

September 19, 2025

Leyla Sahin, Center for Drug Evaluation and Research, Food and Drug Administration,  
Phillip Kurs, Center for Biologics Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002

RE: ***E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials;  
International Council for Harmonisation***  
[Docket No. FDA-2025-D-1797]

Dear Ms. Sahin and Mr. Kurs,

Founded in 2002, the Association of Clinical Research Organizations (ACRO) is non-profit trade association representing the world's leading clinical research and technology organizations, which provide specialized services that are integral to the development of drugs, biologics and medical devices that enable patients to live longer, healthier, and more productive lives. ACRO members provide a wide range of specialized services across the entire spectrum of development—from pre-clinical, proof of concept, and first in human studies through post-approval, pharmacovigilance, and health data research. ACRO member companies employ nearly 400,000 people worldwide and conduct research in every global region.

## **I. General Comments**

ACRO welcomes this ICH E21 guideline on the *Inclusion of Pregnancy and Breastfeeding Individuals in Clinical Trials* and supports the need to generate robust clinical data to support decision-making on treatment options by patients and their healthcare providers. ACRO notes that this population has been underserved by clinical evidence regarding medicines in the past and this guideline represents a significant step forward. ACRO also notes that there is a collective lack of experience and data on how to best design and conduct clinical trials with this population. Because of this, it will be necessary to provide flexibility regarding how to support trials in this area and not simply duplicate approaches for non-pregnant/breastfeeding participants. ACRO therefore recommends that regulators share specific, illustrative case examples in the final guidance where possible.

## **2. General Principles**

Lines 41-49. ACRO welcomes the recommendation that consideration of medicinal use in pregnancy and/or breastfeeding is incorporated throughout product development, including nonclinical studies, through to post-approval use.

Lines 52-57. ACRO welcomes the principle of reducing the burden of study procedures on pregnant and breastfeeding study participants. ACRO notes that the use of decentralized elements may support this principle and recommends that this is included in Line 57 in the final guidance (e.g., “Early engagement with appropriate stakeholders, including patients, provides opportunities to address all relevant aspects of these clinical trials, *including use of decentralized elements* where appropriate”).

Finally, ACRO welcomes the principle for a longer-term approach to data collection and safety monitoring, as reflected in Lines 63-64, 361-363 and 513-515.

### 3. Ethical Considerations

Lines 85-87. ACRO welcomes the clear statement on the ethical need to include pregnant and breastfeeding individuals in clinical trials in order to support safe and effective data-driven use of medicinal products. This is important in order to help address any misconceptions, held by anyone involved in approval, conduct or participation, about the ethics of including pregnant and breastfeeding individuals in clinical trials.

Lines 87-97. ACRO notes the recommendation to use ethics committees with experience with working with pregnant and breastfeeding participants. This is important in order to ensure ethical conduct of the trial and also to ensure that trials are not erroneously rejected due to a lack of understanding of the issues.

### 4. Pregnancy

Lines 221-222. ACRO notes that, should a participant become pregnant within a trial, and the decision is “for treatment with the investigational product to continue, then the participant should be reconsented as a pregnant participant.” ACRO recommends that the need for monitoring as a pregnant participant is highlighted with the inclusion of the following text: “If the conclusion is for treatment with the investigational product to continue, then the participant should be reconsented as a pregnant participant *and monitored as applicable.*”

Lines 264-270. ACRO notes the recommendations regarding sample size. Given the historical lack of clinical trials in pregnant individuals and lack of existing evidence, ACRO notes that data on, for example, withdrawal rates may need to be estimates. ACRO therefore suggests that additional regulatory agency support is available for sponsors to provide advice during the conduct of studies.

Lines 290-292. ACRO welcomes the recognition of the role of modelling approaches. ACRO notes that transparency of the detail behind PBPK models may vary and therefore recommends addition of a line such as “Sufficient details in order to understand the model and the impact on dosing strategy should be reported, such as model assumptions and sensitivity analyses.”

Lines 308–310. ACRO notes that the draft guideline states: “*Pregnant participants should be evaluated with the same efficacy, safety, PK, and PD endpoints as those in the general study population, with the same frequency of evaluation whenever feasible.*” While ACRO agrees with the principle of ensuring standardization of evaluation where possible, ACRO also notes the recommendations in Lines 458-474 regarding minimizing the burden of study procedures on pregnant participants. As highlighted in Lines 469-471 pregnancy may affect the participant’s ability to engage with burdensome study procedures. ACRO therefore suggests rewording Lines 308-310 to “Pregnant participants should be evaluated with the same efficacy, safety, PK, and PD endpoints as those in the general study population, with the same frequency of evaluation whenever feasible, *allowing flexibility for individuals as needed.*”

Line 316. ACRO notes that the draft guideline does not contain any considerations regarding pregnancy loss, beyond it noting it as a “gestational outcome of interest.” ACRO suggests that considerations are included in the guideline to guide sponsors. For example, “standard” clinical trial procedures such as

data collection, withdrawal from the trial or long-term follow-up may need to be modified in order to be sensitive to the participant and their family.

Lines 417–442. ACRO welcomes the emphasis of minimizing burden on pregnant and breastfeeding study participants and the recommendation for early engagement with stakeholders, including patients, to address relevant aspects of the trial.

## **5. Breastfeeding**

Line 626 ACRO welcomes the inclusion of section 4.2.2 describing the expertise needed to support study design and safety monitoring for studies in pregnancy. ACRO recommends a similar section is included in section 5, reflecting the need for expertise to support the studies involving breastfeeding individuals.

Lines 573-577 ACRO notes that the current draft briefly describes different stages of breastfeeding from the perspective of milk composition and quantity. Given that breastfeeding occurs at a time of significant change and potentially stress for the individual and their family, ACRO recommends inclusion of some more participant-centric considerations such as the principle that, where possible, breastfeeding should be established before an individual is recruited into a trial.

Lines 780-781 ACRO recommends that the guideline includes further examples of considerations of prioritization of participant and infant needs. For example Lines 780-781 could be expanded to: “The following should also be considered: timing of sampling and testing; duration of interruption of breastfeeding; the availability of nutritional alternatives to mother’s milk; conditions of their infant (e.g., prematurity) that may affect prioritizing breastmilk provision vs. research participation; and intercurrent illness which could affect the individual’s ability to breastfeed (e.g. reduced volume).”

ACRO thanks the Agency for the opportunity to provide comments on ICH E21. Please do not hesitate to contact ACRO ([knoonan@acrohealth.org](mailto:knoonan@acrohealth.org)) if we can provide additional details or answer any questions.

Respectfully submitted,

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