circumstances, with respect to its current regulations governing the requirement for informed consent when human specimens are used for FDA-regulated *in vitro* diagnostic (IVD) device investigations. See "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", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-informed-consent-vitro-diagnostic-device-studies-using-leftover-human-specimens-are-not

[13] See the FDA Information Sheet "Recruiting Study Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recruiting-study-subjects, for further information.

[14] The regulations allow use of a "short form" consent form when the elements of informed consent are presented orally to the subject (21 CFR 50.27(b)(2)). For a discussion of the short form written consent, see section III.E.4.b, "Short Form."

information or protocol changes occur during the conduct of the study, additional information may need to be given to the subject, and/or the subject may need additional opportunities to ask questions and receive answers throughout the clinical investigation (see section III.C.5, "Providing Significant New Findings to Subjects," and Frequently Asked Question #16).

III. FDA INFORMED CONSENT REQUIREMENTS AND DISCUSSION

The informed consent process and consent form must meet the general requirements of 21 CFR 50.20, and must include the basic elements of informed consent required by 21 CFR 50.25(a) (when used, a short form written consent document states that the elements of informed consent required by 21 CFR 50.25 have been presented orally; see section III.E.4.b "Short Form" for more details). If appropriate to the clinical investigation, one or more of the additional elements of informed consent at 21 CFR 50.25(b) must also be addressed. For "applicable clinical trials" as defined in 42 U.S.C. 282(j)(1)(A) initiated on or after March 7, 2012, an additional element of informed consent (i.e., inclusion of the specified statement regarding ClinicalTrials.gov) is required by 21 CFR 50.25(c).[15] The text of 21 CFR 50.20 and 21 CFR 50.25 is set out in italics below, followed by a discussion of each regulation.

A. General Requirements for Informed Consent

21 CFR 50.20:

- *Except as provided in 50.23, and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.*
- *An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.*
- *The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.*
- *No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.*

[15] For further information, see section III.D, "Element of Informed Consent for 'Applicable Clinical Trials.'"

1. Exceptions to Informed Consent

Informed consent is required for participation in FDA-regulated clinical investigations except under limited circumstances as described in 21 CFR 50.23 (involving certain life-threatening situations, military operations, or public health emergencies) and 21 CFR 50.24 (involving emergency research[16]) (see 21 CFR 50.20). We note that, to implement statutory changes made to the Federal Food, Drug, and Cosmetic Act (FD&C) Act by section 3024 of the 21st Century Cures Act (Cures Act), FDA issued a proposed rule that, if finalized, would allow IRBs responsible for the review, approval, and continuing review of clinical investigations to approve an informed consent procedure that waives or alters certain informed consent elements or that waives the requirement to obtain informed consent for certain minimal risk clinical investigations.[17,18] In addition, FDA issued guidance explaining that until the Agency promulgates regulations implementing the Cures Act amendments to the FD&C Act, FDA does not intend to object to an IRB 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 to an IRB waiving the requirements to obtain informed consent for certain minimal risk clinical investigations under the circumstances described in the guidance.[19] Nothing in FDA's informed consent regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law (21 CFR 50.25(e)).

2. Coercion and Undue Influence

The conditions under which informed consent is sought and the relationship between the subject and the person obtaining consent should be carefully considered to minimize the possibility of coercion or undue influence (21 CFR 50.20). According to the Belmont Report, "Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence,

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[16] See "Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research.

[17] See section 3024 of the Cures Act, Pub. L. 114-255, available at https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf.

[18] See "Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations," (83 FR 57378, November 15, 2018) at https://www.govinfo.gov/content/pkg/FR-2018-11-15/pdf/2018-24822.pdf.

[19] See "Guidance for Sponsors, Investigators, and Institutional Review Boards; IRB Waiver of Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-waiver-or-alteration-informed-consent-clinical-investigations-involving-no-more-minimal-risk.

by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance."[20]

For example, if an employer seeks to enroll employees in a clinical investigation sponsored or conducted by the employer, the informed consent process should contain safeguards to ensure that participation is voluntary and that the possibility of undue influence or coercion by supervisors, peers, or others is minimized. Similarly, because of a potential conflict of interest and the nature of the physician-patient relationship,[21] when the investigator is also the prospective subject's physician, for example, the-investigator should ensure that the prospective subject understands that enrollment in the clinical investigation is voluntary, and that a decision to forgo enrollment will not adversely affect their medical care, in accordance with 21 CFR 50.25(a)(8). The consent process and form should emphasize that an individual's participation is truly voluntary.

Note that coercion and undue influence may be situational, and can affect any population, not just subject populations seen as vulnerable to coercion or undue influence. For example, in a clinical investigation involving the collection of extra tissue samples during a planned surgical procedure, waiting to obtain informed consent until the prospective subject is in the preoperative area would generally fail to minimize the possibility of undue influence. The possibility of undue influence could be addressed by first discussing the study with the prospective subject during a preoperative visit as part of the informed consent process. The prospective subject could be told that the study will be reviewed with them again prior to the procedure and, after all questions are resolved, they will be asked to sign a consent form acknowledging their willingness to participate in the study at that time.

In addition, statements that claim investigational drugs and devices are safe or effective for the purposes for which they are being investigated are prohibited (21 CFR 312.7(a) and 21 CFR 812.7(d)). Likewise, statements that overstate the possibility of benefit may unduly influence prospective subjects by leading them to incorrectly assume that it is known that the investigational product will be of benefit to them, influencing them to agree to participate when they might not have otherwise chosen to do so. For example, wording that refers to the clinical investigation as a "therapeutic trial" could contribute to a

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[20] The Belmont Report was written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission, created as a result of the National Research Act of 1974, was charged with identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and developing guidelines to assure that such research is conducted in accordance with those principles. See Belmont Report, available at https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html.

[21] For the purposes of this document physician means a medical doctor or other appropriate healthcare providers.

prospective subject's misunderstanding that the trial will offer a direct benefit for their disease or condition.

Furthermore, we generally recommend against including statements such as "FDA has given permission for the clinical investigation to proceed" or "FDA has approved the clinical investigation" in the informed consent process, because such statements may suggest to subjects that the investigation has FDA's endorsement. In addition, these statements may not be accurate for the particular clinical investigation at issue (see, e.g., 21 CFR 312.40(b) and 21 CFR 812.2(b)).

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. This topic is also discussed under section III.B.3, "Benefits."

Finally, as discussed in FDA's Information Sheet, "Guidance for Institutional Review Boards and Clinical Investigators, Payment and Reimbursement to Research Subjects," paying research subjects in exchange for their participation is a common and, in general, acceptable practice.[22] FDA recognizes that payment to subjects for participation in clinical investigations, which is not specifically addressed by FDA regulations, may in some cases, raise difficult questions that should be addressed by IRBs. For example, an IRB should 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). However, FDA does not consider payment to research subjects for participating in research a benefit that can be used to justify risk when IRBs evaluate whether risks to subjects are reasonable in relation to anticipated benefit as required by 21 CFR 56.111(a)(2). IRBs should review both the amount of payment and the proposed method and timing of disbursement to assure that they are not coercive and do not present undue influence (21 CFR 50.20). As a general rule, FDA does not believe genuine offers of payment raise questions about coercion; however, an overt threat of harm presented in the guise of an offer of payment (e.g., a threat to withhold payment that had already been promised) would still be coercive.

3. Language Understandable to the Subject or the Legally Authorized Representative

[22] See the FDA Information Sheet, "Guidance for Institutional Review Boards and Clinical Investigators, Payment and Reimbursement to Research Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects.

The information given to the prospective subject, which includes both information provided orally during the consent discussion and written information in the consent form, must be in language understandable to the prospective subject or LAR (21 CFR 50.20). "Understandable" means the information presented to prospective subject is in a language and at a level the subjects can comprehend (including an explanation of scientific and medical terms).

4. Exculpatory Language

The consent process must not include exculpatory language through which a subject, or the LAR, is made to waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agents from liability for negligence (21 CFR 50.20). FDA considers *exculpatory language* to be language that has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt.[23]

The following are examples of exculpatory language that would violate 21 CFR 50.20, and therefore cannot appear in consent forms:

- I waive any possibility of compensation, including any right to sue for injuries that I may receive as a result of being in this study.
- If you suffer an injury as a result of being in this study, neither the institution nor the investigator can assume financial responsibility or liability for the expenses of treatment for such injury.

Examples of language that would not be considered exculpatory are included below (see also section III.B.6, "Compensation and Medical Treatment in Event of Injury"):

- You do not give up any of your legal rights by being in this study, and you may choose to pursue legal action if you are injured by being in the study.
- If you are injured as a result of being in this study, paying for the cost of your medical care will be your responsibility or that of your health insurance company. However, signing this form does not stop you from pursuing legal action for the injury.

[23] For additional discussion of exculpatory language, see the joint draft guidance from the HHS Office for Human Research Protections (OHRP) and FDA, "Guidance on Exculpatory Language in Informed Consent," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exculpatory-language-informed-consent. When finalized the guidance will represent FDA's current thinking on this issue. When finalized, the examples in the draft may be revised.

B. Basic Elements of Informed Consent

As discussed in this section, FDA regulations identify eight basic elements of informed consent to be provided to the subject (21 CFR 50.25(a)). The text of each of the eight elements is italicized below, followed by a discussion of the element. As discussed in section III.E.4.b "Short Form", when a short form written consent document is used, the document must state that the elements of informed consent required by 21 CFR 50.25 have been presented orally to the subject or the subject's LAR (21 CFR 50.27(b)(2)).

> *(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:*

1. Description of Clinical Investigation

> *A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.* (21 CFR 50.25(a)(1))

A clear statement that the clinical investigation involves research is important to make prospective subjects aware that, although preliminary data (bench, animal, pilot studies, literature) may exist, the purpose of the subject's participation is primarily to contribute to research (for example, to evaluate the safety and effectiveness of the test article or to evaluate a different dose or route of administration of an approved drug), rather than to their own medical treatment.

FDA recommends that when discussing the required elements of informed consent with prospective subjects, there should first be a discussion of the care a patient would likely receive if not part of the research, if relevant, and then the potential subject should be provided with information about the research. This sequence allows prospective subjects to understand how the research differs from the care they might otherwise receive. The description of the clinical investigation should identify tests or procedures required by the protocol that would not be part of their care outside of the research; for example, drawing blood samples for a pharmacokinetic study. Note that all experimental procedures must be identified as such (21 CFR 50.25(a)(1)). Procedures related solely to research must be explained (for example, protocol-driven versus individualized dosing, randomized assignment to treatment, blinding of subject and investigator, and receipt of placebo if the study is placebo-controlled) (21 CFR 50.25(a)(1)). In some cases, tests or procedures that would be considered part of usual clinical care will not be performed on study participants; when applicable, this should be discussed as part of the informed consent process.

The description of the clinical investigation must describe the test article (e.g., the investigational product under study) and, if used in the study, the control (21 CFR 50.25(a)(1)). The description should include relevant information on what is known about both the test article and the control. For example, the description should indicate whether the test article is approved or cleared[24] for marketing and describe the use(s) for which it has been approved or cleared. The description should also provide relevant information about any control used in the study: for example, whether the control is FDA approved or cleared for marketing, considered a medically recognized standard of care[25], or is a placebo (including an explanation of what a placebo is). The information provided about the test article and control should include appropriate and reliable information about the potential benefits and risks of each, to the extent such information is available. For 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 consent process should outline what the subject's participation will involve in order to comply with the protocol, for example, the number of clinic visits, maintenance of diaries, and medical or dietary restrictions (including the need to avoid specific medications or activities, such as participation in other clinical investigations[26]). If describing every procedure would make the consent form too lengthy or detailed, FDA recommends providing the general procedures in the consent form with an addendum describing the details of the study procedures to be performed at each visit. It may be helpful to provide a chart outlining what happens at each study visit to simplify the consent form and assist the prospective subject in understanding what participation in the clinical investigation will involve. FDA believes that removing procedural details from the consent form will reduce its length, enhance its readability, and allow the consent document to focus on content related to the risks and anticipated benefits, if any.

The informed consent process must clearly describe the expected duration of the subject's participation in the clinical investigation (see 21 CFR 50.25(a)(1)), which includes their active participation as well as

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[24] For purposes of this guidance, when *"approved or cleared"* is used in discussing devices, the terms refer to FDA permitting the marketing of a device via the premarket approval, premarket notification (510(k)), De Novo classification, or Humanitarian Device Exemption (HDE) pathways.

[25] For the purposes of this guidance only, FDA generally would consider a 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).

[26] For additional information see Frequently Asked Question #11, "Can a subject participate in more than one clinical investigation simultaneously?"

long-term follow-up, if appropriate. Prospective subjects must be informed of the procedures that will occur during such follow-up (21 CFR 50.25(a)(1)), which may be provided in a chart as described above.

