
Informed Consent Information Sheet

Guidance for IRBs, Clinical Investigators, and Sponsors

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health**

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Informed Consent Information Sheet

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Informed Consent Information Sheet **Guidance for IRBs, Clinical Investigators, and Sponsors¹**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide information to institutional review boards (IRBs), clinical investigators, and study sponsors about FDA's informed consent regulations. This guidance, when finalized, will supersede "*A Guide to Informed Consent*," issued in September 1998, by the Office of Health Affairs, FDA. To enhance human subject protection and reduce regulatory burden, the Department of Health and Human Services, Office for Human Research Protections and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This guidance document was developed as a part of these efforts.

The U.S. Department of Health and Human Services announced in 2011 that the federal government is contemplating various ways of enhancing the regulations overseeing research on human subjects. Before developing proposed changes to the regulations – which have been in place since 1991 and are often referred to as the Common Rule – the government issued an Advance Notice of Proposed Rulemaking (ANPRM) seeking the public's input on an array of issues related to the ethics, safety, and oversight of human research. The changes under consideration can be found in the July 26, 2011 Federal Register in an ANPRM titled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators" (available at www.hhs.gov/ohrp/humansubjects/anprm2011page.html). FDA issues this draft guidance while the agencies continue to explore potential changes to the Common Rule. To the extent that issues presented in this draft guidance intersect with the Common Rule FDA plans to coordinate with other relevant federal agencies to facilitate consistency across policies.

¹ This guidance document was developed by the Office of Medical Products and Tobacco (OMPT), the Office of Good Clinical Practice (OGCP), 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).

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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.² The informed consent requirements in 21 CFR part 50 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(c).) If the clinical investigation is conducted or supported by the Department of Health and Human Services (HHS) and involves an FDA-regulated product, then the study is subject to both 45 CFR part 46 and 21 CFR part 50, meaning that both sets of regulations must be followed. Where the regulations differ, the regulations that offer the greater protection to human subjects should be followed.

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 of the word *should* in Agency guidances means that something is suggested or recommended, but not required. The use of the word *must* in Agency guidances means that something is required under the FDA regulations.

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. FDA believes that obtaining a subject’s oral or written informed consent is only part of the consent process. Informed consent involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject’s comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject’s voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires. To be effective, the process must provide sufficient opportunity for the subject to consider whether to participate. (21 CFR 50.20.) FDA considers this to include allowing sufficient time for subjects to consider the information and providing time and opportunity for the subjects to ask questions and have those questions answered. The investigator (or other study staff who are conducting the informed consent interview) and the subject should exchange information and discuss the contents of the informed consent document. This process must occur under circumstances that minimize the possibility of coercion or undue influence. (21 CFR 50.20.)

² 21 CFR part 50 “applies to all clinical investigations regulated by the Food and Drug Administration 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 Food and Drug Administration, 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).

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The consent process begins with subject recruitment, and it includes advertising used to recruit subjects into the clinical trial.³ Once a potential subject is identified, a person knowledgeable about the clinical investigation and capable of answering questions raised by the potential subject should conduct a consent interview.

The consent form must contain information to allow the subject to make an informed decision about participation in a clinical investigation (see [section III](#), FDA Informed Consent Requirements and Discussion).⁴ (21 CFR 50.20 and 21 CFR 50.25.) The consent form serves several purposes, including helping to ensure that the subject receives 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 the subject's voluntary agreement to participate.

The informed consent process often continues after the consent form is signed. Depending on the clinical investigation, additional information may need to be given to the subject, and 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, for a discussion of when findings developed during the clinical investigation must be communicated to subjects.)

III. FDA INFORMED CONSENT REQUIREMENTS AND DISCUSSION

For all FDA-regulated clinical investigations (except as provided in 21 CFR 50.23 and 50.24⁵), legally effective informed consent must be obtained from the subject or the subject's legally authorized representative. Informed consent must meet the requirements of 21 CFR 50.20, and must include the basic information required by 21 CFR 50.25(a). If appropriate to the clinical investigation, one or more of the additional elements of information at 21 CFR 50.25(b) must also be addressed. For "applicable clinical trials" initiated on or after March 7, 2012, an additional element of informed consent is required by 21 CFR 50.25(c).⁶

Below, the sections of 21 CFR 50.20 and 21 CFR 50.25 are set out in italics followed by a discussion of each regulation.

A. General Requirements for Informed Consent

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

³ See the FDA Information Sheet "Recruiting Study Subjects," available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>, for further information.

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

⁵ See [section III.A.1](#), Exceptions to Informed Consent, for further information.

⁶ For further information, see [section III.D](#), Element of Informed Consent for "Applicable Clinical Trials."

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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. (21 CFR 50.20.)

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 research⁷). See 21 CFR 50.20. 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(d)).

2. Coercion and Undue Influence

The conditions under which informed consent is sought and the relationship between the subject and the person obtaining consent must 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, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance.”

For example, when an employing party seeks to enroll employees in a clinical investigation sponsored or conducted by the employing party, the protocol should contain safeguards to ensure that participation is voluntary and that there is no undue influence by supervisors, peers, or others. Similarly, because of a potential conflict of interest and the nature of the physician-patient relationship, when the investigator is also the prospective subject's physician, the physician should be careful to ensure that the prospective subject understands that enrollment in the clinical investigation is voluntary and that a decision to forego enrollment will not adversely affect his/her medical care. The consent form should emphasize that an individual's participation is truly voluntary.

Note that coercion and undue influence may be situational. For example, in a clinical investigation involving the surgical insertion of an investigational device, waiting to obtain

⁷ See "Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research," available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>.

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informed consent until the potential subject is in the preoperative area may fail to minimize the possibility of undue influence.

In addition, statements that claim investigational test articles 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 inappropriately overstate the possibility of benefit should be avoided because they may unduly influence potential subjects. Careful wording is needed in order to avoid overstating potential benefits that may contribute to a subject's therapeutic misconception.⁸

Furthermore, statements such as "FDA has given permission for the clinical investigation to proceed" or "FDA has approved the clinical investigation" should be avoided, because such statements may contribute to the misimpression that the investigation has FDA's endorsement.

