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SCIENCE MEDICINES HEALTH

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An agency of the European Union

3 October 2025
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Overview of comments received — Guideline on inclusion of pregnant and breastfeeding individuals in clinical trials (EMA/CHMP/ICH/149462/2025)

Please note that comments will be sent to the ICH E21 EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	0	0	4.2.11	In this section, consideration should be given to the type of investigational medicinal product, since the benefit.risk balance to continue/discontinue the pregnant participant might be different for a small chemical molecule than for and Advance Therapy or biological medicines.	Add "5. Type of IMP" as factors to be considered
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	0	0	5	From a clinical standpoint, there is a high unmet need to obtain reliable data in certain pedriatric population subsets, such as premature infants, in order to guide the recomendations on whether or not discontinue/encourage breastfeeding during that neonatal period. Taking into account that several chronic and acute maternal medical conditions (e.g., diabetes, hypertension, autoimmune disorders, maternal infections) are significant risk factors for premature births and that those conditions often require pharmacological treatment, it appears mandatory that Sponsors at least consider whether or not these infants should be included as part of the mother-infant pairs in dedicated lactation sudies or even clinical tudies in which breastfeeding mothers are allowed to participate . The guideline poses an opportunity to obtain reliable PK and clinical data from/about breastfinding premature infants in those intances that maybe deemed appropiate (e.g., well-known IMPs in which lactation data is scarce). Consideration should be given to specifically include considerations regarding "premature infants " in the guideline, when appropiate.	See additional comments/suggestions below
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	0	0	5.3.4.	Sponsors should be encouraged to include a Data Monitoring Committee or other safety oversight body as part of the safety monitoring (see section 5.3.1.). A cross-refence should be included in this section in that regard	No specific text changes are proposed.
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	0	0	5.3.5	The details on the reason to discontinue treatment and/or breastfeeding should be collected.	No specific text changes are proposed.

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"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	0	0	5.3.1	In this section, consideration should be given to the type of investigational medicinal product, since the benefit.risk balance to continue/discontinue breastfeeding might be different for a small chemical molecule than for and Advance Therapy or biological medicines.	No specific text is proposed.
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	0	0	Appendix 2	For pregnancy losses occurred during the first trimester, the possibility to study the presence of abnormalities in the embryo/its annexes should be included in Appendix 2, as a gestational outcome if interest. This would be very useful to determine the causes behind an early pregnancy loss.	For pregnancy losses occurred during the first trimester, the possibility to study the presence of abnormalities in the embryo/its annexes should be included in Appendix 2, as a gestational outcome if interest
ACRO	0	0		ACRO, founded in 2002, 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. ACRO welcomes this guideline on the Inclusion of Pregnancy and Breastfeeding Individuals in Clinical Trials and endorses 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. This means it will therefore be necessary to have flexibility in how to support trials in this area and not simply duplicate approaches for non-pregnant/breastfeeding participants. ACRO would therefore recommend that regulators share specific case examples where possible.	Recommendation: sharing, by regulators, of case studies and examples of good practice.
ACRO	0	0		We thank the EMA for the opportunity to provide this feedback. Please do not hesitate to contact ACRO if we can provide additional details or answer any questions. Karen Noonan, Senior Vice President, Global Regulatory Policy	
Certara	0	0	general comment	Overall the document covers many aspects of the issues with including pregnant and breastfeeding women in clinical trials. As currently written it appears that all non-clinical DART work would need to be completed before Women of Child Bearing Potential (WOCBP) could be included in a clinical tria that does not require strict contraception.	It is suggested to include an appendix showing a decision tree for when all DART work prori to a clincial trial would be required, when none would be required or when a weight of evidence (WOE) approach with minimal DART testing or the results of an alternative test for development or reproducttive hazard might be acceptable. Alternative approach to an appendix would be to require a document similar to the "Structured Extrapolation Plan" used in PIPs that outlines the approach for including pregnant and lactating women into clinical trials and still lets first in class, highly benefiicial treaements and new and novel therapies (gene therapies) to get to market as fast as possible without ignoring the need get information on the hazard of exposure during pregnancy or lactation to the moher, fetus and child (see also comment at row #27).
Certara	0	0	general comment	If all DART non-clinical studies are required, the time to an IND would be significantly extended by up to a year or more in the case of an ePPND in NHPs or just a PPND study in rodents. This timing does not include time to produce additional test material which can be considerable for a small molecule and many of these programs will fail in Phase 2	

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Certara	0	0	4.2.4	The concentration of many drug-binding plasma proteins changes continuously during pregnancy, which will impact the fu of drugs binding to these proteins. Changes in fu may impact both PK and PK-PD relationships. Given that in most cases drug efficacy (and safety) is driven by unbound drug concentrations rather than total concentrations, it may not be sufficient to focus the analysis on total drug concentrations only. Fetal exposure and transfer into breastmilk may also to some degree be driven by unbound, rather than total, concentrations.	Include the recommendation to assess potential differences in total as well was unbound drug exposure.
Certara	0	0	5.2	Considerations on age of infant for breastfeeding should be included in the guidance. The WHO guideline consider up to 2 years, but consideration should be included beyond 2 years which is common in some countries e.g. in Africa	
Certara	0	0	appendices	An efficacy extrapolation framework would be useful to support decisions making process for inclusion of pregnant individual in clinical trials. Such a framework could be based on similarity in disease and in response to treatment, drug pharmacology, similarity in target exposure, and how to reach this exposure in pregnant individuals. Safety consideration should also be addressed in such framework. The efficacy/disease/clin pharm-based extrapolation framework presented by Coppola et al. 2024 could be used as reference. Link to this paper is provided in G28.	Medicines in pregnancy: A clinical pharmacology extrapolation framework to address knowledge gaps
Certara	0	0	general comment	It is suggested to plan the submission of a "maternal investigational plan" similarly to the current Structured Extrapolation Plan included in PIPs for peadiatric submissions, in order to have early feedback from regulators.	
Dr Siva Kumar Buddha	0	0	4.2	It would be helpful to provide a decision framework or criteria to help sponsors determine when retention is ethically appropriate versus when withdrawal is necessary.	A simplified decision-making framework is recommended to guide the retention of participants who become pregnant during a clinical trial. First, a scientific and clinical risk-benefit assessment should be conducted to evaluate available nonclinical (e.g., DART) and clinical data, expected fetal exposure, and the potential maternal benefit of continued treatment. Second, the feasibility of ethical and safe monitoring must be ensured, including specialist involvement (e.g., obstetrics) and long-term maternal-fetal follow-up plans. Third, re-consenting of the participant must be performed with transparent communication of risks, and ethics committee approval must be obtained for continued participation. Finally, a multidisciplinary decision involving the investigator, sponsor, medical monitor, and ethics representative should be documented with clear rationale and updated oversight plans. This approach supports ethical consistency, participant safety, and scientific rigor across studies.
Dr Siva Kumar Buddha	0	0	4.1	Consider explicitly recommending the use of real-world data to assess preliminary safety signals before enrolling pregnant individuals.	This aligns with the increasing reliance on RWD in regulatory science and can support more confident risk-benefit decisions in early planning.
Dr Siva Kumar Buddha	0	0	0	The draft does not mention male-mediated exposure and potential risk to pregnancies through paternal use.	Some drugs may affect sperm and indirectly impact fetal outcomes.
EFPIA	0	0	0	This guidance is written to provide guidance for Sponsors, but investigators and sites may also need specific guidance to support pregnant individuals in trials.	Implementation and training plans for this guidance should consider the unique expertise that might be required by investigators and sites and ensure adequate resources are provided to implement this guidance successfully.
EFPIA	0	0	4.1.4	There is a missing discussion about shared decision-making in the context of including pregnant individuals in clinical trials. This approach ensures that both the patient and the physician can weigh the potential risks and benefits together, leading to more informed and personalized treatment decisions.	Consider adding a sentence: It is essential to emphasize the importance of shared decision-making between the patient and the doctor running the trial. If a pregnancy occurs and there is a potential for harm, but the benefits of a drug outweigh the risks, this decision should involve not just a case-by-case discussion but a collaborative decision-making process that respects the patient's values and preferences.

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EFPIA	0	0	4.2.1	The intent of this paragraph is unclear. It references the inclusion of pregnant individuals in trial types other than interventional clinical trials, but does not specify what these other acceptable trial types are. Are observational or non-interventional trials being considered? Clarification is needed to ensure a comprehensive understanding of the study designs applicable for this population.	To enhance clarity, we recommend expanding this paragraph to explicitly outline the types of trials that may be acceptable for the inclusion of pregnant individuals beyond interventional clinical trials. Providing specific examples, such as observational and non-interventional studies, would greatly assist in conveying the intended message
EFPIA	0	0	5.2.2	It would be beneficial to clarify that opportunistic studies are typically conducted for either post-marketing drugs or investigational products that are similar to those currently in development. This distinction is important to ensure a clear understanding of the context in which opportunistic studies are applicable.	We recommend rephrasing the guideline to explicitly state that opportunistic studies are primarily designed for post-marketing medications or for investigational products that share similarities with those already approved. This clarification can help delineate the specific scenarios in which opportunistic studies are appropriate and enhance the overall understanding of the study design.
EFPIA	0	0	0	We support the differentiation made in this guidance between pregnancy and breastfeeding, considering that the risks in pregnancy could be significantly higher than in breastfeeding, since it is always possible to stop breastfeeding and use an alternative method.	No requested change to text
EFPIA	0	0	5.5	Local laws and regulations regarding maternal versus paternal decision making capacity are not addressed in the guidance.	Please consider adding text to address this.
EFPIA	0	0	4.1.2	Should there be a minimum threshold of nonclinical data (e.g., DART studies) before allowing inclusion of pregnant or breastfeeding individuals, or is this left to sponsor discretion? For example, definitive embryo-fetal development studies (as opposed to preliminary EFD studies, per ICH S5 R3) and pre/postnatal development study (PPND study)? Would the fertility and early embryonic development study continue to be only required for phase 3 given that the exposure period is not relevant for this population? Can a weight of evidence approach or NAMs be used instead of animal studies and in what circumstances. This comment is also relevant for clinical data.	Please provide clarification regarding the nonclincial and clinical data that would be needed to support inclusion of pregnant as well as breasfeeding individuals.
EFPIA	0	0	4	Clearer and more specific guidance would be appreciated around establishing a favourable benefit-risk assessment that supports including pregnant/ breastfeeding individuals.	In section 4 relevant aspects are mentioned but wording is often unspecific such as "as early as possible", "appropriately", "generate the necessary evidence". This could be more tangible.
EFPIA	0	0	2	Sponsors… are encouraged to consider strategies…	Wording is often unspecific such as "as early as possible", "appropriately", "generate the necessary evidence". This could be more tangible. A requirement for a plan and regulatory framework with deliverables for products that are likely to be used in WOCBP may be appropriate for this important topic, similar to pediatric development. Include timing of regulatory consultations.
EFPIA	0	0	6	Case studies using weight of evidence approach for some common scenarios would be extremely useful (similar to ICH S11 App.B)	consider adding another Appendix with informative example case studies, including small vs large/biotechnology-derived molecules
EFPIA	0	0	4.2.11	The guideline allows for inclusion of pregnant individuals and continuation in the study if pregnancy occurs. In this context, the rationale for maintaining mandatory contraception requirements in protocols is unclear. Clarification is needed on when contraception requirements are appropriate, and whether they should be removed once sufficient safety data support inclusion or continuation during pregnancy.	
EFPIA	0	0	4.2.11	a substantial number of country IRBs (Ethics commitees) and HAs (Competent Authorities) (not previously consulted) may object to the contraception requirements which would trigger a local/global protocol amendment.	

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EFPIA	0	0	4.1.2	The guideline allows for inclusion of pregnant individuals and continuation in the study if pregnancy occurs. In this context, the rationale for maintaining mandatory contraception requirements in protocols is unclear. Clarification is needed on when contraception requirements are appropriate, and whether they should be removed once sufficient safety data support inclusion or continuation during pregnancy.	
EFPIA	0	0	4.1.3	The guideline allows for inclusion of pregnant individuals and continuation in the study if pregnancy occurs. In this context, the rationale for maintaining mandatory contraception requirements in protocols is unclear. Clarification is needed on when contraception requirements are appropriate, and whether they should be removed once sufficient safety data support inclusion or continuation during pregnancy.	
EFPIA	0	0	4.1.2	a substantial number of country IRBs (Ethics commitees) and HAs (Competent Authorities) (not previously consulted) may object to the contraception requirements which would trigger a local/global protocol amendment.	
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EFPIA	0	0	2	It may be worth considering maternal administration of prodrugs or precursors that are metabolized into active compounds benefiting the infant, especially when the active form is unstable outside the body or due to toxicity cannot be administered by the infant direclly. This approach could be relevant for compounds that cannot be directly administered to the child due to pharmacokinetic limitations. The guideline could acknowledge this as a potential development strategy in specific therapeutic contexts.	
EFPIA	0	0	4.2.8	Clarification is required on the expectation of long term follow-up requirements post study completion, as retention/data quality may be poor. Also to note the consent challenges for this post-study long-tem follow-up.	
EFPIA	0	0	4.2.10	The guideline would benefit from clearer recommendations on statistical methods to ensure data robustness in pregnant and breastfeeding individuals. Given the significant physiological changes during pregnancy that affect drug metabolism, it is important to consider trimester-specific PK/PD modeling, Bayesian and adaptive designs for small sample sizes, longitudinal analysis for repeated measures, causal inference methods to address confounding, and appropriate handling of missing data. These additions would strengthen the reliability of efficacy and safety data and support more informed regulatory decisions.	
EFPIA	0	0	4.3	It is likely that a substantial number of country IRBs (Ethics Committees) and HAs (Competent Authorities) (not previously consulted) object to the inclusion of pregnant individuals which would trigger a local/global protocol amendment.	The guideline should therefore contain provisions to avoid amendments: e.g. require IRB / ethics approval prior to an individual patient be enrolled.
EFPIA	0	0	5.1.1	For breastfeeding, the composition of breast milk is still not fully understood. It changes not only throughout a single feeding session but also with the age and condition of the child. The guideline should provide recommendations on how to ensure robustness of data collected in this context, considering the dynamic nature of breast milk composition.	
EFPIA	0	0	4.1	guidance is nonspecific	proposal is to make the guidance more specific and prescriptive, including when during the development of a molecule to implement these studies, sample size, duration, which trimester of pregnancy, etc.
EFPIA	0	0	0	stages of development for pregnancy and lactation studies	proposal for pregnancy and lactation studies: 1) Lactation studies: should be implemented first, before the pregnancy studies and after an interim analysis for adult phase 3 has been done and peds studies have started with at least blinded safety reviews initiated 2) pregnancy studies should be started with the last trimester first and then first and second trimester studies initiated

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EFPIA	0	0	4.1	guidance is nonspecific	proposal is to make the guidance more specific and prescriptive, including when during the development of a molecule to implement these studies, sample size, duration, which trimester of pregnancy, etc.
EFPIA	0	0	4.2	The unmet need for data and trial participation for pregnant/breastfeeding women is clear, and the paper sets out the arguments well. It will always be difficult to define what is meant by 'robust' data, and also how many participants are adequate.	
EFPIA	0	0	4.1.1	Consider explicitly including assisted reproductive technologies (ART) such as IVF and donor gametes in the planning framework. These modalities may influence disease progression, treatment response, and pregnancy outcomes, and should be accounted for when designing data collection strategies.	Include ART-specific considerations in the planning of pregnancy data collection.
EFPIA	0	0	0	It is questionable if the same guideline should apply for all cases. For example pregnant women invited to participate in a trial for an existing condition (example treatment of lupus during pregnancy or treatment of preterm labor) compared to 1 or 2 cases that accidentally become pregnant during a trial. Propose establishing separate sections: one - for indications in the general population and for indications specific to pregnant or breastfeeding individuals	
EFPIA	0	0	0	In some sections wording is vague or subject to different interpretations. For example: The inclusion of breastfeeding individuals in clinical trials for indications in the general population may be permissible with the appropriate data available …. It is suggested to provide clarification on what constitutes "appropriate data," including examples such as data regarding the concentration of the tested drug in breast milk	
EFPIA	0	0	4.4	Sections 4.4 and 5.5 on informed consent are thorough, but the document could more clearly address how to balance complex information with health literacy needs.	Suggest incorporating principles of plain language, health literacy testing, or layered consent formats that allow for personalized information delivery. This aligns with ICH E8(R1) and global health literacy initiatives.
EFPIA	0	0	0	The guideline alternates between "individuals" and "participants" when referring to pregnant or breastfeeding persons. While this is inclusive, consistent terminology (e.g., "pregnant participants") would enhance clarity and align better with established ICH style in guidelines like E6(R3).	Define preferred terminology early in the guideline (e.g., Section 1.2) and apply consistently throughout.
EFPIA	0	0	0	While the guideline encourages early engagement with stakeholders, it stops short of providing concrete recommendations on how and when to involve pregnant or breastfeeding individuals themselves in protocol design or risk communication.	Include examples or best practices for patient and public involvement (PPI), including participatory research models or co-development of informed consent language.
EFPIA	0	0	5.5	Sections 4.4 and 5.5 on informed consent are thorough, but the document could more clearly address how to balance complex information with health literacy needs.	Suggest incorporating principles of plain language, health literacy testing, or layered consent formats that allow for personalized information delivery. This aligns with ICH E8(R1) and global health literacy initiatives.
EFPIA	0	0	0	The guidance expects proactive planning across all stages of development but does not discuss practical strategies for implementation, such as when DART studies should begin or how to align timelines for pregnancy/lactation studies with regulatory milestones.	Include a high-level schematic or table outlining a possible development timeline for integrating pregnancy/lactation studies within the typical clinical development pathway.
EFPIA	0	0	0	The guideline recommends early dialogue with regulators but lacks specificity on how existing frameworks (e.g., FDA's Pregnancy and Lactation Labeling Rule, EMA's guidance) will harmonize with ICH E21.	Clarify in an appendix or future Q&A document how ICH E21 is intended to align or diverge from existing regional guidances, especially in terms of postmarketing study requirements, labeling, and risk communication.
EFPIA	0	0	0	Throughout the document, the guidance advises Sponsor to make an effort to reduce the burden of trial procedures on the pregnant or breast feeding participant but recommends additional trial procedures specific to the pregnant and/or breastfeeding participants. Procedures for additional PK/PD, measurements of product concentration present in breast milk, prenatal monitoring, infant follow-up would increase the participant burden.	Additonal recommendations on inclusion of pragmatic elements such as obtaining data from obstetrician and pediatrician visits in the trial design would help reduce the participant burden.

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EFPIA	0	0	0	There is guidance throughout the document regarding engagement with external experts such as participant advocacy groups, obstetricians, pediatricians, experts in the therapeutic area, disease state experts, RWD and RWE for product class. Early planning in the development program will be key to the successful inclusion of pregnant and/or breast feeding participants.	Inclusion of a "Points to consider" section similar to ICH E19 would be helpful.
EFPIA	0	0	0	The use of the term "individual" diminishes the scientific basis whereby females have been excluded from medicines development research historically. This is an issue that is entirely limited to the female sex. Given this, females who identify as men (whether they have transitioned - in dress, hormone, surgery, a combination of some or all - or not) are at risk purely because of their female sex, typically derived from the XX chromosomal complement. This is a true biological concept. The issue that drug developers face in assessing if pregnancy and its trimesters impart an effect on PK is directly related to the female sexes ability to produce eggs; when that egg fuses with a male sperm this leads to a pregnant state. This leads to a hormonal cascade which has physiological effects on the female organ systems, and is the whole point as to why we should study investigational medicines in pregnancy to understand if the PK and or PD remains the same or requires adjustment. Respectfully, as a scientific organization laying out global guidance on how to best study highly complex molecules, the ICH should be clear with key terminology. For the E21 guideline, female is the key term - this includes females who identify as men.	The EWG should consider making a global change throughout the document, or at a minimum, including a disclaimer (or a dedicated section) denoting that the guideline is applicable to the female sex, regardless of how one identifies.
EFPIA	0	0	0	General: The idea is hidden somehow in the text, but the way I read it was that a positive benefit risk for pregnant women and or the child must be present. Would it make sense to summarize the criteria before trials in pregnant women can start. I am thinking about some guidance similar to what is available for inclusion of children into clinical trials.	
EFPIA	0	0	0	The definition of infant/child differs among specialities. EMAs definition should be introduced early in the document. From EMA's Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations IV: Paediatric population on page 3.The paediatric population encompasses several subsets. .. the applied age classification of paediatric patients is: • preterm newborn neonates: from day of birth through the expected date of delivery plus 27 days; • term and post-term neonates: from day of birth plus 27 days; • infants (or toddlers): from 1 month (28 days) to 23 months; • children: from 2 years to 11 years	Recommandation. It is important for readers to know EMAs definiton
EFPIA	0	0	0	If possible the document should separated into sections regarding the pregnant women/fetus, the neonate/infant/child and breastfed neonate/infant/child	For users to have easy access of the guidelines for different subgroups
EFPIA	0	0	Appendix 2	A general comment to appendix 2: The most important outcome of the pregnancy (other than the mothers well-being) is the condition of the newborn at birth and the monitoring of neurodevelopment of the child with age – both regarding motor skills and neurological development. This should be monitored more closely after exposure from mothers' medications during the pregnancy. Primarily assessment of the newborn at birth, but also after one month of age. For medications that can have more severe impact to the child, I recommend (as in mentioned in guidelines) a longer period of observation. For neurotropic medication, the child should be evaluated by a pediatric doctor around the age of 9-12 months. I recommend that the appendix 2 should be reviewed by a neonatologist; aligned with the recommendation in the guidelines for the use of experts. Important parameters are not included in the assessment of the newborn: Head circumference is an extremely important parameter: if it is small compared to age, it can be a sign of malnourishment or lack of appropriate developmental of the brain. If HC is larger than normal, one should consider excess cerebral fluid, bleeds during the pregnancy. Length/weight, small for GA, Large for GA, APGAR score are also important measures for the condition of the newborn.	Recommendation
EFPIA	0	0	6	Suggest providing more specific examples for labeling considerations and detailed outcomes for both maternal and infant health in the Appendices.	

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EFPIA	0	0	0	General comment : suggest to have a dedicated section for this population in the paediatric plans (PSP, PIP) and to grant similar rewards (patent extension for devevelopment of drugs in this population, when relevant)	
EFPIA	0	0	0	Thank you for this comprehensive and highly relevant guideline. It reflects a strong evolution of this draft, particularly in clarifying the inclusion of pregnant individuals in clinical trials both pre- and post-marketing. The content is well-structured, aligns with expectations, and addresses key considerations with clarity and depth. It offers a solid foundation for consistent implementation and will undoubtedly serve as a valuable reference going forward. A few suggestions for refinement to improve the overall consistency of the text: Consider using consistent terminology when referring to breastfed individuals—either “breastfed infant” or “breastfed child”—as the latter may imply an older age group. Since the guideline also addresses implications for labeling (see Appendix 1), it would be appropriate to reflect this in the title. References to support any kind of statement (e.g. line 39) is recommended. Very little considerations is given to pre-clinical data and their potential to inform clinical development. Some sections are considered too broad in the way they have been authored compared to others which are more clear and provide reasonable examples.	
EpiSafe Research Team	0	0	0	Who we are: EpiSafe (Optimising outcomes in pregnant women with epilepsy and their babies: Reducing maternal seizure risks and assessing long-term safety of antiepileptic drugs) is a research programe based in the UK. It includes a cluster randomised trial for pregnant women with epilepsy which will be rolled out in 2025 with over 30 UK sites. It is funded by the UK National Institute for Health and Care Research. The research team have consulted with their Patient & Public Involvement Advisory Board (made up of 15 women with epilepsy recently pregnant, some have taken part in clinical trials or research during pregnancy and all are based in the UK). https://www.episafe.org	
EpiSafe Research Team	0	0	0	The current draft places heavier emphasis on fetal/newborn risk, with insufficient focus on maternal health outcomes. Appropriate assessment requires evaluation of both risks and benefits of treatment, for both mother and fetus/newborn, recognising their interdependence.	Throughout the guideline, reinforce that risk–benefit assessment should include maternal outcomes as well as fetal/newborn outcomes.
International Consortium for Innovation and Quality in Pharmaceutical Development	0	0	0	General Comment: Local laws and regulations regarding maternal versus paternal decision-making capacity are not addressed in the guidance.	Please include language addressing this. In addition, reference to local laws regarding pregnancy, pregnancy loss, and maternal/paternal consent should be addressed.
K Richardson	0	0	0	Care must be taken to not regress to a time when females were considered mini-males, and these important sex-based differences should be specified within these guidelines. The FDA requires data to be sex segregated so that differences between males and females regarding dosing safety and efficacy are identified. This is even more pertinent to this guideline which must also consider the safety of the unborn child and the lactating infant.	
K Richardson	0	0	0	Clinical trial guidelines need to be clear, concise and relevant to the population. In this case the population is a sub-set of females. This subset is pregnant and lactating females. Not once in this guideline were the words female/woman/women used. Being a document that will be translated into multiple languages this lack of clarity must be considered. Gender identity idelogy politics have no place in clinical trials.	