2. Risks and Discomforts

A description of any reasonably foreseeable risks or discomforts to the subject. (21 CFR 50.25(a)(2))

The informed consent process must describe the reasonably foreseeable risks or discomforts to the subject. This includes risks or discomforts of tests, interventions and procedures required by the protocol (including protocol-specified standard medical procedures, exams, and tests), with a particular focus on those that carry significant risk of morbidity or mortality. Possible risks or discomforts due to changes to a subject's medical care (e.g., by changing the subject's stable medication regimen or by stopping the subject's current treatment and randomizing them to either the investigational drug or placebo) should also be addressed. Where relevant, participants should also be made aware of the possibility of unintended disclosures of private information and be provided with an explanation of measures to protect a subject's privacy and data, and limitations to those measures.[27] The explanation of potential risks of the test article and control, if any, and an assessment of the likelihood of these risks occurring should be based on reliable and accurate information presented in the protocol, investigator's brochure, labeling, and/or previous research reports. Reasonably foreseeable discomforts to the subject must also be described (21 CFR 50.25(a)(2)). For example, the consent form should disclose that the subject may be uncomfortable having to stay in one position or experience claustrophobia-like symptoms during an MRI. For clinical investigations involving the comparison of an investigational product to one or more standards of care, it may be acceptable to describe the more common and significant risks and discomforts of the standard of care in the informed consent form and provide additional risk information, as appropriate, as part of the consent discussion.

Any reasonably foreseeable risks or discomforts to the subject need to be described in the informed consent form; however, it is not necessary to describe all possible risks, especially if doing so could make the form overwhelming for subjects to read. Information on risks that are more likely to occur and those that are serious should be described so that prospective subjects can understand the nature of the risk. The discussion may include information on whether a risk is reversible, and the probability of the risk based on existing data. Information on what may be done to mitigate serious risks, and risks and discomforts more likely to occur, should also be considered for inclusion.

[27] Note, 21 CFR 56.111(a)(7) requires IRBs to determine, where appropriate, that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The description should not understate the probability and magnitude of the reasonably foreseeable risks and discomforts. If applicable, the consent document should include a description of the reasonably foreseeable risks to the subject, but also the potential for risk to "others" (for example, radiation therapy where close proximity to subjects post-procedure may create some risk to others). In situations where there may be a risk to others, efforts to mitigate the potential risk (e.g., using separate bathrooms) may be included in the consent document or provided in a separate document and given to the subject during the consent discussion.

When appropriate, a statement must be included that a particular treatment or procedure may involve currently unforeseeable risks to the subject (or to the subject's embryo or fetus, if the subject is or may become pregnant) (21 CFR 50.25(b)(1); see section III.C.1, "Unforeseeable Risks"). If unanticipated risks are reported during the investigation, the informed consent discussion and documents may need to be updated with the additional risks (21 CFR 50.25(a)(2); see Frequently Asked Question #16).

3. Benefits

> *A description of any benefits to the subject or to others which may reasonably be expected from the research.* (21 CFR 50.25(a)(3))

Potential benefits should be explained in terms of any direct impact to the prospective subject, in addition to the anticipated societal benefit of the research. The description of potential benefits to the subject from the use of the test article (and control, if appropriate) should include appropriate details, and should be clear, balanced, and based on reliable information to the extent such information is available. For clinical investigations involving the comparison of an investigational product to one or more standards of care, it may be acceptable to generally describe the benefits of the standard of care in the informed consent form and provide more specific information about the standard of care as part of the consent discussion rather than in the consent document. This element requires a description of the potential benefits not only to the subject (for example, "This product is intended to decrease XXX; however, we cannot guarantee that you will receive any benefit from it or from being in the study."), but also to "others" (for example, "Your participation in this research may not benefit you, but information learned from this study may benefit patients with your disease or condition in the future.").

Overly optimistic representations of the benefits of the test article being studied in the clinical investigation may be misleading and may violate FDA regulations that prohibit promotion of investigational drugs and devices (21 CFR 312.7 and 21 CFR 812.7). Where the purpose of the study is to determine the safety and/or effectiveness of the test article, there is usually significant uncertainty regarding whether, and to what extent, the test article provides a benefit. If there is no potential for direct

benefit to the prospective subject, which may be the case, for example, in a phase I study in healthy volunteers, this point should be clearly stated. An example of a way in which to describe in the consent document that an investigational product does not have direct benefits to participating subjects would be to state "There are no direct benefits to you from taking part in this study."

If payments, including reimbursement for research-related expenses incurred by subjects due to participation, are provided, the consent process should not identify them as benefits.[28]

4. Alternative Procedures or Treatments

> *A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.* (21 CFR 50.25(a)(4))

To enable an informed decision about taking part in a clinical investigation, consent forms must disclose appropriate alternatives to entering the clinical investigation, if any, that might be advantageous to the subject (21 CFR 50.25(a)(4)). Prospective subjects must be informed of the appropriate alternatives available to them, including a description of the care they would be likely to receive if they choose not to participate in the research. This includes alternatives such as approved therapies for the patient's disease or condition, other forms of therapy (e.g., surgical) or diagnosis, and when appropriate, supportive care with no disease-directed therapy. This disclosure must include a description of the current medically recognized standard of care, particularly in studies of medical products intended to treat or diagnose serious diseases or conditions. The current medically recognized standard of care may include uses or treatment regimens for a legally marketed drug or device that are not included in the product's approved or cleared uses. 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. However, this information should not be presented in a promotional manner. If a sponsor has questions related to this issue, they may contact FDA for feedback.[29]

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[28] See the FDA Information Sheet "Payment and Reimbursement to Research Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects.

[29] As FDA has recognized in prior guidance, unapproved new uses or treatment regimens for approved or cleared drugs or devices may be important and may even constitute medically recognized standard of care. See FDA "Guidance for Industry; Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," available at https://downloads.regulations.gov/FDA-2008-D-0053-0127/content.pdf.

A statement identifying alternative therapies and indicating that the alternatives will be discussed by the clinical investigator in more detail, if appropriate, may be used if there is more than one alternative. FDA recommends that treatment options lacking evidence of therapeutic value not be included. If 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 (see 21 CFR 50.25(a)(4) and 50.25(b)(5) and Frequently Asked Question #16).

When disclosing appropriate alternative procedures or courses of treatment, FDA recommends that a description of any reasonably foreseeable risks or discomforts and potential benefits associated with these alternatives should be disclosed during the informed consent process, although not necessarily included in the written informed consent document. Where such descriptions or disclosures can contain quantified comparative estimates of the reasonably foreseeable risks or discomforts and potential benefits (e.g., from the clinical literature) between the alternatives, they should do so. The Agency does not believe that providing such quantified comparative estimates for every case would be realistic or appropriate.[30] Where such well-defined estimates are not possible, the Agency believes that a description of the risks and benefits should be sufficient. While this should be more than just a list of alternatives, a full risk/benefit explanation of alternatives may not be appropriate to include in the written document. However, the person(s) obtaining the prospective subject's consent should be able to discuss available alternatives and answer the prospective subject's questions.

It may be appropriate to refer the subject to their primary care provider or another healthcare professional who can more fully discuss the alternatives, for example, when alternatives include various combinations of treatments such as radiation, surgery, and chemotherapy for some cancers. Such discussions with an appropriate healthcare professional should be completed prior to the subject signing and dating the consent form.

While an individual subject may be eligible for more than one clinical investigation, that determination and the decision as to which trial would be most appropriate for a particular subject would need to be made on a case-by-case basis. A discussion of other trials for which the subject may be eligible would generally be more appropriate to address as part of the informed consent discussion, rather than the

[30] *Federal Register*, "Protection of Human Subjects; Informed Consent" (46 FR 8942, January 27, 1981), available at https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/protection-human-subjects-informed-consent; see response to comment 23.

informed consent document.[31] The subject may also wish to seek input from a primary care or other healthcare provider on this issue.

As applicable, the informed consent process should advise that participation in one clinical investigation may preclude an individual's eligibility to participate in other clinical investigations. When there are multiple clinical investigations for evaluating the treatment of a particular disease for which a subject may be eligible, the sequence in which a subject may participate in the clinical investigations may be important and should be discussed with the prospective subject. For example, participation in a study of a drug for a specific therapeutic category may be an exclusion criterion for another study. The prospective subject may wish to discuss the study with their primary care provider, if appropriate.

5. Confidentiality

> *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.* (21 CFR 50.25(a)(5))

The consent process must describe the extent to which confidentiality of records identifying subjects will be maintained (21 CFR 50.25(a)(5)) and should identify all entities, for example, the study sponsor, the research team, regulatory agencies, and/or ethics committee members, who may gain access to the records relating to the clinical investigation. The consent process must also note the possibility that FDA may inspect records (21 CFR 50.25(a)(5)) and should not state or imply that FDA needs permission from the subject for access to the records. Under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, FDA does not need permission to inspect records containing protected health information (45 CFR 164.512). FDA may inspect study records to assess investigator compliance with the study protocol and the validity of the data reported by the sponsor.

FDA may inspect and copy records relating to a clinical investigation (see, e.g., sections 704(a) and 704(e) of the FD&C Act, 21 CFR 56.115(b), 312.58(a), 312.68, and 812.145(b)). FDA generally will not copy records that include the subject's name unless it is necessary to do so for the reasons described in 21 CFR 312.68 and 812.145, such as when there is reason to question whether the records represent the actual cases studied or results obtained. When FDA requires subject names or other information that could connect the individual subject with the personal health information contained in the record, FDA will generally treat such information as confidential, but on rare occasions, FDA may be required to

[31] For additional advice regarding the need to avoid coercion and undue influence during the informed consent process, see Section III.A.2.

disclose this information to third parties, for example, if required by a court of law (see 5 U.S.C. 552(b)(6); see also 21 CFR 20.63(a) and 20.83(a)-(b)). Therefore, the consent process should not promise or imply absolute confidentiality with regard to records that may be inspected by FDA.[32]

6. Compensation and Medical Treatment in Event of Injury

> *For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.* (21 CFR 50.25(a)(6))

For clinical investigations involving more than minimal risk, the informed consent process must describe any compensation and medical treatments available to subjects if injury occurs[33] (21 CFR 50.25(a)(6)). Because available compensation and medical treatments may vary depending on the medical circumstances of the individual subject or the policies of the institution, the consent process should include an explanation to subjects of where they may obtain further information. An example of an adequate statement is:

"The sponsor has made plans to pay for medical costs related to research-related injuries"

followed by an explanation of how to obtain further information.

If no compensation is available, the consent process should include a statement such as:[34]

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[32] When appropriate, a sponsor may request a discretionary Certificate of Confidentiality (CoC). A CoC generally prohibits a researcher from disclosing identifiable, sensitive information about the research participant, created or compiled for purposes of the research, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. There are some exceptions to the prohibition on disclosure of such information. See FDA guidance "Certificates of Confidentiality," available at https://www.fda.gov/media/132966/download.

[33] Investigators should ensure that subjects have access to reasonable medical care for medical problems arising during their participation in the clinical investigation that are, or could be, related to the study intervention. See pages 7-8 of FDA's "Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects.

[34] For additional discussion of exculpatory language, see the joint draft guidance from OHRP and FDA, "Guidance on Exculpatory Language in Informed Consent," which, when final, will represent FDA's current thinking on this topic, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exculpatory-language-informed-consent.

"Because of hospital policy, the hospital is not able to pay for your medical care if you are injured as a result of being in this study. If you are injured as a result of being in this study, you or your insurance will be responsible for paying your medical expenses. However, you do not give up any of your legal rights by being in this study, and you may choose to pursue legal action if you are injured by being in the study."

See section III.A.4, "Exculpatory Language", for additional information.

7. Contacts

> *An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.* (21 CFR 50.25(a)(7))

The consent document (or oral presentation, if a short form is used) must provide information on how to contact an appropriate individual for questions about the clinical investigation and the subjects' rights, and whom to contact in the event that a research-related injury to the subject occurs (21 CFR 50.25(a)(7)). This information should include contact names (or offices), email addresses, and their telephone numbers. FDA recommends that the individual or office named for questions about subjects' rights not be part of the investigational team, because subjects may be hesitant to report specific concerns or identify possible problems to someone who is part of the investigational team. Therefore, an appropriate contact for subjects' rights questions may be the IRB Office, the facility's Patient Advocate Office, or other staff with training regarding the rights of clinical trials subjects. In addition, the consent process should include information on whom to contact and what to do in the event of an emergency, including 24-hour contact information, if appropriate.[35]

If contact information changes during the clinical investigation, then the new contact information must be provided to the subject (21 CFR 50.25(a)(7)). This may be done through a variety of ways, for example, a card providing the relevant contact information for the clinical investigation may be given to the subject during a visit or mailed to the subject in an envelope to protect the subject's privacy.

8. Voluntary Participation

[35] See pages 7-8 of FDA's "Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects.

> *A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.* (21 CFR 50.25(a)(8))

This element requires that subjects be informed that they may decline to take part in the clinical investigation or may stop participation at any time without penalty or loss of benefits to which subjects are entitled (21 CFR 50.25(a)(8)). Language that limits the subject's right to decline to participate or withdraw from the clinical investigation must not be used. If special procedures should be followed for the subject to withdraw from the clinical investigation, the consent process must outline and explain the procedures (21 CFR 50.25(b)(4); see section III.C.4, "Consequences of Subject's Decision to Withdraw"). Written withdrawal from the study by the subject is not a requirement. When possible, the site staff should document the withdrawal and the date it occurred. Note, when a subject withdraws from a study conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.[36]

C. Additional Elements of Informed Consent

FDA regulations identify six additional elements of informed consent to be provided to each subject, when appropriate. (21 CFR 50.25(b))

> *(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:*

The following elements are appropriate to provide to prospective subjects when the IRB determines the information is material to prospective subjects' decisions to participate:

1. Unforeseeable Risks

> *A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.* (21 CFR 50.25(b)(1))

[36] See, "Guidance for Sponsors, Clinical Investigators, and IRBs; Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials," at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-retention-when-subjects-withdraw-fda-regulated-clinical-trials.

