

## Final Concept Paper

### E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials

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*Endorsed by the Management Committee on 11 June 2023*

#### 1. Type of harmonisation action proposed

A new Efficacy guideline to provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breast-feeding individuals in clinical trials (CTs).

#### 2. Background to the proposal and statement of the problem

There is an increasing acknowledgement of the need to generate data for medicinal products in pregnant and breast-feeding individuals. Whilst it is recognized that CTs will usually not be large enough to detect increased risks of rare adverse pregnancy outcomes, it is also recognized that limited clinical information could burden the Health Care Professionals (HCPs) with the task of evaluating the unknown risk and/or benefit of medicinal product use during pregnancy. Inclusion of pregnant and breast-feeding individuals in CTs with appropriate safeguards and informed consent can help to identify pregnancy related changes in pharmacokinetics and/or efficacy needed to provide an appropriate benefit-risk evaluation.

Pregnant individuals are frequently excluded from CTs due to potential safety concerns, and those who become pregnant during a CT are often discontinued from further participation, although they and their child may be followed for safety data. Therapies frequently taken during pregnancy include, amongst others, antimicrobials, anti-hypertensives, antidepressants, anticonvulsants, migraine, diabetes and respiratory medicines, and vaccines<sup>1</sup>. Medicinal product use during pregnancy and breast-feeding may be necessary for disease prevention, and for the treatment of both acute and chronic disorders. This may include their use before the pregnancy is known, and prophylaxis or treatments for conditions that can be pregnancy-specific, worsened by pregnancy, or require continued treatment during pregnancy or breast-feeding. However, lack of data on use of medicinal products during pregnancy can lead to a choice of no treatment or treatment discontinuation for pregnant individuals even when the medication may otherwise be indicated. As a result, risk of morbidity and mortality from the acute or chronic illness may be increased during pregnancy.

Similarly, when data is not available on the levels of medicines in breast milk, HCPs and patients may have limited evidence to make a balanced and shared decision on whether the benefits of breast-feeding outweigh the risk of potential infant drug exposure. For example, pregnant individuals with COVID-19 were less likely than other COVID-19 patients to receive effective medicinal products such as steroids, low molecular weight heparin and antiviral treatments due to the lack of information available to HCPs and pregnant individuals regarding the potential impact on themselves and on the fetus or pregnancy [preliminary data provided by the International Network of Obstetric Survey Systems<sup>2</sup> and the ongoing international COVID-19 pregnancy registry EUPAS39226].

Generally, evidence available in drug labelling on the effect of medicinal products on pregnancy and breast-feeding is typically generated from non-clinical developmental and reproductive animal toxicity studies performed during drug development, with limited human data, if any, at the time of marketing authorisation.

Additional human data such as pregnancy outcome data from registries and real-world data/real-world evidence may be generated in the post-authorisation phase. The time required to acquire and analyse these complex data may mean that information is only incorporated in the drug product labelling long after the product is authorised for use; this does not benefit HCP and patients.

Earlier incorporation of clinical data in product labelling can help inform decision-making for pregnant and breast-feeding individuals. Furthermore, pregnant, and breast-feeding individuals may wish, and should be permitted, if appropriate, to participate in CTs. Inclusion of these individuals in CTs could improve the evidence available, helping HCPs and patients participate in shared decision making about the best choices for the health of the patient during pregnancy and breast-feeding.

Breast-feeding can provide important benefits for both mother and child, as well as for the society in terms of mother-child bonding, mother and child health, and time and cost savings especially considering that breast-feeding may be the only affordable source of nutrition in some parts of the world. Additional information on the use of a medicine in pregnant and breast-feeding individuals can help further inform decision-making and would provide greater certainty regarding benefit-risk. Uncertainties in pregnancy include the immediate or long-term impact of medicinal product use on the fetus or the child, respectively, compared to alternatives. In addition, potential dosage implications that result from physiological changes in pregnancy and the peripartum interval may induce changes in the pharmacokinetics of medicinal products and may ultimately lead to suboptimal efficacy or adverse pregnancy outcomes. Without human lactation studies, it may be unknown whether breast-feeding exposes the neonate or infant to clinically relevant doses of a medicinal product (or its metabolites), the quantity transferred, and whether absorption in the human milk fed child may have safety implications for the child. Without this information, patients may be unnecessarily counselled to interrupt or discontinue breast-feeding, either temporarily or permanently, or initiate compulsory early weaning, which impact both maternal and child health and result in the additional financial costs of having to use formula milk.