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PIPELINE consortium	0	0		We represent the EU-funded PIPELINE project (Pregnancy and Infant Preparedness Platform in Europe [101155825]), a new project established at the start of 2025 to support research on novel diagnostics, vaccines and therapies for infectious diseases in pregnancy and infancy through a dedicated clinical trial platform. We strongly support the ICH E21 Guideline as an essential step towards ensuring inclusion of pregnant and lactating people in clinical trials. The COVID-19 pandemic showed that pregnant people continue to be an underserved population in clinical research, despite longstanding calls to action to address barriers to their inclusion in clinical trials for prevention and treatment of other infections including HIV. We welcome the framework that this guidance provides which will ultimately strengthen maternal and child health.	N/A
Portuguese Pharmaceutical Society	0	0	0	The ICH E21 guideline represents an important step forward in the ethical and scientific inclusion of individuals who have so far been excluded from participation in clinical trials. Although significant challenges exist, its implementation has the potential to transform clinical and regulatory practice, improving global maternal and child health. This document will bring new challenges for pharmacists in promoting the safety of clinical trial participants, raising several issues in its practical application: At the level of recruitment, retention, participant information, and informed consent The inclusion of these patients will bring challenges in terms of safety and enhanced monitoring of pregnant women, breastfeeding mothers, and babies who may benefit from the medicine. It is crucial to strengthen information provision, empowering patients and their families to minimise concerns and doubts, as well as enabling the participation of other professionals in the design of trials. At the regulatory level This may require reinforcement and adjustments to logistical processes and medicine control to enhance safety. Considering social and family contexts, different planning for the medicine pathway may be required, with greater coordination among members of the research team. Pharmacists will need specialised training and must be integral members of the clinical team (e.g. obstetrics, maternal–foetal medicine) to ensure correct treatment management, screening, and support. Study designs must incorporate safety safeguards that minimise risks, as documented in this guideline.	
Portuguese Pharmaceutical Society	0	0	0	At the level of safety and pharmacovigilance In post-treatment follow-up, the collection of relevant data on the use of an investigational product in pregnant and breastfeeding individuals should continue into the post-marketing period. Continuous monitoring of product safety in these populations after authorisation contributes to the identification of safety signals, particularly for rare or late outcomes, which are unlikely to be comprehensively addressed in pre-authorisation clinical trials. Depending on the characteristics and pharmacology of the investigational product and/or the disease/condition, as well as data available from similar medicines, it may be appropriate to design studies that include participants throughout pregnancy, at any stage of pregnancy, or only in specific trimesters (for example, avoiding third-trimester exposure to non-steroidal anti-inflammatory drugs). Clinical trials of prenatal interventions designed to improve foetal/newborn outcomes are not the primary focus of this guideline; however, the principles discussed in this document may still apply in the context of: Recruitment of pregnant women into ongoing and/or subsequent clinical trials; Removal of mandatory contraception requirements in ongoing and/or subsequent clinical trials; Continued participation of women who become pregnant during clinical trials; Implementation of studies specifically designed for pregnant women, if necessary.	

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Prescrire	0	0		Pregnancy section: In general, when a pregnant individual uses a medicine, both the mother and their unborn child are exposed to it. Some of the effects of exposure to the medicine are beneficial, while others are harmful to one or sometimes both individuals. Usually, the medicine is intended to benefit the mother, sometimes with an impact on the well-being of the unborn child. In a few cases, the medicine is primarily intended to benefit the unborn child, for example to prevent preterm delivery. On the whole, little is known about the risks of adverse effects in general, and the risks of malformations in particular, associated with the use of medicines during pregnancy. With the exception of large molecules such as heparins, all medicines reach the unborn child. First, it is important to be aware of the limitations of studies on exposure. It is almost impossible to predict whether a substance is teratogenic, unless it shares chemical similarity with a known teratogen. Other pharmacological data are of little help. The risks are mainly demonstrated using epidemiological studies, since animal studies are not always predictive of effects in humans, though any teratogenic effect in animals serves as a warning (1). Epidemiological studies, such as cohort studies in pregnant individuals, provide useful data for detecting teratogenicity. When an apparently unbiased study fails to show a risk of teratogenicity, it is better to check its statistical power before concluding that no risk exists. This also applies to the results of clinical trials including pregnant individuals: it is important not to conflate the absence of evidence of effects with evidence of the absence of effects. The absence of a statistically significant increase in a risk does not mean that an increased risk is absent. The study may have failed to detect the increased risk due to insufficient statistical power. Before concluding that no risk exists, it is important to take into account the baseline risk, including that of rare but serious malformations, and not to be satisfied with a result concerning the risk of all malformations combined.	
Prescrire	0	0		In summary, this guideline does not clearly specify which disorders are concerned by the inclusion of pregnant individuals in clinical trials. In order to avoid exposing pregnant individuals to substances with an unclear benefit-risk balance in this situation, it is important to only include pregnant individuals in clinical trials on pregnancy-related conditions, such as pre-eclampsia, gestational hypertension and the prevention of preterm birth. The guideline does not state that it is not always necessary to expose individuals in the second and third trimesters of pregnancy to a medicine to understand the clinical consequences on their unborn child, since after the first trimester most of the effects on the child can be deduced from the adverse effect profile in adults. We do not support the fact that the guideline allows for the use of NSAIDs in the first and second trimesters of pregnancy: NSAIDs should be avoided throughout pregnancy, including in the first trimester. In early pregnancy, NSAIDs can cause spontaneous abortion, especially in the first days of pregnancy, and malformations (in particular cardiac defects). In the second and third trimesters, NSAIDs can cause premature closure of the ductus arteriosus in the fetus even after administration of a single tablet, pulmonary arterial hypertension with cardiovascular disorders in utero, cardiorespiratory distress at birth, and renal impairment in utero (oligohydramnios) and at birth (1).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Prescrire	0	0		Aspirin can cause retroplacental haematoma. The guideline fails to set out criteria for assessing whether the risks to which pregnant individuals are exposed can be considered reasonable. The inclusion of pregnant individuals in clinical trials requires an exacting approach to the expected benefits (tangible clinical outcomes of real value to the pregnant individuals concerned) and a cautious approach to the risks (first, do no harm). The guideline also fails to set out criteria for excluding pregnant individuals from clinical trials, including where there is uncertainty about the safety of the substance during pregnancy. The guideline does not explicitly state its position on trials conducted in resource-limited countries, where pregnant individuals are often recruited in a context of increased vulnerability (for example due to precarious backgrounds, high-risk pregnancies, migrant status, a low level of health literacy or being unable to speak the language of the host country). The duration of follow-up for children exposed in utero is left vague. It does not encourage stakeholders to cross-reference the data obtained in trials with real-world pharmacovigilance data, which prevents the detection of safety signals that become apparent in the long term (despite the fact that exposure in utero to diethylstilbestrol and valproic acid is known to have very long term consequences in spite of a normal physical examination at birth), and of uncommon but serious adverse effects. The guideline poses a major problem in relation to confidentiality (including medical confidentiality) and the protection of personal data: despite the fact that personal data must not be transferred without explicit prior consent, it suggests that midwives, home health nurses and prenatal care providers might pass on the contact details of pregnant individuals to sponsors or investigators, without setting out clear conditions. (1) Prescrire Editorial Staff “An approach to preventing adverse drug effects during pregnancy” Prescrire Int 2014; 23 (145): 24-26.	
Prescrire	0	0		Breastfeeding section: From a child health perspective, exclusive breastfeeding for at least the first 6 months of life is generally preferable to formula-feeding (2). Most medicines pass from mother to child during pregnancy and breastfeeding, exposing the baby to the pharmacological effects of the medicines taken by the mother. This intimate connection complicates decisions about whether and how to treat pregnant and breastfeeding individuals, and may require specific monitoring. It must be taken into account when assessing the benefit-risk balance of maternal treatment. Most medicines taken by breastfeeding individuals are present in their milk, and breastfed children are exposed to their adverse effects. Generally speaking, there has been little evaluation of the dose to which children are exposed through breastfeeding and the clinical effects of such exposure, and both are influenced by many factors. The first principle is to avoid exposing the child to unnecessary medicines by establishing whether, from the mother’s perspective, the treatment is important and has a positive benefit-risk balance. Several questions need to be considered. What would happen without treatment? What is the aim of this treatment? What risks are acceptable in order to achieve this aim? It is also important to take into account the breastfeeding individual’s own priorities, the importance they place on the expected benefits and potential risks, their choices and personal values, and their lifestyle, etc. Finally, the perception of the benefits and risks varies in complex ways between individuals, and over a given person’s lifetime (2). In summary, the guideline takes an overly biomedical approach that gives little consideration to the lived experience of breastfeeding individuals and their children. The guideline does not provide adequate clarification about the clinical situations in which it is appropriate to include breastfeeding individuals in clinical trials. The duration of follow-up for children exposed via breastfeeding is left vague. The guideline does not safeguard against the exploitation of patient advocacy groups, or confusion about their role. The guideline acknowledges the burden on participants, but does not set out ways to compensate for it or to provide practical support. The guideline does not introduce an independent ethics committee, does not guarantee families the right to simply withdraw from the study completely, and does not look ahead to the transition to children giving consent for themselves. (2) Prescrire Editorial Staff "Making rational choices about drug treatment while breast-feeding" Prescrire Int 2017; 26 (188): 302-306.	
spm² - safety projects & more GmbH	0	0	4.2.7	In terms of standardization of data collection, the guideline encourages flexibility in assessments but could clarify which data points must be collected across studies for harmonization and regulatory comparability.	
spm² - safety projects & more GmbH	0	0	5.3.5	The guideline advises outlining discontinuation criteria for breastfeeding or teatment in protocols but could benefit from more concrete triggers or thresholds, as well as recommendations for interim safety analyses.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
spm² - safety projects & more GmbH	0	0	Appendix 1	Appendix 1 lists items for labeling, but further instruction on prioritizing information and handling conflicting data, especially from small or postmarketing studies, could help standardize product labeling.	
spm² - safety projects & more GmbH	0	0	Appendix 2	We would suggest providing a template incorporating the mentioned points, e.g. for a pregnancy form. This would help to streamline the process in making sure all relevant points are covered.	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		General Evaluation of Scientific and Ethical Rationale The ICH E21 guideline is clearly motivated by the current lack of evidence regarding medication use in pregnant and lactating individuals. These populations have traditionally been almost universally excluded from clinical trials, resulting in a lack of crucial information in patient leaflets about safety and efficacy during pregnancy and breastfeeding. This forces healthcare providers and patients to make decisions without sufficient evidence, potentially leading to suboptimal treatments and possible harm. The guideline supports this with concrete examples: due to lack of data, necessary treatments are sometimes avoided or discontinued, which may result in deterioration of maternal conditions or harm to the mother, pregnancy, or child. Conversely, the absence of information can lead to the unintentional use of harmful drugs, incorrect dosing (too low or too high, causing under-treatment or side effects), or the unnecessary early cessation of breastfeeding or therapy. The guideline explicitly relies on internationally accepted ethical principles. It states that including pregnant and lactating individuals in research is ethically justified and even supported by the Declaration of Helsinki and ICH standards. This moves away from the traditional idea of "protection by exclusion" toward "protection through research."	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		The recommendations are grounded in well-known scientific insights (such as pharmacokinetic changes during pregnancy) and existing regulatory science. A phased approach is required: only after sufficient non-clinical DART toxicology data and initial safety/efficacy data in non-pregnant individuals may studies involving pregnant individuals commence. The guideline employs a "weight-of-evidence" approach to determine whether the inclusion of pregnant individuals is scientifically justified. All available information is weighed: the indication and medical necessity, non-clinical data (reproductive toxicity, genotoxicity, etc.), biologically plausible risks for embryo/fetus, pharmacology of the product, expected benefits (therapeutic perspective), and the stage of pregnancy during exposure. This comprehensive risk assessment must demonstrate that the expected benefits outweigh the risks to both mother and child before starting a trial involving pregnant individuals. Conclusion of the general evaluation: The guideline presents a compelling scientific and ethical case. It acknowledges that more evidence is needed for the safe treatment of pregnant/lactating individuals, and that it is ethically necessary to no longer systematically exclude this group. The rationale is based on international ethical consensus and logical scientific reasoning, although hard data are still emerging. The overall impression is that ICH E21 offers a solid and necessary framework to responsibly address the current lack of evidence.	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		Obstetric-Gynecological Relevance of the Guideline From an obstetric-gynecological perspective, the guideline addresses many of the clinical needs and risks associated with research in pregnant and breastfeeding individuals. It starts from the reality that many pregnant patients have (or develop during pregnancy/postpartum) chronic or acute conditions requiring treatment. It also emphasizes that pregnancy itself alters the pharmacokinetics and pharmacodynamics of drugs (e.g., increased plasma volume, altered metabolism), necessitating dose adjustments — for example, β-adrenergic drugs being cleared faster in the third trimester or antiepileptic drugs requiring adjusted dosing. The guideline encourages sponsors to take this into account and to explicitly plan PK/PD research across different trimesters and postpartum. The timing of exposure during pregnancy is a recurring theme: study designs may include only certain trimesters if safer (e.g., avoiding exposure to NSAIDs in the third trimester).	

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UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		The mutual influence between disease and pregnancy is also highlighted. Sponsors are expected to assess how pregnancy affects disease progression (e.g., exacerbation risk due to suboptimal treatment), and conversely, how the disease (or lack of treatment) may negatively affect pregnancy outcomes. This is crucial — perinatology offers examples such as uncontrolled epilepsy leading to maternal and fetal risk, or untreated severe asthma causing fetal hypoxia. The guideline implicitly acknowledges that not treating can also be risky. The importance of data on medication safety and effectiveness during pregnancy is thus not merely academic, but directly tied to improved maternal-fetal outcomes. The guideline is also highly relevant for pregnancy-specific conditions. It provides a dedicated section for "Strategies for Obstetric Conditions": for indications unique to pregnancy (e.g., pre-eclampsia, threatened preterm labor), studies involving pregnant individuals are essential to assess efficacy, safety, and dosing. While this may seem obvious, stating it explicitly is important. ICH E21 stresses that for such conditions, data must be collected within the actual target population to support drug registration.	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		In terms of study execution, the guideline makes several obstetrically relevant recommendations: • Multidisciplinary team: Trials involving pregnant individuals must include specialized expertise in study design and monitoring. Neonatal expertise is also implicitly needed for newborn follow-up. • Endpoints and follow-up: In addition to standard endpoints, pregnancy outcomes (miscarriage, congenital anomalies, birth outcomes) must be considered and followed even after delivery. The duration of follow-up should be determined on a case-by-case basis, depending on the drug's half-life and mechanism, and if necessary, extend beyond the study's conclusion. This is especially important from a perinatal perspective: some effects (e.g., teratogenicity) manifest at birth, others later (e.g., child neurodevelopment). Overall, ICH E21 aligns well with obstetric needs: it recognizes both the risks of medication and of not treating, emphasizes monitoring of both mother and child, and integrates obstetric expertise into study design.	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		The guideline also underscores minimizing participant burden and avoiding unnecessary procedures. Belgian centers can utilize established pharmacovigilance pathways for pregnancy, such as the national breastfeeding center, teratology information centers, and the BELpREG registry. Such registries and databases can complement trials, as the guideline suggests via real-world evidence collection. An additional point of attention is sample size and statistical power in pregnancy research: the guideline acknowledges that for non-obstetric indications, the number of pregnant participants in general trials will be small, making rare outcomes (e.g., specific congenital anomalies) hard to detect. The advice is at least to collect pharmacokinetic data during pregnancy (which does not require thousands of participants), and to gradually supplement safety data through post-marketing research and registries.	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		Informed Consent and Ethical Proportionality Consent forms must clearly explain the expected risks and benefits, for both mother and fetus/child. Uniquely, the guideline explicitly states that the risks of not treating or of alternative management should also be described. This aligns with good practice: a pregnant participant can then weigh the implications of participating (with an experimental drug) versus not participating and possibly receiving standard treatment or no treatment at all. _____ Commentary Clear communication about the "paradigm shift" nature of this guideline is crucial: this is not a niche document, but a call to consider the application of all drug development to pregnancy and breastfeeding early on. The message to sponsors and researchers is that inclusion should become the norm, not the rare exception. At the same time, rigorous implementation is essential: ethics committees and investigators must remain committed to minimizing risks and properly supporting participants.	

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UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology - Flemish Society (VVOG)	0	0		Missing or Underemphasized Aspects Overall, the guideline is very comprehensive, but a few points could have been expanded: • Partners and family: The guideline is silent on the role of the partner (e.g., the child's father). Although legally and ethically only the pregnant individual's consent is required, involving partners in the decision-making process could be supportive. A recommendation here — even if not mandatory — could be helpful. • Pregnant minors: Local rules on consent for underage pregnant individuals are briefly mentioned. In Belgium, for instance, a pregnant individual under 18 still requires parental/guardian consent. A more detailed discussion on this vulnerable subgroup (pregnant teens) and how to protect their interests would be valuable. • Concrete inclusion thresholds: While the "weight of evidence" approach is logical, much is left to the sponsor's and ethics committee's judgment. There are no strict criteria — e.g., minimum safety database size or thresholds from DART studies — to clearly define when there is "enough evidence" to safely start involving pregnant individuals. As it stands, this remains somewhat qualitative. • Emergency procedures for maternal or fetal events: Although the guideline notes that protocols must include stopping criteria and risk mitigation plans, it does not elaborate on steps to take when serious fetal abnormalities or pregnancy complications are detected during a study. • Psychosocial support: Participating in a study while pregnant can be psychologically stressful. Explicit mention of providing counseling or psychological support would be a valuable addition. • Long-term follow-up of children: The guideline could clarify how long and in what ways children exposed in utero should be followed up. International best practices (e.g., in vaccine studies) show that monitoring into toddlerhood may be needed to evaluate developmental milestones. A suggested framework — e.g., screening neurodevelopment up to age 2 for drugs with potential neurological effects — would be helpful. • Use of registries: Sponsors should be encouraged to establish or use pregnancy registries alongside clinical trials.	
UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology (EBCOG)	0	0		General support The Guidelines seem quite appropriate, though as a traditionalist and rather concerned about drug trials being carried out on pregnant women and neonates. One can never truly anticipate the short and long-term effects these medications may have on the unborn child. However we welcome EMA's initiative to improve inclusion of pregnant and breastfeeding individuals in clinical trials. The ICH E21 draft guideline represents an essential step toward addressing long-standing evidence gaps in this area. However, there are significant real-world barriers that we believe should be more explicitly acknowledged and addressed in the final guideline. 1. Patient and clinician reluctance to participate •Pregnant women often decline participation in RCTs out of understandable caution about fetal safety. •Referring Obstetricians may also be reluctant to enrol patients, citing liability fears, lack of time or incentives, or ethical objections. •In many countries, antenatal care is delivered largely in private practice even when delivery occurs in public hospitals, making recruitment and follow-up more challenging. Suggestion: The guideline could be strengthened by including strategies to address these barriers, such as: •Improving patient and provider education and engagement during study design. •Developing recruitment models that can better include private practice settings. 2. Limitations of current trial designs •Many published RCTs are open-label rather than blinded, even where placebo control would be ethical, undermining scientific rigor. •Recruitment often takes many years to complete, with studies sometimes recruiting mainly low-risk patients simply to finish faster, reducing applicability to higher-risk groups.	

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UEMS Section of OB GYN - European Board and College of Obstetrics and Gynaecology (EBCOG)	0	0		Suggestion: The guideline should offer practical recommendations to: •Support placebo-controlled and blinded designs where ethical. •Encourage adaptive designs to improve efficiency. •Plan realistic timelines and identify recruitment barriers early. 3. Funding and industry incentives •There is limited industry interest in funding trials in pregnancy, often due to liability concerns and low commercial incentive, particularly for generics or low-cost drugs. •Sometimes manufacturers prefer widespread off-label use without investing in trials that might yield negative results. •In some therapeutic areas (e.g. thromboprophylaxis), research may be led by non-obstetric specialists who have access to funding, while obstetricians themselves often lack resources or infrastructure to lead these trials. Suggestion: The guideline might explicitly acknowledge these economic disincentives and recommend: •Public-private partnerships or government-supported funding mechanisms. •Policies to reduce liability barriers. •Incentives for investigator-led, obstetrician-led research. 4. Need for alternative methodological approaches •Given recruitment challenges, we should also support other rigorous methods beyond traditional RCTs. •Prospective open studies, pragmatic designs, registries, and large-scale observational cohorts can provide valuable data, especially when RCTs are impractical or limited to low-risk populations. The guideline should explicitly encourage: •Pragmatic and hybrid designs that better reflect real-world practice. •Integration with routine care pathways to facilitate recruitment and follow-up. •Use of high-quality observational methods as complementary evidence sources. In summary, while we fully support the principles of the ICH E21 guideline, we suggest that the final version more directly address: •The real-world barriers to recruitment of pregnant and breastfeeding individuals. •The need for financial, regulatory, and policy solutions to improve industry and investigator engagement. •The importance of endorsing flexible, pragmatic, and alternative study designs to ensure timely and relevant evidence generation. WE would like to take this opportunity to underscore that our comments are related to studies primarily carried out in pregnant women to investigate a possible benefit of drugs during pregnancy, such as aspirin for fetal growth restriction or preeclampsia, etc.	

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EpiSafe Research Team	1	39	1	The guideline currently frames inclusion of pregnant and breastfeeding individuals in clinical trials as something to be "considered." This language is not sufficiently directive.	Strengthen the Introduction to state clearly that inclusion of pregnant and breastfeeding individuals in clinical research is expected wherever scientifically and ethically appropriate, not only considered.
EpiSafe Research Team	1	39	1	The guideline does not adequately acknowledge the consequences of current approaches, where medicines are not routinely tested in pregnancy and lactation.	Add a statement in the Introduction highlighting that systematic exclusion of pregnant and breastfeeding individuals from drug development perpetuates inequities and undermines safe, evidence-based care.

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Ethics Committee UZ Leuven	1	2		somewhere in this document it may be useful to use figures of the use of medications in pregnancy, ie more than 50% of women highlighting the need for this guideline.	
EFPIA	4	4	1.1	The referene is made to "breastfeeding individuals" yet later in the document, a distinction is being made for "lactating individuals" and "breastfeeding individuals".	Consider changing to "breastfeeding individuals" to "lactating/breastfeeding individuals" to include both.
EFPIA	5	5	1.1	Generating robust clinical trial data to support evidence-based decision-making may be challenging under certain study designs outlined in the current guidance. Specifically, when only a small number of pregnant individuals are included in an ongoing trial without pre-specified analyses, the resulting data may be insufficient to draw meaningful conclusions. At best, such data may serve to identify potential safety signals rather than provide definitive evidence."	Propose to delete " robust" or to better clarify that some data may be used for signal detection only.
EFPIA	5	5	1.1	What is meant by “robust” in this context? If pregnant and/or breastfeeding women are included (i.e. not excluded from participation) and the trial design (as agreed with a regulatory agency) has no minimum/maximum requirement for enrollment, but only 1 female is ultimately enrolled, is this considered “robust” for purposes of this guideline? Or is "robust" considered by the EWG to call for a dedicated study? As M&S may be sufficient in most scenarios, it would seem the use of the term "robust" without context is problematic.	Delete "~~robust~~"
Global Heart Hub	6	6	2	include patient organisations as an appropriate stakeholder	Early engagement with appropriate stakeholders, including patients and patient organisations, provides opportunities to address all relevant aspects of these clinical trials.
EFPIA	8	16	1.2	It would help the reader to describe and distinguish populations for this guideline more clearly. Inclusion into clinical trials of WoCBP who are already pregnant at study start and WoCBP who are not pregnant at study start but who plan to become pregnant.	When considering including pregnant or breastfeeding individuals in clinical trials, it is important to evaluate the risks and benefits based on all available data, ensure that risks have been appropriately mitigated, and plan studies that can yield scientifically robust data (see Sections 4.1.2 and 5.1.1). Assessing the safety in pregnant and breastfeeding individuals is complex as there are potential impacts on the fetus and breastfed child to consider.
EFPIA	9	10	1.2	"The scope of this guideline includes pre- and postmarketing clinical trials of investigational products" - does this also include Phase I trials in healthy pregnant or breastfeeding individuals?	If no, please consider specifying that. If yes, and there has been a discussion of the ethical aspects of including healthy volunteers that are pregnant or breastfeeding, please consider including some statement about that. If it has not been discussed so far, please consider it.
EFPIA	10	11	1.2	The scope mentions that it includes investigational products for indications in the general population and indications specific to pregnant or breastfeeding individuals. In addition, it states that "all products where individuals of childbearing potential are among the anticipated user population". It is not clear whether the products to treat infertility are in the scope of the guideline.	Please clarify if investigational products to treat infertility are out of the scope of this guideline
EFPIA	10	11	1.2	Why is the phrase "and indications specific to pregnant or breastfeeding individuals" included? The considerations for development of pregnancy and/or lactation specific investigational medicines would by their very definition include these populations. The Concept Paper that was the basis for establishment of the EWG does not include objectives applicable to products developed for indications “specific to pregnant or breastfeeding individuals”.	Delete "~~and indications specific to pregnant or breastfeeding individuals~~".
EFPIA	12	12	1.2	Clarification is requested for the scope about the recommendation to include in Healthy Volunteer studies or disease population. If the emphasis is on patient population, then clarification is needed that this is a PK and a safety trial, so limited efficacy data will be generated.	