When appropriate, the consent process must contain a statement that the particular test article or procedure may involve risks to subjects (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable (21 CFR 50.25(b)(1)). If long-term safety studies (such as bench and animal testing[37]) are not completed, the informed consent process should explain that researchers have not completed studies that may identify potential risks (e.g., carcinogenicity or teratogenicity studies), and that there may be potential risks to subjects (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable (21 CFR 50.25(b)(1)). Sponsors may want to consider whether appropriate birth control measures and notifying the investigator of pregnancy should be included in the protocol and addressed in the informed consent document.

2. Involuntary Termination of Subject's Participation

> *Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.* (21 CFR 50.25(b)(2))

When appropriate, the consent process must inform the subject of anticipated circumstances under which the investigator may end the subject's participation without the subject's consent (21 CFR 50.25(b)(2)). Such circumstances may arise if, for example, the subject is unable to comply with procedures required by the clinical investigation, if the subject meets discontinuation criteria for continuing in the study, or if the site withdraws from the study. A simple statement that the investigator or sponsor may withdraw the subject from participation at any time is inadequate and does not inform the subject of anticipated circumstances that may trigger their withdrawal from the clinical investigation. For example, the consent process may inform the subject that the investigator may withdraw the subject's participation in the clinical investigation if the subject does not follow the instructions given to them by the investigator, such as repeatedly failing to return for protocol-required clinic visits or repeatedly failing to follow dosing or device instructions. If a subject is withdrawn from the study, the clinical investigator should explain to the subject the reasons for withdrawal, discuss other available treatment or research options, and, if appropriate, discuss plans to follow the subject after withdrawal for side effects. The subject should also be informed as to how the data that have already been collected will be handled.

3. Additional Costs to Subject

> *Any additional costs to the subject that may result from participation in the research.* (21 CFR 50.25(b)(3))

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[37] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. FDA encourages sponsors to consult with the relevant review division if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. FDA will consider if such an alternative method is adequate to meet the regulatory need.

If subjects might incur additional expense as a result of taking part in the clinical investigation, the consent process must explain the added costs (21 CFR 50.25(b)(3)). FDA recommends that any additional cost that may be charged to the subject, the subject's insurance, or other reimbursement mechanism be explained as part of the informed consent process. Subjects should be made aware that insurance or other reimbursement mechanisms might not fund the medical care they receive as a result of participating in a clinical investigation even when the care is the standard care they would otherwise receive if not participating in a clinical investigation.[38]

Additionally, insurance or other forms of reimbursement might not pay for care related to complications or injuries arising from participation in a clinical investigation (see section III.B.6, "Compensation and Medical Treatments in Event of Injury"). If the subject's insurance is charged and there are deductibles or copayments, the subject should be informed of whether they will be responsible for these costs. If funds will be available to cover costs not covered by insurance or other forms of reimbursement, the consent form should describe how these funds will be made available to subjects or direct subjects on how to obtain further information. Because these issues may be complex, it may be appropriate to refer the subject to a knowledgeable financial counselor or reimbursement specialist to explain the costs and the insurance and reimbursement issues prior to signing the consent form.

In some cases, the cost of an investigational product may be charged to the subject. In clinical investigations involving investigational devices, the sponsor is permitted to recover the costs of research, development, manufacture, and handling of investigational devices (see 21 CFR 812.7(b)). FDA may authorize sponsors in certain clinical investigations of drugs to recover the direct costs of making the investigational drug available, such as costs to manufacture, ship, and handle (e.g., store) the drug (see 21 CFR 312.8).[39] When these costs are passed to the subject, the consent process must identify these costs (21 CFR 50.25(b)(3)).

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[38] The Patient Protection and Affordable Care Act added section 2709 to the Public Health Service Act (42 U.S.C. 300gg-8). Among other things, this provision prohibits a group health plan or health insurance issuer in the group and individual health insurance market from denying certain individuals' participation in certain clinical trials and from denying or limiting coverage of routine patient costs for items or services furnished in connection with participation in such trials.

[39] See "Guidance for Institutional Review Boards and Clinical Investigators, Charging for Investigational Products," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/charging-investigational-products, and "Guidance for Industry, Charging for Investigational Drugs Under an IND – Questions and Answers," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/charging-investigational-drugs-under-ind-questions-and-answers. Also, sponsors of expanded access INDs and treatment protocols that meet certain requirements may recover other costs than these direct costs. See 21 CFR 312.8(d)(2).

Beyond the costs directly related to participation in the research, it may be appropriate to identify additional costs that may be incurred, such as any costs associated with participation in the clinical investigation, e.g., time off from work, child or elder care, or transportation costs. To aid the prospective subject in understanding these additional costs, the consent process should describe the protocol requirements in sufficient detail (e.g., number and duration of study site visits and procedures) to enable subjects to appreciate how much time they may need to take away from work, child care, or elder care. Prospective subjects should be made aware of direct and indirect costs of participation and informed as to what extent these costs will be covered by the sponsor versus paid by the subject (see section III.A.2, "Coercion and Undue Influence").

4. Consequences of Subject's Decision to Withdraw

> *The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.* (21 CFR 50.25(b)(4))

When appropriate, the consent process must describe the consequences of a subject's decision to withdraw from the clinical investigation and the procedures for orderly termination of participation by the subject (21 CFR 50.25(b)(4)). For example, when withdrawal from a clinical investigation may adversely affect the subject, the informed consent process must explain the withdrawal procedures that are recommended in order to ensure the subject's safety and should specifically state why the withdrawal procedures are important to the subject's welfare. For some clinical investigations, an intervention should be withdrawn gradually, or the investigator may recommend follow-up to ensure the subject's safety when an investigational intervention is prematurely terminated due to a subject's withdrawal. In these cases, the consent process must explicitly inform the subject of the potential adverse effects of premature termination of the investigational intervention. Prospective subjects should be made aware of the number of visits and approximate time required for participation in the study to help them determine if they are able to make the commitment to complete the study. When appropriate, it may be reasonable to counsel prospective subjects that they should not participate in the trial if they do not foresee staying in the study. If applicable, the consent process must explain whether a subject who withdraws early will receive future study payments.[40] The subject should also be informed as to how the data that have already been collected will be handled (see also section III.B.8, "Voluntary Participation").

[40] For further information about the timing of payments to research participants see the "Guidance for Institutional Review Boards and Clinical Investigators, Information Sheet: Payment and Reimbursement to Research Subjects," available at Payment and Reimbursement to Research Subjects | FDA.

5. Providing Significant New Findings to Subjects

> *A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.* (21 CFR 50.25(b)(5))

The consent process must, when appropriate, include a statement that significant new findings that may relate to the subject's willingness to continue participation, such as new risk information, will be provided to the subject (21 CFR 50.25(b)(5)). Significant new findings may include an unexpected adverse event, an adverse event occurring at greater frequency or severity than previously stated in the consent process, results from interim analyses (in some cases), additional alternative procedures or courses of treatment that become available during the course of the clinical investigation, and information from other clinical trials about the effectiveness of the investigational product, the comparator, or other products for the same indication. FDA encourages the inclusion of this statement in the consent form for clinical investigations where knowledge of risk is limited, for example, clinical investigations involving the first use of an investigational product in humans, novel therapies, and new molecular entities, or complex clinical investigations that involve significant risk. Where there are significant new findings, the IRB should consider whether enrolled subjects should be contacted to determine if this information impacts their decision to continue participation in the clinical investigation (see Frequently Asked Question #16).

6. Number of Subjects

> *The approximate number of subjects involved in the study.* (21 CFR 50.25(b)(6))

When appropriate, the informed consent process must state the approximate number of subjects involved in the clinical investigation (21 CFR 50.25(b)(6)). For example, a subject's decision whether or not to participate in the study may be influenced by knowledge that the clinical investigation is a small initial trial of the product (such as a phase 1 or 2 drug clinical investigation or a device feasibility clinical investigation where only a small number of subjects participate).

D. Element of Informed Consent for "Applicable Clinical Trials"[41]

> *When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial*

[41] For further information, see FDA's "Guidance for Sponsors, Investigators, and Institutional Review Boards, Questions and Answers on Informed Consent Elements, 21 CFR § 50.25(c)" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-informed-consent-elements-21-cfr-ss-5025c?source=govdelivery.

> *information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on https://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."* (21 CFR 50.25(c))

All informed consent forms for "applicable clinical trials"[42] initiated on or after March 7, 2012, must contain the above quoted statement, which cannot be modified (21 CFR 50.25(c)).[43] However, additional explanation may be provided, if appropriate. For example, with respect to clinical trials involving investigational devices, an additional statement could be added that information about device trials might not be made publicly available until after a product is cleared or approved by FDA.

E. Documentation of Informed Consent

1. Requirement for Written Documentation of Informed Consent

> *(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.* (21 CFR 50.27(a))

Informed consent must be documented by a signed and dated written consent form except under two specific circumstances as described in FDA's regulations at 21 CFR 56.109(c)[44] (21 CFR 50.27). When

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[42] For the definition of "applicable clinical trial," see 42 USC 282(j)(1)(A) and 42 CFR 11.10(a). It is the responsibility of sponsors and investigators to determine if their clinical trial meets the definition of an "applicable clinical trial" and to ensure compliance with the most current applicable statutory and regulatory requirements. Information on "applicable clinical trials" is available at https://clinicaltrials.gov/ct2/manage-recs/fdaaa.

[43] Note that this statement is not required for child assent.

[44] 21 CFR 56.109(c) states, "*An IRB shall require documentation of informed consent in accordance with section 50.27 of this chapter, except as follows:*

> *"(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or*
>
> *"(2) The IRB may, for some or all subjects, find that the requirements in 50.24 of this chapter for an exception from informed consent for emergency research are met."*

written informed consent is required, the use of electronic, including digital, signatures are permitted under FDA's regulations, provided it is in compliance with applicable regulations.[45]

In the event that an IRB waives the requirement for documentation of informed consent (under 21 CFR 56.109(c)(1)), FDA recommends that the elements of informed consent be reviewed verbally with the subject or the subject's LAR. Additionally, the IRB may require the investigator to provide subjects with a written statement regarding the clinical investigation (21 CFR 56.109(d)). See section III. E.2, "Alternative Methods of Obtaining Informed Consent" below for additional information regarding documentation of consent. FDA recommends that when an IRB waives the documentation requirement for informed consent in circumstances where there is minimal risk of harm under 21 CFR 56.109(c)(1), the consent process and discussion be described and noted in subject case histories required to be maintained under 21 CFR 312.62(b) or 21 CFR 812.140(a)(3).[46]

2. Alternative Methods of Obtaining Informed Consent

Traditionally, informed consent has been obtained and documented in a face-to-face interview using paper consent forms. Technologies are available that may serve as an alternative to the paper consent form in the informed consent process.[47] Parties interested in pursuing alternative methods of obtaining informed consent should discuss their plan with their IRB and are welcome to contact FDA as needed for advice.[48]

Even in the context of paper consent forms, there may be certain circumstances when an alternative to a face-to-face consent discussion may be appropriate. For example, such an alternative may be appropriate

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[45] See 21 CFR part 11, "Electronic Records; Electronic Signatures" and FDA guidance entitled, "*Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application*," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/part-11-electronic-records-electronic-signatures-scope-and-application.

[46] Documentation requirements related to emergency research, as mentioned in 21 CFR 56.109(c)(2), can be found in 21 CFR 50.24. Discussion of these studies is in a separate guidance, "Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research.

[47] For additional information on alternative methods of obtaining informed consent, please see "Guidance for Institutional Review Boards, Investigators, and Sponsors, Use of Electronic Informed Consent in Clinical Investigations," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-informed-consent-clinical-investigations-questions-and-answers, and FDA's MyStudies Application (App) at https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app.

[48] Questions related to alternative methods of obtaining informed consent can be directed to the Office of Clinical Policy at gcpquestions@fda.hhs.gov.

when the subject or the subject's LAR is unable to visit the investigational site to sign the consent form, or if the screening procedures for the clinical investigation require prior activity, such as fasting, that requires consent but does not require a visit to the investigational site.[49] When written documentation of informed consent is required, informed consent cannot be obtained and documented by oral communication through the telephone alone.

Methods other than a face-to-face consent discussion may be acceptable if those methods allow for an adequate exchange of information and documentation, and a method to ensure that the signer of the consent form is the person who plans to enroll as a subject in the clinical investigation or is the LAR of the subject. For example, the consent form may be sent to the subject or the subject's LAR by facsimile or e-mail, and the consent discussion may then be conducted by telephone/videoconference when the subject or subject's LAR can access the consent form during the discussion. After the consent discussion, the subject or the subject's LAR can manually or electronically sign and date the consent form and return the document to the clinical investigator through a secure electronic method, such as by scanning the consent form and returning it through a secure e-mail account, or by posting it to a secure internet address. Alternatively, the subject may bring the signed and dated consent form to their next visit to the clinical site or mail it to the clinical investigator. The signed document must be maintained as part of the subject's case history required under 21 CFR 312.62(b) and 812.140(a)(3). In addition, the person signing the consent form must receive a copy of the consent form (21 CFR 50.27(a)). Although FDA regulations do not require the subject's copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided (see section III.E.3, "Requirement for Dating Consent Form").[50] In situations in which the signed document cannot be retrieved for filing in the study records (e.g., because the subject is in strict isolation due to a highly transmissible infectious disease), 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.