3. Language Understandable to the Subject or the Legally Authorized Representative⁹

The information given to the subject, which could include information provided orally during the consent interview or written information in the consent form, must be in language understandable to the potential subject or legally authorized representative (21 CFR 50.20). "Understandable" means the information presented to potential subjects is in a language and at a level the subjects can comprehend (including an explanation of scientific and medical terms). In ensuring that information is understandable, it should be noted that more than one-third of U.S. adults, 77 million people, have basic or below basic health literacy.¹⁰ Limited health literacy affects adults in all racial and ethnic groups.¹¹ In addition, more than one-half of U.S. adults have basic or below basic quantitative literacy¹² and are challenged by numerical presentations of health, risk, and benefit data.

4. Exculpatory Language

The consent process may not include exculpatory language through which a subject is made to waive or appear to waive any of his or her 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

⁸ The term "therapeutic misconception" is used to describe the assumption of research subjects that decisions about their care are being made solely with their benefit in mind. See Appelbaum, PS, Roth, LH, and Lidz, C, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," International Journal of Law and Psychiatry Vol. 5, (1982): 319-329.

⁹ Also, see [section IV.A.1.a](#), "Adequacy and Appropriateness of Wording," [section V.B](#), "Non-English Speaking Subjects," and [section V.C](#), "Subjects with Low Literacy and Numeracy."

¹⁰ Kutner, M, Greenberg, E, Jin, Y, and Paulsen, C, (2006) *The Health Literacy of America's Adults: Results From the 2003 National Assessment of Adult Literacy* (NCES 2006-483). U.S. Department of Education, Washington, DC, National Center for Education Statistics. <http://nces.ed.gov/pubs2006/2006483.pdf>.

¹¹ Ibid.

¹² Ibid.

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freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt.

The following are examples of exculpatory language that would violate 21 CFR 50.20, and therefore cannot appear in consent forms:¹³

- I waive any possibility of compensation, including any right to sue, for injuries that I may receive as a result of participation in this research.
- If you suffer a research-related injury, neither the institution nor the investigator can assume financial responsibility or liability for the expenses of treatment for such injury.
- In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third party payer.

An example of one potential way to explain that a subject’s legal right to seek to collect compensation for research-related injuries in certain situations is not being waived is included below. Other language that similarly conveys this concept would also be acceptable (see [section III.B.6](#), Compensation and Medical Treatment in Event of Injury, for additional examples):

- In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

B. Basic Elements of Informed Consent

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject: (21 CFR 50.25(a).)

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 so prospective subjects are aware that, although preliminary data (bench, animal, pilot studies, literature) may

¹³ For additional discussion of exculpatory language, see the joint draft guidance from the Office of Human Research Protections (OHRP) and FDA, “Guidance on Exculpatory Language in Informed Consent,” available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM271036.pdf>. When that guidance is finalized, these examples may be revised.

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exist, the purpose of their participation is primarily to contribute to research (for example, to evaluate the safety and effectiveness of the test article, to evaluate a different dose or route of administration of an approved drug, etc.) rather than to their own medical treatment.

FDA recommends that potential subjects first be informed of the care a patient would likely receive if not part of the research and then be provided with information about the research. This sequence allows potential subjects to understand how the research differs from the care they might otherwise receive. The description should identify tests or procedures that would be part of usual care that will not be performed as well as those 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. The information provided should also inform prospective subjects about the potential consequences of these differences in care. Note that all experimental procedures must be identified as such. (21 CFR 50.25(a)(1).) Procedures related solely to research (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) must be explained.

The description of the clinical investigation must describe the test article and the control. The description should include relevant information of what is known about both the test article and the control. For example, the description should indicate whether the test article is approved/cleared for marketing and describe that use. Clarification may be provided that a marketed product may be prescribed by a health care practitioner for the labeled indication as well as other conditions/diseases he/she determines are reasonable. The description should also provide relevant information about any control used in the study. For example, whether the control is a medically recognized standard of care¹⁴ 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 benefits and risks of each, to the extent such information is available.

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 (see [section V.G](#), Subject Participation in More Than One Clinical Investigation)). 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 all study procedures. It may be helpful to provide a chart outlining what happens at each visit to simplify the consent form and assist the 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 its focus to be on more important content, such as the risks and anticipated benefits, if any.

¹⁴ For the purposes of this guidance only, medically recognized standard of care is one evidenced by publication in a peer reviewed journal or recognition by a professional medical society.

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

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 standard medical procedures, exams and tests), especially 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 randomizing to placebo) should also be addressed. 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 information presented in the protocol, investigator’s brochure, package labeling, and 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 the severity and duration of pain from a surgical procedure or the discomfort of prolonged immobilization for MRI.

All possible risks do not need to be described in detail in the informed consent form, especially if it could be overwhelming for subjects to read. Information on risks that are more likely to occur and those that are serious should be included. 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 the most likely to occur and serious risks and discomforts should also be considered for inclusion.

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 not only to the subject, but also to “others” (for example, radiation therapy where close proximity to subjects post procedure may be of some risk to others). When appropriate, a statement must be included that the clinical investigation 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.)

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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).)

The description of potential benefits should be clear, balanced, and based on reliable information to the extent such information is available. 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 benefit”), but also to “others” (for example, “your participation in this research may not benefit you but may benefit future patients with your disease or condition”). Overly optimistic representations of the clinical investigation may be misleading and may violate FDA regulations that prohibit promotion of investigational drugs and devices (see 21 CFR 312.7 and 21 CFR 812.7). Because the purpose of the study is to determine the safety and/or effectiveness of the test article compared to the control, it is not yet known whether the test article may or may not provide a benefit.

FDA considers payment to subjects for participation in clinical investigations to be compensation for expenses and inconveniences, not a benefit of participation in research. If payments are provided, the consent process should not identify them as benefits.¹⁵

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 care they would likely receive if they choose not to participate in the research. This includes alternatives such as approved therapies for the patient’s condition, other forms of therapy (e.g., surgical), and when appropriate, supportive care with no disease-directed therapy.¹⁶ This disclosure must include a description of the current medically recognized standard of care,¹⁷ particularly in studies of serious illness. Standard of care may include uses or treatment regimens that are not included in a product’s approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product’s statement of intended uses).¹⁸ FDA believes that treatment options lacking evidence of therapeutic value do not need to be discussed.

