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

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

ATTN: Leyla Sahin, Center for Drug Evaluation and Research, FDA

September 18, 2025

Re: Comments to Docket No. FDA-2025-D-1797,
E21 Inclusion of Pregnant and Breastfeeding Women 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the opportunity to offer the following comments on the Food and Drug Administration's ("FDA" or "the Agency") draft guidance document for industry from the International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials. There are significant scientific gaps in the knowledge of product safety and efficacy in pregnant and lactating women, and this guidance should help to address those gaps, encouraging the safe and appropriate inclusion of these populations in clinical research. The MRCT Center welcomes this guidance.

The MRCT Center is a research and policy center focused on defining and creating ethical, actionable, and practical solutions for global clinical trials. We achieve this work by acting as a neutral convener by bringing together industry, academia, patients and patient advocacy groups, non-profit organizations, and national 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]

We appreciate the opportunity to comment on the draft guidance presented by ICH and offer our support for the development of appropriate safeguards around the inclusion of pregnant and lactating women through well-designed research that is guided by participant protection. This population has been—and continues to be—understudied, and the result is the exposure of every pregnant woman and breastfed infant to unknown risks. Pregnant and lactating women should have an equal opportunity to engage in evidence-based decision making, which is predicated on population-specific clinical trial data and the analysis of real-world data.

The comments below are meant to support the comprehensiveness and rigor of the guidance and not as criticism; we offer additional perspectives and issues to consider. We offer some general

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

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

recommendations that, we believe, should be addressed in ICH E21 and FDA guidance. Wherein a comment addresses a specific part of the guidance, we have annotated it as such.

Comments and recommendations:

1. We greatly appreciate the clear and declarative statements contained in the guidance, such as the statements that inclusion of pregnant and lactating women is ethical (lines 84-86) and that inclusion is anticipated "unless there exists justification for postponement" (line 130). These statements provide direction in an otherwise complicated minefield. For example, we recommend that the guidance make it clear that signatories to ICH E21 are expected to provide information about how data specific to pregnant and lactating women will be developed and the timing of such data collection.
    a. In the US, this information could be part of the diversity action plans, or elsewhere, if these plans are not required.
    b. We further recommend that FDA encourage sponsors to reach out to the Agency for consultation and advice.
    c. In the US, the FDA should require that the data collection begin prior to final product marketing approval, given the recent authorities afforded FDA.
2. There is insufficient focus on the need for and utility of analysis of real-world data (RWD) of pregnant and lactating women who are prescribed approved products, for which insufficient data has been collected during the product development program. This is an important source of data that poses no incremental risk to the population as the products are prescribed, typically offlabel, for clinical indications. That is not to discourage appropriate clinical trials in these populations, but rather to supplement and backfill the dearth of evidence with which we currently contend. In our opinion, lines 62-68 provide insufficient guidance.
3. In reference to lines 17-22: Studies show that up to 90% of women take over-the-counter medication during pregnancy (source: Garcia et al., 2022; DOI 10.1002/bdr2.2048). It would be helpful to cite how common medication use is during pregnancy and the postpartum period. It would also be useful to highlight that "pregnancy" is not one state but a dynamic one and that pharmacokinetic (PK) and pharmacodynamic (PD) data should be gathered at varying times during pregnancy and the postpartum period. This point is made later in the document, but not in the Background section, where its reference would introduce the reader to consider the timeline and complexity of the pregnancy and postpartum period.
4. Pharmacokinetic (PK) and pharmacodynamic (PD) data need not only be derived prior to product approval. Given that many products are approved without data relevant to pregnant or postpartum women, that these products are nevertheless approved by FDA (and other regulatory authorities), and that physicians prescribe these products, PK/PD studies can be performed when prescribed off-label or as part of a clinical trial. We recommend that the guidance focus on the need for these PK/PD follow-on studies, and we recommend that FDA consider requiring such data as a post-marketing commitment or requirement.
5. The MRCT Center supports the commentary on prescribing information robustness and limitations. However, labels on pharmaceutical products that are vague (e.g., 'may pose a risk to pregnant women') are not sufficiently informative, and do not permit either prescribers or participants to make informed decisions about the product's safety or efficacy. Labeling should describe what is/is not known (e.g., whether the product was tested in pregnant animals,

pregnant women, and/or breastfeeding women) and the specific outcomes of those studies for the mother and the baby. If such information is not available at the time of product approval, the label should be updated regularly as new information, either from clinical trials or real-world evidence (RWE), becomes available. In our opinion, the guidance (lines 77-82 and Appendix 1) should be stronger. Again, we recommend that FDA consider requiring such data as a post-marketing commitment or requirement.

6. It would be helpful for ICH E21 (and FDA) to clarify when, in product development, the inclusion of pregnant and lactating women should be considered or recommended (other than "as early as possible.") Can these populations be enrolled as a sub-study for separate analysis, particularly so that manufacturers (and investigators) are less concerned about the outcomes of the primary study? Specifically, it seems to us that if the product is going to be prescribed following approval to these populations, then initiating PK/PD studies and follow-on appropriate clinical trials should proceed, sequenced to data collected on non-pregnant individuals, and begun prior to market authorization when the product may be used by pregnant women.