For studies involving no more than minimal risk, and no procedures for which written consent is normally required outside the research context, oral consent from a subject or a subject's LAR is permissible under 21 CFR 56.109(c). When oral consent is used, FDA recommends that the consent process and discussion

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[49] See "Guidance for Institutional Review Boards and Clinical Investigators: Information Sheet – Screening Tests Prior to Study Enrollment," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment#:~:text=While%20an%20investigator%20may%20discuss%20availability%20of%20studies,eligibility%20for%20research%2C%20including%20withdrawal%20from%20medication%20%28wash-out%29.

[50] See FDA's guidance "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)" Section 4.8.11; available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1.

be described and noted in subject case histories required to maintained under 21 CFR 312.62(b) or 21 CFR 812.140(a)(3).

3. Requirement for Dating Consent Form

In addition to signing the consent form, the subject or the subject's LAR must enter the date of signature on the form (21 CFR 50.27(a)) to allow confirmation that the subject or the subject's LAR provided consent prior to participation in the clinical investigation, as required by 21 CFR 50.20. In those cases where the subject provides consent on the same day[51] that they begin participation in the clinical investigation, the subject's case history must document that the subject provided consent prior to participation in the research for studies conducted under an IND or IDE, (312.62(b) and 812.140(a)(3)), and the subject's case history should contain the signed and dated consent form. Although FDA regulations do not require the subject's copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided.

4. Forms for Documentation of Informed Consent

Under 21 CFR 50.27:

> *(b) Except as provided in § 56.109(c), the consent form may be either of the following:*
>
> *(1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.*
>
> *(2) A short form written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the*

[51] Prospective subjects should have sufficient opportunity and time to consider enrollment in the research, such that coercion and undue influence are minimized. See section III.A.2, "Coercion and Undue Influence".

> *person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.*

The regulations provide for obtaining written informed consent by two different methods: a long form that embodies all the elements of informed consent (see 21 CFR 50.25), or a short form that states that the elements of informed consent have been presented orally to the subject or the subject's LAR.

a. Long Form

As stated above, the long form must incorporate all the elements of informed consent as required under 21 CFR 50.25. When the long form is used, a copy must be provided to the person signing the form, that is, the subject or the subject's LAR (21 CFR 50.27(a)).

b. Short Form

An IRB may approve a short form to be used in appropriate situations where the elements of informed consent required by 21 CFR 50.25 are presented orally to the subject or the subject's LAR (21 CFR 50.27(b)(2)). For example, IRBs may consider approving the use of a short form in situations where the subject or the subject's LAR is unable to read due to low literacy or visual impairment.[52]

When the short form is used, the IRB is required to approve a written summary of the information to be presented orally (21 CFR 50.27(b)(2)). The information presented orally should be as thorough as the

[52] For additional information see Frequently Asked Question #6, "What should be considered when enrolling subjects with low literacy and numeracy?" and Frequently Asked Question #7, "What should be considered when enrolling subjects with physical or sensory disabilities?" In addition, for information on enrolling individuals with limited English proficiency see Frequently Asked Question #3, "What are some considerations for enrolling non-English speaking subjects?", Frequently Asked Question #4, "What process should be followed when it is expected that subjects who do not understand English will be enrolled?", and Frequently Asked Question #5, "What process should be followed when the enrollment of subjects who do not understand English, or who are limited English proficient, is not expected?"

information contained in the long form.[53] A copy of the short form and the written summary must be given to the person signing the form (that is, the subject or the subject's LAR) (21 CFR 50.27(b)(2)).

Use of the short form requires that there be a witness to the oral presentation of information to the subject or the subject's LAR (21 CFR 50.27(b)(2)). FDA recommends that an impartial third party not otherwise connected with the clinical investigation (for example, clinical staff not involved in the research, a patient advocate or an independent interpreter) serve as the witness. The witness must be present physically or by some other means, for example, by phone or video conference, during the oral presentation, not just the signing of the consent form (21 CFR 50.27(b)(2)). The purpose of the witness is generally to attest to the voluntariness of the subject's consent and the adequacy of the consent process by ensuring that the information was accurately conveyed and that the subject's questions were answered.

The subject or the subject's LAR signs and dates only the short form (21 CFR 50.27(a) and (b)(2)). The witness must sign both the short form and the summary, and the person obtaining consent must sign the summary (21 CFR 50.27(b)(2)). Due 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.

IV. RESPONSIBILITIES FOR INFORMED CONSENT

IRBs, clinical investigators, and sponsors share responsibility for ensuring that the informed consent form and process is adequate and meets FDA's regulatory requirements. The regulatory requirements represent the minimum information to be provided to prospective subjects for informed consent. The consent form should also incorporate any additional information that may affect subjects' rights and welfare or willingness to participate in the clinical research. For example, information about certain financial relationships and interests may be important to the subject (see section IV.A.1, "Review of All Informed Consent Materials" and section IV.B.2, "Financial Relationships and Interests").

[53] See the response to Comment 52 in the preamble to the 1981 final rule issuing regulations for the protection of human subjects (46 FR 8942, January 27, 1981); https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/protection-human-subjects-informed-consent: "The fact that a short form is used to document informed consent does not mean that the subject will get less information than if handed a long, detailed written document…All the 'form' provides [whether long or short] is evidence that the information required by 50.25 has been provided to a prospective subject."

A. The IRB

FDA requires that an IRB review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by the IRB regulations (21 CFR 56.109(a)). A critical part of this responsibility is for the IRB to review and approve a consent form that complies with applicable regulatory requirements at 21 CFR part 50 and to help ensure there is an adequate informed consent process that protects the rights and welfare of subjects participating in clinical investigations (21 CFR 56.109 and 56.111). Below are specific areas that IRBs should consider:

1. Review of All Informed Consent Materials

IRBs must review all materials used in the informed consent process (see 21 CFR 56.109(a)-(b) and 56.111(a)(4)-(5)).[54] This includes recruitment materials[55], such as advertisements, and information provided in addition to the informed consent form (for example, a chart explaining what to expect at each study visit or a document explaining the costs to subjects). The IRB's review is to ensure that information given to subjects as part of the consent process is in accordance with the requirements of 21 CFR part 50 (see 21 CFR 56.109 and 56.111(a)(4)-(5)).

When reviewing clinical investigations, IRBs must ensure that the consent process minimizes the possibility of coercion and undue influence (21 CFR 50.20 and 56.111(a)(4)). When a clinical

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[54] IRBs are not required under 21 CFR part 56 to review stand-alone HIPAA authorizations, so long as an IRB's written procedures, adopted pursuant to 21 CFR 56.108(a), do not require such review and approval. See page 8 of FDA's "Guidance for Industry IRB Review of Stand-Alone HIPAA Authorizations Under FDA Regulations" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-review-stand-alone-hipaa-authorizations-under-fda-regulations).

[55] As described in the FDA Information Sheet "Recruiting Study Subjects" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recruiting-study-subjects), FDA considers advertising, including but not necessarily limited to newspaper, radio, TV, bulletin boards, posters, flyers, and internet postings, to be part of the consent process. However, FDA does not consider listings of basic information about clinical investigations to be advertising for recruitment. We consider basic information to be information such as the title of the clinical investigation, purpose of the clinical investigation, protocol summary, basic eligibility criteria, investigational site locations, and how to contact the site for further information. An example of a basic information listing is the National Institutes of Health clinical trial registry (https://clinicaltrials.gov/), where many FDA-regulated clinical investigations are required to be registered. Any posting about a clinical investigation where the format limits the information provided to basic information does not need to be reviewed by the IRB. However, a posting that provides more than basic information should be submitted for IRB review.

investigation involves subjects who are likely to be vulnerable to coercion or undue influence, IRBs must determine that additional safeguards have been included in the clinical investigation to protect their rights and welfare (21 CFR 56.111(b)). In the event an IRB regularly reviews clinical investigations involving vulnerable subject populations, for such clinical investigations, the IRB membership should include individuals with knowledge about and/or experience working with such subjects, in order to provide expertise and identify techniques for obtaining their informed consent.[56]

The IRB has the authority to require that subjects receive information in addition to what 21 CFR 50.25 requires, if in the judgment of the IRB, the information would meaningfully add to the protection of the rights and welfare of the subjects (21 CFR 56.109(b)). For example, the IRB may determine that local circumstances necessitate the inclusion of additional information relevant to the informed consent process for prospective subjects from that particular community.

HHS recommends that IRBs consider whether subjects should be informed of any financial relationships or interests that are associated with the clinical investigation, such as payments for services, equity interests or intellectual property rights.[57] As indicated in the HHS guidance, some conflicting financial interests in the clinical investigation may affect the rights and welfare of subjects, and IRBs should consider approaches to assure subjects are adequately protected, including providing subjects with information about the financial relationships and interests. IRBs should determine whether subjects should be provided with information regarding the source of funding, funding arrangements, financial interests of parties involved in the clinical investigation, and any financial interest management techniques applied. The IRB should consider the kind, amount, and level of detail of information to be provided to subjects.

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[56] For additional information see Frequently Asked Question #6, "What are some considerations for enrolling subjects with low literacy and numeracy?"; Frequently Asked Question #7, "What are some considerations for enrolling physically challenged subjects?"; and Frequently Asked Question #8, "What are some considerations for enrolling subjects with impaired consent capacity?"

[57] This topic is addressed in the HHS guidance document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection." This guidance, which applies to FDA-regulated clinical investigations as well as human subjects research conducted or supported by HHS, is available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest/index.html.

a. Adequacy and Appropriateness of Wording

The IRB has the authority and responsibility to require that information given to subjects as part of informed consent be in accordance with 21 CFR 50.25.[58] In order to approve the research, the IRB must determine that informed consent will be obtained in accordance with the informed consent regulations (21 CFR 56.111(a)(4)).

Investigators must use an IRB-approved written consent form when documenting informed consent, in accordance with 21 CFR 50.27, except as provided in 21 CFR 56.109(c). Thus, the IRB should review the adequacy and appropriateness of all wording in the consent materials, as well as the overall length and presentation of information. Consent forms that are long, complex, legalistic, and have a high reading level may overwhelm prospective subjects and may inhibit reading of the full document and understanding of the relevant information.

The IRB should ensure that technical and scientific concepts and terms are explained, or common terms substituted, so that the anticipated subject population can understand all provided information (see 21 CFR 50.20).[59] Pictures, diagrams, or other visual aids may be used to improve understanding of medical terms or how an investigational product functions. IRBs may wish to evaluate, through subject discussions, how well the consent materials communicate critical information. Additional guidance on the requirements at 21 CFR 50.20 can be found in section III.A, "General Requirements for Informed Consent" above.

b. Use of Standardized Language

Institutions may develop standard language or a standard format to use in portions of all consent forms (for example, for those elements that deal with confidentiality, compensation, answers to questions, and the voluntary nature of participation) to meet certain FDA regulatory requirements, as well as institutional and other Federal, State, or local requirements.

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[58] See 21 CFR 56.109(b).

[59] Various strategies exist to improve communication with patients, for example, see Doak CC, Doak LG, Friedell GH, Meade CD. Improving comprehension for cancer patients with low literacy skills: strategies for clinicians. CA Cancer J Clin. 1998 May-Jun;48(3):151-62. doi: 10.3322/canjclin.48.3.151. PMID: 9594918.

2. Review of the Consent Process

The investigator should notify the IRB of the consent process to be used. The process may be described in the protocol, or the investigator may provide a brief document describing the process to be used. The materials and procedures used for subject recruitment, which typically include advertisements, must be reviewed and approved by the IRB to ensure that these materials are appropriate, as described in section IV.A.1, "Review of All Informed Consent Materials" (see 21 CFR 56.109(b) and 56.111(a)(4)).[60] The IRB must determine that investigators will seek consent from prospective subjects under circumstances that minimize the possibility of coercion and undue influence (21 CFR 50.20 and 56.111(a)(4)). FDA considers this to include ensuring that the consent process described by the investigator allows sufficient time for prospective subjects to consider the information, provides time and opportunity for the subjects to ask questions and have those questions answered, and allows time and opportunity for the subjects to consider fully whether to participate.

To approve a clinical investigation, the IRB must find that informed consent will be sought from each prospective subject or the subject's LAR and that informed consent will be appropriately documented, in accordance with and to the extent required by 21 CFR part 50 (21 CFR 56.111(a)(4) and (5)). FDA recommends that the IRB inquire as to who will conduct the consent discussion and what procedures will be followed. If procedures other than a face-to-face consent discussion are proposed, such as by telephone, the IRB should consider whether the procedures will provide effective communication and accomplish the goals of the informed consent process. Alternative procedures may be of special concern when the clinical investigation involves complex procedures or when risks may be difficult to comprehend.

FDA regulations authorize the IRB to observe or have a third party observe the consent process, as well as the research (21 CFR 56.109(f)). IRBs should consider using this authority when it may be appropriate[61] or enhance the protection provided to subjects (for example, when the investigator is also

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[60] For further information, see the FDA Information Sheet "Recruiting Study Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recruiting-study-subjects.