¹⁵ See the FDA Information Sheet “Payment to Research Subjects,” available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm>, for further information.

¹⁶ FDA notes that OHRP may hold a different interpretation of “appropriate alternative procedures or courses or treatment” as noted in their regulatory correspondence.

¹⁷ For the purposes of this guidance only, medically recognized standard of care is one evidenced by publication in a peer reviewed journal or recognition by a professional medical society.

¹⁸ As FDA has recognized in prior guidance, “[O]ff-label uses or treatment regimens may be important and may even constitute medically recognized standard of care.” FDA Guidance, “Good Reprint Practices for the

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When disclosing appropriate alternative procedures or courses of treatment, FDA believes a description of any reasonably foreseeable risks or discomforts and potential benefits associated with these alternatives must be disclosed. Where such descriptions or disclosures can contain quantified comparative estimates of risks and benefits (e.g., from the clinical literature), they should do so. The agency does not believe that imposing such a strict requirement for every case would be realistic or appropriate.¹⁹ Where such well-defined estimates are not possible, the agency believes that a description of the risks and benefits will be sufficient.

It may be appropriate to refer the subject to a 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. This referral should be completed prior to the subject signing and dating the consent form.

FDA recognizes that, 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. FDA believes that the discussion of other trials for which the subject may be eligible is best left to the informed consent discussion rather than the informed consent document and may need to include the subject's primary care provider.

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 for the same or other indications. When there are multiple clinical investigations for evaluating the treatment of a particular disease, the sequence in which a subject may participate in the protocols may be important and should be discussed with the subject and the subject's 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, who may gain access to the records relating to the clinical investigation. 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 <http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm>.

¹⁹ *Federal Register*, "Protection of Human Subjects; Informed Consent" (46 FR 8942, January 27, 1981), available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm113818.htm>. See response to comment 23.

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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. Please note that under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, FDA does not need permission to inspect records containing health information (45 CFR 164.512). FDA may inspect study records, for example, to assess investigator compliance with the study protocol and the validity of the data reported by the sponsor.

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA may inspect and copy all records relating to the clinical investigation. 21 U.S.C. § 374(a)(1). See also 21 CFR 312.58(a), 312.68, and 812.145(b). FDA generally will not copy records that include the subject's name unless there is reason to believe the records do not represent the actual cases studied or results obtained. When FDA requires subject names, FDA will generally treat such information as confidential, but on rare occasions, FDA may be required to disclose this information to third parties, for example, to a court of law. See 21 CFR 20.63(a) and 20.83(a)-(b). Therefore, the consent process should not promise or imply absolute confidentiality by FDA.

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.²⁰ (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 statements such as:²¹

- Because of hospital policy, the hospital is not able to offer financial compensation should you be injured as a result of participating in this research. However, you are not

²⁰ FDA expects investigators to ensure that subjects have access to reasonable medical care during their participation in the clinical investigation. See pages 7-8 of FDA’s “Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects,” available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>.

²¹ For additional discussion of exculpatory language, see the joint draft guidance from the Office of Human Research Protections (OHRP) and FDA, “Guidance on Exculpatory Language in Informed Consent,” available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM271036.pdf>. When that guidance is finalized, these examples may be revised.

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precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital.

- Because of hospital policy, the hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge. However, you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital.

Also, see [section III.A.4](#), Exculpatory Language.

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 process must provide information on how to contact an appropriate individual for pertinent 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) and their telephone numbers. FDA recommends that the individual or office named for questions about subjects' rights not be part of the investigational team. Subjects may be hesitant to report specific concerns or identify possible problems to someone who is part of the investigational team. 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.²²

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.

8. Voluntary Participation

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

²² See pages 7-8 of FDA's "Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects," available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>.

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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](#)). Also note that subjects may not withdraw data that was collected about them prior to their withdrawal, as discussed in [Section V.I, Data Retention upon the Withdrawal of Subjects](#).

C. Additional Elements of Informed Consent

The regulations identify additional elements of informed consent to be included, 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).)

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) are not completed, the informed consent process should explain that researchers have not completed studies that may identify potential risks, for example, carcinogenicity or teratogenicity.

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 no longer meets the eligibility 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

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time is inadequate and does not inform the subject of anticipated circumstances that may trigger his/her 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 him/her 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.

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).)

If subjects may incur additional expense because they are taking part in the clinical investigation, the consent process must explain the added costs. (21 CFR 50.25(b)(3).) FDA recommends that the cost of any tests, procedures and/or products 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 because they are participating in a clinical investigation even when the care is the standard care they would otherwise receive if not participating in a clinical investigation.²³

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 also [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 he/she 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.

Beyond the costs directly related to participation in the research, it may be appropriate to identify additional costs that the subject may incur, such as loss of income when the subject takes time off from work to participate in the clinical investigation and transportation costs.

²³ The Patient Protection and Affordable Care Act added section 2709 to the Public Health Service Act. This section, "coverage for individuals participating in approved clinical trials," in general, will prohibit health insurance issuers from dropping coverage because an individual (who requires treatment for cancer or another life-threatening condition) chooses to participate in a clinical trial. Health insurance issuers also may not deny coverage for routine care that they would otherwise provide because an individual is enrolled in a clinical trial.

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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).²⁴ When these costs are passed to the subject, the consent process must identify these costs.

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 they 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. If applicable, the consent process must explain whether a subject who withdraws early will receive future payments.

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 or an adverse event occurring at greater frequency or severity than previously stated in the consent process. FDA encourages the inclusion of this statement in the consent form for clinical investigations where knowledge of risk is limited, for example, clinical investigations of the first use in humans, novel therapies, and new molecular entities, or complex clinical investigations that involve significant risk.

²⁴ Sponsors of expanded access investigational new drug applications (INDs) and treatment protocols may recover other costs than these direct costs. See 21 CFR 312.8(d)(2).

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6. Number of Subjects

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

The informed consent process must state the approximate number of subjects who will be involved in the clinical investigation, when appropriate. (21 CFR 50.25(b)(6).) For example, a subject's decision 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”²⁵

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 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 <http://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.”