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TRT-5 CHV	12	16		This is a matter of access to safer innovative treatments. In the first case, even temporary treatment interruption might not be possible, and the fetus/child will therefore inevitably be exposed. This is why it derserves to be added.	Add: "Chronic conditions for which pregnant and breastfeeding individuals have no choice but to remain on treatment throughout pregnancy and breastfeeding" "Conditions that can be transmitted from mother to child, where the effectiveness of the investigational treatment may impact mother-to-child transmission of the virus (e.g., the principle of HIV and the concept 'undetectable = untransmittable')."
EFPIA	14	15	1.2	The EWG should provide examples of what is defined as "high unmet medical need for treatment in pregnancy or while breastfeeding". According to a 2021 publication (Wesley B, Sewell C, Chang C et al AJOG. 225(1):21-32. 2021.) there have only ever been 9 drugs approved in the US approved for obstetrical conditions; Any drug approved for a non-obstetrical indication that does not contain a contraindication is considered approved though the vast majority have never been studied; and numerous therapeutics are used off-label for pregnancy related conditions. Therefore, it could be considered that nearly every condition occurring co-morbid to pregnancy presents a high unmet medical need.	Either consider being more specific about what is considered "high unmet medical need" in obstetrics, or consider deleting this phrase as the sentence goes on to say essentially that it doesn't matter because everything is in scope.
International Advisory Committee on Clinical Trials in Multiple Sclerosis, National Multiple Sclerosis Society, and European Committee for Treatment and Research in Multiple Sclerosis	17	39	1.3	Pregnant and breastfeeding women with MS are routinely excluded from clinical trials of disease-modifying and symptomatic medicinal therapies. Disease activity changes during pregnancy and post-partum, thus the effects of treatment may be different than in people who are not pregnant although they may be even more important. Continuing and discontinuing disease-modifying therapy during pregnancy and post-partum have differing short- and long- term risks and benefits for patients and their offspring, which remain incompletely understood. We underscore the potential consequences of failing to include pregnant and lactating women in clinical trials, including insufficient information about the safety and efficacy of therapies during the pregnancy and post-partum periods. This means that women with MS and clinicians must make decisions about their health that are not adequately informed and may lead to harm including inadequate treatment.	
EFPIA	20	20	1.3	Clarification is required if all types of medical products this guideline is applicable for or if it is specific for some medical products only.	
EpiSafe Research Team	20	20	1.3	Maternal mental health is mentioned briefly but not integrated across the guidance. Pregnancy and postpartum are recognised periods of vulnerability, and clinical trial participation may increase stress if not supported. Including mental health explicitly would promote participant safety and retention.	Suggest new text be added: "Pregnancy and the postpartum period are recognised as times of increased vulnerability for maternal mental health. Clinical trial design should take account of psychological as well as physical wellbeing."
EFPIA	21	21	1.3	The use of "also" here is a HUGE under-statement - This is the CRITICAL point upon which this entire guideline needs to be built and the actual guidance offered structured. The physiological changes occurring in multiple organ systems (e.g., increased CO, increased blood vol, decreased vascular resistance, increased HR, changes in bp, increased tidal volume, increased GFR, et cetera) can/may directly effect PK and/or PD and therefore should be evaluated in the clinic to assess if a dose adjustment is required to continue to offer benefit and not introduce higher risk to both the pregnant/lactating female and/or their fetus/infant.	This guidance requires significant rework (not just in the background but also the main document) to highlight the essential role of PK assessments across trimesters of pregnancy to determine the appropriateness of the dose/dose regimen in the pregnant population.
EFPIA	21	23	1.3	Physiological changes may also occur and are dynamic during the postpartum period with various maternal physiological systems returning to pre-partem levels at differing rates. These changes could also impact the PK and PD of a medicinal product leading to dosage modification. (Abduljalil et al 2012 Clin. Pharmacokinet.)	Physiological changes during pregnancy and postpartum can also have an impact on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of a medicinal product and there may be a need to modify the dosage of medicinal products in pregnant and breastfeeding individuals.
EFPIA	21	21	1.3	Beside physiological changes, Pregnancy may also change the nature of the disease being treated/managed, thus also necessitating an understanding of changing therapeutic needs during and after pregnancy, (as stated in 5.1.1).	

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Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	21	23	1.3	The guidances states that "Physiological changes during pregnancy can also have an impact on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of a medicinal product and there may be a need to modify the dosage of medicinal products in pregnant individuals." Pregnant patients also develop pathology such as pre-eclampisia which can also affect PK and PD of a medicinal product. Please mention this in the text. See my suggested bold text amendment in next column.	Physiological and pathological changes during pregnancy can also have an impact on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of a medicinal product and there may be a need to modify the dosage of medicinal products in pregnant individuals.
EFPIA	22	23	1.3	The expression "modifying the dosage…" is considered too restrictive and it proposed to talk about the need to adjust dose, administration, etc.	
K Richardson	22	23	1.3	"….there may be a need to modify the dosage of medicinal products in pregnant individuals."	"….there may be a need to modify the dosage of medicinal products in pregnant individuals which may differ from the general non-pregnant female population, and sex-based differences in dosing should be considered."
EFPIA	23	23	1.3	"dosage…"	"dosage and treatment regimen…"
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	24	24	45717	Add that there are hardly any trials performed specifically for disease during pregnancy/pregnancy complications. (another formulation)	Despite the clinical relevance of pregnancy-specific conditions such as preeclampsia and preterm birth, few clinical trials are designed to investigate these indications. Pregnant and breastfeeding individuals are routinely excluded from clinical research, and participants who become pregnant during a trial are frequently withdrawn. Therapeutic interventions targeting pregnancy-specific conditions are rarely developed or systematically evaluated. This has left pregnant and lactating women as drug orphans with very little advancement in the field.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	24	24	45717	Add that there are hardly any trials performed specifically for disease during pregnancy/pregnancy complications. (another formulation)	Despite the clinical relevance of pregnancy-specific conditions such as preeclampsia and preterm birth, few clinical trials are designed to investigate these indications. Pregnant and breastfeeding individuals are routinely excluded from clinical research, and participants who become pregnant during a trial are frequently withdrawn. Therapeutic interventions targeting pregnancy-specific conditions are rarely developed or systematically evaluated. This has left pregnant and lactating women as drug orphans with very little advancement in the field.
EFPIA	26	26	1.3	Consider specifying human pregnancy and breastfeeding specific information in the product labeling given there is usually preclinical assessment of risk.	As a result, human pregnancy and breastfeeding information in the…
EFPIA	28	37	1.3	This lack of data has the following potential consequences for pregnant and breastfeeding individuals:	Lack of data may also have another unintended consequence (uncertain): Imposing pregnancy restrictions (e.g., not allowing a woman to become pregnant) in the absence of a clear teratogenic risk
EFPIA	30	31	1.3	Guideline states, "HCPs and/or patients avoiding or discontinuing indicated treatments leading to exacerbation of the condition or harm to the patient, pregnancy, or the child;" Rationale: Should be "and/or" as harm could occur to the patient and the child.	Suggested addition to text, "HCPs and/or patients avoiding or discontinuing indicated treatments leading to exacerbation of the condition and/or harm to the patient, pregnancy, or the child;"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EpiSafe Research Team	30	30	1	Delays in initiating treatment due to uncertainty could lead to a deterioration in maternal health condition	Suggest new text be added: "delaying" (ie to read:HCPs and/or patients avoiding, delaying or discontinuing indicated treatments...)
TRT-5 CHV	30	37		Lack of diversity in clinical trials and its consequences on therapeutic offers / options must be named in the current context proliferation of drug stockouts.	Add: A limited therapeutic offer, and restrictive therapeutic management recommendations.
EFPIA	31	33	1.3	This should be “fetus/child” in both lines.	Change to "fetus/child"
EFPIA	32	33	1.3	Guideline states, “HCPs and/or patients inadvertently choosing treatments harmful to the patient, pregnancy, or the child;” Rationale: Should be “and/or” as harm could occur to the patient and the child.	Suggested addition to text, “HCPs and/or patients inadvertently choosing treatments harmful to the patient, pregnancy, and/or the child;”
EpiSafe Research Team	35	35	1	Including these new terms provides a more complete and balanced articulation of the clinical risks. NOTE: “Overtreatment” captures the risk that a supratherapeutic dose may result in unnecessarily intensive or excessive treatment, which can cause harm. NOTE: “Unnecessary exposure to treatment” acknowledges that inappropriate dosing can expose pregnant or breastfeeding individuals (and their infants) to risks without corresponding benefit.	Suggest new text be added: ", overtreatment, unnecessary exposure to treatment," (ie to read: Use of a dose or treatment regimen that is sub- or supra-therapeutic, leading to increased risk for under-treatment, overtreatment, unnecessary exposure to treatment, and/or adverse reactions;)
EpiSafe Research Team	35	35	1	By adding “avoidable”, the guideline explicitly recognises that Sub- or supratherapeutic dosing can result in harms that are preventable with appropriate evidence-based prescribing and monitoring. It emphasises the importance of safe, proportionate prescribing and the opportunity to reduce preventable harm. This phrasing aligns with international guidance on risk minimisation (e.g. WHO 2021, EMA GVP Module V), which emphasise reducing avoidable harm through proportionate, preventive measures (eg WHO – Global Patient Safety Action Plan 2021–2030 - https://www.who.int/publications/i/item/9789240032705	Suggest new text be added: "or avoidable" (between 'adverse' and 'reactions')
EFPIA	36	36	1	While the benefits of breastfeeding are acknowledged, there is always an acceptable alternative by using formula feeding. This makes the "avoidance or premature discontinuation of breastfeeding" a clearly lesser medical concern compared to the other items within the list of potential consequences.	Suggest to incorporate this consideration.
Rebekah Burrow, Department of Primary Care Health Sciences, University of Oxford	36	37	1.3	Another potential consequence is avoidance or premature discontinuation of pregnancy to allow for treatment. https://www.cancerresearchuk.org/about-cancer/breast-cancer/living-with/breast-cancer-during-pregnancy	
EpiSafe Research Team	38	38	1	The current list of consequences focuses on clinical decisions and outcomes but does not reflect the personal and professional burden introduced by the absence of evidence. This proposed addition addresses an often overlooked dimension of harm: 1) Patients may experience stress, confusion, or doubt when navigating decisions during pregnancy or breastfeeding without reliable evidence, especially in the context of chronic or complex conditions. 2) Healthcare professionals may struggle to advise or reassure patients confidently, leading to uncertainty in consultations and variation in practice. 3) This lack of clarity can place a significant emotional and practical burden on decision-making and increase the risk of disengagement from care, reduced adherence, or lost opportunities for shared decision-making.	ADD A BULLET POINT AND TEXT "Added stress and decision-making burden for patients and healthcare professionals due to limited evidence, which can make it more difficult to take or support informed and confident decisions about treatment, care, and adherence, and may contribute to disengagement from care."
EpiSafe Research Team	38	38	1	This population often navigates more complex care pathways. Including this bullet recognises the compounded impact of limited data.	ADD A BULLET POINT AND TEXT "Individuals with chronic conditions may face added challenges (such as fragmented care or conflicting advice) making treatment planning more uncertain."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
TRT-5 CHV	38	39			Add : "At the individual level, the lack of robust data and its consequences on therapeutic decisions can impose an additional psychological burden on pregnant or breastfeeding individuals. Switching to a new treatment or being unable to breastfeed can result in the disclosure of a strictly confidential health condition among those around one. The decision to breastfeed despite a medical contraindication may be taken for various reasons (fear of stigma, travel, economic constraints, etc.). This is particularly the case in social contexts where there is strong pressure to breastfeed. Avoidance strategies, unbeknownst to healthcare teams, may be adopted. Giving up breastfeeding is not always well experienced. It can induce or worsen a depressive state in the parent concerned, and may be accompanied by a feeling of guilt."
EFPIA	39		1.3	what are some of the potential public health impacts – there are a few bullets beginning at line 120 later in the document but expanding on this topic is highly supportive of the need for inclusion	
EFPIA	40	57	2	Consider a pregnancy/ breastfeeding investigational plan as part of the development program similar to the PSP/ PIP for the pediatric population to be agreed upon with regulatory agency/ expert committee within the agency. It should be clear that the plan is at the request/agreement with the agency.	
International Advisory Committee on Clinical Trials in Multiple Sclerosis, National Multiple Sclerosis Society, and European Committee for Treatment and Research in Multiple Sclerosis	40	97	2.0 and 3.0	We strongly support the principle that the plan for development of any investigational product thoughtfully and comprehensively consider use in pregnancy and breastfeeding. Pregnant women can consent to participation in clinical trials in discussion with their health care providers when sufficiently informed about potential risks and benefits; blanket exclusions of women of childbearing potential do not respect their autonomy as individuals. Specific rationales for their exclusion should be stated based on the mechanisms of action of the drug, existing clinical information based on use for other indications and pre-clinical data. We recognize that the relative risks and benefits of participation differ between Phase I/II, III and IV trials because the body of evidence about safety of the medicines being tested is relatively limited for all individuals in Phases I/II. The perspectives of women who are pregnant, breastfeeding or might be in the future should be obtained when developing these investigational plans, including determining when (in what phase) and how information about pregnancy outcomes should be obtained.	
ACRO	41	49	2	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.	
EFPIA	41	62	2	These paragraphs state recommendations to collect data for pregnant and lactating women earlier in product development, leaving the reader wanting instructions on how to do this, which is later covered in the guidance.	Add a sentence or statment saying the purpose of the guidance is to provide recomendations how to achieve this goal.
EFPIA	41	46	2	Careful considerations and planning is advised for this population and we encourage the guideline to support sponsors in creating an internal strategic pregnancy and lactating investigation plan as part of their clinical development plan and regulatory strategy.	
EFPIA	43	43	2	"product development from nonclinical studies through post-approval use of the product" - are nonclinical studies meant to involve pregnant or breastfeeding animals or just cells/tissues of pregnant or breastfeeding humans?	If no, please consider specifying that. If yes, and there has been a discussion of the ethical aspects of performing nonclinical studies on pregnant or breastfeeding animals, please consider including some statement about that. If it has not been discussed so far, please consider it.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	45	45	2	This statement would be clearer if the EWG strove to define the breadth of possible clinical studies. This should include a range of relevant options that could be more than sufficient to satisfy the necessary information to inform on adequacy of dose/dose regimen, and certainly should not be limited to an E&S (Efficacy & Safety)/confirmatory study. Also, it would be better emphasized to take the current parenthecized text and make a new sentence.	Change to "... and clinical studies (e.g., pharmacokinetic studies, modeling and simulation, inclusion in clinical trials or within dedicated clinical trials or the rationale for not obtaining data) should be done ...". Add "Sponsors should include a rationale within study protocols as to why a pregnant and/or lactating population has not been included."
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	46	46	2	It would be best with a mandatory plan to e.g. have concentration data in breast milk, umbilical cord blood, plan for register follow-up, build a register for follow-up?	...investigational product. Studies on concentration in breast milk should be part of the study protocol if possible. If adequat post-market introduction follow-up data for pregnancy should be obtained by e.g. setting up a volunatry registry, measurement of umbilical cord concetrations etc. In countries with existing health- or quality registers this should be a requirement IRBs should ask for when giving ethical apporval.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	46	46	2	It would be best with a mandatory plan to e.g. have concentration data in breast milk, umbilical cord blood, plan for register follow-up, build a register for follow-up?	...investigational product. Studies on concentration in breast milk should be part of the study protocol if possible. If adequat post-market introduction follow-up data for pregnancy should be obtained by e.g. setting up a volunatry registry, measurement of umbilical cord concetrations etc. In countries with existing health- or quality registers this should be a requirement IRBs should ask for when giving ethical apporval.
EFPIA	47	55	2	I find this section (and many others that follow) to be unhelpful in that there are aspirational suggestions followed by warnings, both of which we all know but neither of which provides help in implementation- e.g. talk to us early, include them early, but make sure the drug is safe first and don't overburden them.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	47	49	2	Currently, there are no obligations for pharmaceutical trials to include pregnant and breastfeeding women and these individuals are considered to pose a too high risk for pharma-industry in phase 2 and 3 trials. We would wish for a stronger formulation here regarding the safety of women in reproductive age where new compounds SHOULD be trialled in women of reproductive age to ensure safety and future trials in pregnancy specifically.	Suggest to add a stronger statement here around inclusion of women in reproductive age, pregnancy and lactation. Instead of "are encouraged" -> "should consider"
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	47	49	2	Currently, there are no obligations for pharmaceutical trials to include pregnant and breastfeeding women and these individuals are considered to pose a too high risk for pharma-industry in phase 2 and 3 trials. We would wish for a stronger formulation here regarding the safety of women in reproductive age where new compounds SHOULD be trialled in women of reproductive age to ensure safety and future trials in pregnancy specifically.	Suggest to add a stronger statement here around inclusion of women in reproductive age, pregnancy and lactation. Instead of "are encouraged" -> "should consider"
ENTIS (European Network of Teratology Information Services)	49	52	2	Professional counseling with experts in the field of teratology should be sought. ENTIS (European Network of Teratology Information Services) is an international organization dedicated to teratology and includes the leading specialists in this field.	It is recommended to consult with experts in the field of pregnancy and lactation, teratology information centers (TIS).
Gedeon Richter plc.	49	52	2	Could you please clarify what is meant by "consulting with regulatory authorities as early as possible"? Specifically: What volume of toxicology data is expected at this stage? Should reproductive toxicity data be included? If so, which segment(s)? Is a teratogenicity study required? Should a comparative pharmacology study be provided, including a gold standard reference? Additionally, could you please clarify what form of regulatory interaction would be recommended for this consultation?	
EFPIA	50	50	2	"as early as possible" should be clarified. Is it acceptable to start planning before the reprotox data are available? The plan will be very different depending on the reprotox results.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ACRO	52	57	2	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. ACRO would suggest that this is included in line 57 e.g. “Early engagement with appropriate stakeholders, including patients, provides opportunities to address all relevant aspects of these clinical trials, including use of decentralised elements where appropriate”.	Recomendation: inclusion of the following text in line 57: “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”.
EFPIA	52	55	2	The text in the 2nd part ('undue influence & coercion') of the following sentence is not entirely clear: "Every effort should be made to reduce the burden of study procedures on pregnant and breastfeeding study participants and it is essential to avoid any undue influence or coercion when pregnant or breastfeeding individuals are included or planned to be included in clinical trials."	Please provide some examples to clarify the intended meaning undue influence & coercion?
EFPIA	54	55	2	Guideline states, “…participants and it is essential to avoid any undue influence or coercion when pregnant or breastfeeding individuals are included or planned to be included in clinical trials” This is true for all study participants. Is there any specific reason (or not) as to why pregnant and/or breastfeeding individuals are any more susceptible to undue influence and/or coercion?	
EFPIA	55	56	2	It would be helpful to clarify what is meant by early in "early engagement".	
EFPIA	56	56	2	Care partners play an important role for patients, It's good to acknowledge this at the beginning of this guide and especially as a care partner could also be the co-parent to-be.	including patients -> proposal to add patients and their care partners
EpiSafe Research Team	56	57	2	Rationale for including “co-design” - Referring to co-design reflects evolving international expectations to embed the perspectives of those most affected by clinical trials into trial design from the outset. Rationale for including “inclusive, acceptable, and aligned with real-world priorities” - This wording reinforces the need for trial protocols to reflect real-life complexity, particularly for populations historically excluded from evidence generation. Ref: UK Standards for Public Involvement / CIOMS International Ethical Guidelines (2021), Guideline 7	ADD TEXT: "co-design trials that are inclusive, acceptable, and aligned with real-world priorities." (ie to read Early engagement with appropriate stakeholders, including patients, provides opportunities to co-design trials that are inclusive, acceptable, and aligned with real-world priorities.)
EFPIA	57	57	2	"All" is an over-statement - "relevant" sufficiently addresses the point being made.	Delete "~~all~~"
EpiSafe Research Team	57	57	2	The guideline highlights stakeholder engagement but could further stress that early involvement of potential participants improves confidence, acceptability, recruitment, and retention.	Suggest new text be added: “Early involvement of potential participants and patient representatives in study planning is recommended to improve acceptability, recruitment, and retention.”
EFPIA	58	62	2	Suggest to put the thoughts into the right sequence	
EFPIA	58	62	2	We consider this an appropriate section to mention risk evaluation in relation to pre- or post-marketing authorisation and also suggest that the assessment should be done in light of the potential benefit not only the risk for both the mother and the fetus.	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	58	59	2	The individuals in a pregnancy include both the mother and the fetus(es). I suggest to amend this text below to make this apparent: "Assessing the safety in pregnant and breastfeeding individuals is complex as there are potential impacts on the fetus and breastfed child to consider." See suggested bold text amendment in the next column	Assessing the safety in pregnant and breastfeeding individuals is complex as there are potential impacts on the mother, fetus(es) and breastfed child to consider.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	59	0	2	should also include embryo, as fetal stage starts after 10-12 weeks and women maybe exposed at embryo stages as well, these are various stages of pregnancy and risks of drugs in pregnancy are different if you are in fetal or embryonic stage	include 'embryo'
EFPIA	60	60	2	Proposal to clarify "... to evaluate the risks and benefits for the mother and the fetus/breastfed child based on all available data..."	... to evaluate the risks and benefits for the mother and the fetus/breastfed child based on all available data…
EFPIA	61	61	2	What does it mean" all availlable data" ?	Outline the data that should be considered
ACRO	63	64	2	ACRO welcomes the principle for longer-term approach to data collection and safety monitoring, as reflected in lines 63-64, 361-363 and 513-515.	
EFPIA	64	69	2	The 'post-marketing period' should not be the only timeframe considered; after a registrational study demonstrates a favorable benefit-risk (B/R) ratio, an early access program prior to market entry could provide data, including information on special populations not included in the registrational study.	Proposed wording: Ongoing safety monitoring of product use in these populations in the postmarketing period as well as early access programs contribute to the identification of safety signals, especially for rare or delayed outcomes, that are unlikely to be thoroughly addressed in pre-authorization clinical trials. Real-world data (RWD) used to generate real-world evidence (RWE) can be helpful in assessing the usage and potential benefits or risks of an investigational product in pregnant and breastfeeding individuals.
EpiSafe Research Team	64	67	2	The current draft places disproportionate emphasis on potential fetal risks without adequately recognising maternal risks from stopping or avoiding treatment. Uncontrolled maternal disease can cause indirect harm to the fetus as well as direct harm to the mother. Clarifying that postmarketing safety monitoring should include both maternal and fetal/child outcomes ensures balanced evaluation and encourages continued treatment where clinically appropriate.	Add focus on maternal outcomes alongside fetal/child outcomes (Suggest new text be inserted: "should include assessment of both maternal and fetal/child outcomes") Proposed edit (changes highlighted in bold) - Collection of data pertinent to use of an investigational product in pregnant and breastfeeding individuals should continue into the postmarketing period. Ongoing safety monitoring of product use in these populations in the postmarketing period should include assessment of both maternal and fetal/child outcomes, recognising that inadequate treatment of maternal conditions can result in...
EpiSafe Research Team	64	67	2	The current draft places disproportionate emphasis on potential fetal risks without adequately recognising maternal risks from stopping or avoiding treatment. Uncontrolled maternal disease can cause indirect harm to the fetus as well as direct harm to the mother. Clarifying that postmarketing safety monitoring should include both maternal and fetal/child outcomes ensures balanced evaluation and encourages continued treatment where clinically appropriate.	Add statement on indirect harm from untreated maternal disease (Suggest new text be inserted: "recognising that inadequate treatment of maternal conditions can result in indirect harm to the fetus as well as risks to the mother") Proposed edit (changes highlighted in bold) - Collection of data pertinent to use of an investigational product in pregnant and breastfeeding individuals should continue into the postmarketing period. Ongoing safety monitoring of product use in these populations in the postmarketing period should include assessment of both maternal and fetal/child outcomes, recognising that inadequate treatment of maternal conditions can result in indirect harm to the fetus as well as risks to the mother.
EFPIA	66	66	2	We suggest explicitly stating that safety signal detection should include maternal, fetal, and neonatal outcomes separately to ensure clarity in pharmacovigilance planning.	The guidance should clarify which safety signals should be considered.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Consortium for Innovation and Quality in Pharmaceutical Development	66	66		Recommend to explicitly state that safety signal detection should include maternal, fetal, and neonatal outcomes separately to ensure clarity in pharmacovigilance planning.	The guidance should clarify which safety signals should be considered.
EFPIA	67	69	2	Already generated RWD for a given condition and/ or therapeutic class/ similar treatments should serve as data source where possible. Also the difficulties to fulfill previous RWD commitments re. pregnancy use/ pregnancy and infant outcome for other therapeutics for the condition should be considered.	
TRT-5 CHV	67	69		In France, a cohort on breastfeeding and HIV has recently been established.”	Add : “In this respect, the establishment of European cohorts to monitor pregnancies and breastfeeding among individuals with chronic conditions transmissible to the child should be encouraged. The pooling of national data should also be promoted."
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	69	69	2	Add recommendation for countries with existing registers	...breastfeeding individuals. In countries with existing medication-, patient and birthregisters, register follow-up should be incorporated into the planning of investigational product development.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	69	69	2	Add recommendation for countries with existing registers	...breastfeeding individuals. In countries with existing medication-, patient and birthregisters, register follow-up should be incorporated into the planning of investigational product development.
EFPIA	70	73	2	The ongoing assessment of an investigational product is mainly drawn from other sources than the clinical trial.	Suggest replacing “assessment of an investigational product during pregnancy and breastfeeding ~~may draw from a variety of data sources~~ can be enriched with various sources, such as…."
EFPIA	70	73	2	Suggestion to include preclinical toxicological assessments of an experimental medicine, which may provide vital information to enable clinical trials in pregnant and/or breastfeeding individuals. Unclear if this paragraph focuses only on the postmarketing period. Suggest to consider merging with preceding paragraph to clarity if this is the intention.	Ongoing assessment of an investigational product during pregnancy and breastfeeding may draw from a variety of data sources, such as nonclinical development and reproductive toxicity test, pharmacovigilance-generated data, electronic health records, medical claims or health insurance databases, medicinal product or disease registries, or other sources (such as digital health technologies).
EFPIA	70	73	2	Ongoing assessment of an investigational product during pregnancy and breastfeeding may draw from a variety of data sources, such as pharmacovigilance-generated data, electronic health records, medical claims or health insurance databases, medicinal product or disease registries, or other sources (such as digital health technologies).	Change to "Initial and ongoing…."
ENTIS (European Network of Teratology Information Services)	70	73	2	Add ENTIS as an entity from which information can be drawn for postmarketing investigation	“Ongoing assessment of an investigational product during pregnancy and breastfeeding may draw from a variety of data sources, such as pharmacovigilance-generated data, electronic health records, medical claims or health insurance databases, medicinal product or disease registries, teratology information services (TIS), or other sources (including digital health technologies).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	72	73	2	There are limitations/ insufficient sample size in claims data to generate robust results re. pregnancy/ infant outcome with pregnancy/ beast feeding exposure based on claims data/ registries.	
EFPIA	73	77	2	Can examples of post approval data collection platforms be given?	
EFPIA	73	75	2	Please clarify what does “platform” mean.	Suggestion to add : “(e.g non-interventional studies, registries…)”.
EFPIA	74	75	2	Who does ICH believe is responsible for building, maintaining these platforms? Each sponsor for each individual drug, or is this a societal ask? Is this feasible? Do obstetricians globally have the bandwidth to enter data into hundreds of “platforms” all designed differently to capture this data, or would the ideal be a single platform, or even better integrative platforms where data can be seamlessly and efficiently captured from RWD?	Strongly suggest that the EWG takes the opportunity to make a strong international call for cohesive data systems that allow for mother-baby interlinkage, and universal data standards so that data can be more easily accessible and analyzable. Otherwise, delete this statement, as it is an unachievable ask that has already been proven (i.e. in the decades of poorly recruiting pregnancy registries) to be highly inefficient and of questionable use.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	74	75	2	stronger formulation	...such as mother-child linkage, platforms for post-approval data collection should be prepared proactively and background information ... should be collected to assist with data interpretation.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	74	75	2	stronger formulation	...such as mother-child linkage, platforms for post-approval data collection should be prepared proactively and background information ... should be collected to assist with data interpretation.
EFPIA	78	79	2	Sentence should be updated to clarify that we don't automatically include any data on pregnancy in the label. There needs to be an assessment of the quality, quantity and therefore robustness of the data before inclusion.	Below Text is proposed for inclusion in the sentence: "Available data and assessment of investigational product benefits and risks during pregnancy and breastfeeding are expected to be included (after evaluation of the quality and quantity of data available), and updated as necessary in labeling documents."
EFPIA	78	83	2	No added value as CDS and regional labeling requirements already address what should be captured in product labels.	Delete. This is not a labeling guideline.
EFPIA	78	78	2	It is worth adding benefits and risks for the mother and the fetus	Available data and assessment of investigational product benefits and risks for the mother and the fetus during pregnancy and breastfeeding are expected to be included and updated as necessary in labeling documents.
ENTIS (European Network of Teratology Information Services)	80	83	3	While the guideline rightly emphasizes that prescribing information on pregnancy outcomes should reflect the robustness and limitations of the data, it is important to also state that, in the absence of adequate data, restrictive or prohibitive wording should be avoided. Instead, labeling should use permissive language that acknowledges uncertainty without discouraging treatment or labeling use as contraindicated. Overly restrictive language in such circumstances may unnecessarily limit therapeutic options and negatively affect.	However, the absence of information should not, by itself, justify establishing a contraindication and/or restricting use.
ACRO	85	87	3	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.	
Rebekah Burrow, Department of Primary Care Health Sciences, University of Oxford	85	91	3	"...have responsibility for evaluating whether the risks of conducting the trial are reasonable in relation to anticipated benefits." Can it be emphasised that the risk does not need to be zero, or minimal? Rather, the present risk does need to be balanced against potential benefits. Lyerly, A. D., et al. (2021). "Ending the evidence gap for pregnancy, HIV and co-infections: ethics guidance from the PHASES project." J Int AIDS Soc 24(12): e25846.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	86	86	3	Guideline states, "…data-driven use of medicinal products is ethical and supported by the Declaration of Helsinki." The way this sentence is worded is that inclusion is ethical regardless of the study design. As such, it needs to be qualified.	Options include "can be ethical" or "is ethical with appropriate study designs."
EFPIA	86	86	2	My understanding is that there are multiple versions of the Declaration of Helsinki and that not all countries have signed on to the most current version.	Please add reference to the verison that is being cited.
EFPIA	86	86	3	We support the principle that is mentioned here but proposes a modification to say it "...is, in principle, ethical" in order to support the rest of this section. Additionally, it should be highlighted that the results of reprotox studies are to be taken into account.	"… data-driven use of medicinal products is, in principle, ethical and supported by the Declaration of Helsinki"
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	87	90	3	Sponsors' responsibilities are not well reflected in the draft guideline and appear diluted (lines 87-90). It would facilitate comprehension to clearly state these resposibilities or, at least, include a cross refernece to realted guidedance (e.g., ICH E6).	Add a clarification of the Sponsors' responsibilities mentioned in this section
ACRO	87	97	3	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.	
EFPIA	87	87	3	ICH E6(R3): How does this guideline support inclusion of pregnant or breastfeeding individuals in clinical trials? It only mentions "follow-up of participants after… other events such as pregnancies" in section B.9.4, but this could refer to intercurrent pregnancy cases and not specifically to inclusion of pregnant individuals. Breastfeeding is not mentioned at all.	Revisit appropriateness of reference to ICH E6(R3)
EFPIA	87	87	3	This section has failed to provide context in relation to existing ICH guidance contained in ICH M3(R2) Section 11.4 'Pregnant Women', ICH S5(R3) 'Detection of Toxicity to Reproduction for Human Pharmaceuticals'.	Add M3(R2) and S5(R3).
EFPIA	87	91	3	These two sentences, and in particular the 2nd sentence "Consideration should be given to the use of IRBs or ECs experienced in working with pregnant and breastfeeding participants" while accurate, are something that a sponsor (user of this guideline) does not have much control over. Investigators/sites work through (and with) their IRB/IEC - therefore, it is unclear why this statement is included in a guideline intended for sponsors and regulatory agencies.	Consider relaying to the end user why this statment matters - i.e. investigators/sites should be selected that have the ability to utilize an IRB/IEC that contains relevant expertise; otherwise delete.
Prescrire	87	90	3	"For evaluating whether the risks of conducting the trial are reasonable in relation to anticipated benefits": What are the criteria? The various criteria need to be clearly stated, in order to eliminate any ambiguity about the criteria for determining whether the risks can be considered reasonable.	Set out the criteria for determining whether the risks can be considered reasonable. The inclusion of pregnant individuals in clinical trials requires an exacting approach to the expected benefits (tangible clinical outcomes of real value to the pregnant individuals concerned) and a cautious approach to the risks (first, do no harm).
EFPIA	88	91	3	Consideration to use IRBs/ECs experienced with pregnancy/ breastfeeding participants.	This experience in the composition of IRBs/ECs could be mandatory or at least emphasized more strongly
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	90	91	3	The sentence "IRB/EC experienced in working with pregnant and breastfeeding participants" could be better explained by adding examples of said "expertise".	"...use of IRBs or ECs experienced in working with pregnant and breastfeeding participants (e.g., e.g., such as those with obstetitric, pediatric, neonatologist members or capability to consult them ad hoc)"
EFPIA	90	93	3	At all levels obstetric and neonatologist/ pediatric experts should be involved at the sponsor site, the agency evaluating the developmental plan, as well as IRBs and ECs.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	90	93	3	"Consider" is too weak. All nations should have an IRB/EC experienced in working with pregnant or breastfeeding participants. Include also sequeles for infants who are not breastfed.	All countries should establish an organization so that trials involving women of reproductive age are handled by IRBs or ECs exoerienced and trained in working with... For protocols involving pregnant or breastfeeding individuals, this responsibility involves considerations for the participant, for their pregnancy, and the fetus or (breastfed) infant.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	90	93	3	"Consider" is too weak. All nations should have an IRB/EC experienced in working with pregnant or breastfeeding participants. Include also sequeles for infants who are not breastfed.	All countries should establish an organization so that trials involving women of reproductive age are handled by IRBs or ECs exoerienced and trained in working with... For protocols involving pregnant or breastfeeding individuals, this responsibility involves considerations for the participant, for their pregnancy, and the fetus or (breastfed) infant
EFPIA	91	91	3	Proposal to state that the IRBs or ECs either be experienced in studies (instead of working with) with pregnant and beastfeeding participants, or have expertise in studies in pregnant and breastfeeding participants. Additionally, considerations should be given to consult additional experts before providing their opinion if they don't have experience.	… Consideration should be given to the use of IRBs or ECs experienced in studies with pregnant and breastfeeding participants. …
EFPIA	92	0	3	should also include embryo, as fetal stage starts after 10-12 weeks and women maybe exposed at embryo stages as well, these are various stages of pregnancy and risks of drugs in pregnancy are different if you are in fetal or embryonic stage	include 'embryo'
EFPIA	93	93	3	Guideline states, "...considerations for the participant, for their pregnancy, and the fetus or breastfed infant" Above, "child" is used. "Infant" is more appropriate, in my opinion, as it covers up to 12 months of age. The document should be consistent throughout.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	97	97	3	Give concrete examples what ethical boards handeling this type of protocols need to have dicussed/be aware of, maybe add a table with points that need to have be discussed. If possible recommendation that: second parent does not need to consent for the woman's participation in case of pregnancy and no need for second parent consent for collection of umbilical cord blood (rational: no pain for the child, value of sampling after exposure is higher than second parent consent), no second parent consent for national register-based child follow-up through existing medical or quality registers (rational: data i collected anyway and potentially available for research, value of follow up higher than second parent consent), information on possibility to deviate from AE/SAE reporting with adequate explanation, option to inform on studies in general by posters at the ward and include patients in acute situations without prior consent - and asking for consent afterwards	IRBs/ECs evaluating clinical trials including pregnant and breastfeeding individuals need to have competence/be aware of ethical issues related to: 1) consent of the other parent (when to give - before/after birth; for which type of follow up: umbilical cord blood, further sampling, available register data for the offspring, data specifically collected for the study), 2) AE and SAE reporting (almost all birth take place at a hospital, birth include pain, bleeding, infections are usual, treatments at the time point of birth cannot affect risk for congenital malformations, every c-section leads to a persisnant change/damage of the body), 3) in some countries midwives have much broader competences/responsibilities than in other countries).