[61] In the "Institutional Review Board; Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research," published in the *Federal Register*, November 30, 1978 (43 FR 56174), the Commission stated: "Observation of the consent process or conduct of research is both a difficult and delicate task. The designation of staff or members of the IRB to observe research activities can impose a substantial strain on the limited resources of the IRB. Further, such observation may intrude on confidential relationships or the privacy of individual subjects. IRBs should take these factors into account when determining appropriate means for continuing review of a protocol, and alternatives such as investigator reporting requirements should be considered. However, certain research will warrant observation to assure the protection of subjects, and in such cases IRBs have an obligation to take suitable measures." Id. at 56179.

the treating physician for a prospective subject, when the person conducting the consent interview is relatively inexperienced, or when the clinical investigation involves vulnerable subjects). In addition to observing a sample of consent discussions, the IRB could interview subjects to assess the consent process and evaluate the subjects' understanding of the clinical investigation.

3. IRB Review of Updated Informed Consent Documents

All information given to subjects as part of the consent process is to be reviewed and approved by the IRB (21 CFR 56.109(a)-(b) and 56.111(a)(4)-(5)).[62] During the clinical investigation, new information about the research or changes to the clinical investigation may arise that affect the rights or welfare of subjects. FDA recommends that IRBs have procedures in place for the timely, efficient, and effective review of such new information or changes. This would include procedures for the clinical investigator and/or sponsor to notify the IRB of any significant new findings that arise during the clinical investigation relevant to a subject's decision to continue participation (see section III.C.5, "Providing Significant New Findings to Subjects", and Frequently Asked Question #16). When new information or changes in the clinical investigation warrant revisions of the consent form (and any accompanying changes to the protocol), such revisions must be reviewed and approved by the IRB before the revisions are initiated, except when necessary to eliminate apparent immediate hazards to subjects (21 CFR 56.108(a)(3)-(4)).

Some changes may be reviewed and approved by expedited means, as provided for by 21 CFR 56.110. For example, an IRB may decide expedited review is appropriate for changes to the consent form that reflect minor changes in the protocol or recruitment plan (e.g., new advertising for subjects following initiation of the clinical investigation when the advertisement incorporates wording from the approved consent form). When expedited review is used, if the IRB reviewer is unsure whether the change qualifies for expedited review under 21 CFR 56.110(b), FDA recommends that the reviewer (if other than the IRB chair) consult with the IRB chair. If doubts persist as to whether the change qualifies for expedited review, then the change should be reviewed at a convened meeting of the IRB.[63]

Administrative changes, such as the correction of typographical and spelling errors, and changes in telephone numbers, may be submitted to the IRB at any time, including during continuing review, and do not require formal review and approval. Although such changes do not need IRB review, updated

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[62] This would include all addenda to the consent form and other materials used in the consent process.

[63] As indicated at section IV.B, when new information is added to the consent form that might affect the willingness of already enrolled and actively participating subjects to continue in the clinical investigation, the IRB should determine the need to inform the previously enrolled subjects of the new information and determine their willingness to continue in the research.

versions of the consent form should be sent to the IRB so that they have current copies of the informed consent form on file.[64]

4. Identification of Revised Consent Forms

The IRB should ensure that there is a way to identify a revised consent form so that continued use of a previously approved version does not occur. While not required by FDA regulations, the use of date stamps is one possible mechanism for ensuring use of the most recently approved version of the consent form.

B. The Clinical Investigator

The clinical investigator is responsible for protecting the rights, safety, and welfare of subjects during a clinical investigation, and for ensuring that, unless an exception applies, legally effective informed consent is obtained from each subject or the subject's LAR before that subject takes part in the clinical investigation (see 21 CFR 50.20(a), 312.60, and 812.100). Legally effective informed consent includes meeting all applicable Federal, State, and local laws that require additional information in the informed consent form beyond what FDA regulations require. Sponsors and investigators may wish to seek legal guidance regarding specific local consent requirements applicable to their research.

The clinical investigator should notify the IRB regarding the consent process, including who (e.g., the investigator or another study team member) will conduct the consent discussion. Any information that will be given to subjects to review and discuss as part of informed consent must be submitted to the IRB for review and approval (21 CFR 56.109(a)-(b) and 56.111(a)(4)-(5)). An investigator may not begin the informed consent process with prospective subjects until the IRB reviews and approves the clinical investigation, consent form, and any other information to be given to subjects as part of the consent process (21 CFR 50.20, 50.27, and 56.109).

The clinical investigator's institution may have standard language or a standard format for consent forms (for example, for those elements that deal with confidentiality, compensation, answers to questions, and the voluntary nature of participation). FDA recognizes that investigators may also need to identify and

[64] See section IV.A.4 for guidance regarding identification of the most up-to-date version of the informed consent form.

meet institutional requirements and incorporate them into the consent form for the IRB's initial review of the clinical investigation.

During the clinical investigation, the investigator may need to revise the consent form to address new information that might arise during the conduct of the trial, such as a change to the protocol or new safety information. The investigator will need to obtain IRB review and approval of the revised consent form (21 CFR 50.27 and 56.109). In addition, because the consent form is being modified to reflect new information that might affect the willingness of already enrolled and actively participating subjects to continue in the clinical investigation, the IRB should determine the need to inform the previously enrolled subjects of the new information and determine their willingness to continue in the research (see Frequently Asked Questions #16).

Any new information that is part of the consent process must be reviewed and approved by the IRB as a change in approved research before it is initiated, except where necessary to eliminate apparent immediate hazards to the subject (see 21 CFR 56.108(a)(4)). In the rare event that urgent safety information is provided to the subject prior to IRB approval, the IRB should promptly be notified of both the safety issue and the notification of subjects.

Below are specific areas for consideration by the clinical investigator:

1. Delegation of Consent Discussion

FDA regulations require that the investigator obtain the legally effective informed consent of subjects (21 CFR 50.20, 312.60 and 812.100). If the investigator delegates this responsibility, FDA expects that the individual to whom the responsibility is delegated be qualified by education, training, and experience to perform this activity. The individual obtaining informed consent should be knowledgeable about the clinical investigation and have the appropriate training and credentials to 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. The investigator should have a detailed plan for the supervision and training of staff, and oversight of the clinical investigation, including the informed consent process.[65] Even when a task is delegated to another individual, the investigator remains

[65] See FDA's "Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects" at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects.

responsible for ensuring that legally effective informed consent is obtained for all subjects in accordance with 21 CFR part 50.

2. Financial Relationships and Interests

The clinical investigator should consider whether information related to financial relationships or interests should be provided to subjects.[66] Clinical investigators should consider the potential effects that a financial relationship might have on the clinical investigation or on interactions with subjects. When there are financial relationships or interests, clinical investigators should consider the following actions:

- Including information in the informed consent form, such as:
  - The source of funding and funding arrangements for the conduct and review of the clinical investigation, or
  - Information about a financial arrangement or interest (e.g., stock in the study sponsor, patent on the investigational product) of an institution or an investigator and how it is being managed.

- Using special measures to modify the informed consent process when a potential or actual financial conflict exists, such as:
  - Having another individual who does not have a potential or actual conflict of interest involved in the consent process, especially when a potential or actual conflict of interest could influence the tone, presentation, or type of information presented during the consent process.
  - Using independent monitoring of the consent process.

Although the clinical investigator should consider these issues regarding financial relationships and interests, 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 (see 21 CFR 56.109 and 56.111(a)(4)-(5)).

[66] See the HHS guidance document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest/index.html#.

C. The Sponsor

Sponsors often provide clinical investigators with a model consent form that may be adapted by the clinical investigator to meet local needs. When the consent form for studies that require an IND or IDE application is submitted to FDA for review, FDA's comments are generally directed to the sponsor (see section IV.D.1, "Investigational New Drugs and Biologics," and section IV.D.2, "Investigational Medical Devices"). The sponsor should promptly provide the clinical investigator with any necessary modifications required to satisfy the regulations at 21 CFR 50.25 so that changes can be made to the consent forms. A modified model consent form reflecting the changes may be used to convey the necessary edits. Because the clinical investigator must receive IRB approval before starting the clinical investigation (see 21 CFR 312.66 and 21 CFR 812.110(a)), the sponsor should work closely with the clinical investigator to make certain the modified consent form is reviewed and approved by the IRB. The clinical investigator should provide the sponsor with a copy of the consent form approved by the IRB.

Below are specific areas for consideration by the sponsor:

1. Considerations for Multicenter Clinical Investigations

For multicenter clinical investigations, changes may need to be made to the consent form to address local and institutional requirements. For multicenter clinical investigations reviewed by more than one IRB, when local IRB review results in substantive modifications to the consent form, i.e., changes that affect the rights, safety, or welfare of the subjects, FDA expects the sponsor to share the revisions with all investigators and their IRBs. In this situation it may be more efficient to share the changes with the sites using a modified model consent form, when appropriate. If the multicenter clinical investigation has a central IRB cooperating with local IRBs or human research protection offices, the revisions should be forwarded to the central IRB.[67] Alternatively, local issues may be addressed by the central IRB depending on the review agreement between the local IRB(s) and central IRB. Note that for medical

[67] See "Guidance for Industry, Using a Centralized IRB Review Process in Multicenter Clinical Trials," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/using-centralized-irb-review-process-multicenter-clinical-trials.

device studies that require submission of an IDE application, such changes must be submitted to FDA.[68, 69]

2. Sponsor Personnel

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.[70]

D. The FDA

FDA's regulations for drug (including biologic) and device investigations have different requirements for the submission of informed consent materials (see sections IV.D.1, "Investigational New Drugs and Biologics," and IV.D.2, "Investigational Medical Devices," for additional information). Sponsors are not required to submit informed consent materials to FDA for all clinical investigations (see, for example, 21 CFR 312.2(b) and 21 CFR 812.2(b) and (c)); however, FDA may require that they be submitted in some cases as discussed below.

Generally, when informed consent materials are submitted, FDA reviewers assess the adequacy of the consent form by considering its communication of reasonably foreseeable risks or discomforts to the

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[68] See 21 CFR 812.35(a).

[69] The 2018 Common Rule requires that any institution located in the United States that is engaged in cooperative research conducted or supported by a Federal Department or Agency must rely upon approval by a single IRB for that portion of the research that is conducted in the United States, unless the research is not subject to the provision (45 CFR 46.114(b)). The compliance date for research subject to this provision was January 20, 2020. On September 28, 2022, FDA issued a proposed rule to harmonize with this requirement to the extent practicable and consistent with statutory provisions (see https://www.federalregister.gov/documents/2022/09/28/2022-21089/institutional-review-boards-cooperative-research). The January 19, 2017, final rule revising the Common Rule is available at https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html.

[70] See "Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects.

subject and other elements required by 21 CFR 50.25. In some situations, FDA may find a consent form to be misleading, inaccurate, or incomplete in a way that would make informed consent inadequate and noncompliant with 21 CFR part 50. In these cases, FDA may require that specific revisions be made to address the concern(s) before the clinical investigation can proceed (21 CFR 312.42 and 812.30).

FDA's review of the consent form as part of an IND or IDE application submission does not substitute for the responsibility or authority of the IRB to review and approve the consent form and consent process as a condition for the clinical investigation to begin (21 CFR 56.103(a)). IRBs are responsible for ensuring the adequacy of the information in the consent form and may require modification as appropriate (21 CFR 56.109(a)-(b)).

Below are specific areas FDA considers in its review of the consent form:

1. Investigational New Drugs and Biologics[71]

The IND regulations (21 CFR part 312) do not specifically require submission to FDA of the consent form with the IND. However, if FDA determines that review of the consent form is necessary to make the determination of whether the clinical investigation may safely proceed, the Agency will request that the sponsor submit the consent form for review under 21 CFR 312.23(a)(11).

As a general matter, FDA will review the informed consent form for treatment INDs and treatment protocols (21 CFR part 312, subpart I) and INDs for studies conducted under the Exception From Informed Consent Requirements for Emergency Research (21 CFR 50.24) for consistency with 21 CFR 50.25 (see 21 CFR 50.24(a)(6)).

For other clinical investigations of drugs, FDA often considers the following factors in determining whether to require submission and review of the consent form:

- Nonclinical studies submitted in support of the first administration of a drug in humans have identified an unusual toxicity.
- Unusual known toxicity is associated with the investigational drug, the drug class to which the drug belongs, or with a different drug with characteristics similar to those of the study drug.

[71] For the purposes of this document, unless otherwise specified, all references to "drugs" or "drug products" include human drug products and biological products that are also drugs.

- The study subject population is particularly vulnerable.
- The study design is unusual for the therapeutic class.
- The clinical investigation is a postmarketing safety clinical trial, required under section 505(o) of the FD&C Act to assess a serious risk.
- The clinical investigation has significant potential for serious risk to human subjects.
- The clinical investigation involves asking subjects to forgo or delay effective treatment that is known to decrease long-term mortality or irreversible morbidity.
- FDA has other confidential or proprietary information not available to an IRB that affects the assessment of whether the informed consent form adequately addresses risks.

After reviewing the consent materials, if the FDA review divisions have specific concerns about the adequacy or compliance of the consent materials with 21 CFR part 50, details about these concerns normally will be conveyed to the sponsor in writing. In rare circumstances, FDA may find a consent form to be misleading, inaccurate, or incomplete in a way that makes informed consent inadequate and noncompliant with 21 CFR part 50 to the extent that subjects would be exposed to an unreasonable and significant risk of illness or injury. In these cases, FDA may require that specific revisions be made to address the concern(s) before the clinical investigation can proceed (21 CFR 312.42).