Some regional guidance documents, such as those mentioned in Transclerate's Points to Consider for the drug product lifecycle (preclinical, clinical and post-marketing periods) concerning the evaluation of medicines in pregnancy and women of childbearing potential that may become pregnant, have been issued and initiatives started that demonstrate the growing importance of the topic. There have been increasing calls from stakeholders, including the healthcare community and public to improve information to support decision making for use of medicinal products in pregnancy and breast-feeding<sup>3,4</sup>. Nevertheless, the COVID-19

pandemic has illustrated the opportunities currently being missed. For instance, a review of studies for non-biological treatments against COVID-19 found that 80% (124/155) of COVID-19 CT specifically excluded pregnant women<sup>5</sup>. The limited data on COVID-19 vaccines, in which pregnant individuals were excluded from Phase III trials, resulted in conditional marketing authorisations in Europe, containing statements of limited experience with use of COVID-19 vaccines in pregnant individuals, which led to delayed vaccine administration in many pregnant individuals despite the high morbidity and mortality risks to both the pregnant individuals and her infant associated with COVID-19 infection in pregnancy. Although there is work ongoing to improve this situation in specific therapeutic areas such as HIV<sup>6,7</sup> and anti-malarials<sup>8</sup>, and more broadly the IMI ConcePTION<sup>9</sup> project, at present HCPs and patients are left without much information to guide the use of newly developed medicinal products or those that have established benefit-risk profiles in non-pregnant populations, yet which are required to treat medical conditions in pregnant individuals<sup>10</sup>.

Although it is encouraging to see the level of global interest in this area, there is a risk that development of multiple individual guidelines could introduce complexity due to inconsistent recommendations, which could impede the enrolment and retention of pregnant and breast-feeding individuals in multinational studies and the consequent generation of critical data for medicine use in these populations. In addition, there are certain areas that are currently vague in existing guidelines such as situations in which inclusion of pregnant individuals in research is not appropriate<sup>11</sup>. Therefore, there is a need for harmonised regulatory guidelines for conducting CTs in pregnant and breast-feeding individuals that would enable the safe conduct and robust data collection from these trials to enable regulatory acceptance for inclusion in the product label information.

### **3. Issues to be resolved and expected deliverable(s)**

To ensure the appropriate inclusion and/or retention of pregnant and breast-feeding individuals in CTs conducted to study product safety, efficacy, and dose/dosing regimens in these populations, this global harmonised guideline will address scientific and high-level regulatory principles such as:

- The data required to define appropriate timing of inclusion and/or retention of pregnant and breast-feeding individuals or retention of individuals who become pregnant in CTs, and when contraception requirements can be removed or relaxed.
  - Considerations for the use of existing data sources (e.g., non-clinical developmental and reproductive toxicology animal studies [DART]), real world evidence of use in pregnancy or breast-feeding, data from drugs of the same pharmacological group, availability of physiologically based pharmacokinetics [PBPK] models incorporating known physiological changes and predicted pharmacokinetics.
  - Considerations for the type of therapeutic:
    - There may be different considerations related to CT design regarding whether the drug is a biological medicine such as monoclonal antibody or vaccine versus a small molecule drug.