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	97	97	3	Give concrete examples what ethical boards handeling this type of protocols need to have dicussed/be aware of, maybe add a table with points that need to have be discussed. If possible recommendation that: second parent does not need to consent for the woman's participation in case of pregnancy and no need for second parent consent for collection of umbilical cord blood (rational: no pain for the child, value of sampling after exposure is higher than second parent consent), no second parent consent for national register-based child follow-up through existing medical or quality registers (rational: data i collected anyway and potentially available for research, value of follow up higher than second parent consent), information on possibility to deviate from AE/SAE reporting with adequate explanation, option to inform on studies in general by posters at the ward and include patients in acute situations without prior consent - and asking for consent afterwards	IRBs/ECs evaluating clinical trials including pregnant and breastfeeding individuals need to have competence/be aware of ethical issues related to: 1) consent of the other parent (when to give - before/after birth; for which type of follow up: umbilical cord blood, further sampling, available register data for the offspring, data specifically collected for the study), 2) AE and SAE reporting (almost all birth take place at a hospital, birth include pain, bleeding, infections are usual, treatments at the time point of birth cannot affect risk for congenital malformations, every c-section leads to a persisnant change/damage of the body), 3) in some countries midwives have much broader competences/responsibilities than in other countries).
EFPIA	100	103	4.1	Proposal to include the "risks associated with not medicating or withdrawing medication from individual patients" here.	… the duration of treatment, the strength of the available evidence and indication being sought and intended population, and the risks associated with not medicating or withdrawing medication from individual patients.’
EFPIA	100	103	4.1	The risks for the mother and the fetus associated with treatment discontinuation before or during pregnancy should be added to this sentence.	
EFPIA	102	103	4.1	Proposal to reword to ‘strength of the available evidence and indication being sought and intended population’	… the duration of treatment, the strength of the available evidence and indication being sought and intended population.’
EFPIA	103	104	4.1	differential approach by pregnancy stage/trimester: Current wording is too vague.	Consider adding specifics for minimum evidence for 1st trimester, 2nd trimester, 3rd trimester
EFPIA	103	105	4.1	Guideline states. “In addition, the approach may differ based on the anticipated trimester of pregnancy of participants to be included in the clinical trial.” The anticipated trimester of exposure will only vary for pregnancy-related disorders, not chronic diseases during which an individual becomes pregnant (as this would invariably involve first trimester exposure). This should be made clear.	
EFPIA	103	104	4.1	This is the first use of a critically important concept in pregnancy research - "trimester". Throughout the guideline there is frequent reference to first or third trimester without any clarity or contextualization on why they matter to the point you're making. Further, the guideline has failed to outline why consideration of pregnancy trimesters matter when evaluating the PK (and its role in determining the appropriateness of dose/regimen), efficacy and/or safety (maternal and fetal) of investigational medicines. Some time should be spent outlining why/how conducting research in different trimesters may impact program design to both capture relevant PK, efficacy and/or safety information. For example, outline that 1st trimester is the crucial time period for fetal development where for certain IMPs, EFD and PPND are critically important. A trimester specific approach will be essential to enable drug developers and reviewers identification of critical design elements to inform on benefit-risk.	Add background on pregnancy trimesters and their importance to generating data in IMP research.
EFPIA	107	141	4.1.1	Ethical considerations regarding minumum sample size requirements for robust data analysis should be provided in the guidance.	Please provide guidance on this topic specifically when there are small sample sizes.
Rebekah Burrow, Department of Primary Care Health Sciences, University of Oxford	107	141	4.1.1	All non-obstetric trials should collect data on pregnancy and breastfeeding status so that we know when we are generating evidence in these people, and when we are not.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	108	109	4.1.1	Consider including preventative measures in factors to consider on evidence collection for pregnant individuals.	Suggest inclusion of the following text or similar: "Incorporating evidence collection for pregnant individuals into the development strategy starts with considering the targeted condition, patient population, and existing treatments and/or preventative measures (e.g, vaccines, prophylactic treatments).
EFPIA	109	116	4.1.1	This section describes factors to consider when planning for Pregnancy Data Collection. Considerations how pregnancy can influence the disease and how the disease may impact pregnancy should be taken into account. Additionally, a third consideration should be included: the potential effects of studied drug(s) on pregnancy.	consider adding that as a 3rd factor Proposed change: ...he disease state (e.g., potential worsening of the disease/condition if under- or untreated), how the patient's disease (and its treatment), as well as how potential effects of studied drug(s) could impact the pregnancy and its outcomes
EFPIA	109	111	4.1.1	Based on the condition and the mode of action of a given treatment, it should also be considered at which time point, i.e. after sufficient control of the underlying disease a pregnancy may be advisable to mitigate certain risks.	
EFPIA	109	109	4.1.1	Proposal to replace "existing treatments" with "current standard of care" which is considered of higher importance to pregnant or breastfeeding women.	Incorporating evidence collection for pregnant individuals into the development strategy starts with considering the targeted condition, patient population, and current standard of care.
EFPIA	110	111	4.1.1	This is an odd example - it's as if the EWG is asking sponsors to evaluate stopping or not initiating treatment with an IMP. The whole point of this guideline is inclusion of pregnant females in clinical trials, therefore, it would seem that what is essential to be considered is what is the known impact (if any) of pregnancy on the specific disease being studied, regardless of whether or not the patient is on concomitant treatment, and whether or not treatment would potentially be altered due to starting study drug. This would be critical to know so that the study is designed to capture data that demonstrates if treatment with study drug (IMP) alters the historically understood disease impact from pregnancy (for the better, worse, or neutral).	Delete the e.g.
EFPIA	112	113	4.1.1	Should also consider adding the long-term impact for the mother and infant at the end of the sentence.	
PIPELINE consortium	112	113	4.1.1	Suggested additional example	Could add risk of vertical transmission of infection as a specific example here alongside adverse pregnancy outcomes
EFPIA	113	113	4.1.1	Proposal to add to the end of this sentence "…due to inadequate disease control) and whether there is evidence of potential for and/or enhanced susceptibility to drug-related risks in the developing foetus".	…due to inadequate disease control) and whether there is evidence of potential for and/or enhanced susceptibility to drug-related risks in the developing foetus.
EFPIA	115	115	4.1.1	This is confusing. Are you trying to say here, if a trial includes WOCBP and one becomes pregnant it would be useful to have a pre-considered set of analyses to capture additional information that can be used for purposes of informing PK? Or, is the intention to say that it helps WOCBP to have data on fetal outcomes to inform whether or not they'll try to get pregnant while on the IMP (once authorised)?	Depending on which this is, modify the sentence.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	115	130	45661	There are no examples given here which would strengthen the argument	Suggest to add examples of the COVID-19 pandemic when pregnant women were excluded from trials even though they were a high risk group of adverse outcomes and DEATH. This delayed the vaccination of pregnant women and caused a surge in maternal mortality during this time period
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	115	130	45661	There are no examples given here which would strengthen the argument	Suggest to add examples of the COVID-19 pandemic when pregnant women were excluded from trials even though they were a high risk group of adverse outcomes and DEATH. This delayed the vaccination of pregnant women and caused a surge in maternal mortality during this time period
EFPIA	116	0	4.1.1	should also include embryo, as fetal stage starts after 10-12 weeks and women maybe exposed at embryo stages as well, these are various stages of pregnancy and risks of drugs in pregnancy are different if you are in fetal or embryonic stage	include 'embryo'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	116	117	4.1.1	Clinical studies in pregnant individuals anticipated to include pharmacodynamics/biomarkers to demonstrate proof of mechanism, suggest to include PD as likely included data.	When the investigational product is likely to be used by individuals of child-bearing potential, collecting data on safety, efficacy, PK and PD during pregnancy, and predicted exposure ot the fetus is important to support informed decision-making.
EFPIA	116	116	4.1.1	Safety and efficacy data will unlikely be informative at this stage, however PK in pregnancy and predicted exposure to the fetus would inform how data on safety and efficacy will be collected. Clarification on this wording is requested.	
EFPIA	116	116	4.1.1	Efficacy' could be measured when conducting efficacy studies but information on efficacy will remain limited when conducting PK pregnancy studies. Clarification on expectations is requested.	
EFPIA	117	118	4.1.1	The guideline has failed to outline why consideration of pregnancy trimesters matter when evaluating the PK (and its role in determining the appropriateness of dose/regimen), efficacy and/or safety (maternal and fetal) of investigational medicines. Some time should be spent outlining why/how conducting research in different trimesters may impact program design to both capture relevant PK, efficacy and/or safety information.	Add background on pregnancy trimesters and their importance to generating data in IMP research.
EFPIA	117	118	4.1.1	This sentence could be misunderstood to mean "as early as possible *in the pregnancy*" and a revision of the wording is proposed.	"Data should be collected ~~as early as possible and~~ at the appropriate~~ly~~ time~~d~~ in product development, which will be case-by-case."
Gedeon Richter plc.	117	118	4.1.1	Could you please clarify during which phase(s) of development pregnant or breastfeeding individuals should be included? The guideline indicates that pharmacokinetic (PK) data collection is required, but also notes that initial data may need to be obtained from non-pregnant women. From an ethical and safety perspective, we believe that pregnant and breastfeeding individuals should only be included in the later phases of development—once efficacy and safety have been adequately demonstrated in non-pregnant/non-breastfeeding women—unless the investigational product is intended to treat a life-threatening condition.	Pregnant and breastfeeding individuals should not be included in clinical trials before Phase III, when sufficient safety and efficacy data is present.
EFPIA	118	119	4.1.1	Early engagement with with regulators, patients groups etc would be highly beneficial to ensure alignment and to ensure their buy-in early in the development process. It is proposed to address this missing aspect in this paragraph.	
EFPIA	120	129	4.1.1	We suggest removing these bullet points as most diseases left untreated would have a potential for adversely affecting the health of the mother and therefore of the fetus/child. We do not see a need to point out just some of them.	
Ethics Committee UZ Leuven	120	121		We also need an expert of the pregnancy physiology on board given its complexity. For example. The first trimester of the pregnancy is the most vulnerable so where possible we avoid mediaction in this trimester. BUT, drugs that request a placental transporter to pass to the fetal compartment will pass maximally in third trimester when the concentration of receptors is highest; and they will not pass during the first trimester.	
Prescrire	120	133	4.1.1	The inclusion scenarios listed do not include pregnancy-related conditions (pre-eclampsia, gestational hypertension and gestational diabetes). They should then be restricted to situations related to pregnancy and substances for which the benefit-risk balance is favourable outside of pregnancy. This applies to both the investigational product and the standard treatment to which the new medicinal product is being compared.	
EFPIA	125	127	4.1.1	Recommend adding embryo when discussing teratogenicity, in addition to fetus.	Proposed Change: ...and/or the health of the embryo/fetus/child
EFPIA	127	127	4.1.1	Clarification of the term "not satisfactory" is requested. Is it supposed to mean "not recommended" or "not effective in the pregnant individual" or "without a positive Benefit/Risk in the pregnant individual" or "not compatible" or something else?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	128	129	4.1.1	Guideline states, "…known to carry high risks for the pregnant individual and/or the fetus/child (e.g., known or suspected teratogenicity or increased risk of pregnancy loss)." If a treatment is known to be teratogenic, the emphasis on data collection seems to assume that the exposure should continue (assuming it is inadvertent as it should be in this case). Prevention of someone becoming pregnant would seem to be the appropriate emphasis here. Data collection if a pregnancy happens is important, but this specific fact pattern seems to be lumped in with the others. Rather than "early acquisition of data from pregnant individuals," should pregnancy prevention be the emphasis?	
EFPIA	131	131	4.1.1	Unclear what type of 'justifications' for postponement of early data acquisition would be considered appropriate and legitimate. Suggestion to elaborate on the interpretation of 'justification' within the scope of this Guideline to increase clarity and consistent interpretation. For example, are practical considerations or the development stage of the product considered appropriate justifications?	
EFPIA	133	133	4.1.1	"At a later stage" in the cited paragraph seems to contradict the aim for early acquisition of data mentioned in the beginning. Clarification is requested as to what is referred to by "later stage" and what it is supposed to mean. Even better would be to remove it completely or replace it by 'as soon as possible'.	
EFPIA	134	138	4.1.1	NSAID example is appreciated, but more could be helpful, e.g. about placental transfer in humans of (monoclonal) antibodies by pregnancy stage	consider adding more examples.
EFPIA	134	135	4.1.1	"... from other similar medicinal products" Please provide Training Material examples where this has been allowed by a Health Authority for the study of an IMP (not an already authorised product). If there are no examples, please provide a theoretical Training Material example that is the model for how this is likely to be accomplished. Further, the EWG should expand Section 4.2.4 to provide more useful guidance on the role for mathematical modelling approaches to yield predictive data when leveraging data from within the IMP's program and/or from other products. AND the EWG should propose to the Management Committee a separate guideline on Pregnancy Extrapolation, as this is likely to be the most effective and efficient approach to generating useful data to inform on Benefit-Risk.	Training Materials needed, plus expand Section 4.2.4 and propose a Pregnancy Extrapolation guideline.
Prescrire	134	138	4.1.1	After the first trimester of pregnancy, many of the adverse effects on the pregnant individual and the unborn child can be deduced from the substance's pharmacology. It is not always necessary to expose individuals in the second and third trimesters of pregnancy. NSAIDs should be avoided throughout pregnancy, including in the first trimester. In early pregnancy, NSAIDs can cause spontaneous abortion, especially in the first days of pregnancy, and malformations (in particular cardiac defects). In the second and third trimesters, NSAIDs can cause premature closure of the ductus arteriosus in the fetus even after administration of a single tablet, pulmonary arterial hypertension with cardiovascular disorders in utero, cardiorespiratory distress at birth, and renal impairment in utero (oligohydramnios) and at birth. NSAIDs, including aspirin at analgesic doses, inhibit prostaglandin synthesis, slow down uterine contractions and prolong or even delay labour. NSAIDs can cause haemorrhage during labour and thrombosis in the mother (1).	
EFPIA	135	135	4.1.1	"and available data from other similar medicinal products" may not be relevant here. Phrase could be removed.	
EFPIA	136	138	4.1.1	There needs to be a broader discussion on the role of evolving physiology during pregnancy (somewhere in this guideline) and the differences that are observed across trimesters, as well as its potential impact on PK and/or PD. This paragraph is otherwise not useful in advising drug developers on how to consider which pregnancy trimesters may be relevant for consideration of inclusion.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	139	141	4.1.1	Guideline states," Clinical trials of prenatal interventions intended to improve outcomes of the fetus/neonate are not the focus of this guideline, however the principles discussed in this guideline may still apply." This caveat should be stated in the beginning of the document.	
EFPIA	139	141	4.1.1	It is not clear which prenatal interventions intended to improve outcomes of the fetus/neonate are not in the focus of the guideline. Term prenatal interventions is broad and includes screening and diagnosis, medical treatments, nutritional support.	Suggest clarifying "prenatal interventions excluding medical treatments"
EFPIA	139	141	4.1.1	As the EWG stated at the start of the sentence, this is not the focus of this guideline, therefore, this second half of the statement is inappropriate. The first half of this statement should be moved to Section 1.2 Scope.	Delete 2nd half of sentence, move 1st half of statement to Section 1.2 Scope.
EFPIA	139	140	4.1.1	To be clarified: is this excluding treatments for prevention of diseases of the fetus?	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	139	141	4.1.1	The guidance states that "Clinical trials of prenatal interventions intended to improve outcomes of the fetus/neonate are not the focus of this guideline, however the principles discussed in this guideline may still apply". I have two issues with this statement: (1) It is often difficult to separate out that a prenatal intervention is only improving the outcome for the fetus and not the mother's outcome. An intervention might appear to only improve the fetal outcome but could also impact the mother's mental health through this improvement to her fetus. We know this from trials of pregnancy interventions that show pregnant women value the option of prenatal therapy as they feel something is being done. How will applicants be able to separate out the two beneficiaries? I am not certain they will be able to. (2) In many cases, a mother who receives a prenatal intervention intended to improve the outcome of the fetus, has an improvement in her healthcare outcome also. A prenatal intervention to prevent preterm labour, if effective, is likely to improve the maternal condition as a preterm labour carries risk to the mother's health such as chorioamnionitis for example. It is therefore almost impossible to separate out the two beneficiaries of an intervention. And both individuals - mother and fetus - need to be monitored for adverse events. I would suggest this section is reworded to reflect this or even deleted.	
PIPELINE consortium	139	141	4.1.1	In addition, a single interventional product may have benefits for fetus/infant and the pregnant person	
International Consortium for Innovation and Quality in Pharmaceutical Development	142	142		Should there be a minimum threshold of nonclinical data (e.g., DART studies) before allowing inclusion of pregnant or breastfeeding individuals, or is this left to sponsor discretion? For example, definitive embryo-fetal development studies (as opposed to preliminary EFD studies, per ICH S5 R3) and pre/postnatal development study (PPND study)? Would the fertility and early embryonic development study continue to be only required for phase 3 given that the exposure period is not relevant for this population? Can a weight of evidence approach or NAMs be used instead of animal studies and in what circumstances. This comment is also relevant for clinical data.	Please provide clarification regarding the non-clinical and clinical data that would be needed to support inclusion of pregnant as well as breastfeeding individuals.
Rebekah Burrow, Department of Primary Care Health Sciences, University of Oxford	142	142	4.1.2	We should not have a default of inclusion, or a default of exclusion. Rather, the default should be consideration and a scientifically, medically and ethically sound justification for exclusion.	
EFPIA	146	148	4.1.2	Please expand on the appropriate stage of development for inclusion of pregnant participants	Outline by phase potential points for inclusion for prenancy/lactation
EFPIA	146	148	4.1.2	This sentence should reference existing ICH guidance ICH M3(R2) Section 11.4 'Pregnant Women', ICH S5(R3) 'Detection of Toxicity to Reproduction for Human Pharmaceuticals' which should be considered when a program is working to include pregnant females during the investigational development program.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gedeon Richter plc.	146	147	4.1.2	Could you please clarify what volume and type of nonclinical data should be available prior to including pregnant individuals in clinical studies? Specifically, if reproductive toxicity has not been fully investigated (i.e., not all three segments—fertility and early embryonic development, embryo-fetal development, and pre-/postnatal development—have been completed), but the molecule otherwise has an acceptable toxicological profile, could it still be considered eligible for inclusion in a Phase 1 study involving pregnant participants?	
Prescrire	149	151	4.1.2	Persistent ambiguity about the exclusion criteria for pregnant individuals.	The guideline should be more explicit about the criteria that make inclusion of pregnant individuals definitively unacceptable. These might include a medicine that is teratogenic in at least one animal species, or a medicine with adverse effects that could disrupt the pregnancy (such as preterm birth or hypertension) or impair organ function in the unborn child.
spm² - safety projects & more GmbH	149	159	4.1.2	The guideline outlines a "weight of evidence" approach for including pregnant individuals in trials, but does not specify precise thresholds or types of data required at each stage. Clearer guidance on the minimum data requirements (nonclinical and clinical; e.g. toxicity studies) for inclusion could help sponsors navigate decision-making.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	151	151	45661	Definition of this expression: "a weight of evidence approach"	Please add a definition - we are unsure of the meaning?
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	151	151	45661	Definition of this expression: "a weight of evidence approach"	?
EFPIA	152	159	4.1.2	For a proper benefit/risk assessment it is important to understand whether the disease under investigation (that may exacerbate during pregnancy) will abate/resolve after pregnancy	add respective bullet
EFPIA	152	159	4.1.2	Consider including anticpated duration of treatment as a factor to consider, as it may be difficult to enrol participants if treatment/ exposure is over a very short duration (e.g, 5 day treatment courses of antibiotics). Also consider including degree of systemic exposure as products intended for local action (e.g: administered via inhalation or topicaly as is the case with retinoids) may have a degree of absoprtion.	Consider including the following text in (or similar): Anticipated duration of treatment; The clinical pharmacology of the investigational product, including systemic absorption of products intended for local action;
EFPIA	152	159	4.1.2	Individually listed factors like "Nonclinical data," "The prospect of benefit," "The clinical pharmacology," etc	We agree with the Agency's approach of taking a "weight of evidence approach" and consideration of multiple factors for inclusion of pregnant women or women who may become pregnant in clinical trials. It might be helpful to understand how different types of evidence will be considered in various contexts , e.g. -The clinical pharmacology of the investigational product, particularly its PK and PD characteristics and their potential alteration during pregnancy; •Biological plausibility of harm due to pregnancy exposure based on MoA and structural similarity to known teratogens.....” This additional clarity will help sponsors collect evidence that will facilitate the approach outlined by the Agency.
EFPIA	152	159	4.1.2	Proposal to include a first bullet with ‘high medical need’ to better frame the context and to re-emphasize the lack of treatment options available.	Addition: high medical need