2. Investigational Medical Devices

For clinical investigations of medical devices for which an IDE application is required to be submitted to FDA, the sponsor must include in the application copies of all forms and informational materials that will be provided to subjects to obtain informed consent (21 CFR 812.20(b)(11)). FDA reviews the consent form to ensure that it conforms to the requirements of 21 CFR part 50. After review, FDA may send the sponsor a letter citing deficiencies regarding the consent form (21 CFR 812.30(a) and (b)(4)). The clinical investigation may not begin until the sponsor has corrected these deficiencies (21 CFR 812.30(a) and 812.42). In the event an IRB requires substantive changes to the informed consent document after IDE approval, i.e., changes that affect the rights, safety, or welfare of the subjects, the sponsor must submit the revised informed consent document to FDA for its review and approval prior to implementing the changes to the document (see 21 CFR 812.35(a)).

V. FREQUENTLY ASKED QUESTIONS

This section of the guidance document is intended to provide answers to frequently asked questions about FDA's regulations for the protection of human subjects. The numbers assigned to the questions are intended for ease of reference and do not represent the frequency with which these questions are asked.

1. What are some considerations for enrolling a child[72] into a clinical investigation?

FDA regulations provide additional safeguards for children enrolled in clinical investigations, as described in 21 CFR part 50, subpart D.[73] If a child is to be enrolled in a clinical investigation, parental or guardian permission must be obtained in accordance with the requirements for informed consent in 21 CFR part 50 (21 CFR 50.55(e)) [74] and be documented in accordance with 21 CFR 50.27 (21 CFR 50.55(f)). When appropriate, the assent of the child also must be obtained (see 21 CFR 50.55(a)-(d)). As with informed consent for adult subjects, the exceptions to informed consent requirements described in section III.A.1, "Exceptions to Informed Consent", apply to research involving children.

The IRB may determine that the permission of one parent is sufficient for clinical investigations involving no greater than minimal risk to children to be conducted under 21 CFR 50.51, or clinical investigations involving greater than minimal risk to children but presenting the prospect of direct benefit to individual subjects in accordance with 21 CFR 50.52 (21 CFR 50.55(e)(1)).

For clinical investigations to be conducted in accordance with either 21 CFR 50.53 or 21 CFR 50.54,[75] where permission is to be obtained from parents, the permission of both parents is required unless one

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[72] For purposes of 21 CFR part 50, the term *children* means "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted." See 21 CFR 50.3(o).

[73] FDA promulgated 21 CFR part 50, subpart D, "Additional Safeguards for Children in Clinical Investigations," as an interim rule in April 2001 (see 66 FR 20589, April 24, 2001; https://www.govinfo.gov/content/pkg/FR-2001-04-24/pdf/01-10008.pdf), and issued a final rule in February 2013 (see 78 FR 12937, February 26, 2013; https://www.govinfo.gov/content/pkg/FR-2013-02-26/pdf/2013-04387.pdf).

[74] Note that the waiver of parental permission found in 45 CFR 46.408(c) is not available under FDA's regulations.

[75] 21 CFR 50.53 applies to clinical investigations presenting greater than minimal risk and no prospect of direct benefit to the individual subjects, but that are likely to yield generalizable knowledge about the subjects' disorder or condition. 21 CFR 50.54 applies to clinical investigations that do not meet the requirements of 21 CFR 50.51, 50.52, or 50.53 but present a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child (21 CFR 50.55(e)(2)).[76]

The general requirements for informed consent, found in 21 CFR 50.20, 21 CFR 50.25 and 21 CFR 50.27, apply to parental permission (21 CFR 50.55(e)-(f)). When obtaining parental permission, in the event the parents of a child do not understand English, the parental permission must be obtained and documented in language that is understandable to the parents (21 CFR 50.20). The 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. Similarly, if child assent is required, the information given to the child should be in language that is understandable to the child.

"Assent" means a child's affirmative agreement to take part in a clinical investigation, not just the failure to object (21 CFR 50.3(n)). Child assent, when appropriate, and parental (or guardian) permission taken together meet the ethical requirement to obtain informed consent. Absent a waiver of the assent requirement (21 CFR 50.55(d)), the IRB must determine that there are adequate provisions for soliciting the assent of children when, in the IRB's judgment, the children are capable of providing assent (21 CFR 50.55(a)). In deciding whether children are capable of providing assent, the IRB must consider the ages, maturity, and psychological state of the children to be involved in the clinical investigation (21 CFR 50.55(b)).[77] A child does not need to fully understand the clinical investigation in order to provide assent, provided the child is capable of understanding the interventions and the related procedures. For example, a child may be able to understand and provide assent if the child understands and agrees to the interventions and/or procedures in the trial (e.g., drawing a blood sample for a test), even though the child may not be capable of understanding a randomized clinical trial.

An IRB may determine that assent is not necessary or may waive the assent requirement in certain situations (21 CFR 50.55(c) and (d)). For example, the assent of children is not a necessary condition for proceeding with a clinical investigation if the IRB determines that the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation (21 CFR 50.55(c)(2)). Also, the IRB may waive the assent requirement for children capable of assenting if the IRB finds and documents that the clinical investigation involves no more than minimal risk to the subjects; the waiver will not adversely affect the rights and welfare of the subjects; the clinical investigation could not practicably be carried out without the waiver; and, when appropriate, the subjects will be provided with

[76] For additional discussion on what is meant by "not reasonably available," see the Secretary's Advisory Committee on Human Research Protections (SACHRP) recommendations at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-d-november-13-2018/indes.html.

[77] FDA recognizes that IRBs may adopt procedures setting an age below which children are presumed incapable of providing assent.

additional pertinent information after participation (21 CFR 50.55(d)). Parental permission requirements (to the extent consent is required under 21 CFR part 50) remain in these circumstances.

When the IRB determines that assent is required, it must also determine whether and how assent must be documented (21 CFR 50.55(g)). Some of the same considerations noted above for determining capability of children to provide assent should be considered when determining whether assent should be in writing or oral.

When a written assent process is appropriate or required by the IRB, FDA does not require the use of a written assent form (21 CFR 50.55(g)), but FDA strongly encourages the use of a separate assent form that is "child-oriented" and developmentally appropriate. A separate assent form does not need to include all of the elements of a consent document but should focus on those aspects of the clinical investigation that may impact on a child's willingness to participate.

Parental permission and child assent should be viewed as an ongoing process throughout the duration of a clinical investigation. If and when a child who was enrolled in a clinical investigation with parental permission reaches the legal age of consent, that subject no longer meets the definition of a child under 21 CFR 50.3(o), and the investigator should obtain the subject's informed consent under 21 CFR part 50, subpart B, prior to performing any further research interventions and/or procedures involving that subject.

In addition, § 50.3(o) defines children as "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted". However, in some situations, a State may grant certain minors of a specific age the right to consent to treatments or procedures on their own behalf. These mature minors do not meet the definition of children for purposes of a clinical investigation that involves solely those "treatments or procedures" for which they can give consent outside the research context and thus, the requirements of 21 CFR part 50, subpart D, do not apply to the research with respect to these minors. Similarly, minors deemed ''emancipated'' by State law, such that they may provide consent to treatments and procedures in the clinical setting, also do not meet the definition of children under § 50.3(o), and the requirements of 21 CFR part 50, subpart D do not apply to the research with respect to these emancipated minors. In these cases, the mature or emancipated minors can consent to participation in FDA-regulated research without the need for parental or guardian permission. For example, if a clinical trial is being conducted in a jurisdiction that has laws that explicitly allow a minor of a particular age, to consent to receive specific sexual transmitted disease (STD) services in the clinical setting, these minors may be able to provide informed consent for participation in a clinical trial of a product intended to treat or diagnose an STD.

2. Are there any additional protections required when enrolling children who are wards of the state?

Children who are wards of the state or any other agency, institution, or entity can be included in a clinical investigation that is approved under 21 CFR 50.53 and 50.54 provided the clinical investigation is either: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards (21 CFR 50.56). In other words, one of these criteria must be satisfied in order for children who are wards to be enrolled in clinical investigations involving greater than minimal risk and no prospect of direct benefit, but likely to yield generalizable knowledge about the subjects' disorder or condition (21 CFR 50.53) or clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (21 CFR 50.54).

If a clinical investigation is approved under 21 CFR 50.56(a), the IRB must require that an advocate be appointed for each child who is a ward (21 CFR 50.56(b)). The IRB must ensure that such an advocate is in place, but the IRB itself is not required to appoint the advocate. The advocate, who may serve as an advocate for more than one child, serves in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*[78] (21 CFR 50.56(b)(1) and (2)). The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation (21 CFR 50.56(b)(3)). The appropriate expertise for an advocate should include, but is not limited to, education and/or experience in pediatric medicine, law, child advocacy, foster parenting, behavioral sciences, or child psychology. The advocate should be adequately informed about the potential risks and benefits of the proposed clinical investigation, and about how the intervention is likely to affect the individual child. The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization (21 CFR 50.56(b)(4)).

Wards of the state can participate in clinical investigations approved under 21 CFR 50.51 (i.e., research involving no more than minimal risk) and 21 CFR 50.52 (i.e., research involving greater than minimal risk but presenting the prospect of direct benefit), and FDA regulations do not require the appointment of an advocate for children who are wards involved in clinical investigations approved under these sections. However, IRBs should consider the appointment of an advocate in such clinical investigations in order to ensure that there is someone who will act in the best interest of the ward(s) for the duration of their participation in the clinical investigation. Before enrolling any child who is a ward in a clinical investigation approved under 21 CFR 50.51 or 21 CFR 50.52, IRBs should ensure that each child has a

[78] FDA considers an individual acting *in loco parentis* to be an individual having the legal authority and responsibility to act in place of a parent.

guardian and/or advocate with the background, experience and commitment to act in the best interest of the child.

3. What are some considerations for enrolling non-English speaking subjects[79]?

Prospective subjects who do not understand English may ask or be asked to participate in a clinical trial in locations where English is the predominant language. The investigators and the IRBs that review such research should carefully consider the ethical ramifications of enrolling or excluding prospective subjects when a language barrier may exist between the investigator(s) and some or all of the prospective subjects. Consistent with the requirement that selection of subjects be equitable (21 CFR 56.111(a)(3)), individuals should not routinely be excluded from participating in research simply because they do not understand English.

When prospective subjects who do not understand English are to be enrolled in a clinical study, IRBs and investigators must ensure that the information given to such prospective subjects or their LARs is in language understandable to the subjects or their LARs (21 CFR 50.20). FDA considers *understandable* to mean that the information presented to prospective subjects is in a language and at a level they can comprehend, including an explanation of scientific and medical terms.

The IRB must review and approve consent documents (long form or short form with written summary) that are to be used by investigators to document the informed consent of subjects (21 CFR 50.27(a) and 21 CFR 56.111(a)(4) and (5)). When translation and interpretation are needed for written and oral information that is to be presented to subjects, FDA recommends that the IRB review, and if appropriate, approve reasonable procedures for ensuring that the translations will be prepared by a qualified individual or entity, and that interpretation assistance is available.

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[79] FDA strongly encourages stakeholders to ensure that informed consent documents are accessible to individuals with limited English proficiency. To the extent an organization receives Federal financial assistance from HHS, Title VI of the Civil Rights Act of 1964 and its implementing regulations require the organization to take reasonable steps to provide meaningful access by individuals with limited English proficiency. See 42 U.S.C. 2000d, *et seq*; 45 CFR part 80; *see also* Section 1557 of the Affordable Care Act, 42 U.S.C. 18116, which provides similar protections as those under Title VI in health programs and activities receiving Federal financial assistance. This guidance provides information to assist institutional review boards (IRBs), clinical investigators, and sponsors in complying with FDA's informed consent regulations for clinical investigations. It does not provide guidance on how to comply with any regulatory obligations stemming from a source outside of the statutes FDA administers and FDA's regulations.

A protocol amendment in which the investigator proposes to include use of translated informed consent documents for a study already approved by the IRB with English language consent documents may be considered no more than a minor change to the research and may qualify for an expedited review procedure under FDA regulations at 21 CFR 56.110(b).

FDA notes that informed consent should be viewed as an ongoing process throughout the course of a subject's involvement in the research. Therefore, FDA recommends that whenever subjects who do not understand English are involved in research, appropriate interpreter services be made available throughout the course of the research.

4. What process should be followed when it is expected that subjects who do not understand English will be enrolled?

When investigators reasonably expect that the subject population for a proposed study will include individuals who do not understand English and can anticipate the specific language(s) that these individuals will understand, the investigator should submit to the IRB, prior to its initial review, appropriately translated consent documents (i.e., either a long form or a short form with written summary). The investigators should also provide the IRB with a description of how interpreters for oral communication will be made available to subjects during the research. For example, if the investigators reasonably expect that the subject population for a proposed research protocol will include individuals who only understand Spanish and others who only understand Russian, the investigators should submit to the IRB, prior to its initial review, consent documents (i.e., either a long form or a short form with written summary) translated into Spanish and Russian along with a description of how interpreters for oral communication in Spanish and Russian will be made available during the research. The next Frequently Asked Question describes the process that may be followed when the enrollment of a subject who does not understand English is unexpected and no prior arrangements for this possibility have been made.