- The necessity for a CT in pregnant individuals and that the design of a CT needs to consider whether a monoclonal antibody, a small molecule, a vaccine, or an advanced therapy medicinal product, may have differing effects based on exposure to the fetus/breast milk/nursing infant.
- Considerations for uncertainties:
  - How to assess the potential benefits of the investigational medicinal product and CT participation on pregnant/breast-feeding individuals and their fetuses/neonates against the uncertainty and potential harms or risks, including the risks of no or alternative treatment.
- Types of the data to be collected and evaluated from CTs
  - The strategies and methodologies that may be used to generate and evaluate the data from CTs involving pregnant / breast-feeding individuals.
- Planning how and when to include pregnant / breast-feeding individuals in CT
  - Including pregnant / breast-feeding individuals in pre-authorisation CTs or CTs once the product has received marketing authorisation.
  - Consideration for the therapeutic area and unmet medical needs (treatment needs in pregnant/breast-feeding individuals of the disease and the prospect of benefiting from a product with a therapeutic advantage compared to current standard of care) and/or impacts of non-treatment (e.g., irreversible damage from disease flares, disease progression).
  - The types of trial design that might be considered
  - Bridging principles to other ICH guidelines related to pregnancy and breast-feeding [e.g., GCP guidelines, ICH S5(R3) and M3] and planning DART non-clinical studies to facilitate the inclusion of pregnant and breast-feeding individuals in CTs.
- Situations in which the inclusion of pregnant / breast-feeding individuals in a CT is not recommended.
- Ethical considerations.

The guideline will also provide practical guidance for planning CTs including pregnant and/or breast-feeding individuals, such as protocol descriptions, informed consent, data collection considerations, and mother and child follow-up (with reference to other ICH and PV guidelines [e.g. ICH E6, E2A and E11]). Guidance for a comprehensive communication and stakeholder engagement plan will also be included.

Effects of exposure on the fetus during pregnancy to drugs that may impact *in utero* and/or post-natal development need to be known to ensure safety of the fetus, the new-born, and the child as some exposures during pregnancy may have lifelong repercussions.

A new overarching guideline that will cover principles and practices to enable the collection of a sufficiently robust set of safety, efficacy, and/or pharmacokinetic data in pregnant and breast-feeding individuals will better inform clinical decision-making in medicinal product use (e.g., improved product labelling). The guideline will establish a common understanding between regulatory authorities, industry, and other stakeholders and harmonise strategies and

methodologies for enrolment and retention of pregnant and/or breast-feeding individuals into CTs and overall drug development plans.

#### **4. Planning**

The composition of the Expert Working Group (EWG) is expected to be diverse and should include representatives with expertise in relevant areas (e.g., non-clinical, clinical, regulatory, safety, pharmacovigilance, CT design, obstetrics, paediatrics/paediatric neurodevelopment, neonatology, developmental and reproductive toxicology, oncology, etc). *Ad hoc* consultations with experts such as the ICH S5, statisticians, researchers, medical ethicists, neonatologists, nonclinical toxicologists, epidemiologists, obstetricians/obstetric physicians, midwives, etc. and/or additional experts as determined by the Topic Leaders may need to be added to address certain technical components of the guideline. Additional resources may also include the need to meet face-to-face on a regular basis to achieve alignment on this topic across EWG members.

An informal Working Group was launched in October 2022 to finalize the Concept Paper prior to the formation of an ICH EWG. The EWG aims to achieve *Step 1* technical consensus document /*Step 2* signoffs within 18 months of the establishment of the EWG. It is expected that the work of the EWG will take approximately 3 to 4 years to complete.

#### **5. Impacts of the project and post-hoc evaluation**

Harmonisation of strategies and methodologies for enrolment and retention of pregnant and breast-feeding individuals into CTs and overall drug development plans will result in sustainable availability of information regarding a product's benefit-risk during pregnancy and breast-feeding and help reduce the risk of pregnant and/or breast-feeding patients being prescribed medicinal products without adequate evidence in this patient population.

This topic is expected to be implementable globally as the main deliverable is a set of technical principles to enable the collection of data that is based on currently accepted guidelines by global regulatory authorities. A global level agreement is needed to improve the situation for pregnant and breast-feeding individuals who need medicines, and to be inclusive of all patient populations. In addition, a global guideline will ensure consistent application and ethical/equivalent data generation within global trials.

The need for an evaluation plan will be considered during the preparation of the guideline.

## References

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