All informed consent forms and processes for “applicable clinical trials”²⁶ initiated on or after March 7, 2012, must contain the above quoted statement.²⁷ While additional explanation may be provided, the statement may not be modified.

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).)

When obtaining informed consent, informed consent must be documented by a signed and dated written consent form except under two specific circumstances, as described in FDA's regulations

²⁵ For further information, see FDA's guidance, “Questions and Answers on Informed Consent Elements, 21 CFR § 50.25(c)” available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf>.

²⁶ 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 <http://clinicaltrials.gov/ct2/manage-recs/fdaaa> and the document “Elaboration of Definitions of Responsible Party and Applicable Clinical Trial” available at <http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf> (see pages 4-10).

²⁷ Please note that this statement is not required for child assent.

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at 21 CFR 56.109(c).²⁸ (21 CFR 50.27.) When written informed consent is required, the use of electronic, including digital, signatures is permitted under FDA’s regulations, provided it is in compliance with applicable regulations.²⁹

In the event that an IRB waives the requirement for written 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 legally authorized representative. Additionally, the IRB may require the investigator to provide subjects with a written statement regarding the clinical investigation. (21 CFR 56.109(d).) FDA recommends that when an IRB waives the documentation requirement for informed consent in circumstances where there is minimal risk of harm as allowable under 21 CFR 56.109(c)(1), the consent process and discussion be described and noted in the records relating to the clinical investigation.³⁰

2. Alternative Methods of Obtaining Informed Consent

Traditionally, informed consent has been obtained in a face-to-face interview using paper consent forms. New technologies are becoming available that may serve as an alternative to the paper consent form in the informed consent process. Parties interested in pursuing alternative methods of obtaining informed consent are encouraged to contact FDA.³¹ Currently, FDA is considering alternative methods using these new technologies and would be interested in comments on these alternative methods.

Even in the context of paper consent forms, there may be certain circumstances when an alternative to a face-to-face consent interview may be appropriate. For example, such an alternative may be appropriate when the subject or the subject’s legally authorized representative 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. When written informed consent is required, informed consent cannot be obtained solely by telephone. For studies involving no more than

²⁸ 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.”

²⁹ See [21 CFR Part 11](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf), Electronic Records; Electronic Signature. Guidance is also available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf>, entitled, “Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application.”

³⁰ 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 <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>.

³¹ The FDA review division for the product area that is the subject of the investigation may be contacted to discuss alternative methods of obtaining informed consent.

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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 legally authorized representative is permissible under 21 CFR 56.109(c). When oral consent is used, FDA recommends that documentation of the process (information provided, name of individual obtaining consent, date consent obtained) be included in the study records (see 21 CFR 312.62(b) and 21 CFR 812.140(a)(3)).

Methods other than a face-to-face consent interview 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 legally authorized representative of the subject. For example, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's legally authorized representative can read the consent form during the discussion. After the consent discussion, the subject or the subject's legally authorized representative can sign and date the consent form and return the document to the clinical investigator by facsimile, 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 his/her next visit to the clinical site or mail it to the clinical investigator. The signed document should be filed with the subject's case history. See 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.

3. Requirement for Dating Consent Form

In addition to signing the consent form, the subject or the subject's legally authorized representative must enter the date of signature on the form (21 CFR 50.27(a)) to allow confirmation that the subject or the subject's legally authorized representative 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 day³² that he/she begins participation in the clinical investigation, the subject's case history must document that the subject provided consent prior to participation in the research (see 21 CFR 312.62(b) and 21 CFR 812.140(a)(3)). The person signing the consent form must receive a copy of the consent form (21 CFR 50.27(a)), 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.

³² The potential subject 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.

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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 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 legally authorized representative.

a. Long Form

The long form embodies 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 legally authorized representative. (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 legally authorized representative. (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 legally authorized representative is unable to read due to illiteracy or blindness (see [section V.C](#), Subjects with Low Literacy and Numeracy, and [section V.D](#), Physically Challenged Subjects).

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 is to

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be the same quantity and quality of information as when a long form is used.³³ 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 legally authorized representative). (21 CFR 50.27(b)(2).)

Use of the short form requires that a witness be present to the oral presentation of information to the subject or the subject’s legally authorized representative. (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 or a patient advocate), serve as the witness. FDA recommends that the witness be present (physically or by some other means, for example by phone or video conference) during the entire consent process, not just the signing of the consent form. 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 legally authorized representative only signs and dates 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).)

IV. RESPONSIBILITIES FOR INFORMED CONSENT

IRBs, clinical investigators, and sponsors have responsibility for ensuring that the informed consent process is adequate and meets FDA's regulatory requirements. The regulatory requirements represent the minimum information to be provided to potential subjects for informed consent. IRBs, sponsors, and investigators should consider providing additional information as appropriate.

A. The IRB

FDA requires that an IRB review and 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 ensure there is an adequate informed consent process that protects the rights and welfare of subjects participating in clinical investigations (21 CFR 56.109(b) and 56.111(a)(4)).

1. Review of All Informed Consent Materials

IRBs must review all materials used in the informed consent process.³⁴ This includes recruitment materials³⁵ and information provided in addition to the informed consent document

³³ See preamble to final rule in the *Federal Register*, January 27, 1981 (46 FR 8949).

³⁴ IRBs are not required to review stand-alone Health Insurance Portability and Accountability Act (HIPAA) authorizations under 21 CFR part 56 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

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(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 contains the elements identified in 21 CFR 50.25 and meets the requirements of 21 CFR 50.20 (see 21 CFR 56.109(a), 56.109(b), and 56.111(a)(4)).

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 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.³⁶ (21 CFR 56.111(b).) In the event an IRB regularly reviews clinical investigations involving vulnerable 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 ensuring informed consent.

The IRB has the authority to require that information, in addition to that specifically mentioned in 21 CFR 50.25, be given to subjects when, 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, local circumstances may necessitate the inclusion of additional information relevant to the informed consent process for potential 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.³⁷ As stated in the HHS guidance referenced in the footnote, some financial interests in the clinical investigation may affect the rights and welfare of subjects and IRBs should consider approaches to assure subjects are

HIPAA Authorizations Under FDA Regulations” (available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126952.pdf>).