5. What process should be followed when the enrollment of subjects who do not understand English is <u>not</u> expected?

FDA recognizes that investigators on occasion face circumstances where: (1) a prospective subject who does not understand English is eligible for an IRB-approved research protocol; and (2) the investigator has an IRB-approved English language long form but does not have an appropriate IRB-approved written translation of the long form or written summary for the study. This may occur because neither the investigator nor the IRB reasonably expected enrollment of a subject for whom a translation would be needed.

For some research, the timeframe for subject enrollment may provide sufficient time for the preparation of an appropriately translated long form or an appropriately translated written summary to be used with a short form. When translation or interpretation is needed for written and oral information that is to be presented to subjects, FDA recommends that the IRB review, and if appropriate, approve reasonable procedures for ensuring that the translations will be prepared by a qualified individual or entity, and that interpretation assistance is available.

For other research, the timeframe for enrollment of a subject who does not understand English may not provide sufficient time for preparation of appropriately translated consent documents. As a contingency for this situation, many IRBs have arranged for translation of a generic short form in multiple languages that satisfies the requirements of FDA regulations at 21 CFR 50.27(b)(2) and have prospectively approved the use of such short forms for enrollment of subjects who do not understand English as needed for any research protocol. In such circumstances, FDA considers procedures that include the following sequential steps to be one acceptable way of obtaining and documenting the informed consent of the subject:

Step 1 – Determine That There is Sufficient Justification to Enroll the Subject Without Using a Translated Long Form to Document the Subject's Informed Consent

The investigator, in consultation with the IRB chairperson (or another IRB member designated by the chairperson, hereafter referred to as designee) whenever feasible, determines that there is sufficient justification (e.g., due to a limited therapeutic window) for obtaining the subject's consent without waiting for a translated long form to be reviewed and approved by the IRB prior to enrollment of the subject. In making a decision to allow enrollment of a subject who does not understand English into a research protocol without waiting for a written translation of the long form, the investigator (and whenever feasible the IRB chairperson or designee) should consider whether the consent process, under this circumstance, will provide the subject with sufficient opportunity to understand the information being presented. If consent is sought and the investigator believes that the prospective subject has not understood the information presented, then the individual should not be enrolled in the research.

Step 2 – Obtain and Document the Subject's Informed Consent in Accordance with FDA Regulations at 21 CFR 50.20, 21 CFR 50.25 and 21 CFR 50.27 Using a Translated Short Form and the English Language Version of the Long Form as the Written Summary

In accordance with the requirements of 21 CFR 50.27(b)(2), informed consent is documented using a short form that has been translated into a language understandable to the prospective subject and approved by the IRB. As a prerequisite to using this procedure, the investigator must have available a short form written in a language understandable to the prospective subject or LAR and previously approved by the IRB (21 CFR 50.20 and 21 CFR 50.27(a)). To meet this prerequisite, the IRB must

require that the sponsor or investigator arrange for translation of a generic short form into a language understandable by the prospective subject or LAR, and the IRB must have approved the prospective use of such short forms for enrollment of subjects who do not understand English, as needed. Additionally, the IRB must approve a written summary of what is to be said to the subject or the LAR (21 CFR 50.27(b)(2)). The IRB-approved English long form often serves as this written summary. The translator should be fluent in both English and in the subject's language. It may be appropriate to have a translator available for all subsequent study visits to relay information between the subject and study personnel.

The procedure for obtaining and documenting the subject's informed consent with a translated short form and an English version of the long form includes the following:

(1) The investigator (or their designee) obtaining informed consent, with the assistance of an interpreter if needed (e.g., if the investigator is not bilingual), provides orally to the subject the elements of informed consent required by FDA regulations at 21 CFR 50.25 and any additional pertinent information included in the IRB-approved English version of the long form. This presentation may be an oral translation of the IRB-approved English version of the long form. The oral presentation must be in language understandable to the subject (21 CFR 50.20). The investigator, with the assistance of an interpreter if needed, answers any questions from the prospective subject. There must be a witness to the oral presentation who must not be the person obtaining informed consent (21 CFR 50.27(b)(2)). Furthermore, FDA strongly recommends the witness be fluent in the language of the oral presentation. The witness must, at a minimum, have sufficient proficiency in the language of the oral presentation to be able to attest to the information that was to the presented orally to the prospective participant (21 CFR 50.27(b)(2).) In addition, if possible, the witness should not be related to the subject.

(2) At the time informed consent is sought, the subject is given the IRB-approved translated short form and a copy of the IRB-approved English version of the long form, which serves as the written summary.

(3) The short form is signed and dated by the subject or LAR.

(4) The witness signs both the short form and the copy of the IRB-approved English version of the long form. (Note that when an interpreter assists the person obtaining consent, the interpreter may serve as the witness, but is not required to do so.)

(5) The person actually obtaining consent signs the copy of the IRB-approved English version of the long form.

Step 3 – Take Additional Actions Following Subject Enrollment

After the subject has been enrolled in the research, the investigator takes the following additional actions:

(1) If a subject was enrolled in the research using an untranslated long form to serve as the written summary, and if the investigator did not consult with the IRB chairperson (or designee) prior to enrollment of the subject who does not understand English, the investigator should promptly notify the IRB chairperson (or designee) that such a subject was enrolled.

(2) The investigator must obtain a translated copy of the IRB-approved English version of the long form that served as the written summary, which should be done promptly. The investigator promptly submits it to the IRB for review and approval. Once the translated long form/written summary is approved by the IRB, the investigator must provide it to the subject or LAR and should do so as soon as possible. FDA considers this step essential to the requirement that informed consent be documented by the use of a written consent document and that the subject be provided a copy (21 CFR 50.27). Many of the clinical investigations regulated by FDA involve ongoing interventions and may involve long-term follow-up. For this reason, translation of the long form is critically important as a means of providing subjects or their LAR an ongoing source of information understandable to them.

Additionally, as noted above in Frequently Asked Question #3, FDA recommends that whenever subjects who do not understand English are involved in research, appropriate interpreter services be made available throughout the course of the research.

6. What should be considered when enrolling subjects with low literacy and numeracy?

Although a competent person who does not read and write well can give informed consent and enroll in a clinical investigation, the sponsor, clinical investigator, and IRB should consider whether any modifications to the informed consent process are necessary to ensure that the informed consent process is understandable.

For subjects with apparent low literacy and/or low numeracy, oral presentation of the information contained in the consent document is especially important. When the elements of informed consent are presented orally to the subject or the subject's LAR, the IRB may want to consider approving the use of a short form and written summary (21 CFR 50.27(b)(2)), which includes a witness to the oral presentation of the informed consent elements who also signs the consent document (see section III.E.4.b, "Short Form"). It should be noted that, even if the information is presented orally, the subject or the subject's LAR is required to sign the consent form (whether the long form or short form is used) unless the IRB has waived documentation of informed consent under 21 CFR 56.109(c).

Subjects who cannot write can indicate their consent by "making their mark" on the consent document, in lieu of signing and dating the consent form when consistent with applicable law. In these situations, a note should be included in subject case histories required to be maintained under 21 CFR 312.62(b) or 21

CFR 812.140(a)(3) indicating the reason for the lack of a signature and date as required by 21 CFR 50.27(a). The date consent was obtained should be recorded in this note.

7. What should be considered when enrolling subjects with physical or sensory disabilities?

A person with physical or sensory disabilities (for example, physically unable to talk or write or has hearing or visual loss) can enroll in a clinical investigation if competent and able to signal consent consistent with applicable law. Enrolling such subjects into a clinical investigation 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. The records relating to the clinical investigation must include documentation of the informed consent process (21 CFR 50.27) unless excepted under 21 CFR 56.109(c). FDA recommends including in subject case histories required under 21 CFR 312.62(b) or 21 CFR 812.140(a)(3) a description of the specific means by which the prospective subject communicated agreement to take part in the clinical investigation and how questions were answered. FDA recommends that investigators provide reasonable modifications and auxiliary aids and services when necessary to meet the specific needs of the study population.[80] For example, for subjects with vision disabilities, the investigator could use an audio recording of the contents of the consent form or a consent form with enlarged font, depending on the degree of impairment.

8. What should be considered when enrolling adult subjects with impaired consent capacity? [81]

Consent capacity is a person's ability to understand information relevant to the decision to enroll in a study, that is, to weigh the risks and benefits of participation, to appreciate the available alternatives (including nonparticipation), to reach an informed and voluntary decision regarding participation, and to communicate that decision. Consent capacity also depends, in part, on the complexity of the decision that

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[80] FDA strongly encourages stakeholders to ensure that informed consent documents are accessible to individuals with disabilities. To the extent an organization receives Federal financial assistance from HHS, the organization must comply with the Rehabilitation Act of 1973. This guidance provides information to assist IRBs, clinical investigators, and sponsors in complying with FDA's informed consent regulations for clinical investigations. It does not provide guidance on how to comply with any regulatory obligations stemming from a source outside of the statutes FDA administers and FDA's regulations.

[81] For further information on consent capacity, see "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider," National Institutes of Health (NIH), Office of Extramural Research, available at https://grants.nih.gov/grants/policy/questionablecapacity.htm and SACHRP's "Recommendations Regarding Research Involving Individuals with Impaired Decision-making," available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2009-july-15-letter-attachment/index.html.

confronts the prospective subject, which may take into account such factors as study design, risks, and anticipated benefits.

Impaired consent capacity may involve partial impairment, impairment that fluctuates over time, or complete impairment. For example, consent capacity can be affected by a wide range of disorders and conditions, such as dementia, stroke, traumatic brain injury, intellectual and developmental disabilities, serious mental illness, intoxication, and delirium.

Enrollment of subjects with partial impairment may require modifications to the consent form and process to enable those subjects to consent on their own behalf. When a subject's consent capacity is sufficiently impaired that the subject is unable to provide legally effective informed consent, the subject may not be enrolled unless the subject's LAR consents on the subject's behalf (21 CFR 50.3(l) and 50.20).

IRBs and investigators should carefully consider whether the inclusion in research of individuals who lack consent capacity is ethically appropriate and scientifically necessary. Whenever individuals with impaired consent capacity (partial, fluctuating, or complete) are or may be enrolled in clinical studies, ethical and procedural challenges arise. Considerations that may help address these challenges and provide additional safeguards include:

- Assessing consent capacity of prospective subjects, for example, through use of an independent, qualified professional and a process that includes: (1) documentation of elements of capacity (such as understanding information, showing evidence of choice, showing rational reasoning, understanding the nature of the situation, and showing reasonable understanding of outcome of choice); and (2) assessments at the time of consent, at periodic intervals, and when a subject's family member expresses concern about the subject's study participation.
- Establishing a waiting period in the decision-making process to allow additional time for decision-making.
- Using methods to enhance consent capacity, for example through (1) simplification and/or repetition of information, (2) involvement of a subject advocate or trusted family member/friend to assist when sharing information about the clinical investigation, and (3) refraining from discussions during periods of heightened impairment, when possible.
- Assessing a subject's understanding after information about the clinical investigation has been imparted, for example, through use of a questionnaire.
- Re-assessing consent capacity after initiation of the clinical investigation for subjects with progressive disorders whose cognition may decline.
- Involving an LAR either initially or later in the clinical investigation if consent capacity diminishes.

- Assessing whether prospective subjects who cannot provide legally effective consent on their own behalf may nonetheless be able to provide some form of oral agreement at the outset of the study and, as appropriate, throughout the course of the research (e.g., for subjects with progressive disorders), and how such oral agreement would be documented. In such a circumstance, an LAR would need to provide documented written consent.
- Emphasizing the voluntary nature of the decision to participate and the right to withdraw at any time.
- Determining whether the IRB or a third party should observe the consent process.

9. Who can serve as a legally authorized representative (LAR) and what is their role?

FDA regulations define an LAR as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" (21 CFR 50.3(l)). The key point to consider when determining who may serve as an LAR is that the LAR must be authorized under applicable law to consent on behalf of the prospective subject to the procedure(s) involved in the clinical investigation.

In the United States, the legal authority for who may serve as an LAR is determined by State and local law. Where applicable law exists to determine who is authorized to serve as an LAR to consent to an individual's participation in research, consent must be obtained from an LAR in accordance with this law. Institutions, IRBs, and investigators should have the ability to access information regarding applicable laws for the clinical investigations they conduct or oversee, when necessary. If the IRB, investigator, or sponsor is uncertain about State and local laws governing who can serve as an LAR, they should consult with their institution and/or legal counsel.

Once identified, an LAR may sign the informed consent form for the prospective subject, should that individual be incapable of providing their own informed consent. Additionally, the LAR should be consulted to make decisions on behalf of the subject and to assure that any such decisions are in the subject's best interest throughout the duration of the subject's participation in the clinical investigation.

The inclusion of individuals who lack the ability to consent for themselves presents unique ethical and procedural challenges for IRBs and investigators. In such situations, consent to research by an LAR is an acceptable alternative under FDA's regulations. 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 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. In a situation in which a prospective subject is capable of providing informed consent at the onset of a clinical investigation but is 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 once the subjects' conditions warrant it.

10. How can informed consent be obtained through electronic methods?

FDA supports the use of electronic processes to obtain informed consent.[82] Electronic media are being used to provide information usually contained within a paper informed consent form, to evaluate the subject's comprehension of the information presented, and to document the consent of the subject or the subject's LAR. Electronic processes to obtain informed consent may use 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. Additional guidance on the use of electronic informed consent in clinical investigations can be found in the FDA guidance entitled, "*Guidance for Institutional Review Boards, Investigators, and Sponsors, Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers*".[83]

11. Can a subject participate in more than one clinical investigation simultaneously?

Some subjects may wish to participate simultaneously in more than one clinical trial. Enrollment in more than one clinical investigation 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 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). 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.