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EFPIA	152	159	4.1.2	Proposal to add a bullet: the impact of the disease on pregnancy	Addition: the impact of the disease on pregnancy
EFPIA	152	159	4.1.2	Proposal to add bullet: harm due to investigational product discontinuation for individuals who become pregnant	Addition: harm due to investigational product discontinuation for individuals who become pregnant
Global Heart Hub	152	152	4.1.2	I'm not sure if this is part of the scope, but it'd be interesting to gather data on whether there are different responses to treatment related to, e.g., type of pregnancy; IVF/natural; number of children, etc.	n/a
EFPIA	153	153	4.1.2	EFD and PPND, or something else?	Add "(e.g., EFD and PPND)"
Pfizer Clinical Research Unit, Brussels	153	153	4.1.2	Nonclinical data: as this is already a general requirement for clinical development to progress further, it is not clear whether the nonclinical data in reference here should involve information collected during pregancy and/or milk production in the general/specific models	Add some clarification about the context of that nonclinical data: e.g. Nonclinical data from DART/PPND studies, genotoxicity or others
EFPIA	154	154	4.1.2	Guideline states, “The prospect of benefit;” Benefit is mentioned, but no discussion of risks. There should be data on the risks of the intervention on non-pregnant patients (for diseases which are not pregnancy-related).	
EFPIA	154	154	4.1.2	For the mother only, or the mother and fetus? Clarify in the text.	
EFPIA	154	154	4.1.2	A rewording to clarify prospect of therapeutic benefit for the mother is proposed	Suggest changing to: The prospect of therapeutic benefit for the mother
EFPIA	155	155	4.1.2	clinical pharmacology: modeling missing	consider adding PK modeling
EFPIA	156	156	4.1.2	For the mother only, or the mother and fetus? Clarify in the text.	
EFPIA	156	156	4.1.2	Proposal to clarify "Biological plausibility of harm for the mother and the fetus due to drug exposure during pregnancy" Proposal to add "based on product known safety profile in non-pregnant individuals" after Biological plausibility of harm due to pregnancy exposure to make clear which data to assess the biological plausability of harm.	… Biological plausibility of harm for the mother and the fetus due to drug exposure during pregnancy based on product known safety profile in non-pregnant individuals …
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	157	157	4.1.2	Clarification suggested, since it's the usual terminology	When during the pregnancy (i.e., gestational trimester) the investigational product would be administered
EFPIA	157	157	4.1.2	Suggestion to replace "when" by "which trimester" or to re-write as "timing of administration during pregnancy"	Which trimester during the pregnancy...
EFPIA	157	157	4.1.2	Proposal to add a additional point on breastfeeding similar to and following line 157	
EFPIA	158	158	4.1.2	"similar to the investigational product". Do you mean within the same class, or is something else implied here? Clarify in the text.	
EFPIA	160	162	4.1.2	What does an "integrated assessment" look like? Is it asking to how the ICH E11A mapped evaluating similarity of disease? Do some of the data in a "weight of evidence" approach have a hierarchical superiority in the assessment? Please clarify and consider adding a diagram. This will better inform the text in Lines 184-186 as well.	Clarify in the text what is meant by "integrated assessment". Provide a Training Material example.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	160	160	4.1.2	Suggest to replace "the plan for collection of clinical data" by "the plan for inclusion of pregnant individuals in clinical trials.."	… In the development strategy, the plan for inclusion of pregnant individuals in clinical trials…
EFPIA	162	177	4.1.2	The guideline is not specific enought which DART studies are absolutey needed prior to inclusion of pregnant individuals. Is e.g. the PPND study necessary, which usually is only required for marketing?	Add which nonclinical studies are required prior to inclusion of pregnant individuals in any case, e.g. EFD studies (if appropriate rodent and non-rodent models are available) and which studies are only needed under specific circumstances (e.g. PPND study).
EFPIA	163	166	4.1.2	It is unclear if the recomendation is to use all of these tests as part of the strategy, or if a combination of a few of them would suffice? Is it up to the Sponsor to put together a scientific argument using the appropriate testing that can be a few of these examples?	Clarify in the text if all of these are required or if it is acceptable to use few as long as the scientific rationale is sound.
EFPIA	164	174	4.1.2	Could more specific recommendations on timing of DART studies be included?	
EFPIA	166	166	4.1.2	"... and any relevant modeling." This is the 1st use of the term modeling in the guideline. However, it is unclear how you intend the end users to interpret what you mean by modeling. As you are discussing nonclinical data in the paragraph, it would seem that you do not mean pharmacometric modeling, but rather model based studies utilizing a pregnant disease model. Please clarify.	
EFPIA	166	169	4.1.2	This statement is non-specific and applicable to all study populations. In reading the paragraph I'm not convinced it's even a necessary statment. You can delete this sentence, and the "For instance," (Line 169) and you do not loose anything. It actually is a stronger paragraph without the non-specific sentence included.	Delete "It is necessary to assess the nonclinical studies on how informative these studies would be on the safety of the investigational product for the intended patient population and make necessary adjustments to the type of studies needed and/or the study design. For instance, t", and capitalize "The".
EFPIA	166	166	4.1.2	To provide an example of relevant modeling	and any relevant modeling (*including Pharmacokinetic/Pharmacodynamic relationship in non pregnant and pregnant species*)
EFPIA	166	166	4.1.2	Please specify to what in this extract "qualified / validated alternative tests" is supposed to mean. Is it meant to say "aternative to standard nonclinical studies"? The sentence rather sounds like "tests" mean "testing kits or methods" .	
International Consortium for Innovation and Quality in Pharmaceutical Development	166	166	4.1.2	Recommend to consider the "relevant modeling" phrase be further clarified, such as to characterize impact of pregnancy in PK over stages of development or exposure-response modeling from translational assessments	
EFPIA	173	174	4.1.2	"... potential risk to a pregnancy." Do you mean viability of the pregnancy, fetal risk or something else? Clarify.	
EFPIA	174	177	4.1.2	If nonclinical data identifies a risk, what is the scenario whereby this EWG believes any company would conduct further studies to facilitate inclusion of pregnant females in the confirmatory program, or any HA and/or IRB would allow inclusion? I can understand the EWG suggesting that further elucidation purely to characterize risk for purposes of Contraindication labeling, but it seems disconnected with reality that further studies would be conducted to facilitate inclusion. Delete or clarify what the purpose of these "further investigations" are designed to do.	
Certara	178	198	4.1.2	The draft guidance states that the necessary quantity and type of data from non-pregnant participants will typically be similar to the data needed for an investigational product to proceed through clinical development. Hower, in some the drug PK exposure in non-prgnant individuals may not be representative of the exposure expected in pregnant population e.g. some CYPs/UGTs activity either increases or decreases during pregnancy leading to altered drug levels. This should be investigated (e.g. using predictive tools) before decisions to include pregnant individual in clinial trials are made and the dose should be informed accordingly to avoid efficacy or safety issues.	The assessment of the alteration of PK exposure due to pregnancy should be considered as key factor and included in the list of approaches/actions needed to be considered in the development strategy.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	178	179	4.1.2	Include consideration as to if pediatric data is needed	In addition to gathering the nonclinical data needed to proceed to studies in pregnancy, acquiring clinical data in non-pregnant individuals, and if relevant in paediatric patients, will also usually be necessary.
EFPIA	178	179	4.1.2	This statement should be more specific: How much safety in non-pregnant individuals is needed (End of Ph2? end of Ph3?)	
EFPIA	179	181	4.1.2	Please further define non pregnant participants, is this refined to individuals capable of pregnancy but not currently pregnant? And does this refer to Phase 1 studies?	
EFPIA	179	179	4.1.2	The word "usually"... Are there instances when this data would not be needed?	
K Richardson	179	181	4.1.2	"Generally, clinical data that support safety and prospect of benefit in non-pregnant study participants could reasonably be expected to be applicable for pregnant individuals."	It should be clarified here that the non-pregnant individuals are females. It does not make sense to assume pregnant female data is comparable with male data, especially when we know there are sex-based differences in treatments.
EFPIA	180	185	4.1.2	This paragarph is a bit confusing. One cannot assume that what is considered safe for non-pregnant individuals is also safe for pregnant individuals. This is why it is important to study these groups separately.	Consider revising the paragraph for clarity to ensure it conveys the message more effectively. It may help to simplify the language and structure to reduce confusion.
EFPIA	181	183	4.1.2	"The necessary quantity and type of data from non-pregnant participants will *typically be similar* to the data needed for an investigational product to proceed through clinical development." What does the EWG define as a scenario that is atypical?	Would be beneficial to have some discussion of the atypical scenarios in the guideline, or alternatively please prioritize developing this as an example within Training Materials.
EFPIA	181	183	4.1.2	While we understand it may be difficult to provide precise information on good timing, this sentence lacks some clarity and seems vague; it may be difficult to define when such a point is reached for further development or End of Phase2 or between Phase 3 and regulatory filing.	
EFPIA	184	187	4.1.2	"…the necessary nonclinical and clinical data…" Vague wording, more specific needed	Provide more specific guidance especially on the timing of the components to support which scenario (pregnant / breastfeeding). Also consider specifics to reproductive toxicity when non-human primates are the relevant species, which per current guidelines are usually conducted in parallel to late-stage clinical development.
EFPIA	184	186	4.1.2	Guideline states, "When the necessary nonclinical and clinical data become available, the sponsor should perform a benefit-risk assessment that incorporates all relevant information described above, using a weight of evidence approach."	Agree with this statement. This sentence supports the need to add risk to the bullet points in line 154.
ENTIS (European Network of Teratology Information Services)	184	187	4.1.2	Risk assessment needs clearer and explicit criteria for what constitutes adequate pre-clinical evidence and how to interpret non-pregnant clinical data in the context of pregnancy-related physiological changes, in order to have balanced risk-benefit assessment.	The objective of this assessment should be to determine whether the risks of proceeding with trials in pregnancy are reasonable given the anticipated benefits. Clear, explicit and evidence-based criteria should be implemented during drug development.
EFPIA	185	186	4.1.2	Explanation is requested on what is meant by "using a weight evidence approach".	
EFPIA	186	187	4.1.2	The phrase on the objective for the benefit-risk assessment may be clarified "The objective of this assessment should be to determine whether the risks of proceeding with trials in pregnancy are reasonable given the anticipated benefits"	Suggest alternative wording "The objective of this assessment should be to determine whether the risks of proceeding with trials in pregnancy for the fetus are reasonable given the anticipated benefits for the mother"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	186	187	4.1.2	"... proceeding with trials in pregnancy ...". Does the WOE (weight of evidence) approach then only apply to trials that are specific to the pregnant population? If no, then this sentence should be revised to reflect that the WOE is intended to be utilized to assess the appropriateness of studying the IMP in pregnant females (regardless as to whether this is in a study inclusive of a pregnant population OR dedicated trials in a pregnant population).	
EFPIA	187	187	4.1.2	Suggestion to add "and/or allowing drug continuation during pregnancy" after "in pregnancy"	… The objective of this assessment should be to determine whether the risks of proceeding with trials in pregnancy and/or allowing drug continuation during pregnancy are reasonable given the anticipated benefits. …
EFPIA	188	190	4.1.2	Guideline states, "If the sponsor determines that proceeding with trials in pregnancy is not yet reasonable, they should seek to obtain further data unless there is a rationale for not studying the investigational product in pregnancy."	What type of "further data" is being referred to here? More of the data being referred to above? Section 4.1.3 appears to discuss this. The bullet points below seem to be premature, and perhaps should be moved later in the document or put a reference to that section
EFPIA	188	192	4.1.2	"... proceeding with trials in pregnancy ...". Does the WOE (weight of evidence) approach then only apply to trials that are specific to the pregnant population? If no, then this sentence should be revised to reflect that the WOE is intended to be utilized to assess the appropriateness of studying the IMP in pregnant females (regardless as to whether this is in a study inclusive of a pregnant population OR dedicated trials in a pregnant population).	
EFPIA	190	191	4.1.2	If the sponsor determines… Is regulatory consultation expected here?	Consider regulatory consultation.
Ethics Committee UZ Leuven	193	195		For clinical studies, it can be assumed that contraception will generally remain standard practice, and in any case a thorough benefit–risk analysis will be necessary. A final evaluation of potential risks should be based on real-world pregnancy follow-up data, as clinical trials will usually not include enough cases to allow for a definitive assessment. In most cases, particularly in studies with new IMPs, this is extremely challenging: efficacy is not yet established in healthy women, let alone in pregnant women. The guideline is written in a relatively open manner, mainly providing points for consideration. From this perspective, we can follow the document in most respects. However, we find the statements in lines 193–195 somewhat far-reaching, as they might encourage an overly permissive inclusion of pregnant women in clinical trials. The guideline should not be interpreted as a blanket reference to allow inclusion of pregnant women or to waive contraception requirements. A more nuanced approach is essential, and careful attention should be paid to the wording of the guidance.	
EFPIA	194	195	4.1.2	If mandatory contraception requirements are to be removed from on-going and/or subsequent clinical trials, then it is very important that the study participant is fully aware of the risks and potential benefits if they allow themselves to become pregnant. Text to this effect should be added here. Also, the impact of including or keeping pregnant participants in ongoing studies must be carefully considered. It may postpone the availability of a treatment option overall for all patients.	
Global Heart Hub	194	195	4.1.2	This is very important and should apply to both sexes	n/a
EFPIA	197	198	4.1.2	This approach should be favored, so suggest that the"if needed" is removed.	Implementation of study(ies) specifically designed to be conducted in pregnant individuals ~~if needed.~~
EFPIA	199	222	4.1.3	If the trial was initially evaluated not to be fit for pregnant individuals, it is unlikely that it will change during the investigation. The guidance does not clearly state how to handle cases where it is not appropriate to include pregnant individuals.	These sections should address the cases as described in the titles 'When all data necessary to support a favorable benefit-risk assessment are not yet available' and 'When existing data suggest a safety concern for pregnancy' and clearly state that in these cases, investigation in pregnant individuals is not recommended.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	199	199	4.1.3	The section above under line 150 mentions that data and evidence needed applies to "ongoing participation of individuals who become pregnant" but more clarification is required why the guideline distinguishes B/R for these participants vs those who are not already in a CT but can be enrolled during their pregnancy.	
EFPIA	199	199	4.1.3	Proposal to tweak the existing section title because the term 'favourable'is considered as too strong for use in a clinical trial context. Consider adding potential in front of favorable	
International Consortium for Innovation and Quality in Pharmaceutical Development	199	235		If the trial was initially evaluated not to be fit for pregnant individuals, it is unlikely that it will change during the investigation. The guidance does not clearly state how to handle	These sections should address the cases as described in the titles 'When all data necessary to support a favorable benefit-risk assessment are not yet available' and 'When existing data suggest a safety concern for pregnancy' and clearly state that in these cases, investigation in pregnant individuals is not recommended.
EFPIA	208	209	4.1.3	If mandatory contraception is an inclusion criterion (with many regions requiring a double hurdle as stipulated by national health authorities and ethics committees), any pregnancy occurring during the study should lead to study discontinuation. Based on current experience, implementing exemption rules will be challenging. Additional details might be warrented i.e. how to continue with the patient outside of the study (e.g. named patient access, compassionate use, a substudy...)	
EFPIA	208	222	4.1.3	Remember the vast majority of current confirmatory trials are studying diseases that are not unique to pregnancy (e.g., hypertension, diabetes, multiple sclerosis), therefore the WOCBP enrolled in these studies are likely enrolled by a disease area specialist who may not be a maternal-fetal specialist. Therefore it is surprising that the guideline fails to discuss whose decision it is to proceed - primarily the study participant - nor does it discuss whom sponsors should request of their site investigators to consider having as sub-Is (sub-investigators) to help advise WOCBP study participants to make the best informed decision about how to proceed (stay on trial on or off IMP or discontinue from trial).	
Gedeon Richter plc.	209	222	4.1.3	Could you please clarify whether the guidance should also address regulatory and legal requirements that may mandate the withdrawal of pregnant participants? While the listed circumstances are important, institutional policies, local laws, and national regulations may also require exclusion or withdrawal of pregnant individuals from clinical trials. It would be helpful if the guidance explicitly acknowledged these factors as part of the decision-making framework.	
EFPIA	212	213	4.1.3	The availability of data from molecular entities or treatments similar to the investigational product may also be informative	•Information obtained to date regarding the safety in pregnancy of the investigational product (nonclinical as well as any clinical findings and data from molecular entities or treatments similar to the investigational product)
EFPIA	212	213	4.1.3	Information available when a pregnancy occurs despite mandatory contraception may be more extensive than at the time of study start. The most up to date data can be taken into account by the sponsor. Advice is requested about what would be the way for the sponsor to communicate to Health Authorities / Ethics Committees to support the potential decision on how continuation of the investigational treatment.	
Prescrire	212	213	4.1.3	Persistent ambiguity about the objective inclusion criteria for pregnant individuals in cases when all the data necessary to establish the drug's favourable benefit-risk balance are not yet available, and when pregnancies occur despite mandatory contraception.	The guideline should be more explicit about the criteria that make the inclusion of pregnant individuals definitively unacceptable. These might include a medicine that is teratogenic in at least one animal species, or a medicine with adverse effects that could disrupt the pregnancy (such as preterm birth or hypertension) or impair organ function in the unborn child.
EFPIA	215	215	4.1.3	Consider also consultation with the obstetrician / HCP that monitor the pregnant patient, especially if participant becomes pregnant while taking an investigational product in the 1st trimester, be informed of the patient' s participation to a clinical study with some information about the investigational product.	•The advice from the obstetrician / HCP that monitor the pregnant patient (including informing of the patient' s participation to a clinical study with some information about the investigational product), especially if partcipant becomes pregnant while taking an investigational product in the 1st trimester.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	216	218	4.1.3	"teratogenicity" just refers to one possible toxicity to embryo-fetal development (see ICH S5 R3)	Change "teratogenicity" to "malformation or embryo-fetal lethality"
ACRO	221	222	4	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." Given the importance of monitoring, ACRO would recommend 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"*.	Recommendation: inclusion of the following text in lines 221-222: "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"*.
Certara	221	222	4.1.3	It is stated that in case pregnancies occur during clinical trials and if the conclusion is for treatment with the investigational product to continue, then the participant should be reconsented as a pregnant participant. However, in some cases dose adjustment may be needed due to pregnancy-related PK levels and this should be taken into account in the benefit-risk assessment.	Evaluation of potential dose adjustment should be included in the decision making process when pregnancies occur during clinical trials (similarly to the approach in 4.2.4). Consideration on fetal exposure assessment are needed as well
EFPIA	221	222	4.1.3	Proposal to clarify the sentence with the proposed amendment "... to continue based on benefit risk assessment for the mother and for the fetus, then the participant should be reconsented as a pregnancy participant with appropriate monitoring for the rest of the study."	... to continue based on benefit risk assessment for the mother and for the fetus, then the participant should be reconsented as a pregnancy participant with appropriate monitoring for the rest of the study."
Pfizer Clinical Research Unit, Brussels	221	222	4.1.3	reconsenting as pregnant participant if conclusion of assessment is treatment to be continued: particularly in Phase 1 trials, there may be a logistic gap if that pregnant participant consent form is not available immediately (IRB/ICE approved) at pregancy discovery, the risk being then a treatment discontinuation until consent is signed. In principle, that consent would not have been prepared as the study was with mandatory contraception	Instead of having a reconsent as pregnant participant, the original consent may content language on possible continuation of therapy if a pregnancy occurs despite contraception (a participant not willing to expose her child would then withdraw consent at the moment)
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	222	222	4	But default should be that the data of the participant remain in the study and that there is a plan for analysing these data. For countries with existing registers, register-based follow-up should be a must.	If the conclusion is for treatment with the investigational product to continue, the participant is able to consent and plan to continue the pregnancy, then the participant should be reconsented as a pregnant participant. Irrespective of conitnuation and re-consent as pregnant participant, there should be a plan for analysis and follow-up in the study protocol. In countries with registers, register-based follow-up should be mandatory.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	222	222	4	But default should be that the data of the participant remain in the study and that there is a plan for analysing these data. For countries with existing registers, register-based follow-up should be a must.	If the conclusion is for treatment with the investigational product to continue, the participant is able to consent and plan to continue the pregnancy, then the participant should be reconsented as a pregnant participant. Irrespective of conitnuation and re-consent as pregnant participant, there should be a plan for analysis and follow-up in the study protocol. In countries with registers, register-based follow-up should be mandatory.
EFPIA	223	235	4.1.4	If the trial was initially evaluated not to be fit for pregnant individuals, it is unlikely that it will change during the investigation. The guidance does not clearly state how to handle cases where it is not appropriate to include pregnant individuals.	These sections should address the cases as described in the titles 'When all data necessary to support a favorable benefit-risk assessment are not yet available' and 'When existing data suggest a safety concern for pregnancy' and clearly state that in these cases, investigation in pregnant individuals is not recommended.
EFPIA	223	233	4.1.4	The paragraph states that there might be cases were the benefit might outweigh the risk of using a potential developmental toxicant druing pregnancy. This is of course correct but the follwing examples and the proposal to include pregnant women on a case-by-case basis is impractical. The methotrexate example needs further explanation, as there are alternative treatment besides this already known teratogen.	Rephrase the paragraph.
EFPIA	223	223	4.1.4	A similar section is not included for breastfeeding, but is also relevant for this study population. Suggest to add similar paragraph for breastfeeding population.	Make similar section for infants/breastfed population

