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 of Women's Health (OWH)
Office of Clinical Policy (OCLP)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Food and Drug Administration (FDA)
5630 Fishers Lane, Rm. 1061, Rockville, MD 20852

March 11, 2025

Re: **FDA-2024-D-4245**
Draft Guidance: Study of Sex Differences in the Clinical Evaluations of Medical Products; Guidance for Industry
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("MRCT Center") appreciates the opportunity to comment on the Food and Drug Administration's ("FDA" or "the Agency") draft guidance document entitled "Study of Sex Differences in the Clinical Evaluations of Medical Products; Guidance for Industry," published January 7, 2025, by the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we appreciate the intra-agency collaboration of FDA, involving OWH, OCLP, CDER, CBER, CDRH, and OCE, issuing a joint draft guidance.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We commend the forward thinking and clarity of the FDA draft guidance and only offer these few recommendations to enhance its understanding and implementation.

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

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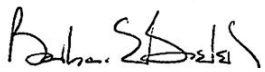
Comments

1. The guidance appropriately differentiates sex and gender, terms that have often been used interchangeably when they are not. The clarification that this guidance applies to sex differences is helpful. The guidance should clarify how to designate and include intersex individuals in FDA (and OWH, OCLP, CDER, CBER, CDRH, and OCE) research. While likely beyond the scope of the guidance, it would also be helpful to address whether and how to report on transgender individuals who are on hormone therapies.
2. The guidance provides recommendations on statistical approaches for evaluating sex differences. While we endorse the transparency in reporting subgroup analyses, including non-significant results, it would be helpful to know whether and when trials should (or must) be powered to detect differences in safety or efficacy by sex, and when post-marketing studies are likely to be required.
3. We appreciate the emphasis on including individuals who are pregnant or lactating, a historically underrepresented group. Understandably, however, sponsors are hesitant to include pregnant individuals because of the unknown risks to the fetus. Specific reference to FDA guidance on the inclusion of pregnant people would be helpful.
4. We encourage FDA to segregate the concerns of lactating women from the concerns about inclusion of pregnant people (and the attendant risks to the unborn developing fetus). First, FDA can recommend that the investigational product be tested for its presence in breast milk. Second, FDA can recommend alternatives to lactation be considered, particularly for clinical trials that are addressing unmet medical needs.
    - Specific guidance on lactating (as opposed to pregnant) people would be welcome.
    - Guidance on the inclusion of pregnant and lactating people could be updated to include a discussion of ethical considerations and informed consent processes for this population, particularly regarding risk communication. We encourage the guidance to address and potentially require long-term follow-up studies to assess the effects of medical products on maternal and child health, including developmental outcomes.
5. The guidance could consider specific language regarding the use of real-world data and real-world evidence (RWD/RWE) to support decision-making in this context. Specifically, strengthening the use of RWD/RWE in post-marketing requirements to monitor sex differences in safety and effectiveness will help confirm safety and efficacy in setting in which the pivotal trials have been either inconclusive or underpowered.

We commend FDA's effort in addressing sex differences in the clinical evaluation of medical products. The draft guidance is an important step toward ensuring research is more inclusive, equitable, and reflective of the diverse populations that medical products serve, while

acknowledging historical underrepresentation. We appreciate the opportunity to provide feedback and welcome continued engagement.

Respectfully submitted,
on behalf of the MRCT Center



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