Brigham and Women's Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Office for Human Research Protections (OHRP)
Oncology Center of Excellence (OCE)
Food and Drug Administration (FDA)
5630 Fishers Lane, Rm. 1061, Rockville, MD 20852

February 24, 2025

Re: **FDA-2024-D-2402**
Draft Guidance: Considerations for Including Biopsies in Clinical Trials
Submitted electronically via Regulations.gov

To whom it may concern,

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard ("MRCT Center") appreciates the opportunity to comment on the Food and Drug Administration's ("FDA" or "the Agency") draft guidance document entitled "Considerations for Including Biopsies in Clinical Trials; Draft Guidance for Industry, Investigators, Institutions, and Institutional Review Boards; Availability," published January 7, 2025, by the Department of Health and Human Services. This guidance is welcome.

The MRCT Center is a research and policy center that seeks to improve the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. It functions as an independent convener to engage stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges, and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. The responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators nor with the institutions with which its authors are affiliated.[1]

Of note, we greatly appreciate that FDA and HHS, and specifically OHRP, have collaborated on issuing a joint draft guidance. This commitment to harmonization significantly benefits the regulated community; it reduces administrative complexity and burden.

We commend the forward thinking and clarity of the FDA and OHRP draft guidance and only offer these few recommendations to enhance its understanding and implementation.

Recommendations

1. The draft guidance distinguishes between required and optional biopsies (Lines 47-50, Lines 52-60). We support the FDA's guidance that required biopsies should be justified based on the necessity participant eligibility, primary or key secondary endpoints, or treatment response. However, we recommend further clarification

[1]Brigham and Women's Hospital, Mass General Brigham, Harvard Medical School, and Harvard University.

Smith Center #771, 1350 Massachusetts Ave, Cambridge, MA 02138 75 Francis Street, Boston, MA 02115
Tel: 617-827-7413 | Email: bbierer@bwh.harvard.edu www.MRCTCenter.org

on what constitutes a "key secondary endpoint" to prevent unnecessary exposure to invasive procedures. Providing specific examples of key secondary endpoints that justify requiring a biopsy for trial participation would be helpful.

2. We fully agree that less invasive and/or alternative approaches should be considered, but we believe that this should be a first and threshold consideration, and a principle enumerated explicitly in the guidance. In other words, a biopsy should only be considered if a less invasive or alternative approach would not be sufficient for the purpose proposed. Currently, less invasive approaches appear to be called out in biopsy cases of "tissue sites that pose higher risk" (Lines 70-71), but why, for instance, would one permit a skin biopsy if a photograph would suffice?

3. We agree with FDA that "the purpose of the biopsies, the reason(s) for their inclusion, and the associated risks" (Lines 67-68) should be considered whenever biopsies are considered, as the risks vary based on the biopsy proposed. However, the risk of the biopsy site is not the only dimension of risk that should be considered in the guidance, and even the same site may vary in incremental risk. Consider the following examples:

    a. A deep tissue biopsy (e.g. prostate, brain, bowel) is an invasive procedure, but the risks and invasiveness of the procedure that is conducted to obtain a sample for research purposes are very different from a research biopsy that is obtained as an incremental task (e.g., an extra needle biopsy, additional adjacent tissue) to a necessary and indicated clinical procedure.

    b. While very rarely true for adults, children often require sedation to obtain a bone marrow aspirate and biopsy. A research bone marrow sample would not be considered minimal risk given the requirement for sedation and, therefore, could not be performed as an optional biopsy. However, if a child is being sedated for one purpose (e.g., for insertion of a central line), obtaining a bone marrow aspirate or biopsy does not necessarily present the same concern, given that sedation is required for clinical reasons. Greater clarification is requested.

    c. The draft guidance specifically does not address the "acquisition of fluid samples such as samples of blood, urine, or saliva from trial participants" (footnote 6), implying that there is no need to distinguish required from optional biospecimen collection if the biospecimen is in a fluid state. We argue that it is not the state of matter that is determinative; rather, it is the invasiveness of the procedure to obtain the specimen. We realize that the title of the draft guidance only addresses "biopsies" and that may be the

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reason that fluid samples[2] are not considered, but a plain language read of footnote 6 allows for other interpretations. Consider:

i. In our opinion, the same considerations in terms of invasiveness and necessity would apply to obtaining cerebrospinal fluid (CSF) and might well be considered in this current draft guidance.

ii. Similar logic applies to obtaining certain other "liquid" specimens, such as bronchial washings.

We recommend that the intention of footnote 6 be clarified.

4. The draft guidance does not address whether the required or optional biopsies may be retained for future secondary research and, if so, under what conditions. If a biopsy is required for specific purposes (e.g., determination of eligibility, primary or key secondary endpoints, or treatment response), consent for future research unrelated to the trial should be subject to a separate and specific consent for unspecified future research, and that consent should not imperil eligibility or retention. If there are scenarios in which separate and specific consent for unspecified future use would not be appropriate or sought, the rational and scientific justification should be explicitly stated.

   Note: we appreciate that separate consent is already envisioned by the current draft guidance, but the guidance speaks to optionality if the purpose of the biopsy is for "non-key secondary and exploratory endpoints." (Lines 122-123) and, separately, for "specimens that will be stored and used for future unspecified research" (Lines 25-26). Consistent with the recommendation above and the principle of respect for persons, we believe that consent for each purpose should be separate and clear to the participant. Participants may well consent to an optional biopsy to obtain incremental information related to the trial or disease condition (and/or other uses that are specified) but not agree to storage and use for future unspecified research.

5. The guidance can be strengthened in regard to its IRB considerations. Specifically, IRBs should be instructed to ensure that the protocol has justified why (1) less invasive and/or alternative approaches are not feasible and then (2) how risks have been minimized, and finally (3) the rationale and scientific justification for the inclusion of any biopsy. Additionally, the IRB should ensure that consent is obtained for either required or optional biopsies closely proximal to the proposed procedure.

   Note: the current statement "Participants must consent to any and all biopsies, required or optional, before they are performed" (Lines 153-154) does not specify

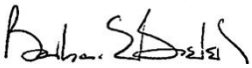
[2] Fluid samples are often termed "biospecimens" rather than "biopsies."

when that consent must be obtained. A plain language read would permit consent at the time of enrollment for any future biopsy.

6. The draft guidance rightly states that biopsies for unspecified future research should be optional (Lines 52-60, 125-126). We believe that the draft guidance should enumerate the required elements of the informed consent documents or refer to other guidance and regulations. Consent documents should include information about the conditions for storage, transfer, access, and identifiability, as well as potential genomic sequencing, biomarker identification, and third-party data-sharing practices related to biopsy-derived samples.

We commend FDA's effort to enhance the ethical rigor, scientific validity, and participant protections in the use of biopsies for clinical research. By clarifying criteria for required biopsies, reducing participant burden, strengthening informed consent protections, and ensuring equity in trial access, the final guidance can foster greater public trust and inclusivity. We appreciate the opportunity to provide feedback and welcome continued engagement.

Respectfully submitted,
on behalf of the MRCT Center



Barbara E Bierer, MD

Faculty Director, MRCT Center