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	223	235	45661	This section suggest that some compounds are not considered safe in pregnancy. Unfortunately, this is the case for most drugs where a minority are tested in clinical trials in pregnant women. This is usually why pregnant women are excluded. Should it rather not be stated that pre-clinical models of placental passage and consideration of drug treatment in different phases of pregnancy should be considered rather than that the compound has not been proven safe in pregnancy? There is a big problem with women with chronic disease having to stop their current medication due to safety issues and this should be a compulsory part of drug evaluation so that these women can safely continue with the best medication for their condition. Otherwise risks with treatment are transfered to clinic with no or less rigorous follow-up and no systematic monitoring.	Add a section about the potential of testing placental transfer of drugs and to use drugs in different parts of pregnancy depending on drug profile and findings
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	223	235	45661	This section suggest that some compounds are not considered safe in pregnancy. Unfortunately, this is the case for most drugs where a minority are tested in clinical trials in pregnant women. This is usually why pregnant women are excluded. Should it rather not be stated that pre-clinical models of placental passage and consideration of drug treatment in different phases of pregnancy should be considered rather than that the compound has not been proven safe in pregnancy? There is a big problem with women with chronic disease having to stop their current medication due to safety issues and this should be a compulsory part of drug evaluation so that these women can safely continue with the best medication for their condition. Otherwise risks with treatment are transfered to clinic with no or less rigorous follow-up and no systematic monitoring.	Add a section about the potential of testing placental transfer of drugs and to use drugs in different parts of pregnancy depending on drug profile and findings
EFPIA	224	226	4.1.4	"If nonclinical and/or clinical data suggest that the investigational product is potentially harmful to the pregnant individual and/or the fetus, the sponsor may conclude that inclusion of pregnant individuals in clinical trials is initially not warranted." The nonclinical studies can identify a potential risk and very high exposure margins compared to the highest recommended human dose. Suggest clarifying that the harmful effects occur at "therapeutically relevent exposures".	
EFPIA	224	225	4.1.4	The following specification of the line to the pregnant individual and/or fetus is warrented: or if they indicate the changes of drug transfer is high.	… If nonclinical and/or clinical data suggest that the investigational product is potentially harmful to the pregnant individual and/or the fetus or if they indicate the changes of drug transfer is high, the sponsor …
EFPIA	225	0	4.1.3	should also include embryo, as fetal stage starts after 10-12 weeks and women maybe exposed at embryo stages as well, these are various stages of pregnancy and risks of drugs in pregnancy are different if you are in fetal or embryonic stage	include 'embryo'
EFPIA	226	227	4.1.4	The guidance states that 'for some investigational products, the benefits of use in pregnancy may still outweigh the potential risks' - This would have been defined in the initial assessment of the IMP and it is not clear for situations where the risk outweighs the benefit, what addtional data would change the benefit-risk or mitigate the risk.	This section should expand on situations where it is not appropriate to include pregnant individuals in the clinical trial due to the potential risks, and provide guidance on what additional data would change the benefit-risk or mitigate the risk. Also, expand on the benefit-risk differences between trimesters, and how data can be generated/used to assess risk by trimester to guide enrollment.
International Consortium for Innovation and Quality in Pharmaceutical Development	226	227		The guidance states that 'for some investigational products, the benefits of use in pregnancy may still outweigh the potential risks' - This would have been defined in the initial assessment of the IMP and it is not clear for situations where the risk outweighs the benefit, what additional data would change the benefit-risk or mitigate the risk.	This section should expand on situations where it is not appropriate to include pregnant individuals in the clinical trial due to the potential risks and provide guidance on what additional data would change the benefit-risk or mitigate the risk. Also, expand on the benefit-risk differences between trimesters, and how data can be generated/used to assess risk by trimester to guide enrollment.
EFPIA	230	230	4.1.4	"(e.g., methotrexate for SLE)". The guideline should include what the safety risk is, otherwise you are leaving end users unfamiliar with MTX to guess at what the risk is, and whether the risk is limited to SLE or is present for all conditions treated with MTX.	Please expand the example.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EpiSafe Research Team	230	230	4.1.4	The draft guideline does not acknowledge that medicines with known or suspected teratogenic risk in early pregnancy may still be appropriate later in pregnancy or during breastfeeding. Excluding such products outright risks denying treatment where maternal benefit outweighs risk. Some agents that may be unsafe in the first trimester (e.g. associated with teratogenicity) can be safely and appropriately reintroduced in the second or third trimester, or may be suitable during breastfeeding. Balanced consideration is needed to avoid unnecessary harm from undertreatment while maintaining fetal and maternal safety.	Suggest new text be added: "In some cases, medicines with safety signals such as teratogenic risk in early pregnancy may be considered for reintroduction in the second or third trimester, or for initiation during breastfeeding, where the potential maternal benefit outweighs the risk."
Prescrire	230	231	4.1.4	Ambiguity about the inclusion criteria for pregnant individuals when existing data suggest a safety concern for pregnancy. The guideline refers to assessment "on a case-by-case basis", but does not provide a clear minimum threshold of evidence for the inclusion of pregnant individuals. This leaves sponsors and authorities a wide margin of interpretation that could result in inconsistent practices.	
EFPIA	231	231	4.1.4	"case-by-case basis". Does the EWG mean participant-by-participant or trial-by-trial?	Please clarify, or alternatively, succinctly elucidate the examples which should make this point clearer.
EFPIA	231	231	4.1.4	The sentence states that inclusion of pregnant individuals may be considered on a case-by-case basis but this is considered to be always the case. Clarification is requested what is special about this scenario.	
EFPIA	231	234	4.1.4	Guidance is requested or direction about which additional data to collect and ways to mitigate potential risks.	
EFPIA	235		4.1.4	provide more information on the potential risks within the different trimesters	
EFPIA	236	241	4.1.5	Examples of obstetric conditions are given, but no examples of "data needed to proceed in clinical development and support a marketing application specific to the condition" are given.	Provide examples of data needed or reference relevant sections of the guidance describing data needed.
EFPIA	236	241	4.1.5	How different is this relative to the conditions above? The risk benefit ratio may be different but the process is the same, so, we feel a separate section is not needed.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	236	236	38356	Add on repurposing drugs. Add a section on drugs that we already use in clinical routine but off-lable, suggesting that those indications should be formalized? As it is now, we cannot even run academic trials on other questions in case an off-lable product is involved without running the study as a medical product trial with extreme costs for monitoring, safet reporting etc	Drugs and medical products used off-lable in clinical routine should be approved for the condition. Companys and countries are encouraged to sponsor trials /studies that collect necessary information for applying for the pregnancy-related condition so that post-market data can be collected systematically and future trials using on-lable products can be performed.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	236	236	38356	Add on repurposing drugs. Add a section on drugs that we already use in clinical routine but off-lable, suggesting that those indications should be formalized? As it is now, we cannot even run academic trials on other questions in case an off-lable product is involved without running the study as a medical product trial with extreme costs for monitoring, safet reporting etc	Drugs and medical products used off-lable in clinical routine should be approved for the condition. Companys and countries are encouraged to sponsor trials /studies that collect necessary information for applying for the pregnancy-related condition so that post-market data can be collected systematically and future trials using on-lable products can be performed.
EFPIA	237	241	4.1.5	...."will be specific to the condition." It would be helpful to elaborate on what types of data would be needed for this scenario that is different from inclusion of a pregnant woman in any other type of clinical trial. Consider also referencing M3(R2) Section 11.4.	
EFPIA	237	241	4.1.5	The draft guideline clearly points to a case by case evaluation. It is proposed to provide more insights on external comparators/patients' own history considering the challenges of control groups in such a population.	
Prescrire	242	242	4.2	Persistent ambiguity about the inclusion criteria: The guideline refers to assessment "on a case-by-case basis", but does not provide a clear minimum threshold of evidence for inclusion. This leaves sponsors and authorities a wide margin of interpretation that could result in inconsistent practices.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Advisory Committee on Clinical Trials in Multiple Sclerosis, National Multiple Sclerosis Society, and European Committee for Treatment and Research in Multiple Sclerosis	242	406	4.2	Multiple disease-modifying therapies are available for women with MS now, and some are known to be safe in pregnancy. As such, inclusion of women who are pregnant, breastfeeding or of childbearing potential may be most feasible in Phase IV studies. These studies should be designed to assess pharmacokinetics of the drug being tested, transfer of the drug to the placenta, transfer of the drug in breast milk, maternal health outcomes, as well as neonatal and long-term neurodevelopmental and immunological outcomes of the child. While inclusion in Phase IV trials is logical, the guideline should also encourage exploration of adaptive designs or nested pregnancy cohorts within Phase III programs, especially when preclinical and early clinical safety data are reassuring. Delaying inclusion of all therapies until Phase IV risks prolonging knowledge gaps that impact clinical decision-making. Moreover, we recommend the guideline explicitly acknowledge the role of real-world evidence (RWE) and pragmatic trials in supplementing conventional explanatory interventional trials for pregnant and breastfeeding women. Leveraging observational data, registries, and linked health records is essential to generating robust evidence on maternal and fetal outcomes. The EMA should encourage international interoperable, disease-specific or therapeutic-class registries, with minimum data standards. This would avoid fragmentation and facilitate signal detection. Requests for data linkage should be included in the consent processes for all trial phases and registries to reduce the burden on women of capturing some of these outcomes.	
EFPIA	243	244	4.2	What about clinical trials where WOCBP are enrolled but there is no contraception requirement?	Add to this sentence ", and trials enrolling WOCBP that have no requirement for contraception."
EFPIA	244	246	4.2	The title mentions "Inclusion of pregnant individuals in CTs." However, the text mentions individuals with childbearing potential, and that is not exactly the same population.	Please clarify.
EFPIA	246	247	4.2	You would also get early pregnancy data from studies where contraception is mandated as you are still likely to get some pregnancies	expand sentence accordingly
EFPIA	246	248	4.2	How does the EWG define "early pregnancy"? Consider using broadly acceptable medical terminology so that there is clarity on recommendations. For example, consider utilizing "during conception", "during implantation" or "during the first trimester of pregnancy".	
EFPIA	246	248	4.2	The aspect of acquiring data on medicinal products during early pregnancy could also occur in trials with contraception required in case of unexpected pregnancy. It is proposed to consider this aspect and to rephrase the sentence accordingly.	
EFPIA	251	253	4.2.1	While this guideline focuses mainly on the inclusion of pregnant individuals in interventional clinical trials, other trial types may be acceptable if they are appropriate for inclusion of pregnant individuals.	Please elaborate and provide examples. We would suggest a tiered appropach (more complex to less complex) in applying principles.
EFPIA	251	256	4.2.1	This section does not provide much in the way of guidance as it irelates to design and implementation. -In Line 252 the EWG should just spell out "non-interventional and observational" instead of inferring and using the phrase "other trials". - The EWG should at a minimum make cross-reference to E8, E9, and E10 as it would then imply that existing internationally implemented guidelines are relevant to the pregnant population. If these guidelines are not relevant to trials evaluating pregnant females then this should be described here.	
Global Heart Hub	251	256	4.2.1	The guidelines should spell out the need to include patient organisations and pregnant and lactating patients in protocol design – particularly given that patients at this important life juncture may not wish to participate in CTs – safety concerns/ new baby taking priority	n/a
International Consortium for Innovation and Quality in Pharmaceutical Development	251	253		While this guideline focuses mainly on the inclusion of pregnant individuals in interventional clinical trials, other trial types may be acceptable if they are appropriate for inclusion of pregnant individuals.	Please elaborate and provide examples of other trial types. We would suggest a tiered approach (more complex to less complex) in applying principles.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	252	253	4.2.1	Guideline states, "…clinical trials, other trial types may be acceptable if they are appropriate for inclusion of pregnant individuals." This statement is unclear. Is it saying that other trial types may be appropriate/acceptable for the inclusion of pregnant individuals? As worded, the trial is acceptable if it includes pregnant individuals (which is unclear).	
EFPIA	252	252	4.2.1	Clarification is requested what kind of "other trials may be acceptable" or to give examples.	
EFPIA	253	253	4.2.1	The wording would benefit from additional clarification because the term study design is considered very broad.	… which study design including the dose/dosage regimen being investigated in the study being concerned, in relation to dosing intended upon marketing authorisation…
EpiSafe Research Team	253	253	4.2.1	This suggested new addition strengthens the guideline's focus on inclusive trial design by explicitly recognising that structural inequalities can prevent equitable participation. Including this language supports more representative and generalisable evidence for pregnant populations.	Suggest new text be added: "Study design should consider and reduce structural barriers that may limit participation, such as disability, migration status or other social determinants of health."
EFPIA	254	254	4.2.1	Both aspects, study design and considerations on how to control the study for pregnant individuals is proposed to be captured in this sentence. It may not be feasible to have the same standard of care as control group in pregnant versus not pregnant patients, there may be some potential differences on the standard of care, in addition to maybe some more ethical considerations on keeping pregnant patients with "placebo" standard of care.	
EFPIA	255		4.2.1	it's difficult to discuss comparators and concomitant medications in this context given that the study drug has been rigorously tested with non-clinical and clinical results supporting administration to pregnant participants	
EFPIA	255	256	4.2.1	proposal to reword "i.e., test and comparator products" with "i.e., investigational product and comparator products"	(i.e., investigational product and comparator products)
EFPIA	255	256	4.2.1	It is going to be challenging to be able to fully consider the safety impact of the comparator products, clarification is requested if this can be removed.	
Prescrire	255	256	4.2.1	Provide details of what this evaluation entails	
ENTIS (European Network of Teratology Information Services)	257	262	4.2.2	The European Network of Teratology Information Services (ENTIS) is an international professional organization comprising specialized centers that provide scientifically based information and counseling regarding medicinal and chemical exposures during pregnancy and lactation.	"Given the specialist knowledge required for investigational product and disease impacts on pregnancy, embryo-fetal development, and neonatology, consultation with relevant specialist (e.g., obstetrician or maternal fetal medicine specialist, teratology information services experts and pharmacoepidemiologists with methodological experience on medicines in pregnancy)...."
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	257	262	45692	In this section, there is a lack of discussion around the difficulties to report AE and SAE in pregnancy trials. Surrently, the recommended reporting of SAE and AE do not apply to pregnancy. An obvious example is hospital care where a majority of pregnant women (at least in HIC) give birth in a hospital and therefore hospital care can not be considered an SAE. Revised recommendations for reporting of AE and SAE in pregnancy research is needed	Add a suggestion of revised list of AE and SAE for pregnancy research to help the set-up of clinical trials in pregnancy
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	257	262	45692	In this section, there is a lack of discussion around the difficulties to report AE and SAE in pregnancy trials. Surrently, the recommended reporting of SAE and AE do not apply to pregnancy. An obvious example is hospital care where a majority of pregnant women (at least in HIC) give birth in a hospital and therefore hospital care can not be considered an SAE. Revised recommendations for reporting of AE and SAE in pregnancy research is needed	Add a suggestion of revised list of AE and SAE for pregnancy research to help the set-up of clinical trials in pregnancy
EFPIA	258	262	4.2.2	This section should also detail the need for trials designed to assess the E&S (Efficacy & Safety) of IMPs being studied for non-obstetric indications to include sites that have access to/ include sub-Investigators who are expert in maternal-fetal health (e.g., should a WOCBP become pregnant or should the trial enroll pregnant females).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	258	262	4.2.2	Proposal to broaden the perspective and to include additionally "... and to provide advice regarding study conduct." in line 262	... to help interpret any AEs reported during pregnancy and to provide advice regarding study conduct.
Prescrire	258	262	4.2.2	Pharmacologist teams from specialist pregnancy pharmacovigilance centres (in France, these are located in Toulouse and Lyon) could also be included	
EFPIA	259	259	4.2.2	Guideline states,"… pregnancy, embryo-fetal development, and neonatology,…" Neonatology is a field of study/practice, not an area of impact. "embryo-fetal and neonatal development" would be better.	Suggest text replacement, "… pregnancy, embryo-fetal development, and neonatal development..."
EFPIA	260	260	4.2.2	Guideline states,"… (e.g., obstetrician or maternal fetal medicine specialist)…"	Suggest text addition, "… (e.g., obstetrician, maternal fetal medicine specialist, or neonatologist) …"
EpiSafe Research Team	260	260	4.2.2	Pregnancy and breastfeeding studies involve complex maternal, fetal, and neonatal considerations. Expertise from obstetric physicians and neonatologists can help interpret any adverse events reported during pregnancy.	Suggest new text be added: "obstetric physicians" and "neonatologists" (e.g., obstetrician, obstetric physicians, maternal–fetal medicine specialists, and neonatologists)
EFPIA	261	261	4.2.2	DMC should help in defining specific stopping rules	
EFPIA	263	273	4.2.3	The section on sample size should be carefully reassessed and be more specific on expectations. Guidance for the analysis strategy of primary/secondary endpoints of the overall population is missing. There is a little bit of advice regarding sample size estimation, however, it would have been helpful to get advice how to treat pregnant women in the overall analysis when they get dose adjustments, rescue medication, etc. Innovative statistical models/extrapolation should be considered and be acceptable, when appropriate.	
International Consortium for Innovation and Quality in Pharmaceutical Development	263	263		Ethical considerations regarding minimum sample size requirements for robust data analysis should be provided in the guidance.	Please provide guidance on this topic specifically when there are small sample sizes.
ACRO	264	270	4	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 e.g. withdrawal rates may need to be estimates. ACRO would suggest that additional regulatory agency support is available for sponsors to provide advice during the conduct of studies including pregnant individuals.	Recommendation: additional regulatory agency support is available for sponsors to provide advice during the conduct of studies including pregnant individuals.
EFPIA	264	266	4.2.3	What does the EWG mean by "proportion"? The EWG should consider that any product currently authorized for use in an adult population IS authorized for use in pregnant females unless there is a specific Contraindication statement in the label. Therefore, this paragraph should be cautious about inferring that a "proportion" (typically inferring a minimum n sample) of the study population should be pregnant. Is that actually necessary in all cases? If PK, PK/PD has been able to demonstrate similar exposure to effective dose between a pregnant population and WOCBP, is the recruitment of any pregnant patient into the confirmatory trial essential to making regulatory conclusions on B:R? The EWG may benefit from reading ICH E11A on pediatric extrapolation and the draft M15 MIDD guideline as there are numerous sections that are relevant to seeking innovative means of generating/evaluating data in addition to robust (RCTs) and "proportionate" (typically inferring minimum n sample) sample sizes.	Address and minimally consider reference to M15.
EFPIA	264	273	4.2.3	Is the number of women enrolled by trimester potentially important for patient representation and statistical analysis?	Include whether or not this is critical or not in this section.
Global Heart Hub	264	273	4.2.3	These guidelines could have a negative impact on the recruitment of women of childbearing to go to CTs – it could seem too potentially complicated. Trial centres should be given targets for numbers/%s to be included in trials and should be held accountable, to overcome this potential issue. Perhaps smaller trial groups should be accepted for these patients, accepting that fewer will want to participate in CTs vs the general population.	n/a

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	267	268	4.2.3	Guideline states, "For clinical trials with non-obstetric indications, estimating the number of pregnant participants can help determine assessable endpoints." Is the assumption that this study does not include contraceptive requirements? This statement should be more clear.	
EFPIA	267	268	4.2.3	What does the EWG want an end user to do with this sentence (i.e. what is the point here)? Designing a trial starts with understanding the target population and the clinically relevant endpoints that are essential for analyzing the effectiveness of the IMP. Are you suggesting that if including a pregnant population you may need to select a surrogate marker (only for the pregnant population) to be used as the primary endpoint? Why would the pregnant population need a separate endpoint? If the disease process is the same (similar) and the dose/dose regimen has been established for the pregnant population to be included in the trial with other adults (e.g., men, and WOCBP), shouldn't their data analysis be a part of the overall study analysis dataset?	Please revise this statement.
Gedeon Richter plc.	267	270	4.2.3	The guideline acknowledges that "low participant numbers may limit safety conclusions, especially for rare adverse outcomes such as specific birth defects." According to the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/2005), a minimum of 300 exposed pregnancies is generally considered necessary to draw meaningful safety conclusions regarding teratogenic risk. Could you please confirm whether our understanding is correct—that this minimum sample size requirement applies specifically to pregnancy- and breastfeeding-related indications, and that no such threshold is defined for other indications not directly involving these populations?	Please confirm explicitly that there is no requirement regarding the number of pregnant and/or breastfeeding individuals in case of an indication not directly related to pregnancy and/or breastfeeding.
EFPIA	269	270	4.2.3	If the study had low participant numbers that limit safety conclusions, would this have to be stated as a caveat to the data in the label?	Include information in this section.
EFPIA	270	270	4.2.3	Proposal to change to "safety or efficacy conclusions"	… may limit safety or efficacy conclusions, especially ...
ACRO	271	273	4	It is not clear what is meant by the sentence: "The number of participants required to determine an efficacy endpoint should be achieved by design for clinical trials of investigational products used for obstetric indications or in trials designed for pregnant individuals only."	Recommendation: rephrase to be clearer.
EFPIA	271	273	4.2.3	In most cases, it is not advisable to rely solely on estimates from obstetrical trials or trials that focus exclusively on pregnant women. The participant numbers in obstetrical trials can be quite high. Therefore, if you are conducting a trial that aims to include pregnant women, you may significantly exceed the number of participants, which can make the study impractical.	Provide an alternative strategy for determining an approximate sample size.
EFPIA	271	273	4.2.3	What is the EWG trying to say here? This sentence is unclear. Is it specific to obstetric specific study design, if so, start with that, and then state what is essential in order to conclude on B:R in pregnant females. Please refer to existing relevant ICH guidelines (e.g., E8, E9, and even E10).	
EFPIA	271	271	4.2.3	Safety endpoints should be mentioned for obstetric indication trials	suggestion
EFPIA	271	273	4.2.3	The section would benefit from further clarifications when it is obstetric indication (where a control arm may not be ethically plausible) vs non obstetric indications. Earlier in the guidance it mentions to include pregnant population in clinical trials within non pregnant population, for non obstetric indications. Would the efficacy endpoint and sample size calculation be different then and specific for the pregnant subpopulation within the study? And a specific control arm required? Or historical control would be possible?	
Gedeon Richter plc.	271	273	4.2.3	Could you please confirm whether our understanding is correct—that dedicated studies in pregnant or breastfeeding individuals are only required for pregnancy-related indications?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	274	298	4.2.4	Take ethnicity, age of the pregnant individual into consideration.	Line 290: suggestion to add: In addition to pregnancy-related physiological changes, factors such as ethnicity and the pregnant individual's age should be considered when determining dosing strategies
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	274	298	45692	In this section, a parapgraph about the potential differences in PK in pregnancy and some pregnancy induced disorders would be helpful. For example in preeclampsia, there is often a need for an increased dosage due to loss in the urine secondary to endothelial injury.	Add an example that PK profiles may further differ in pregnancy specific disorders such as preeclampsia and should be taken into consideration when planning the trial.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	274	298	45692	In this section, a parapgraph about the potential differences in PK in pregnancy and some pregnancy induced disorders would be helpful. For example in preeclampsia, there is often a need for an increased dosage due to loss in the urine secondary to endothelial injury.	Add an example that PK profiles may further differ in pregnancy specific disorders such as preeclampsia and should be taken into consideration when planning the trial.
EFPIA	275	275	4.2.4	Modify to "dose, treatment regiment, and frequency"	Modify : "dose, treatment regimen or frequency"
EFPIA	277	279	4.2.4	Provision of some examples could be beneficial for description of physiological changes during pregnancy	Suggest the following modification: "The physiological changes that occur during pregnancy may affect absorption, distribution, metabolism, and elimination of the product potentially leading to an altered PK/PD profile of the investigational product. This will change the exposure and related response (e.g., the volume of distribution for drugs like penicillin increases due to increased plasma volume, potentially leading to subtherapeutic levels if standard dosing is used).
EFPIA	277	283	4.2.4	This paragraph, in its current simplistic form is sufficient for this section on PK and Dosing. However, it is inadequate as the only attempt at some discussion of the role of pregnancy-induced changes in physiology across trimesters (and its implications) within the guideline draft. The EWG should develop a section within the Background that has a more definitive discussion on the trimester related physiologic changes that impact considerations regarding PK and dosing, which is the fundamental reason that this guidance is needed (i.e., do the physiologic changes impact exposure, and ultimately impact response).	
EFPIA	277	283	4.2.4	Alteration to absorption, distribution, metabolism and elimination of a drug would impact its PK, and not only its PK to PD relationship. Changes to PK itself (drug exposure) could have safety considerations. PD changes during pregnancy would be dependent on the drug's mechanism of action and disease. As written, PK/PD may be interpreted only as PK to PD relationship. Throughout this section, suggest to write out "PK and PK/PD" in place of PK/PD for clarity that pregnancy would not only alter the PK to PD profile/relationship.	The physiological changes that occur during pregnancy may affect absorption, distribution, metabolism and elimination of the product potentially leading to an altered PK profile of the investigational product that could have safety considerations and/or altered PK to PD relationship (PK/PD). In addition, the extent of these physiological changes can vary over the course of pregnancy, so PK and PK/PD should be assessed during different trimesters and postpartum. Depending on the duration of treatment, PK and PK/PD measures should be assessed from the same participant wherever possible. The postpartum period should be sufficiently long to understand PK and PK/PD changes until the return to pre-pregnancy state.
Gedeon Richter plc.	277	294	4.2.4	Could you please clarify whether it is possible that a lack of efficacy is due to insufficient exposure? If so, how could this be demonstrated clinically in patients who are already ill?	
EFPIA	278	278	4.2.4	Proposal to add 'catabolism' after metabolism - to account for monoclonal antibodies and proteins	...distribution, metabolism, catabolism, and elimination…