³⁵ As described in the FDA Information Sheet “Recruiting Study Subjects” (available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>), 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. Basic information about a clinical investigation is: 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 (<http://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. Any posting that provides more than basic information is subject to IRB review.

³⁶ Vulnerable populations identified in FDA regulations include children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons (21 CFR 56.111(a)(3) and (b)); however, IRBs may consider additional populations to be vulnerable to undue influence and may decide to provide additional protections to these populations.

³⁷ This topic is addressed in the Department of Health and Human Services 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, is available at <http://www.hhs.gov/ohrp/policy/fguid.pdf>.

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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.

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 50.25.³⁸ In its review of a clinical investigation, the IRB can disapprove a clinical investigation if informed consent will not 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 level³⁹ may overwhelm potential 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 (21 CFR 50.20).⁴⁰ Pictures or diagrams may be used to improve understanding of medical terms or how an investigational product functions. IRBs may wish to evaluate, through subject interviews, how well the consent materials communicate critical information.

b. Use of Standardized Language

IRBs should also address institutional requirements and applicable Federal, State, and local laws and regulations. (21 CFR 56.103(c) and 56.112.) 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 these requirements.

³⁸ See 21 CFR 56.109(b).

³⁹ A recommendation that consent forms be written at an eighth grade or lower reading level was made by the working group formed by the National Cancer Institute (NCI), along with the Office for Protection from Research Risks (now the Office of Human Research Protections, OHRP) and FDA in the 1998 “Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials” available at <http://www.cancer.gov/clinicaltrials/conducting/simplification-of-informed-consent-docs/page2>.

⁴⁰ 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,” *Cancer: A Journal for Clinicians* Vol. 48, No. 3 (May/June 1998): 151-162, <http://onlinelibrary.wiley.com/doi/10.3322/canjclin.48.3.151/full>.

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2. Review of the Consent Process

The investigator should advise the IRB of the consent process to be used. The materials and procedures used for subject recruitment, which typically include advertisements, must be reviewed by the IRB to ensure that these materials are appropriate.⁴¹ The IRB must ensure that investigators seek consent from 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 investigators allow sufficient time for subjects to consider the information, provide time and opportunity for the subjects to ask questions and have those questions answered, and allow time and opportunity for the subjects to consider fully whether to participate. The IRB must review all information given to subjects describing recruitment incentives, such as payments to reimburse potential subjects for expenses and inconveniences related to their participation (21 CFR 56.109(b)). In addition, the IRB must review the proposed amount and schedule of payments to subjects to ensure payments are appropriate to the time commitment and study procedures, and that subjects will not be unduly influenced by these incentives.⁴²

To approve a clinical investigation, the IRB must find that informed consent will be sought from each prospective subject or the subject's legally authorized representative and that informed consent will be appropriately documented. (21 CFR 56.111(a)(4) and (5).) FDA recommends that the IRB inquire as to who will conduct the consent interview and what procedures will be followed. If procedures other than a face-to-face consent interview 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 believes it is appropriate⁴³ and will enhance the protection provided to subjects (for example, when the investigator is also the treating physician for a potential 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 interviews, the IRB

⁴¹ For further information, see the FDA Information Sheet “Recruiting Study Subjects” available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>.

⁴² For further information, see the FDA Information Sheet “Payment to Research Subjects,” available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm>.

⁴³ 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.

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could interview subjects to assess the consent process and evaluate the subjects' understanding of the clinical investigation.

3. IRB Review Procedures

All information given to subjects as part of the consent process is to be reviewed and approved by the IRB.⁴⁴ (21 CFR 56.109(a) and (b)). 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 and that were provided to subjects (see [section III.C.5](#), Providing Significant New Findings to Subjects). When new information or changes in the clinical investigation require 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).)

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, such as new advertising for subjects following initiation of the clinical investigation when the advertisement incorporates wording from the approved consent form and the advertisement can be easily compared to 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.

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. The investigator can then photocopy the date-stamped consent form for use in the trial.

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 legally effective informed consent is obtained from each subject before that subject takes part in the clinical investigation (see 21 CFR

⁴⁴ This would include all addenda to the consent form and other materials used in the consent process.

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50.20, 312.60, and 812.100). The clinical investigator should advise the IRB regarding the consent process, including who will conduct the consent interview. 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) and (b).) An investigator may not begin the informed consent process with subjects until the IRB reviews and approves the clinical investigation, consent form, and the information to be given to subjects as part of the consent process. (21 CFR 50.20, 56.103(a), 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 will also need to identify and meet such institutional requirements and incorporate them into the consent form for the IRB's initial review of the clinical investigation.

When organizing the information in the consent form, FDA recommends that the clinical investigator consider the order in which the information is presented so that the elements most significant to the subject's decision to participate are presented first. The clinical investigator is also encouraged to incorporate any additional information of interest to subjects that may affect their rights and welfare. For example, information about financial relationships and interests may be important to the subject (see [section IV.B.2](#), Financial Relationships and Interests).

During the clinical investigation, the investigator may need to revise the consent form to address changes to the protocol or new information, such as significant new findings. The investigator will need to obtain IRB review and approval of the revised form. (21 CFR 56.109.) In addition, because the consent form is being modified to reflect changes to the protocol or new information, either of which may affect the willingness of already enrolled and actively participating subjects to continue in the clinical investigation, the IRB should determine the need to re-consent these enrolled subjects. To diminish confusion about the change, the investigator may use a prepared summary of the change to aid in an informative presentation to the enrolled subject. However, this summary does not constitute the revised informed consent document.

1. Delegation of Consent Interview

FDA regulations require that the investigator obtain or ensure that the legally effective informed consent of subjects is obtained.⁴⁵ If the investigator delegates this responsibility, FDA recommends 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; and the investigator should have a detailed plan for the supervision and oversight of the clinical investigation, including the informed consent process.⁴⁶ Even when a

⁴⁵ See 21 CFR 312.60 and 812.100.

⁴⁶ See FDA's "Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects", October 2009, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>.

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task is delegated to another individual, the investigator remains responsible for ensuring the clinical investigation is conducted according to applicable FDA regulations and for protecting the rights, safety, and welfare of subjects during the clinical investigation (21 CFR 312.60 and 21 CFR 812.100).

