Considerations for Including Tissue Biopsies in Clinical Trials

Guidance for Industry, Investigators, Institutions, and Institutional Review Boards

DRAFT GUIDANCE

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Considerations for Including Tissue Biopsies in Clinical Trials Guidance for Industry, Investigators, Institutions, and IRBs[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) on this topic. It does not establish any rights for any person and is not binding on FDA, OHRP, or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA or OHRP staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to industry, investigators, institutions, and institutional review boards (IRBs) regarding considerations for tissue biopsies that may be conducted in adults and in children[2] as part of clinical trials that evaluate investigational medical products and/or that are conducted or supported by the Department of Health and Human Services (HHS).[3,4,5] For the purposes of this guidance, a biopsy is a procedure that involves acquisition of

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), and Office of Clinical Policy and Programs (OCPP) at the Food and Drug Administration (FDA) and the Department of Health and Human Services Office for Human Research Protections (OHRP).

[2] FDA's regulations at 21 CFR 50.3(o) define children as "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted." HHS's regulations at 45 CFR 46.402(a) define children as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."

[3] This guidance applies to FDA-regulated clinical investigations of medical products. For the purposes of this guidance, all references to *medical products* mean human drugs and biological products, devices, and combination products that are regulated by CDER, CBER, or CDRH. This guidance also applies to HHS-supported or conducted nonexempt human subjects research that is a *clinical trial* as defined in 45 CFR 46.102(b).

[4] For purposes of this guidance as it applies to FDA-regulated clinical investigations, the terms *clinical trial*, *trial*, *clinical investigation, investigation,* and *study* are used interchangeably and have the same meaning.

[5] *Clinical investigations*, as defined in 21 CFR 50.3(c) and 56.102(c), of medical products may be subject to various requirements under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations, including sections 505(i) and 520(g) of the FD&C Act and 21 CFR Parts 50, 56, 312, and 812, as applicable. Clinical trials conducted or supported by HHS are subject to 45 CFR Part 46.

tissue[6] from a trial participant as part of a clinical trial protocol.[7] Biopsies needed to inform routine clinical care are not included in this guidance.

In general, FDA's and OHRP's guidance documents 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.

II. BACKGROUND

Biopsies inherently include varying degrees of risk. In some circumstances, biopsied tissue(s) may be the only way to obtain information that is necessary to answer the questions of interest in a clinical trial, such as to identify eligible trial participants or evaluate treatment effects (e.g., evaluate treatment response, determine the mechanism of action, understand resistance mechanisms, or evaluate and monitor toxicities).

When biopsies are needed because they are the only way to obtain data to ensure that the participants enrolled in the trial have the intended target condition (e.g., have a cancer that has a specific tumor biomarker, etc.), to obtain data needed to otherwise determine eligibility, or to evaluate the clinical trial's primary endpoint(s) or a key secondary endpoint,[8] requiring biopsies as a condition of trial participation may be reasonable. Sponsors should consider, among other things, whether the risks of the biopsies and any other risks of the trial are reasonable in relation to the anticipated benefit(s), if any, to the participants, and the importance of the knowledge that may be expected to result.[9] For the purposes of this guidance, "required" biopsies refer to those

[6] This guidance does not address acquisition of fluid samples, such as samples of blood, urine, or saliva from trial participants.

[7] For purposes of this guidance, the terms *trial participant, participant,* and *subject* are used interchangeably and have the same meaning.

[8] For clinical trials that involve human drugs or biological products and that include multiple endpoints, the guidance for industry *Multiple Endpoints in Clinical Trials* (October 2022) may be a helpful resource. FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] Under 21 CFR 812.30(b), FDA may disapprove, or withdraw approval of, an investigational device exemption (IDE) application if the Agency finds that "there is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained," among other reasons. Further, under section 520(g)(8) of the FD&C Act, FDA may place a clinical investigation on clinical hold if the Agency determines that "the device involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation," taking into account certain specified factors. Additionally, under 21 CFR 312.42(b), FDA may place a clinical investigation being conducted under an investigational new drug application on clinical hold if the Agency finds that "[h]uman subjects are or would be exposed to an unreasonable and significant risk of illness or injury," among other reasons. Under 21 CFR 56.111(a)(2) and 45 CFR 46.111(a)(2), IRB approval requires that risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result. See section IV of this guidance for discussion of additional requirements for clinical trials involving children as participants.

that are specified in the clinical protocol as a condition of trial participation. In general, it may be reasonable to include required biopsies in the clinical protocol as necessary study procedures for the purposes described in this paragraph.