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	279	281	4.2.4	Obstetric conditions such as pre-eclampsia, fetal growth restriction, have huge impacts on pregnant individual's physiology for example altering liver funtion, platelet number and albumin concentration and are common in pregnancy. It is important to point this out. I suggest that mention of this be added into this section (see additional text in next column in bold.) "The physiological changes that occur during pregnancy may affect absorption, distribution, metabolism, and elimination of the product potentially leading to an altered PK/PD profile of the investigational product. In addition, the extent of these physiological changes can vary over the course of pregnancy, so PK/PD should be assessed during the different trimesters and postpartum. In addition, the extent of these physiological changes can vary over the course of pregnancy, so PK/PD should be assessed during the different trimesters and postpartum".	"The physiological changes that occur during pregnancy and the pathology of obstetric diseases may affect absorption, distribution, metabolism, and elimination of the product potentially leading to an altered PK/PD profile of the investigational product. In addition, the extent of these physiological changes can vary over the course of pregnancy, so PK/PD should be assessed during the different trimesters and postpartum. n addition, the extent of these physiological and potential pathological changes can vary over the course of pregnancy, so PK/PD should be assessed during the different trimesters and postpartum."
EFPIA	282	283	4.2.4	More guidance is requested on the length of the postpartum assessment period to understand PK/PD changes.	
EFPIA	283	283	4.2.4	The term "pre-pregnancy state" is used here and elsewhere in the Guidance. It would be helpful to understand how the EWG defines this - specifically, what endpoints should be at "pre-pregnancy state"? Is the lactation period included?	
K Richardson	284	286	4.2.4	"... it is essential to include in the protocol whether pregnant participants should receive the same dose as non-pregnant participants or a different dose"	Sex-based differences in dosing matters. Propose "..whether pregnant participants should receive the same dose as non-pregnant female participants or a different dose, where sex-based differences apply to dosing."
EFPIA	286	288	4.2.4	Dose adjustments should also be considered when the rate of adverse events are observed.	Please consider rephrasing: 'Dose adjustments may be needed for pregnant participants in cases where efficacy becomes suboptimal because of insufficient systemic exposure, or where the therapeutic index or safety margins are narrow, or where adverse events are observed.'
International Consortium for Innovation and Quality in Pharmaceutical Development	286	288		Recommend to include dose adjustments should also be considered when the adverse events are observed. Please consider including the bolded text in next column.	Please consider rephrasing: 'Dose adjustments may be needed for pregnant participants in cases where efficacy becomes suboptimal because of insufficient systemic exposure, or where the therapeutic index or safety margins are narrow, or where adverse events are observed.'
EFPIA	287	287	4.2.4	Clarification is required if "becomes suboptimal because insuffient systemic exposure, or where the therapeutic index or safety margins are narrow" should be consistent with the previous text "dose or treatment regimen that is sub- or supra-therapeutic" as mentioned in section 1.3.	
International Consortium for Innovation and Quality in Pharmaceutical Development	288	289	4.2.4	For initial dose recommendations suggest adding information from nonclinical species as well.	"non clinical data from appropriate animal models" should be added prior to "and clinical dose-exposure data....."
K Richardson	288	290	4.2.4	"To initially estimate the dosage/dosing regimen for pregnant participants, clinical and dose-exposure data from non-pregnant participants could be considered."	Propose "..clinical and dose-exposure data from non-pregnant females could be considered, where sex-based differences are known."
EFPIA	289	290	4.2.4	Propose change text from "could" to "should" in "data from non-pregnant participants could be considered"	… data from non-pregnant participants should be considered ...
ACRO	290	292	4	ACRO welcomes the recognition of the role of modelling approaches. ACRO notes that transparency of the detail behind PBPK models may vary and recommends including a statement stating that sufficient details should be reported.	Recommendation: 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"*.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Pfizer Clinical Research Unit, Brussels	292	294	4.2.4	Any observed PK alterations in pregant participants… this statement is confusing as the intention of the sentence is collection of information for proper dose selection for pregant participants. Except in cases where proper dose selection (last portion of sentence) refers to subsequent participants/cohorts in the study or new studies, it is uncler where the PK alterations in pregnant participants would have been observed	Clarification required Suggestion: Any observed PK alterations in pregnancy models….
EFPIA	297	297	4.2.4	Which "clinical trial"? Consider revising this to reflect the iterative nature of new data generation throughout a development *program* for a novel IMP.	"...on the findings of the data generated during the clinical trial development program (e.g., new safety findings and its impact on understanding of risk, new PK data and its impact on dosing and/or regimen concerns in the trial and the clinical impact of overexposure or underexposure)."
EFPIA	298	298	4.2.4	Suggest adding after underexposure additional clarification as proposed	… or underexposure) during the conduct of the study and finally confirmed at the end of the study based on all available evidence and benefit risk profile of the drug.
EFPIA	299	315	4.2.5	Does this also apply to pregnant partners when becoming pregnant during clinical trial	Consider to at expectations for pregnant partners in the guideline overall where applicable.
EFPIA	299	306	4.2.5	There are no nonclinical models mentioned in this section. Does the EWG consider a qualified/validated non-clinical model acceptable to determine/predict fetal exposure?	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	299	306	45692	There is no mentioning of in vitro assessment of placental passage	There are new models emering, such as placenta on a chip, that can accelerate evaluation of drug safety for fetal exposure and can be added here.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	299	306	45692	There is no mentioning of in vitro assessment of placental passage	There are new models emering, such as placenta on a chip, that can accelerate evaluation of drug safety for fetal exposure and can be added here.
EFPIA	300	306	4.2.5	This section would benefit from suggestion of how to obtain fetal exposure data (cord sampling, neonatal sampling upon delivery in a range of gestational durations (aka pre-term and full-term neonates) etc.). Similarly, adding a section in the document to talk about the data that can inform PBPK, like ePPND studies at diff. stages of pregnancy, to inform on fetal exposure predictions would benefit the guideline.	
EFPIA	301	306	4.2.5	This section should also mention that enhanced fetal surveillance may need to be considered as part of fetal exposure assessments.	
EFPIA	302	303	4.2.5	Please clarify the meaning of the sentence starting with "Currently, it is challenging…"	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	302	304	4.2.5	"Currently, it is challenging to evaluate fetal exposure with available methods such as umbilical cord blood sampling." I agree with this statement. But please include that ex vivo placental perfusion expeirments are another way to explore fetal exposure with the advantage that studies can be done in placentas from pregnancies with pathology such as fetal growth restriction. See additional text in the next column.	"Ex vivo placental perfusion expeirments are another way to explore fetal exposure with the advantage that studies can be done in placentas from pregnancies with pathology such as fetal growth restriction."
EFPIA	303	306	4.2.5	Nonclinical studies (ePPND) could also be informative to estimating fetal exposure.	However, nonclinical studies as well as PBPK modeling could be infomative to estimating fetal exposure.
EFPIA	303	303	4.2.5	PBPK to be written in its entirety	However, *Physiologically based Pharmacokinetic modelling*