2. Financial Relationships and Interests

The clinical investigator should consider whether information related to financial relationships or interests should be provided to subjects.⁴⁷ 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 document, 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.

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 is submitted to FDA for review, FDA’s comments are generally directed to the sponsor. See [section IV.D.1](#), Investigational New Drug and Biologics, and [section IV.D.2](#), Investigational Medical Devices. The sponsor should promptly provide FDA’s comments to the clinical investigator so that changes can be made to the consent forms. Because the clinical investigator must receive IRB approval before starting the clinical investigation (see 21 CFR 312.66 and 21 CFR 812.110(a)),

⁴⁷ This topic is addressed in the Department of Health and Human Services guidance document, “Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection.” This guidance, which applies to FDA-regulated research, is available at <http://www.hhs.gov/ohrp/policy/fguid.pdf>.

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the sponsor should work closely with the clinical investigator to make certain the modified consent form is reviewed and approved by the IRB. FDA recommends that the clinical investigator provide the sponsor with a copy of the consent form approved by the IRB.

1. Considerations for Multicenter Clinical Investigations

For multicenter clinical investigations, minor changes may need to be made to the consent form to address local and institutional requirements. When IRB review results in substantive modifications to the consent form, i.e. changes that affect the rights, safety, or welfare of the subjects, FDA recommends that the sponsor share the revisions with the investigators and their IRBs. If the clinical investigation has a central IRB working in cooperation with local IRBs, the revisions should be forwarded to the central IRB.⁴⁸ Alternatively, local issues may be addressed by the central IRB depending on the review agreement between the local IRB(s) and central IRB.

D. The FDA

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)). FDA's regulations for drug (including biologic) and device investigations have different requirements for the submission of informed consent materials in applications (see sections [IV.D.1](#), Investigational New Drugs and Biologics, and [IV.D.2](#), Investigational Medical Devices, below).

Generally, when informed consent materials are submitted, FDA reviewers assess the adequacy of the consent form by considering its communication of reasonably foreseeable safety issues 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 makes informed consent inadequate and noncompliant with 21 CFR part 50. In these cases, FDA will 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 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.)

1. Investigational New Drugs and Biologics⁴⁹

The investigational new drug (IND) regulations (21 CFR part 312) do not specifically require submission to FDA of the consent form with the IND application. However, if FDA determines

⁴⁸ See "Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials" available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm>.

⁴⁹ 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.

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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, the informed consent form will be reviewed for treatment INDs and treatment protocols (21 CFR part 312, subpart I) and INDs conducted under the exception from informed consent requirements for emergency research (21 CFR 50.24) consistent with 21 CFR 50.25 (see 21 CFR 50.24(a)(6)).

For other clinical investigations, 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 identify 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;
- The study 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 forego 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 in such a manner as 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 investigational device exemption (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

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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 makes substantive changes to the informed consent document after IDE approval by FDA, 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. (21 CFR 812.35(a).)

V. ADDITIONAL CONSIDERATIONS

A. Review of 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 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.⁵⁰ Sponsors and investigators will need to comply with all applicable HIPAA privacy protections 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 potential 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 does not require informed consent.⁵¹ Even though informed consent is not required by FDA in these instances, proper maintenance of these records includes safeguarding the privacy and confidentiality of the patient's information. 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 if he or she is eligible for the clinical investigation, additional information may need to be gathered from the

⁵⁰ For a clinical investigation that is conducted or supported by HHS, the activities described here generally would be considered research involving human subjects, but could be exempt under 45 CFR 46.101(b)(4). If the study is not exempt, the requirements for obtaining and documenting the informed consent of the subjects (or the requirements for waiving the informed consent requirements) under the HHS regulations would need to be satisfied in order for these activities to be conducted.

⁵¹ Ibid.

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potential 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,”⁵² for a discussion of when informed consent would be required under the regulations.

The records of a subject who was previously enrolled in a clinical investigation may be reviewed retrospectively, without reconsenting the subject, to collect additional 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. In cases where the additional information goes beyond what was identified in the original protocol and disclosed in the original consent form, obtaining informed consent for the additional information would be required. (21 CFR 50.20 and 50.25.) Where possible, FDA recommends that the clinical investigator anticipate the need for obtaining further information and obtain consent as part of the initial consent process.

In all of the above situations, there are privacy and patient confidentiality issues that need to be addressed. The clinical investigator, sponsor, and institution should consider whether institutional policies or other statutory or regulatory requirements exist to address this (such as under the Health Insurance Portability and Accountability Act (HIPAA), the HIPAA Privacy Rule (45 CFR parts 160 and 164) or HHS human subject protection regulations at 45 CFR part 46).⁵³

B. Non-English Speaking Subjects⁵⁴

Individuals 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 potential subjects when a language barrier may exist between the investigator(s) and some or all of the potential 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 individuals 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 legally

⁵² This Information Sheet is available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm>.

⁵³ Please contact the Office for Civil Rights (<http://www.hhs.gov/ocr/hipaa/>) for additional information on HIPAA and the Privacy Rule or the Office for Human Research Protections (<http://www.hhs.gov/ohrp/>) for additional information on 45 CFR part 46.

⁵⁴ For HHS-funded or -conducted research, see OHRP’s guidance, “Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English” at <http://www.hhs.gov/ohrp/policy/ic-non-e.html>. FDA notes that OHRP’s guidance document on this topic is unchanged.

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authorized representatives is in language understandable to the subjects or their representatives (21 CFR 50.20). *Understandable* means the information presented to potential 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 all English and non-English language versions of any 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 reviewing proposed informed consent procedures involving translation of written and oral information that is to be presented to subjects, FDA recommends that the IRB review, and if appropriate, approve procedures for ensuring that the translations will be prepared by a qualified individual or entity.

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.

1. Informed Consent Procedures when Enrollment of Subjects who do not Understand English is Expected

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 they 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.

2. Informed Consent Procedures when Enrollment of Subjects who do not Understand English is Unexpected

FDA recognizes that investigators on occasion face circumstances where: (1) an individual who does not understand English is eligible for an IRB-approved research protocol; and (2) the

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investigator has an IRB-approved English language long form, but does not have an appropriate IRB-approved written translation of the long form, short form, or written summary. 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 time frame for subject enrollment may provide sufficient time for the preparation and IRB review of an appropriately translated long form or an appropriately translated short form and written summary. When this is the case, translated consent forms are to be reviewed and approved by the IRB prior to enrollment of the subject.