However, when results of biopsies are not needed to determine eligibility for trial participation or will be used solely for evaluation of non-key secondary endpoints and/or exploratory endpoints specified in the clinical protocol, or solely for facilitating unspecified future research uses,[10] requiring biopsies may unnecessarily increase risk to or create undue burden for the trial participant, limit access to clinical trials, and/or discourage participation. In general, when biopsies are to be conducted for evaluation of non-key secondary endpoints and/or exploratory endpoints or for unspecified future research uses, they should be optional. For the purposes of this guidance, "optional" biopsies refer to those that are specified in the clinical protocol but not as a condition of trial participation.

III. CONSIDERATIONS FOR CONDUCTING TISSUE BIOPSIES IN ADULTS IN CLINICAL TRIALS

When including biopsies as part of clinical trials involving investigational medical products or other study interventions, the following should be considered: the purpose of the biopsies, the reason(s) for their inclusion, and the associated risks.[11] The degree of risk involved in the biopsy also should be considered, as biopsies of different tissues have inherently different types and levels of risk (for example, shave biopsy of the skin vs. biopsy of brain tissue). For tissue sites that pose higher risk, alternative approaches to the biopsy should be considered and a strong scientific justification for the critical need for the biopsy in the clinical trial should be provided.

FDA encourages sponsors to discuss their medical product development plan, including any potential biopsies, with the appropriate review division responsible for the medical product early in development, including the benefits and risks of performing biopsies.[12] For clinical trials conducted or supported by HHS, OHRP encourages investigators to discuss any potential biopsies with their IRB, including the benefits and risks of performing biopsies. When designing

[10] An example of a situation involving unspecified future research would be to require that trial participants undergo a research biopsy for the sole purpose of contributing to a biobank for future research.

[11] If biopsies are included as part of a clinical trial involving a human drug or biological product and an in vitro companion diagnostic device, the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices* (August 2014) may be a helpful resource. See also the draft guidance for industry and FDA staff *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product* (July 2016) for additional information. When final, this guidance will represent the FDA's current thinking on this topic.

[12] Sponsors should follow each FDA center's procedures for engaging with the Agency in the context of a development program. For information on meetings regarding drugs and biological products, see the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (August 2023). For medical devices, see the draft guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (March 2024). When final, these guidances will represent the FDA's current thinking on these topics.

clinical trials, the following should be considered when including one or more biopsies as part of the clinical trial:

- Including a required biopsy in the clinical protocol may be reasonable in relation to anticipated benefits if the information cannot be obtained from existing pathology specimens or other less invasive means, and the information from the biopsy is necessary to, for example:

  - identify participants who may derive clinical benefit from the investigational medical product or other study interventions, such as selecting a patient population for trial enrollment whose diseases are associated with specific findings and thus may be more likely to respond to a particular intervention (e.g., human epidermal growth factor 2 [HER2] positive disease for HER2-targeted therapies, etc.);[13]

  - identify participants who should not be enrolled in the study due to the risk of certain side effects or toxicities associated with an investigational medical product (e.g., increased toxicities for patients with Kirsten rat sarcoma viral oncogene homolog [KRAS]- and/or neuroblastoma Ras viral oncogene homolog [NRAS]-mutated colon cancer treated with certain epidermal growth factor receptor antagonists);

  - identify participants whose current disease state would render it unlikely for them to derive benefit from the investigational medical product or other study interventions (e.g., a patient whose kidney biopsy shows predominantly scar tissue without signs of active inflammation and who would thus not benefit from immunosuppression);

  - evaluate the primary endpoint(s) or key secondary endpoint(s) of the clinical trial;

  - evaluate treatment response (e.g., bone marrow biopsies and/or aspirates in patients with certain hematologic malignancies, etc.);

  - obtain histological diagnosis of tissue to support performance testing of diagnostic investigational medical products by providing a "truth standard."[14]

- The protocol should clearly state the rationale and scientific justification for the inclusion of each biopsy in the clinical trial.

