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**Via Electronic Submission**

March 10, 2025

Sara Brenner, MD, MPH  
Acting Commissioner  
U.S. Food and Drug Administration  
5630 Fishers Lane Room 1061  
Rockville, MD 20852

Molly Klote, MD  
Director  
HHS Office for Human Research Protections  
1101 Wootton Parkway Suite 200  
Rockville, MD 20852

**Subject: Considerations for Including Tissue Biopsies in Clinical  
Trials ([Docket No. FDA-2024-D-2402](#))**

Dear Dr. Brenner,

The Association for Clinical Oncology (ASCO) appreciates the opportunity to provide feedback on the joint Food and Drug Administration's (FDA) and Office for Human Research Protections (OHRP) draft guidance, "Considerations for Including Tissue Biopsies in Clinical Trials." We applaud the Agencies' recommendations for trial designers to consider the inclusion of tissue biopsies in trial protocols and explain decisions about whether a biopsy should be required or optional for adults and children. The draft guidance aligns with ASCO's ongoing efforts to improve the ethics of research biopsies, especially those that are a mandatory condition of research participants' enrollment on trials.

ASCO is an organization representing more than 50,000 oncology professionals who care for patients with cancer. Through research, education, and promotion of the highest-quality, patient care, our members are committed to ensuring access to evidence-based care

for the prevention, diagnosis, and treatment for all Americans. ASCO supports robust quality initiatives that enhance performance measurement and improvement, clinical practice guidelines, big data analytics, and the value of cancer care.

In 2019, ASCO released an ethical framework for researchers on incorporating research biopsies in cancer clinical trials.<sup>1</sup> The framework offered recommendations to enhance the ethics of research biopsies by focusing on three goals: maximizing scientific utility, minimizing participant risk, and strengthening oversight. The framework emphasizes best practices such as designing trials to minimize risks by collecting only the tissue necessary for planned analyses, using the safest procedures to obtain sufficient tissue for research objectives, and developing eligibility criteria that account for research biopsy requirements. ASCO appreciates that the joint FDA-OHRP draft guidance also addresses risk and benefit considerations in clinical trials involving children and reinforces the importance of consent. We overwhelmingly support the proposal to make biopsies for evaluation of non-key secondary endpoint(s) and/or exploratory endpoints—or for unspecified future research uses—optional. We believe the draft guidance seeks to improve ethical use of tissue biopsies in clinical trials and offer the following comments:

- The joint draft guidance emphasizes the need to ensure tissue biopsy risks are balanced with expected benefits to the research participant. We agree that sponsors should provide clear rationales and scientific justifications for the need to include biopsies in their protocols. ASCO's concerns have centered around the fact that most research biopsies in oncology clinical trials have not provided direct benefits to research participants, except in a limited number of circumstances, such as the identification of patients for trial enrollment. We believe research biopsies add a potential safety risk to research participants and may cause discomfort and inconvenience. Therefore, we recommend that the Agencies and Institutional Review Boards (IRBs) ensure the informed consent forms are very carefully written to avoid misleading research participants about the potential benefits of research biopsies and their scientific importance.
- We recommend the FDA and OHRP add clarity to the draft guidance regarding the definitions of secondary, non-key secondary, and exploratory endpoints. The draft guidance refers to key secondary endpoints but the FDA's prior guidance in 2017 and 2022 on endpoints in clinical trials only distinguishes between primary,

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<sup>1</sup> Laura A. Levit et al., Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement. JCO 37, 2368-2377(2019). DOI:10.1200/JCO.19.01479

secondary, and exploratory endpoints.<sup>2,3</sup> There is no distinction made between key vs. non-key secondary endpoints, and we believe these terms should explicitly be defined in the final guidance.

- We also recommend the draft guidance provides clarification around the reporting of serious adverse events. The 2019 ASCO framework recommended that regulators consider serious adverse events that result from research biopsies to be study-related and require sponsors to collect and report them. However, we note this issue is not addressed in the draft guidance.
- We recommend clarifying FDA recommendations regarding IRB roles in managing active protocols whose biopsy requirements are not in compliance with the guidance (e.g., mandatory biopsies for non-key secondary or exploratory endpoints). We believe implementation of the guidance in these circumstances should lead to protocol amendments related to the categorization of endpoints and may also require that biopsies deemed mandatory in certain protocols be changed to optional.
- There have been inconsistencies in oversight by IRBs and regulators regarding research biopsies. We recommend IRBs better ensure ethical conduct of research biopsies and assess participant risk, scientific justification, and the informed consent process.
- Finally, we believe it is important for the guidance to emphasize the expectation and commitment to high-quality ethical clinical research and the need for the use of rigorous scientific design, wherein any required biopsies would be used to test a specific well-justified scientific hypothesis, using well-validated methods, and with an appropriate statistical plan. In general, our ethical framework permits optional research biopsies regardless of risk level because competent adults can decide whether to consent after being given complete and clear information.

Notwithstanding these further recommendations for finalizing this draft guidance, ASCO strongly supports FDA and OHRP's proposed guidance on tissue biopsies and believes it

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<sup>2</sup> Multiple Endpoints in Clinical Trials: Guidance for Industry. U.S.HHS Food and Drug Administration. January 2017. <https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf>

<sup>3</sup> Multiple Endpoints in Clinical Trials: Guidance for Industry. HHS Food and Drug Administration. October 2022. <https://www.regulations.gov/docket/FDA-2016-D-4460>.

outlines needed changes that are particularly relevant to cancer clinical trials and the development of new oncology products.

In conclusion, we believe this draft guidance will raise attention regarding the inclusion of research biopsies in oncology clinical trials. We also believe the scientific community should strengthen protection for research participants undergoing biopsies, that protocols meet these high ethical standards, and that researchers report accurate and thorough information to ClinicalTrials.gov and the peer reviewed literature. ASCO will continue to work with cancer researchers, lawmakers, and regulators to improve the ethics, design, and conduct of cancer clinical trials. Thank you again for the opportunity to contribute to the Agencies' efforts to improve the ethics of research biopsies, and we look forward to working with you. Please contact Shimere Williams Sherwood, PhD at [Shimere.Sherwood@asco.org](mailto:Shimere.Sherwood@asco.org) with any questions and for further discussions.

Sincerely,



Eric P. Winer, MD, FASCO  
Association Chair of the Board  
Association for Clinical Oncology