For other research, the timeframe for enrollment of a subject who does not understand English may not provide sufficient time for preparation and IRB review 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 50.25 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 and previously approved by the IRB (21 CFR 50.27(a)). To meet this prerequisite, the IRB or investigator must have arranged for translation of a generic short form into a language

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understandable by the prospective subject 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 legally authorized representative. (21 CFR 50.27(b)(2).) The IRB-approved long form can be used as this written summary.

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

- (1) The investigator obtaining informed consent, with the assistance of an interpreter if needed, 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, the witness should be fluent in the language of the oral presentation.
- (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.
- (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 without waiting for a translated long form (which served as the written summary) to be reviewed and approved by the IRB, 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.

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- (2) For FDA-regulated research, the investigator must promptly obtain a translated copy of the IRB-approved English version of the long form, which served as the written summary. 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 provides it to the subject 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. FDA believes that translation of the long form is critically important as a means of providing subjects an ongoing source of information understandable to them.

C. 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, oral presentation of the information contained in the consent form is especially important. When the elements of informed consent are presented orally to the subject or the subject's legally authorized representative, 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 form (see [section III.D.4.b](#), Short Form). It should be noted that, even if the information is presented orally, the subject or the subject's legally authorized representative 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 form, when consistent with applicable State law. In this situation, a progress note in the subject's case history should indicate the reason for the lack of a signature.

D. Physically Challenged Subjects

A person who is physically challenged (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 when consistent with applicable State 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 that the subject's case history include 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 accommodate the specific needs of the study population. For

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example, the investigator could use an audio tape of the contents of the consent form or a form with enlarged font, depending on the level of impairment of the visually impaired subjects.

E. Impaired Consent Capacity⁵⁵

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 confronts the individual, 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, developmental disorders, 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 legally authorized representative consents on the subject’s behalf. (21 CFR 50.3(l) and 50.20.)

FDA regulations expressly identify “mentally disabled persons” as a vulnerable category of subjects in clinical investigations for which IRBs may need to assume increased responsibilities. (21 CFR 56.107(a) and 56.111(b).) For example, when reviewing studies that involve “mentally disabled persons” who are likely to be vulnerable to coercion or undue influence, IRBs must ensure that additional safeguards have been included in the study, which may include modifying the informed consent process, to protect the subjects’ rights and welfare. (21 CFR 56.111(b).)

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 potential subjects, for example, through use of an independent, qualified professional⁵⁶ and a process that includes: (i) documentation of elements of capacity (such as understanding information, showing evidence of choice,

⁵⁵ 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 <http://grants.nih.gov/grants/policy/questionablecapacity.htm>.

⁵⁶ A professional with the appropriate background, training and experience in working with individuals with impaired consent capacity. See reference in footnote 55 for additional information.

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showing rational reasoning, understanding the nature of the situation, and showing reasonable understanding of outcome of choice); and (ii) 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 (i) simplification and/or repetition of information, (ii) involvement of a subject advocate or trusted family member/friend to assist when sharing information about the clinical investigation, and (iii) 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 a legally authorized representative either initially or later in the clinical investigation if consent capacity diminishes.
- Assessing whether individuals who cannot provide legally effective consent on their own behalf may nonetheless be able to provide some form of oral agreement (e.g., assent) 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, a legally authorized representative would need to provide documented written consent.
- Determining whether the IRB or a third party should observe the consent process (see [section IV.A.2](#), Review of the Consent Process, for more information).

F. Children as Subjects⁵⁷

If a child is to be enrolled in a clinical investigation, the parent(s) or guardian must provide permission, with the assent of the child when appropriate. (21 CFR 50.55). Parental or guardian permission must be obtained in accordance with the requirements for informed consent (21 CFR 50.55(e))⁵⁸ and be documented in accordance with 21 CFR 50.27. (21 CFR 50.55(f).) FDA regulations provide these safeguards for children enrolled in clinical investigations, as described in 21 CFR part 50, subpart D.⁵⁹ As with informed consent, the exceptions under 21 CFR 50.23 or 21 CFR 50.24 also apply to the requirement for parental permission.⁶⁰ (21 CFR 50.55(e).)

⁵⁷ For purposes of 21 CFR part 50, 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).

⁵⁸ Note that the waiver of parental permission found in 45 CFR 46.408(c) is not available under FDA’s regulations.

⁵⁹ FDA adopted 21 CFR part 50 subpart D, “Additional Safeguards for Children in Clinical Investigations”, as an interim final rule in April 2001 (21 CFR part 50, subpart D) (subpart D) (see 66 FR 20598, April 24, 2001), and issued a final rule in February 2013 (see 78 FR 12937, February 26, 2013).

⁶⁰ The exception under 21 CFR 50.23 involves certain life-threatening situations where there is no suitable alternative therapy and there is insufficient time to obtain informed consent, military operations, and public health emergencies. The exception under 21 CFR 50.24 involves emergency research.

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FDA regulations also require the IRB to determine whether the assent of the child participant is appropriate as discussed below. (21 CFR 50.55(a).)

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

For clinical investigations approved by the IRB under either 21 CFR 50.53 or 21 CFR 50.54,⁶¹ where permission is to be obtained from parents, the permission of both parents is required unless one 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).)

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).) 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.) FDA recommends that a child not be used as a translator, 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.⁶² (21 CFR 50.55(b).) 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 a complex clinical trial, a child may be able to understand and provide assent if he/she appreciates and agrees to the interventions and/or procedures in the trial (e.g., drawing a blood sample for a test), even though he/she 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

⁶¹ 21 CFR 50.53 applies to clinical investigations presenting greater than minimal risk and no prospect of direct benefit to the individual subject, 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 fall within the scope 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.

⁶² FDA recognizes that IRBs may adopt procedures setting an age below which children are presumed incapable of providing assent.