[13] If such an approach is part of an enrichment strategy to increase efficiency of drug development and support precision medicine, the following guidance for industry may be helpful: *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019).

[14] For a description of "truth standard," see the guidance for industry *Developing Medical Imaging Drug and Biological Products, Part 2: Clinical Indications* (June 2004).

- When biopsy information is used in endpoint analyses (i.e., primary endpoint, secondary endpoint, exploratory endpoint, etc.), the statistical analysis plan should clearly state how the results of the biopsy will be analyzed.

- Biopsies should be optional in the clinical protocol when information from the biopsy will be used to evaluate non-key secondary and exploratory endpoints.[15]

- Biopsies should be optional when the purpose of the biopsy is solely to obtain specimens that will be stored and used for future unspecified research.

- At any time during the trial, participants retain the right to withdraw consent to undergo any biopsy. Where the biopsy is required, the withdrawal of consent may impact the participants' ability to continue participation in the trial.[16] Declining to undergo one or more optional biopsies should not negatively impact the participant as it pertains to trial enrollment, participation in other aspects of the trial, care the participant will receive during the trial, or other study considerations.

- In all instances (required or optional biopsies), it is important to minimize risks to participants.[17] Eligibility criteria for trials with required biopsies should exclude participants for whom a biopsy would present an unacceptable level of risk.

- Investigators are responsible for protecting the rights, safety, and welfare of trial participants in FDA-regulated clinical trials.[18] Investigators are also responsible for ensuring that only trial participants who provide informed consent to have a biopsy as part of the clinical trial (whether required or optional) undergo the biopsy.[19] Investigators should also generally communicate to the healthcare provider performing the biopsy, if the investigator does not perform it, whether the biopsy is required or optional, as applicable. Investigators should ensure that the healthcare providers performing the biopsy minimize risk to the extent possible for the trial participant (e.g., identifying the least invasive approach if several biopsy sites are possible).

[15] Requiring biopsies in clinical protocols for the purpose of evaluating non-key secondary and exploratory endpoints could unnecessarily expose subjects to risk. Under 21 CFR 56.111(a)(1) or 45 CFR 46.111(a)(1), to approve research covered by 21 CFR Part 56 or 45 CFR Part 46, respectively, the IRB must determine, among other things, that the risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

[16] Where the biopsy is required, withdrawal of consent to undergo biopsy may be one of the anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent to discontinue trial participation. See 21 CFR 50.25(b)(2) and 45 CFR 46.116(c)(2).

[17] See 21 CFR 56.111(a)(1) and 45 CFR 46.111(a)(1).

[18] See 21 CFR 312.60 and 812.100. For additional information on this topic, see the guidance for industry *Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects* (October 2009).

[19] See 21 CFR 50.20; 45 CFR 46.116(a)(1).

- When deciding whether biopsies should be required or optional, the conditions under which informed consent is sought should be carefully considered to minimize the possibility of coercion or undue influence.[20] Both the clinical protocol and informed consent document should clearly state whether each biopsy is required or optional. Participants must consent to any and all biopsies, required or optional, before they are performed.

- The informed consent document must include certain basic elements specified in 21 CFR 50.25 and/or 45 CFR 46.116, as applicable. These elements include any reasonably foreseeable risks or discomforts to the participants. Therefore, it is important for the informed consent document for the clinical trial to include, among other information, a description of the reasonably foreseeable risks – including physical risks from the biopsy procedure itself and informational risks (e.g., related to disclosure of identifiable private information learned from the biopsy, etc.) – and discomforts of the biopsy to the participant.[21]

IV. CONSIDERATIONS FOR CONDUCTING TISSUE BIOPSIES IN CHILDREN IN CLINICAL TRIALS

The considerations described above for conducting biopsies in adults in clinical trials are generally also relevant for clinical trials involving children as participants. FDA's and HHS's human subject protection regulations at 21 CFR Part 50, subpart D and 45 CFR Part 46, subpart D, respectively (collectively, "subpart D"), provide additional safeguards that must be considered when children are enrolled in clinical trials. Under those regulations, an IRB reviewing a clinical trial involving children as subjects must only approve those clinical trials that satisfy the requirements in 21 CFR 50.51, 50.52, or 50.53 and/or 45 CFR 46.404, 46.405, or 46.406 and the conditions of all other applicable sections of subpart D.[22]

A biopsy (and the biopsy's associated procedures, such as procedural sedation) conducted solely for research purposes and not needed for clinical management or routine clinical care should be evaluated to determine whether it offers prospect of direct benefit to the enrolled child. [23] For example, a biopsy conducted as part of a clinical trial may offer prospect of direct benefit to the

[20] See 21 CFR 50.20 and 45 CFR 46.116(a)(2).