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[82] Please see footnote 80.

[83] See FDA "Guidance for Institutional Review Boards, Investigators, and Sponsors, Use of Electronic Informed Consent in Clinical Investigations – Questions and Answers," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-informed-consent-clinical-investigations-questions-and-answers.

Sponsors generally include prohibitions related to the use of concomitant medications in the protocol or restrict (via exclusion criteria) inclusion of subjects who have participated in another clinical investigation within a specified period of time (for example, the washout period before a subject can enroll in a new clinical investigation). Implied in the prohibitions on concomitant medications is the idea that subjects should generally not participate in more than one clinical investigation at a time. Investigators should inquire about multiple enrollments and, when appropriate, discourage this practice in the consent document and during informed consent discussions. Further, 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.

12. How should data be handled when an enrolled subject decides to withdraw from a trial?

Under FDA regulations, data collected on subjects up to the time of withdrawal from clinical investigations of drugs and devices conducted under an IND or IDE must remain in the study database (see, e.g., 21 CFR 312.62(b) and 812.140(a)(3)).[84] If a subject withdraws from a study, removal of data that were already collected would undermine the scientific validity, and therefore the ethical integrity, of the research. Such removal of data could also put enrolled subjects, future subjects, and eventual users of marketed products at an unreasonable risk and could compromise FDA's ability to perform its mission to protect public health and safety by assuring the safety and effectiveness of regulated medical products.

FDA recommends that subjects be advised in the consent document that the data collected on them up until the point of their withdrawal will remain part of the study database and may not be removed. An investigator should ask a subject who is withdrawing whether they wish to withdraw from the investigational interventions only and are willing to continue in the clinical investigation for follow-up of associated clinical outcome information. If a subject withdraws from the interventional portion of the clinical investigation but agrees to continued follow-up not addressed in the original consent document, the investigator must obtain the subject's informed consent for this limited participation using an IRB-approved consent document (21 CFR 50.20 and 50.27(a)). If a subject withdraws from the interventional portion of a clinical investigation and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access the subject's medical record or other confidential records that would require additional consent from the subject (21 CFR 50.20). However, such records

[84] FDA regulations (see 21 CFR 312.62 and 812.140(a)(3)) require investigators to prepare and maintain adequate case histories recording all observations and other data pertinent to the investigation on each subject. For further discussion, see FDA "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-retention-when-subjects-withdraw-fda-regulated-clinical-trials; and OHRP guidance, "Withdrawal of Subjects from Research Guidance," available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-withdrawal-of-subject/index.html.

may be accessed consistent with the original consent process, without additional consent under FDA's regulations, to obtain information collected prior to the subject's withdrawal from the study.

An investigator may consult publicly available sources of information to determine a subject's vital status (and if deceased, cause of death) after a subject withdraws from a clinical investigation. This activity does not require subject consent because the information is publicly available.

13. What steps should be taken to inform subjects when a study is suspended or terminated? [85]

A clinical trial may be suspended and possibly terminated for a variety of reasons. When a study is suspended, IRBs, sponsors, and investigators should consider whether subjects should be notified, and if so, when, especially given that during a study suspension, complete information may not be available. Although the IRB has the authority to require that information be provided to subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects (21 CFR 50.109(b)), all parties should consider what information should be shared with subjects in order to ensure that their rights and welfare are protected, that they are not put at risk, and that they receive appropriate care, if indicated. The parties involved, including the subjects' treating physicians (if different from the investigator), as appropriate, may need to help determine whether it is in the best interests of currently enrolled subjects to (a) continue receiving the interventions that were being administered to subjects under the study at the present site, (b) be transferred to another study site (if the study is only suspended at certain sites) so that participation of the subjects in the study may continue, or (c) be transitioned to medical management outside of the research context. Continuation of subjects on the test article may be appropriate, for example, when the test article holds out the prospect of direct benefit to the study subjects or when withholding the test article poses increased risk to study subjects. In general, information about these considerations should be shared with subjects so that they may understand the changes affecting their participation in the study and to allow them to make informed decisions about their continued participation.

If a study is terminated, study subjects should be provided with as much information as possible regarding the reason for the termination. Such a discussion not only recognizes their valuable participation in the study but also helps explain the scientific value of the information obtained due to their willingness to participate in clinical research. Such a discussion provides an opportunity to address questions subjects may have about an investigational product that was administered to them (e.g., immediate safety

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[85] For further discussion, see "Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-continuing-review-after-clinical-investigation-approval. See section III.H.2, "Suspension or Termination of IRB Approval."

concerns, ability to participate in another clinical trial, and appropriate waiting period to do so) and what long-term follow-up may be available or necessary. If the reason for the study termination involves a safety concern that may impact the future medical care of the study subjects, it would be important to discuss appropriate follow-up procedures with the subjects and possibly the subjects' primary care provider(s).

14. Should subjects be informed of aggregate study results at the completion of a trial?

FDA recognizes that subjects are frequently interested in the aggregate results of the clinical investigation in which they were enrolled. FDA supports the return of aggregate research results and recommends that they be returned to subjects in a clear and comprehensible manner. Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA), including its implementing regulations in 42 CFR part 11, requires the "responsible party" (usually the sponsor or principal investigator) of certain clinical trials of drug products (including biological products) and device products (referred to in FDAAA as "applicable clinical trials") to register the trials and submit summary results information to the government-operated clinical trials data bank, www.ClinicalTrials.gov, within a certain time period.[86] Summary results information submitted to ClinicalTrials.gov is made publicly available in the databank.[87] As discussed in section III.D, "Elements of Informed Consent for Applicable Clinical Trials" above, FDA issued a final rule[88] that amends the informed consent regulations (21 CFR 50.25) to require that the informed consent documents for applicable clinical trials include the specific statement that is provided in the regulation to inform subjects that clinical trial information for such clinical trials will be available at www.ClinicalTrials.gov but it will not include information that can identify subjects individually.

For clinical trials that are not "applicable clinical trials," the sponsor or principal investigator may voluntarily register the clinical trial and submit summary results information to the databank.[89] If a sponsor or principal investigator plans to submit summary results information from the trial voluntarily, nothing would prevent an investigator, sponsor, or IRB from informing prospective subjects of the plan to

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[86] See section 801(a) of FDAAA, Pub. L. 110-85, adding 42 U.S.C. §282(j); https://uscode.house.gov/view.xhtml?req=(title:42%20section:282%20edition:prelim)%20OR%20(granuleid:USC-prelim-title42-section282)&f=treesort&edition=prelim&num=0&jumpTo=true . See also 81 FR 64982 (September 21, 2016), available at https://www.govinfo.gov/app/details/FR-2016-09-21/2016-22129.

[87] See 42 U.S.C. § 282(j)(3)(B)(ii). https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=87

[88] 76 FR 256 (January 4, 2011), available at https://www.govinfo.gov/content/pkg/FR-2011-01-04/pdf/2010-33193.pdf.

[89] We note that if a sponsor or principal investigator does choose to voluntarily register a clinical trial or submit summary results information for it, they may be subject to additional requirements. See 42 CFR 11.60.

submit such information in an appropriate manner. Informed consent forms can direct subjects to www.ClinicalTrials.gov, where subjects can obtain certain overall aggregated summary study results information. Investigators and sponsors can describe other plans in the consent form for informing subjects of the outcomes of the clinical investigation.

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. However, if the plan to share aggregated study results is developed after the study is closed with the IRB, the IRB does not need to review the sponsor's plan to share the aggregate results.[90]

15. Is informed consent required to review patient records?

Sponsors and investigators may seek to review patient medical records for a variety of reasons related to a clinical investigation. Whether the record review is considered part of the clinical investigation, as defined under FDA's regulations at 21 CFR 50.3(c) and 21 CFR 56.102(c), is determined by the IRB on a case-by-case basis. If the record review is part of the clinical investigation, then informed consent from the subject for the record review is required under 21 CFR part 50.

A survey of patient records at a site may be performed to determine whether the site has a sufficient number of patients with the condition of interest for the clinical investigation to be feasible. Such a survey is in preparation for a clinical investigation and does not fall within the definition of a clinical investigation and, therefore, does not require informed consent under FDA's regulations. However, sponsors and investigators will need to comply with all applicable requirements under HIPAA and other applicable laws in these circumstances.

A patient's records may be reviewed to determine whether the patient is eligible for a clinical investigation. In order to facilitate this process, limited information about the prospective subject may be recorded. It should be noted, however, that only information to establish the patient's eligibility for the study and contact information should be recorded. This 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. Even though

[90] For additional discussion of the return of aggregate study results and IRB review, see SACHRP's recommendations on this topic at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2015-april-24-attachment-d/index.html.

informed consent is not required by FDA regulations in these instances, 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). Many institutions have privacy boards to help fulfill this function or they may give the IRB this responsibility. Review by these entities may be required by the institution prior to these record review activities.

If a patient's record does not include the basic information necessary to determine whether the patient is eligible for the clinical investigation, additional information may be needed about the prospective subject. Obtaining informed consent may be required prior to obtaining the additional information. Please see the FDA Information Sheet "Screening Tests Prior to Study Enrollment,"[91] for a discussion of when informed consent would be required under FDA regulations.

The records of a subject who was previously enrolled in a clinical investigation may be reviewed retrospectively to collect information under certain limited circumstances, consistent with the original consent process. If this retrospective review is to gather information that was intended to be collected but was missed (that is, the protocol required collection of the information, but it was not reported in the case report form and the purpose of the review is merely to fill in gaps in the record), then this review is considered to be covered by the previous informed consent obtained for the clinical investigation and further consent from the subject is not required.[92]

In cases where the additional information to be collected goes beyond what was identified in the original protocol and disclosed in the original consent document, obtaining informed consent for the collection of additional information for use in a clinical investigation would be required (21 CFR 50.20). FDA recommends that the clinical investigator anticipate the need for obtaining further information and obtain consent for medical records review and data collection as part of the initial consent process.

In all of the above situations, privacy and patient confidentiality issues should be considered. The clinical investigator, sponsor, and institution should consider whether institutional policies or other statutory or regulatory requirements are applicable to the review of patient records (such as under the HIPAA Privacy

[91] FDA Information Sheet "Screening Tests Prior to Study Enrollment" is available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment.

[92] For further guidance regarding the consequences of a subject's decision to withdraw from a clinical investigation see section III.C.4.

Rule (45 CFR parts 160 and 164, subparts A and E) or the HHS human subject protection regulations at 45 CFR part 46).[93]

16. How should subjects be informed of new information that may affect their willingness to continue participation in the research?

During the conduct of a clinical investigation, significant new information (e.g., protocol changes, new findings related to safety) may arise that could affect a subject's willingness to continue their participation in the clinical trial. When this occurs, the IRB should determine whether currently enrolled subjects should be provided with the new information and given an opportunity to affirm their willingness to continue in the research. In the research community this process is frequently referred to as "reconsent." FDA regulations do not use or define the term reconsent, nor do FDA regulations specify the process an IRB should use to determine the need or method to inform subjects who are already enrolled in the study of the new information. As such, IRBs have flexibility to establish procedures they think are appropriate to provide for subjects to have an opportunity to affirm their willingness to continue in the research.

As a consequence of new information, the investigator may need to revise the consent form to include the new information for new enrollees and obtain IRB review and approval before it is used (see 21 CFR 50.27(a) and 56.109). Because the consent form is being modified to reflect the new information, the IRB should determine whether the investigator should provide currently enrolled subjects with the new information either with the revised informed consent document or an alternative method such as a consent addendum or information sheet describing the new information.

When a revised consent form is used to inform enrolled subjects of new information and to document their willingness to continue in the trial, the investigator may use a prepared summary of the change(s) to reduce confusion about the change(s) and aid in presenting the new information. After the discussion of the new information and an acknowledgement of understanding by the enrolled subject, the enrolled subject should be asked to sign and date the revised consent document if they are willing to continue participating in the research. When an alternative method is used, such as a consent addendum or information sheet, the enrolled subject should be asked to sign and date the consent addendum or

[93] Please contact the Office for Civil Rights (https://www.hhs.gov/programs/hipaa/index.html) for additional information on HIPAA, including the Privacy Rule, or the Office for Human Research Protections (https://www.hhs.gov/ohrp/) for additional information on 45 CFR part 46.

information sheet.[94] FDA recommends that a copy of the signed and dated consent addendum or information sheet be provided to the subject.

In general, FDA does not believe it is necessary for subjects who have completed their active participation in the study to be informed of new information unless the new information relates to risks that may manifest after such participation. In this situation, it may be appropriate to provide previously enrolled subjects with counseling regarding any risk that may be warranted. Similarly, FDA does not believe it is necessary to inform subjects who are still actively participating of new information when the change will not likely affect their decision to continue in the study (e.g., an increase in the number of study subjects). However, IRBs may recommend that the investigator provide the above-discussed summary to all subjects (previously and currently enrolled subjects) for their awareness.

[94] For additional discussion on providing new information to previously enrolled subjects, see SACHRP's recommendations on the topic at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/april-7-2020-attachment-a/index.html.