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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 can 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 additional pertinent information after participation. (21 CFR 50.55(d).) Parental permission requirements 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. If the IRB determines oral assent is appropriate, the assent process should be described and noted in the subject's records relating to the clinical investigation. For clinical investigations involving children from whom the IRB has determined written assent is required, a permission form that follows the regulations at 21 CFR 50.20 and 50.25 for parents to give permission is required, and FDA recommends that an assent form for children that outlines the clinical investigation be used.

FDA does not require the use of a written assent form (see 21 CFR 50.55(g)); however, when a written assent process is appropriate or required by the IRB, 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 form, but should focus on those aspects of the clinical investigation that may impact on a child's willingness to participate.

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 that two conditions are met. First, 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(a)(1) and (2).) In other words, children who are wards may only 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 one of these two conditions is met.

Second, if the IRB approves an investigation under 21 CFR 50.53 or 50.54 after determining 21 CFR 50.56(a) is met, the IRB must require that an advocate is 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 does not need to appoint the advocate. The advocate, who can 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 (i.e., has the legal authority and responsibility to act in the place of a

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parent). (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. The appropriate expertise for an advocate may 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 in 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.

FDA regulations do not address the appointment of an advocate for children involved in clinical investigations approved under 21 CFR 50.51 (i.e., research involving no more than minimal risk) or 21 CFR 50.52 (i.e., research involving greater than minimal risk but presenting the prospect of direct benefit). 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, IRBs should ensure that each child has a guardian and/or advocate with the background, experience and commitment to act in the best interest of the child.

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 is no longer considered a child for purposes of 21 CFR part 50 Subpart D, see 21 CFR 50.3(o), and the investigator must 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. (21 CFR 50.20.)

G. Subject Participation in More Than One Clinical Investigation

Some subjects may wish to participate simultaneously in more than one clinical trial or enroll in a single clinical investigation multiple times. FDA strongly discourages these practices as 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. In addition, the subjects may find it difficult to understand all the risks and proposed benefits, much less meet the demands, of multiple protocols. Moreover, there may be potential drug or device interactions, and the simultaneous use of more than one investigational product may confound the results of the clinical investigations.

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 not participate in more than one clinical investigation

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at a time. Investigators should inquire about multiple enrollments and discourage this practice in the consent form and during any informed consent discussions.

H. Suspension/Termination of a Study⁶³

A clinical trial may be suspended and possibly terminated for a variety of reasons. Such reasons could include the identification of a significant safety issue, lack of effectiveness, or a concern about investigator misconduct. Often, when one of these issues is first identified, a study may be temporarily suspended while the issue is investigated. Depending upon the type and seriousness of the concern, changes to the study protocol or to the informed consent (due to significant new findings as discussed previously in [section III.C.5](#)) may be needed, or a decision may be made to terminate the study. In other cases, a sponsor may terminate a study or entirely abandon development of a product for business 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. 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 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 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 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. Moreover, such a discussion provides an opportunity to address questions subjects may have about the investigational product that was administered to them (e.g., immediate safety 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, appropriate follow-up procedures would need to be discussed with the subjects and possibly the subject's primary care provider.

⁶³ For further discussion, see "Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval" available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>. See section III.H.2, "Suspension or Termination of IRB Approval."

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I. Data Retention upon the Withdrawal of Subjects

Under FDA regulations, data collected on subjects up to the time of withdrawal from the clinical investigation must remain in the study database.⁶⁴ See 21 CFR 312.62(b) and 812.140(a)(3). If a subject withdraws from a study, removal of data that were already collected may undermine the scientific, 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 products.

Subjects should be advised in the consent document that the data collected on them up until the point of their withdrawal remains part of the study database and may not be removed. An investigator should ask a subject who is withdrawing whether he/she wishes to withdraw from the investigational interventions only and is 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 form, the investigator must obtain the subject’s informed consent for this limited participation using an IRB-approved consent form. (21 CFR 50.25(a)(1).) 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 and 50.25(a)(1).) However, such records may be accessed consistent with the original consent process, without additional consent, 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.

K. Reporting Aggregate Results of the Clinical Investigation

FDA recognizes that subjects are frequently interested in the aggregate results of the clinical investigation in which they were enrolled. Aggregate research results should be returned to subjects in a clear and comprehensible manner. Title VIII of FDAAA requires the “responsible party” (usually the sponsor or principal investigator) of certain clinical trials of drugs, devices,

⁶⁴ For further discussion, see “Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials” available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>. FDA regulations (see, for example, 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 individual treated with the drug or exposed to the device. Please also see OHRP’s guidance on this topic, “Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues” available at <http://www.hhs.gov/ohrp/policy/subjectwithdrawal.pdf>.

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and biological products (referred to in FDAAA as "applicable clinical trials") to register the trials and submit summary results to the government-operated clinical trials databank, www.ClinicalTrials.gov, within a certain time period.⁶⁵ The summary results of these clinical trials will be made publicly available in the databank.⁶⁶ As explained above in [section III.D](#) (Element of Informed Consent for “Applicable Clinical Trials”) of this guidance, FDA has issued a final rule⁶⁷ that amends the informed consent regulations (21 CFR 50.25) to require that the informed consent documents for applicable drug, biologic, and device clinical trials include the specific statement that is provided in the regulation that clinical trial information for such clinical investigations will be available at www.ClinicalTrials.gov. This website will not include information that can identify enrollees individually.

For clinical trials that are not “applicable clinical trials,” subject to Title VIII of FDAAA, the sponsor or principal investigator may voluntarily register and report results to the databank. If a sponsor or principal investigator plans to submit trial results voluntarily, nothing would prevent an investigator, sponsor, or IRB from informing potential subjects of the plan to submit such information in an appropriate manner. Informed consent forms can direct subjects to www.ClinicalTrials.gov, where subjects can obtain certain overall study results. Investigators and sponsors can describe other plans in the consent document for informing subjects of the outcomes of the clinical investigation.

⁶⁵ See section 801(a) of the Food and Drug Administration Amendments Act of 2007, Pub. L. 110-85, adding 42 U.S.C. §282(j).

⁶⁶ 42 U.S.C. §282(j)(2)(A)(ii)(II).

⁶⁷ The final rule (Federal Register, Volume 76, pages 256-270) is available at <http://edocket.access.gpo.gov/2011/pdf/2010-33193.pdf>