[21] For additional information on informed consent, see the FDA guidance for IRBs, clinical investigators, and sponsors *Informed Consent* (August 2023).

[22] If the IRB believes that the clinical trial does not meet the requirements in either 21 CFR 50.51, 50.52, or 50.53 and/or 45 CFR 46.404, 46.405, or 46.406, the IRB may refer the clinical trial to FDA or HHS, as applicable, for further review if the IRB first finds that the clinical trial presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. See 21 CFR 50.54 and 45 CFR 46.407.

[23] See Section III.E of the draft guidance for industry, sponsors, and IRBs, *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022) for more information on assessing the prospect of direct benefit and risks of a particular intervention or procedure. When final, this guidance will represent the FDA's current thinking on this topic.

child by providing information that identifies whether the child will or will not be likely to have a favorable response to an investigational medical product that itself offers prospect of direct benefit. If a biopsy conducted as part of a clinical trial is determined to offer the prospect of direct benefit, the risks of the biopsy should be justified by the anticipated benefit of the biopsy to the child and the relation of the anticipated benefit to the risk should be at least as favorable to the child as that presented by available alternative approaches.[24]

If the biopsy does not offer prospect of direct benefit, the risks of the biopsy should be limited to "minimal risk" [25] or a "minor increase over minimal risk." [26] If the risk of a biopsy that does not offer prospect of direct benefit exceeds "minimal risk" and is limited to "a minor increase over minimal risk," the biopsy must be likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the child's disorder or condition.[27] When evaluating the risks of a biopsy, the potential for harm, the invasiveness, the frequency of the planned biopsy, and the risks of any procedural sedation during the conduct of the biopsy that would not be needed for the child's clinical care, should be considered.

For example, a single muscle biopsy has been considered, in many circumstances, to be a procedure that does not exceed a *minor increase over minimal risk*.[28] However, FDA and OHRP would generally consider large internal organ biopsies, for example a liver or kidney biopsy, to exceed a *minor increase over minimal risk*. Therefore, absent a prospect of direct benefit to the child, a large, internal organ biopsy generally should not be conducted in children as part of a clinical trial unless the procedure is performed as part of the routine clinical care for that child in the treatment of their condition.

The IRB must determine that permission of each child's parent(s) or guardian is granted and that adequate provisions are made for soliciting the assent of the child when in the judgment of the

[24] See 21 CFR 50.52 and 45 CFR 46.405.

[25] See 21 CFR 50.51 and 45 CFR 46.404. "Minimal risk" is defined in the FDA and HHS regulations as the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 21 CFR 50.3(k) and 56.102(i) and 45 CFR 46.102(j).

[26] See 21 CFR 50.53 and 45 CFR 46.406. "Minor increase over minimal risk" should be understood to mean a slight increase over minimal risk that poses no significant threat to the child's overall health or well-being. Department of Health, Education, and Welfare, Research Involving Children: Report and Recommendations of National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. See the *Federal Register* of January 13, 1978 (43 FR 2084 at 2112). Also see the draft guidance for industry, sponsors, and IRBs *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[27] See 21 CFR 50.53 and 45 CFR 46.406.

[28] Snyder D, Lee C, and Nelson R. (2018). Invasive Placebos, Patient Burdens and Community Advocacy: A Federal Ethics Panel Protocol Review. In Kodish, E and Nelson, R. (Eds). Ethics and Research with Children, A Case-Based Approach (2nd ed.). New York, NY: Oxford University Press.

IRB the children are capable of providing assent.[29] The parental permission form should describe any foreseeable risks or discomforts and any benefits to the child that are associated with the biopsy. In determining whether children are capable of providing assent, the IRB should take into account the ages, maturity, and psychological state of the children. If the IRB determines that the children are capable of providing assent, developmentally- and age-appropriate information about the biopsy should be included in the assent process.

[29] See 21 CFR 50.55 and 45 CFR 46.408.