7. We recommend clarifying that for study eligibility criteria, any exclusion/s for women who could become pregnant, who are pregnant, or who are breastfeeding should be accompanied by a justification for the exclusion that clearly states the scientific, safety, and/or ethical reasons for the exclusion. This justification should be included in the protocol eligibility section so that the ethics committee and the regulatory authority reviewers can readily find and evaluate the reasons offered.

8. We applaud the distinction between pregnancy and lactation and the need to consider the risks and benefits of each separately. We recommend that the guidance clarify that the exclusion of pregnant persons and of breastfeeding women must each be justified. These two physiological conditions should always be considered separately.

9. In reference to lines 206-220: Currently, if a participant becomes pregnant while on a trial, the text directs that the participant could either drop out or, if they choose to remain, be reconsented as a pregnant participant if they choose to continue as a pregnant person. We recommend that this section provide information about counseling regarding these options and information about keeping a pregnancy once detected, with due consideration for local laws, particularly in cases where the treatment is teratogenic, but the well-being of the mother is at risk without treatment.

    a. Whenever a participant becomes pregnant while on a trial, the informed consent process and document should specify known and potential incremental risks to the pregnant woman and fetus, whether any additional data collection will be needed, and whether the neonate and/or infant will be assessed and/or monitored over time. In the US, if the neonate and/or infant will be assessed and/or followed, the applicability of Subpart D should be considered.

10. Because legislation regarding pregnancy and its outcomes varies by state across the United States (and by country globally), it would be valuable to include language regarding the risks to loss of privacy and confidentiality, particularly in the setting of pregnancy loss, termination, or adverse outcome. In this setting, the risks of legal liability to the investigator, clinician, and participant should be mentioned. Privacy risks are mentioned briefly in the section on

recruitment of pregnant women, but these risks exist at other times as well (e.g., if a participant becomes pregnant when already on a clinical trial). Further, recommendations for de-identification and anonymization of data, etc., should be included.

11. Pregnant women who have a documented pregnancy but not a documented birth can be at risk of their privacy being compromised (see lines 439-446.) This risk varies by state within the United States well as other sovereign nations, and should be given additional, site-specific consideration by investigators during recruitment. Risks should be communicated clearly to potential trial participants during the informed consent process, and at the point of a reported pregnancy.
12. The guidance should acknowledge that, under certain conditions, confidentiality commitments can be overridden (e.g., through federal or state legislation requiring reporting) and the potential consequences of disclosure. We recommend that this information be included in the informed consent document, as appropriate.
13. The guidance should discuss whether there are situations in which both the pregnant person and the parent partner, if one exists, should consent to participation and, similarly, when the lactating woman and the parent partner, if one exists, should consent to participation. In the US, certain studies on infants and children require two-parent consent. In the context of breastfeeding while participating in a clinical trial, would, and when would, one- or two-parent consent be required?
14. Section 5.4.2 addresses reducing the burden on participants. The introduction of decentralized elements in the clinical trial should be emphasized. Further, the MRCT Center recommends that the bulleted list include an expectation, and not simply a consideration, that hospital-grade pumps, pump accessories (e.g., extra tubes, valves, cups, breastmilk storage containers [e.g., breastmilk freezer bags with ounce labels]), and any other specialized equipment or resource be issued to participants for use during their breastfeeding period. Trial participants should not have to pay out-of-pocket costs to participate in a trial.
15. The MRCT Center recommends that the FDA guidance be harmonized with OHRP guidance and regulations, when applicable, prior to finalization. We further recommend that the 2018 draft FDA guidance be finalized to be consistent with ICH E21 (and OHRP).
16. We recommend that the guidance include guidance on both expectations for and clinical trials related to the study participant's pregnant partner.
17. We recommend that the guidance include considerations of and suggestions for trials involving both significant risk and non-significant devices.
18. We recommend that the guidance include considerations of and suggestions for vaccine development. In addition to general guidance, we suggest that the following settings also be addressed:
    a. The risk/benefit analysis may need to be reevaluated by the ethics committee, as the susceptibility of the pregnant (and post-partum) woman, fetus, and infant to infection is often increased.

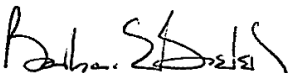
b. A vaccine that is administered to a woman who is later identified as pregnant or who becomes pregnant. The vaccine recipients appear to be ideal candidates for breast milk analysis, and the infants for protection from the target of the vaccine.

19. We recommend that the guidance provide recommendations on short-term and long-term follow-up, when appropriate, focusing on safety and considering the risk of the product and product class.

In summary, the MRCT Center welcomes the ICH and FDA efforts to protect pregnant and breastfeeding women through inclusion in clinical trials. Aligning regulatory standards for including this population is an important step forward in the development of medicines within the United States and globally.

Please feel free to contact me (bbierer@bwh.harvard.edu) if we can be helpful or you wish to discuss.

Respectfully submitted,



Barbara Bierer, MD
Faculty Director, MRCT
Professor of Medicine, Harvard Medical School