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	303	303	4.2.5	PBPK is an important tool but not reasonable in every instance and softening of the language is proposed.	...However PBPK modelling may be a...
EFPIA	304	305	4.2.5	"Despite the limitations, fetal exposure data could contribute to the overal pharmcologic and safety profile of the invstigational product in fetuses and infants." Clarification is requested why "could" would not be "would".	
EFPIA	307	315	4.2.6	Need to consider situations where data availability to determine retention of pregnant women may differ between 2 arms and you are comfortable allowing women to continue in one arm if they get pregnant but not the other, which is a situation we have had. You then need to decide how to deal with that in your analysis without disadvantaging your more investigational arm. i.e. otherwise you have more discontinuations in one arm even if equal numbers get pregnant in both arms. It would be helpful to have standardised guidance on this from regulatory agencies but what we have done is censor efficacy data on all pregnant women at the time of pregnancy diagnosis but allow them to continue in the study on order to collect PK and safety data.	
ACRO	308	310	4	ACRO notes that the draft guideline says "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". Whilst ACRO agrees with the principle of ensuring standardisation of evaluation where possible, ACRO also notes the recommendations in lines 458-474 regarding minimising the burden of study procedures on pregnant participants. As highlighted in lines 469-471, pregnancy may affect participant's ability to engage with burdensome study procedures. ACRO would therefore suggest rewording lines 308-310 to allow flexibility to minimise burden for participants.	Recommendation: rewording of 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"*.
EFPIA	308	311	4.2.6	PK/PD is mentioned on line 308 and then again as an example in line 311. Please explain if there are different or additional PK/PD endpoints that would be needed for pregnant participants that are not conducted for those in the general population.	
EFPIA	308	310	4.2.6	Proposal to reword this sentence, since lines 53-56 (& 5.3.2) correctly point out the issue of study burden for pregnant participants. The way it is currently placed comes out too strong.	Consideration should be given, as applicable, to evaluating the same....
EFPIA	308	315	4.2.6	It is considered of value to extend the scope to maternal health and neonatal/infant outcomes in this section for completeness rather than just mentioning the pregnancy period.	
EFPIA	309	310	4.2.6	This sentence would benefit from additional clarification by adding 'to ensure consistency in data collection and comparability of outcomes'. Also, the frequency of evaluation should be performed based on expected risks of pregnancy and disease.	...with the same frequency of evaluation whenever feasible, to ensure consistency in data collection and comparability of outcomes (for ...
EFPIA	310	311	4.2.6	This sentence directly contradicts the sentence in Line 308-311. Are the PK and PD endpoints/ frequency the same or are they different/additive. This paragraph would benefit from some nuancing of the text to relay that often the endpoints/ frequency will be the same, however, they will be certain scenarios where additional data may be needed (e.g., additional frequency of PK samples due to physiologic changes throughout the trimesters of pregnancy). The EWG should also include an e.g. OR better, plan to develop a specific Training Materials example outlining when a different efficacy or PD endpoint is needed for a pregnant population than the general study population.	Revise text and develop Training Material example.
EFPIA	310	311	4.2.6	PK/PD (PK to PD relationship) is not often an endpoint in clinical studies. With the PK and PD endpoints mentioned in the first sentence (line 308), unclear what additional PK/PD data may be collected in pregnant participants. Suggest to remove "PK/PD data" in the parenthesis.	Additional endpoints may also be needed for pregnant participants ~~(e.g., PK/PD data)~~.
EFPIA	311	313	4.2.6	The CT scan example confuses your point. What do I mean by this, what happens if CT scans are the tool measuring the primary efficacy outcome? In this case, should the trial even be enrolling pregnant study participants? Consider adding some statement that acknowledges certain ley efficacy endpoints may preclude the inclusion of pregnant participants.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ACRO	316	316	4	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 would suggest that considerations are included in the guideline to guide sponsors in this area.	Recommendation: inclusion of examples of "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.
EpiSafe Research Team	316	350	4.2.7	Clearer direction is needed to ensure both short- and long-term infant outcomes are assessed, and that communication about uncertainty is transparent.	Suggest new text be added: "Protocols should include assessment of both short- and long-term infant outcomes. Risk–benefit information provided to participants should clearly state the level of certainty in the evidence and reflect input from relevant specialists to ensure the infant's health is well considered."
EFPIA	317	318	4.2.7	Clarification for this sentence is proposed: "Pregnancy-related assessments should be specified in the protocol and include those that are impacted by the disease."	… Pregnancy-related assessments should be specified in the protocol and those that are impacted by the disease should be highlighted. …
EFPIA	322	324	4.2.7	"...a plan to follow and collect pregnancy-specific outcome data systematically is needed to evaluate the impact of the investigational product on maternal and fetal/infant/child health. How this is best achieved will need to be considered on a study specific basis..."	Suggest emphasizing the importance of standardized definitions for outcomes and the use of relevant classifications: "...a plan to follow and collect pregnancy-specific…….evaluate the impact of the investigational product on maternal and fetal/infant/child health. This plan should include predefined definitions for all relevant pregnancy and infant outcomes, using established classification systems to ensure data comparability and interpretability. The plan should be discussed and agreed upon before the start of each study. How this is…..on a study specific basis..."
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	322	335	4.2.7	Please mention MFAET in this section. MFAET is the first and only standardised international maternal and fetal adverse event criteria that are now available for use in investigational clinical trials. The terminology provided 19 new fetal and 12 new maternal definitions that were mapped to MedDRA in 2016 and have been graded through international consensus process published in 2021. See https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6047 Spencer RN, Hecher K, Norman G, Marsal K, Deprest J, Flake A, Figueras F, Lees C, Thornton S, Beach K, Powell M, Crispi F, Diemert A, Marlow N, Peebles DM, Westgren M, Gardiner H, Gratacos E, Brodszki J, Batista A, Turier H, Patel M, Power B, Power J, Yaz G, David AL. Development of standard definitions and grading for Maternal and Fetal Adverse Event Terminology. Prenatal Diagnosis 2022;42:15-26. PMID 34550624. doi: 10.1002/pd.6047 Further details about this can be added to Appendix 2 - see comment further below.	Add in details of MFAET and link to resources: See https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6047 Spencer RN, Hecher K, Norman G, Marsal K, Deprest J, Flake A, Figueras F, Lees C, Thornton S, Beach K, Powell M, Crispi F, Diemert A, Marlow N, Peebles DM, Westgren M, Gardiner H, Gratacos E, Brodszki J, Batista A, Turier H, Patel M, Power B, Power J, Yaz G, David AL. Development of standard definitions and grading for Maternal and Fetal Adverse Event Terminology. Prenatal Diagnosis 2022;42:15-26. PMID 34550624. doi: 10.1002/pd.6047 https://www.ucl.ac.uk/population-health-sciences/womens-health/research/maternal-and-fetal-medicine/prenatal-therapy-0/current-projects-professor-anna-david-prenatal-therapy/maternal-and-fetal-adverse-event-terminology-mfaet
EFPIA	333	334	4.2.7	don't need 'child' as newborn/infant will suffice as child is passed the newborn stage	Consider removing 'child' from the sentence
EFPIA	333	334	4.2.7	This should be as limited as possible and as best as possible integrated into routine post-natal pediatric care.	
Prescrire	333	334	4.2.7	Despite the goal of reducing the burden of assessments, some of the recommendations (such as repeated evaluations and extended follow-up of the child) may considerably increase the burden on participants, and could jeopardise fully informed consent by further adding to day-to-day demands.	
EFPIA	334	334	4.2.7	Why use "newborn" here and not in any other places? Suggest changing to be consistent	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	335	335	4.2.7	Please elaborate on what "additional information" the EWG would anticipate to help in the interpretation of the safety profile.	
EFPIA	340	342	4.2.7	Can this be set up as a sub-study, mandatory for pregnant participants?	Might make it easier e.g. for Informed consents
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	340	342	4.2.7	Add in the use of fetal heart rate monitoring which is standard of care to assess fetal wellbeing alongside fetal ultrasound. See text in bold in the next column.	Local routine pregnancy monitoring for trial participants may be part of study-specific assessments. These may include prenatal and postpartum follow-up visits, neonatal consultations, fetal heartrate monitoring, ultrasound scans, and blood and urine tests.
Prescrire	340	342	4.2.7	Despite the goal of reducing the burden of assessments, some of the recommendations (such as repeated evaluations and extended follow-up of the child) may considerably increase the burden on participants, and could jeopardise informed consent by further adding to day-to-day demands.	
EFPIA	343	346	4.2.7	We welcome the considerations to the use of mobile study visits, virtual telemedicine study visits and home health nurses to aleviate the burden of pregnant individuals after birth, especially considering the post-partum follow-up could take a long time.	No requested change to text
EFPIA	343	346	4.2.7	Acknowledged that this starts with "where feasible", however, for non-obstetric trials (which are the overwhelming majority for novel IMPs), the request to move visits to coincide with routine pregnancy visits is highly impractical/unfeasible. Study visits tend to have precise visit windows, how does the EWG recommend sponsors capture this in the CRF? Will every out of visit obstetrical visit turned research visit now need to be captured as a deviation? How does this impact the statistical analysis plan? Further, the EWG has provided no operational guidance on the need to have each site contain an obstetrical sub-I anywhere in the guideline. Should an investigator bring in an obstetrical sub-I to the team, will every study participant need to use that one obstetrical sub-I or may they keep their own obstetrician? Will each new obstetrician have to now be trained to be a sub-I? Will each site investigator need to hire/ask for a line item to cover a visiting research nurse to go to each of the obstetrical visits to carry out the site visit? Will that obstetrical site have the necessary tools (lab techs, imaging, et cet) to carry out the visit? The guideline	
EFPIA	343	343	4.2.7	Could be applicable for section 4.3.2 "Reducing Burden and Harm on Pregnant Individuals in Clinical Trials" as well	suggestion
EFPIA	347	348	4.2.8	Is there a recommended minimum follow-up duration for neurodevelopmental outcomes? Should this vary by product class? For reference, an existing guidance for evaluation of neurodevelopmental safety recommends evaluation up to at least 2 years of age for products for use in neonates.	Please consider adding text to address this.
EFPIA	347	357	4.2.8	Assessment and data collection for infants	It would be useful to propose a follow-up period, especially to access developmental delays.
EFPIA	347	357	4.2.8	It is suggested to clarify the distinction between participating in a trial with a one-year follow-up for the baby, including neurodevelopment assessments, versus extending the follow-up duration if required by health authorities. Additionally, it would be beneficial to determine the extent to which all these trials should be considered mandatory post-marketing surveillance for baby follow-up. References to certain publications or guidances could be beneficial (e.g. FDA guidance "Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development" 2024)	
EFPIA	347	357	4.2.8	Consider making Section 4.2.8 a sub-section of 4.2.9 as it is solely about infant outcomes (safety) with no efficacy or PK expectations. Therefore, assessments and data collection in infants born to mothers exposed to IMP during study is a component of safety monitoring.	Makes 4.2.8 a sub-section of 4.2.9.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Consortium for Innovation and Quality in Pharmaceutical Development	347	348		Consider including a recommended minimum follow-up duration for neurodevelopmental outcomes. and if this should this vary by product class. For reference, an existing guidance for evaluation of neurodevelopmental safety recommends evaluation up to at least 2 years of age for products for use in neonates.	Please consider adding text to address duration of follow-up.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	347	357	45692	An issue in pregnancy research is that ethical boards often require partner's consent for follow up of the neonate. This is not reasonable since the woman is included during pregnancy and the neonate has been exposed to a drug in the womb. The mother's consent should be enough for follow up of the neonate since this regards safety issues of the original trial where the neonate was exposed in utero. Currenlty, safety data and important outcome measures are hampered by the fact that the research team might not receive consent from the other parent after birth, either due to practical reasons (the partner is physically not there) or that the partner choose not to sign.	Emphasize that the partner's consent is not needed for follow up of a treatment that was initiated in pregnancy or at least not umbilical blood sampling, register-based follow-up or other examinations such as collecting growth data that do not cause any harm to the infant.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	347	357	45692	An issue in pregnancy research is that ethical boards often require partner's consent for follow up of the neonate. This is not reasonable since the woman is included during pregnancy and the neonate has been exposed to a drug in the womb. The mother's consent should be enough for follow up of the neonate since this regards safety issues of the original trial where the neonate was exposed in utero. Currenlty, safety data and important outcome measures are hampered by the fact that the research team might not receive consent from the other parent after birth, either due to practical reasons (the partner is physically not there) or that the partner choose not to sign.	Emphasize that the partner's consent is not needed for follow up of a treatment that was initiated in pregnancy or at least not umbilical blood sampling, register-based follow-up or other examinations such as collecting growth data that do not cause any harm to the infant.
EFPIA	348	357	4.2.8	Duration of follow-up will depend on a number of factors, however the guidance needs more specificity.	Add guidance on duration of infant follow-up e.g. 1 year minimum, 2 years for neurological outcomes
ENTIS (European Network of Teratology Information Services)	348	357	4.2.8	As ENTIS members have established methodologies for long term follow up, they could be consulted for methodological input	"Options may include subgroup-specific safety follow-up studies, enrollment in existing programs such as pregnancy registries, or other appropriate methods to ensure longer-term data collection on infant outcomes. Experts at ENTIS, who are highly experienced with established follow-up methodologies, should be consulted"
Prescrire	348	352	4.2.8	Persistent ambiguity about the criteria: a non-exhaustive list of substances requiring long-term follow-up is therefore needed here.	
spm² - safety projects & more GmbH	348	357	4.2.8	We understand that duration, and thereby probably also frequency, of follow-up for affected infants depends on a lot of factors and is decided on a case-by-case basis. Would it be possible to provide concrete examples, e.g. a pregnancy during an oncological study with pregnancy as an exclusionary criterion and pointers on the timeframe (how often, how long) follow-up of the infant would be recommended (maybe even 5 or 10 years after birth) or also autoimmune studies.	
Ethics Committee UZ Leuven	353	353		It can be a combination of physical examination and assesment of the neurocognitive outcome and a questionnaire. In the latter children are examined when there is an indication to do so in the questionnaire completed by the parents	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	353	357	4.2.8	In the case of very long term follow-up, potentially in a trial sub-study, the issue of getting consent from the grown-up infant might apply when the child reaches the age of consent under country law. This should be added in as a very specific issue related to trials in pregnant and lactating individuals. Suggested text in bold in the next column	"It is recognized that the follow-up may extend until past the clinical trial completion date, sometimes into adulthood of the infant offspring from the clinical trial. Sponsors should ensure a mechanism for such follow-up is in place. This may include getting consent when the child reaches the age of consent under country law. Options may include subgroup-specific safety follow-up studies, enrollment in existing programs such as pregnancy registries, or other appropriate methods to ensure longer-term data collection on infant outcomes."
Prescrire	353	354	4.2.8	Specify the minimum duration of follow-up	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	357	357	4.2.8	Proposal to change wording from "data collection on infant outcomes" to "data collection on infant/child outcome" as effects could last past infancy.	… data collection on infant/child outcome ...
EFPIA	358	367	4.2.9	This section may require adaptations to differentiate between adverse events due to the medicine being investigated and adverse events due to the pregnancy (e.g., nausea).	Please consider clarifying how sponsors can differentiate the safety monitoring plan taking into consideration adverse events potentially due to the investigational product and adverse events potentially due to symptoms of the pregnancy.
EFPIA	358	358	4.2.9	Safety monitoring for breastfeeding individuals is very detailed. There should also be a safety monitoring plan for infants.	suggestion
International Consortium for Innovation and Quality in Pharmaceutical Development	358	367		This section may require adaptations to differentiate between adverse events due to the medicine being investigated and adverse events due to the pregnancy (e.g., nausea).	Please consider clarifying how sponsors can differentiate the safety monitoring plan taking into consideration adverse events potentially due to the investigational product and adverse events potentially due to symptoms of the pregnancy, and document accordingly.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	358	358	45692	Add a section on IRB /DSMB/monitor training regarding obstetric trials.	The common definition of AE and SAE may be problematic for trials during pregnancy and especially birth (pain, bleeding, infection, hospitalization, c-sections...). IRBs, DSMB and monitors working with this type of trials should have experience and training in this sort of trials.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	358	358	45692	Add a section on IRB /DSMB/monitor training regarding obstetric trials.	The common definition of AE and SAE may be problematic for trials during pregnancy and especially birth (pain, bleeding, infection, hospitalization, c-sections...). IRBs, DSMB and monitors working with this type of trials should have experience and training in this sort of trials.
EFPIA	359	360	4.2.9	Not quite sure where this would go and whether too detailed but maybe there should be some wording around normal laboratory ranges and how they can change in pregnancy (like alk phos for example) and that you need to consider how to interpret those with regard to AEs. Also the need to be able to interpret liver enzyme changes for example which may be due to obstetric issues like obstetric cholestasis and which may be incorrectly attributed to the IMP. That may all be covered by the section which recommends having an obstetrician or fetal medicine expert involved in the protocol and safety review.(i think 4.2.2)	
EFPIA	359	359	4.2.9	Provide examples for "pregnancy-related AEs". It's unclear if you're referring simply to something such as fetal loss, or you also mean to include pregnancy complications such as pre-eclampsia.	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	359	361	4.2.9	"Participants should be closely monitored for pregnancy-related AEs, with appropriate management plans if required." Please amend to discuss that both the mother and the fetus) should be closely monitored for AEs. This goes beyond the traditional concept of pregnancy-related AEs that are often confined to just consideration of maternal hypertension, new-onset diabetes etc. There is plenty of information that can be identified about the fetus and their development using imaging such as ultrasound and fetal heart rate monitoring. This should not be underestimated. See amended text in bold.	"Participants should be closely monitored for maternal and fetal AEs, with appropriate management plans if required."
Pfizer Clinical Research Unit, Brussels	360	361	4.2.9	The impact of the investigational product on the health of the pregnancy and infant … : health of pregnancy sounds unfamiliar	The impact of the investigational product on pregnancy and infant's health …
EFPIA	365	367	4.2.9	The sentence could be misleading i.e that only published data could be sufficient "Sources for the detection of a signal could include clinical trials and post-trial follow-up, from clinical use during pregnancy or pediatric use, or published data, if applicable."	Suggest alternative wording " Sources for the detection of a signal could include clinical trials and post-trial follow-up, from clinical use during pregnancy or pediatric use, and/or– published data, if applicable.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EpiSafe Research Team	367	367	4.2.9	Without recognising background rates, there is a risk of wrongly attributing common adverse pregnancy outcomes to the investigational product. This could lead to inappropriate discontinuation of therapy, misclassification of SUSARs, and biased trial results. Clear guidance is needed to ensure that both investigators and sponsors interpret these outcomes in the correct clinical context.	Suggest new text be added: "When monitoring for pregnancy-related AEs (including miscarriage, stillbirth, congenital abnormalities, and preterm birth), sponsors should recognise these as known adverse outcomes of pregnancy with established background rates. These background rates must be taken into account in study design, safety signal detection, and reporting of SUSARs."
K Richardson	370	371	4.2.10	"whether the efficacy, dosing, and safety of the investigational product in pregnant individuals are similar to the general population."	Propose "...whether the efficacy, dosing, and safety of the investigational product in pregnant individuals are similar to the female population and the wider general population.
EFPIA	371	372	4.2.10	Clarify this is the case for safety and also efficacy. Product labeling should only include data from studies that have been designed with SAP for pregnancy data analysis.	
Gedeon Richter plc.	371	376	4.2.10	The guideline acknowledges that small numbers of pregnant participants can be informative, but does not provide quantitative guidance. Is there a proposed minimum sample size or statistical power recommended for the inclusion of pregnant individuals in clinical trials that would balance the need for safety signal detection with feasibility?	
EFPIA	374	376	4.2.10	It may be better to use different phraseology to capture what you are intending here. It's not that it's difficult, it's that analysis of a pregnant sub-population will likely not be adequately powered so the strength of any conclusion based solely on this small subset analyses may be limited. Therefore, caution is warranted.	
EFPIA	374	376	4.2.10	In addition, PK data from a small set of pregnant participants can help to reinforce data from models approximating exposure in the pregnant population at large. A rewording is suggested.	... In addition, PK data from a small set of pregnant participants can help to validate models approximating exposure in the pregnant population. …
EFPIA	375	376	4.2.10	Additional details on mitigation strategies to tackle the difficulty with interpreting adverse pregnancy outcomes in small populations, such as considering for example the Confidence Intervals, is requested.	
EFPIA	377	383	4.2.10	This paragraph is repetitious with what has been mentioned many times: benefit risk assessment	
EFPIA	380	383	4.2.10	Consider changing "pregnancy" to "pregnant individual and/or fetus" in ….whether and how treating the underlying health condition with the investigational product benefits the pregnancy	….whether and how treating the underlying health condition with the investigational product benefits the pregnant individual and/or fetus
EFPIA	383	383	4.2.10	Guideline states, "…benefits the pregnancy."	Suggest text addition, "…benefits the pregnancy and infant."
EFPIA	386	386	4.2.10	This paragraph would benefit from adding potential confounders and the inclusion is proposed. More specifics around these possible confounders is proposed to be included.	
ENTIS (European Network of Teratology Information Services)	386	386	4.2.10	Emphasizing the underlying disease condition as a confounding factor	Possible confounders, explicitly confounding by indication should also be considered.
EFPIA	387		4.2.10	provide more information on the potential risks within the different trimesters	
EFPIA	389	391	4.2.10	It is proposed to reword this paragraph to faciliate its meaning. Specifically, clarification is requested if such data can be considered acceptable as an alternative to a control arm in a clinical trial involving a pregnant population with the disease.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Certara	392	406	4.2.11	The potential need of dose adjusment should be investigated and added to the considerations for pregnancies occurring during clinical trials. This may need to be re-assessed as pregnancy advances e.g., in case of long term studies	
EFPIA	392	392	4.2.11	Address female partners of a male who is in a study and management of pregnancy related outcomes in this section.	
EFPIA	392	406	4.2.11	Continuing the pregnant patient in the study and remaining on IP has challenges as noted elsewhere in the document, but even continuing off IP may be challenging due to other study requirements such as colonoscopy under anesthesia. How to address without encouraging PDs? I know they reccomend writing the protocol to allow pregnant individuals to not complete some requirements, but these may be key outcomes. Pregnancy may also effect other measurements directly (weight, labs, etc.)	
EFPIA	392	392	4.2.11	While the guidance is focusing on female participants, the data should also be collected on partners or male participants. It is recommended to include some consideration concerning the standard guidance for male contraception and of not impregnating rules.	
EFPIA	394	394	4.2.11	The term "mandatory contraception" is used several times in the document but does not distinguish between "effective" and "highly effective" contraception. Typically, a Sponsor will make a distinction on the level of contraception based on the results of the EFD studies - no risk identified at a nice safety margin, effective contraception; a risk identified at a low safety margin, highly effective contraception. Since pregnancies are currently not desired in clinical trials, sponsors will typically require WOCBP to use some level of contraception so "mandatory contraception" is normally in place for all clinical trials for WOCBP at some level. However, the risks to the embryo/fetus are different.	Consider differentiating between a drug that requires highly effective contraception due to an identified risk versus one that requires effective contraception because of a desire not to have pregnancies in the trial even though an adverse effect has not been identified.
Pfizer Clinical Research Unit, Brussels	399	401	4.2.11	reconsenting as pregnant participant	may require edit depending on the outcome of suggestion to section 4.1.3
Prescrire	399	401	4.2.11	Persistent ambiguity about the objective inclusion criteria for pregnant individuals	The guideline should be more explicit about the criteria that make the inclusion of pregnant individuals definitively unacceptable. These might include a medicine that is teratogenic in at least one animal species, or a medicine with adverse effects that could disrupt the pregnancy (such as preterm birth or hypertension) or impair organ function in the unborn child.
Prescrire	402	403	4.2.11	Despite the goal of reducing the burden of assessments, some of the recommendations (such as repeated evaluations and extended follow-up of the child) may considerably increase the burden on participants, and could jeopardise informed consent by further adding to day-to-day demands.	
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	404	406	4.2.11	We agree that a spontaneous pregnancy should not be an automatic reason for unblinding: Reasons/conditions to do so should be considered during early stages of planing. In that sense, consideration should be given to involve the pregnant participant in the decision to unblind the treatment in her particular case.	Add the consideration to involve the pregnant participant in the decision to unblind the treatment in her particular case
EFPIA	404	404	4.2.11	There should be consideration of local laws and regulations regarding reproductive rights of IOCBP and pregnant individuals.	Please add a statement to consider local laws around contraception when designing studies.
EFPIA	404	404	4.2.11	Does this also apply to pregnant partners when becoming pregnant during clinical trial	Consider to at expectations for pregnant partners in the guideline overall where applicable.
EFPIA	404	406	4.2.11	Regarding the need for unblinding, could the EWG provide some examples for when unblinding is recommended and when it is not recommended. One example may be when highly effective contraception is required and there is a diference in risk between the cohorts, e.g., placebo versus a drug with an identified embryofetal risk.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	407	407	4.3	need a section describing how pregnant participants are educated on the non-clinical and clinical results supporting a trial in pregnancy (acknowledging the ICF section which is later in the document but educating the participants needs to be well planned and done over a specific period of time. They will require time to digest the information and ask questions. Section 4.4, the ICF, should be relatively smooth after the period of education about the non clinical and clinical results.	
EFPIA	407	423	4.3	Two headings on recruitment? - please make these sections shorter	suggestion
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	407	442	4.3	Please add text to recognise the likely intersection of pregnancy with other factors linked to research inclusion which include but are not limited to ethnicity and multiple indices of deprivation, and the consequent need to consider these factors in recruitment and retention to ensure representation of pregnant individuals in trials is reflective of the pregnant population. This is particularly important given the relationship of these factors with high risk pregnancy and adverse pregnancy outcomes. Currently there is recognition of cultural differences but this is not linked to research inclusion and other factors are not considered.	Recruitment and retention planning should consider the need for research inclusion and recognise that pregnancy is likely to intersect with other factors related to under-representation in clinical trials which include ethnicity and multiple indices of deprivation, particularly where these factors are linked to higher incidence of adverse pregnancy outcomes.
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	407	474	4.3	Please include wording that makes it clearer that 'stakeholder organisations' like charities and parent/patient groups specifically should not only be involved at early stages of trial design (to help with recruitment and retention strategies), but also continue to be involved during trial to support with potential / unforeseen recruitment and retention challenges that may occur. They are also key in raising awareness especially for the pregnancy trials where many people are understandably likely to have concerns about participation. Stakeholder organisations should be included on signposting for advice on how best to involve people in Patient Public Inclusion for trials, and participation renumeration etc, not just IRBs and ethics committees who may not have the relevant knowledge.	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	407	474	4.3	There is a gap around processes and guidelines for communicating with pregnant women, birthing people and parents when a pregnancy loss or death of a baby happens during a trial/study. This can happen to seemingly low-risk women as our obstetric tools to predict late miscarriage, preterm birth and stillbirth are poor. This includes speaking to participants about their ongoing involvement and what might happen to their data etc. Please add this in. Having clear communication processes around this difficult time is vital to ensure that the clinical trial is conducted in a supportive and thoughtful way for participants.	
EFPIA	410	416	4.3	The statement serves no purpose - remove?	suggestion
EpiSafe Research Team	410	412	4.3	The original wording risks undervaluing the complexity of autonomy during pregnancy. The revised version recognises the multifaceted experiences and foregrounds the person, it reflects the real-life complexity of decision-making during pregnancy. REF Declaration of Helsinki (2024) highlights that the participant's welfare must always take precedence over the interests of science and society	Replace "a time when social and/or family interests are enhanced compared to the health of a non-pregnant individual" TO "a time of significant physical, emotional, and social change" Replace "Such interests may influence a pregnant individual's autonomy" TO "during which individual autonomy may be influenced by family, societal, or healthcare pressures" NEW SECTION TO READ: "Pregnancy is a time of significant physical, emotional, and social change, during which individual autonomy may be influenced by family, societal, or healthcare pressures. These influences may either unduly encourage or deter participation in a clinical trial."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	411	411	4.3	Guideline states, "…of a non-pregnant individual. Such interests may influence a pregnant individual's autonomy…" "Autonomy" may not be the correct word here. A person retains their autonomy even if they are influenced by others. "Decision" may be a better word.	Suggest replacement text, "…of a non-pregnant individual. Such interests may influence a pregnant individual's decision…"
EFPIA	413	416	4.3	Propose to move this section as additional bullet point to next section.	suggestion
PIPELINE consortium	413	421	4.3	Lines 413-416 could be better linked with the following paragraph, to improve clarity around meaning of "wider awareness". A range of other stakeholders, including researchers other than clinicians (such as social scientists), may have relevant experience in conducting such research and understanding of facilitators and barriers to clinical trial participation.	It is suggested that the text specifically mentions people with lived experience (not limited to "patients' advocacy groups") as well as either expanding the list or indicating that this is just a selected list of groups to engage with.
EFPIA	414	416	4.3	"future pregnant individuals" is essentially any female. To make your point more clearly use precise language that has been well understood generationally in medicines development.	" ... ~~Future pregnant individuals~~ WOCBP with the same disease or condition who may want to become pregnant can help....
EpiSafe Research Team	414	416	4.3	Including "accessible" ensures that study information is understandable and usable by all participants, supporting ethical recruitment and informed consent. Including "how it may benefit the individual's own health and pregnancy" recognises that participants are more likely to engage in research when the personal relevance and potential benefit to their health and pregnancy are clearly communicated. Together, these changes help address concerns, strengthen respect for autonomy, and improve equitable recruitment.	Add "and accessible" to emphasise that information must not only be comprehensive but also understandable and usable by diverse populations. Insert "including" clarifies the scope of what should be covered in study information. Added "and how it may benefit the individual's own health and pregnancy" shifts the focus from purely future benefit to also recognising potential direct benefit to the current participant, which strengthens respect for autonomy and informed decision-making. NEW SECTION TO READ: "Providing detailed and accessible information on the proposed study, including its potential impact on future pregnant individuals with the same condition and how it may benefit the individual's own health and pregnancy, can help address concerns and improve recruitment for these trials."
Global Heart Hub	414	416	4.3	Patient organisations could play a role in the development of culturally adapted materials in lay-terms and the dissemination of the information	n/a
Prescrire	414	416	4.3	Importance of fully informing pregnant individuals and their partners.	
ACRO	417	442	4	ACRO welcomes the emphasis of minimising burden on pregnant and breastfeeding study participants and the recommendation for early engagement with stakeholders, including patients, to address relevant aspects of the trial.	
EpiSafe Research Team	417	417	4.3	This change ensures that people with lived experience are recognised in their own right (not only via formal groups or clinicians). Including them explicitly reflects best practice in inclusive, patient-centred research design. REF Declaration of Helsinki (2024) NIHR UK Standards for Public Involvement (2019), Standard 2	ADD "individuals with lived experience," after "patients' advocacy groups," NEW SECTION TO READ: "Engaging with patients' advocacy groups, individuals with lived experience, organizations managing disease-specific registries,"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Prescrire	417	421	4.3	Risk of exploitation of patient advocacy groups, or muddying their role. Patient advocacy groups are referred to here as channels of recruitment, which may muddy their role as an independent representative and source of support. There is a danger that they will be perceived as jointly running the trial, despite being neither sponsors nor investigators.	
Rebekah Burrow, Department of Primary Care Health Sciences, University of Oxford	417	421	4.3	"Engaging with patients' advocacy groups, organizations managing disease specific registries and clinicians experienced in conducting research in pregnant individuals before clinical trial initiation may help reduce challenges…" This is a statement of fact rather than a guide to do (or not do) something. Clinical trialis for all products where individuals of childbearing potential are among the anticipated user population should be actively involving people with recent experience of pregnancy in trial design. Trialists should be actively attempting to recruit and retain people who are pregnant, and measuring their success in this.	
International Consortium for Innovation and Quality in Pharmaceutical Development	418	419		Sponsors should confirm that study sites have appropriate infrastructure and medical experts for studying pregnant individuals (high risk pregnancy teams, Neonatal ICUs).	Please add text emphasizing the importance of having the right clinical site infrastructure and resources in addition to the 'clinicians experienced' to encourage participation by pregnant subjects. This would include ensuring that the site and investigators are appropriately qualified to see a pregnant patient, factor pregnancy into their study-related decision making and refer patient for follow-up with a pregnancy-related specialist would be important.
EFPIA	419	420	4.3	Sponsors should confirm that study sites have appropriate infrastucture and medical experts for studying pregnant individuals (high risk pregnancy teams, Neonatal ICUs).	Please add text emphasizing the importance of having the righ site infrastructure and resources to encourage participation by preganant subjects.
ENTIS (European Network of Teratology Information Services)	422	423	4.3	ENTIS centers provide specialized, evidence based counseling regarding medicinal and chemical exposures during pregnancy and breastfeeding. They constitute a trusted and safe resource for women in relation to pharmacotherapy during pregnancy. Accordingly, ENTIS should be regarded as part of the multidisciplinary supportive team assisting women in making informed decisions about clinical trial participation and in addressing their concerns, as their involvement may facilitate overcoming recruitment challenges and participation barriers.	Involving potential participants and other stakeholders such as relevant healthcare teams (e.g., obstetric and maternal-fetal medicine professionals) early in the study design stages, could provide input on patient-oriented outcomes of interest and/or reducing burdens for inclusion of pregnant individuals in clinical trials (see Section 4.3.2). In addition, collaboration with organizations such as ENTIS (European Network of Teratology Information Services), which operates specialized counseling centers, could further support recruitment and retention efforts.
EpiSafe Research Team	422	422	4.3	This addition ensures the text explicitly acknowledges that participants with lived experience offer valuable insight distinct from professionals or theoretical participants. It aligns with ethical commitments to respect, relevance, and inclusion in research design, and helps ensure that burdens, outcomes, and recruitment approaches are genuinely informed by those affected.	ADD "including individuals with lived experience," after "potential participants," NEW SECTION TO READ: Involving potential participants, including individuals with lived experience, and other stakeholders such as relevant healthcare teams ...)
EFPIA	427	428	4.3	Correction	Consideration of cultural differences regarding aspects of the birth, cord blood, and placenta (and use of placental samples) may help identify important aspects'
EFPIA	427	428	4.3	Can the EWG think of a scenario where they will expect a non-obstetric IMP trial to add in cord blood analysis and/or placental sampling as endpoints, and the implication of adding such endpoints to identification of non-obstetric researchers (pulmonologists, immunologists, cardiologists) to agree to become a trial investigator? If this is only theoretical, then this example should be deleted as this guideline is specfic to inclusion studies, not obstetric trials.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Consortium for Innovation and Quality in Pharmaceutical Development	427	428		Recommend to add text ‘help’	Consideration of cultural differences regarding aspects of the birth, cord blood, and placenta (and use of placental samples) may help identify important aspects'
EFPIA	428	428	4.3	Suggest deleting "may identify importan aspects" - The meaning is not clear and the remainder of bullet is considered sufficient.	Consideration of cultural differences regarding aspects of the birth, cord blood, and placenta (and use of placental samples) ~~may identify important aspects~~;
EFPIA	429	431	4.3	We welcome the considerations to the use of mobile study visits, virtual telemedicine study visits and home health nurses to aleviate the burden of pregnant individuals after birth, especially considering the post-partum follow-up could take a long time.	No requested change to text
Global Heart Hub	429	431	4.3	Think also of minorities and marginalised groups- what would be needed for them to participate in clinical trials?	n/a
Prescrire	429	431	4.3	Lack of clarity about informed consent in the pre-recruitment phase. This bullet point suggests that HCPs (e.g. midwives and home health nurses) may pass on the contact details of pregnant individuals to sponsors or investigators. This poses a major problem in relation to confidentiality (including medical confidentiality) and the protection of personal data. Personal data must not be transferred without explicit prior consent.	
Prescrire	432	435	4.3	Underappreciation of the social pressure related to pregnancy The idea of “educating” healthcare professionals to encourage participation could easily slide into an implicit moral prescription (“you should take part to help other pregnant individuals...”). At a time when individuals may be vulnerable (due to pregnancy, stress and medicalisation), this may undermine the true autonomy of their decision to take part.	
EpiSafe Research Team	434	434	4.3	Guidance should clarify that HCPs should provide consistent advice and integrate trial participation into routine care to help supprot women.	Suggest new text be added: “Healthcare professionals involved in routine care should provide ongoing support and consistent advice to participants. Training should include awareness of maternal mental health and communication of uncertainties.”
EpiSafe Research Team	438	438	4.3	This addition addresses the need for representativeness in recruitment, especially for diseases with ethnic or regional variation in prevalence. It reinforces that equity in trial participation is not just ethical, but also scientific ensuring relevant safety and efficacy data across populations. REF Declaration of Helsinki (2024) NIHR INCLUDE Ethnicity Framework (2020)	ADD text after "resources": "...while also supporting trust, reducing burden, and promoting fair and respectful participation. Recruitment should aim to reflect the diversity of the population affected by the condition, including ethnicity, language, and other factors, particularly for conditions more common in specific groups."
EFPIA	439	442	4.3	In 4.3 discusses retention of the pregnant individual - and then 4.3.1 recruitment - is a sentence or section needed also for retention/recruitment about sites when additional efforts are needed to follow-up infant outcomes (aka the site has to stay open, the infant is followed-by another provider), etc.	
EpiSafe Research Team	442	442	4.3	A respectful and fair retention approach must prioritise the wellbeing of participants by maintaining regular, agreed communication and avoiding unexpected contact after long periods of silence. This helps prevent distress and promotes trust. Equally, addressing practical and financial pressures (e.g. lost income, childcare, or travel costs) through appropriate reimbursement and compensation is essential to support continued participation and reduce inequity.	Proposed addition (add-on sentence) “Retention strategies should be respectful and fair, with regular, agreed communication rather than unexpected contact after long periods of silence. Practical and financial pressures (e.g., childcare, work commitments, travel costs) should be addressed through appropriate reimbursement and compensation, with safeguarding needs considered where relevant.”

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	443	457	4.3.1	There is no mention in this section of the need for each site to consider the addition of a obstetric sub-Investigator as a core member of their research team.	Add discussion regarding obstetric sub-Investigators.
Prescrire	443	457	4.3.1	Absence of caution in relation to the patient's socioeconomic status and vulnerability This paragraph does not include any specific precautions for limiting biased recruitment of vulnerable individuals, meaning those with precarious backgrounds, with high-risk pregnancies, migrants or individuals with a low level of health literacy and individuals who do not speak the language of the host country. ➞ Risk of exploitative recruitment, in a vulnerable population without adequate support.	
International Advisory Committee on Clinical Trials in Multiple Sclerosis, National Multiple Sclerosis Society, and European Committee for Treatment and Research in Multiple Sclerosis	443	457	4.3.1	The EMA guideline provides general guidelines related to the recruitment and retention of pregnant individuals in clinical trials, but more specific guidance would be helpful (such as how much flexibility could be allowed in study procedures without harming the overall trial).	
PIPELINE consortium	444	445	4.3.1	This applies to obstetric conditions but may be less relevant for other investigational products.	
EpiSafe Research Team	450	450	4.3.1	Helps address patient concern around unexpected contact or pregnancy status being revealed without consent.	ADD ", and appropriate safeguards put in place to ensure this is done respectfully and without causing distress." NEW SECTION TO READ: ...If recruited through obstetric clinics or electronic healthcare records, consideration should be given to local privacy laws regarding disclosing pregnancy status, and appropriate safeguards put in place to ensure this is done respectfully and without causing distress.
EFPIA	451	457	4.3.1	"Recruitment at earlier timepoints of pregnancy……..clinical care or who become pregnant in a trial (see Section 4.1.3)."	Suggest adding scientific justification about the need for early pregnancy data and proactive strategies: "Recruitment at earlier……..to identify through electronic health records or obstetric/antenatal care units. However, first-trimester data collection is critical, being a period of major organogenesis and high risk of teratogenic effects. Reaching out to specialized care physicians……a trial (see Section 4.1.3).
EpiSafe Research Team	457	457	4.3.1	To ensure research is relevant, ethical, and generalisable, recruitment strategies must reflect the diversity of the populations affected by the condition under study. Without proactive efforts to include under-served groups research risks reinforcing health inequities and missing important safety or efficacy data for those most affected.	ADD "Recruitment strategies should also aim to reach diverse populations affected by the condition under study, including efforts to include individuals from under-served communities."
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	457	457	4	...a trial (see Section 4.1.3).	...a trial (see Section 4.1.3). The above mentioned methods for recrutiment are examples and other recruitment ways could also be used.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	457	457	4	...a trial (see Section 4.1.3).	...a trial (see Section 4.1.3). The above mentioned methods for recrutiment are examples and other recruitment ways could also be used.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	458	474	4.3.2	As much as possible, efforts should be made to coodinate study visits with routine prenatal visits to minimize time toxicity for participants	
EFPIA	458	474	4.3.2	Is there any recommendation on using DCT elements, e.g. home care, home nursing etc.. - if local regulations allow of course. Applies t0 5.4.2 as well	May further reduce burden of pregnant individuals
Gedeon Richter plc.	458	474	4.3.2	Could you please clarify whether a sponsor has the right to modify a clinical trial protocol in such a way that pregnant participants are treated under less stringent conditions compared to the general population enrolled in the same study?	
Global Heart Hub	458	474	4.3.2	There is no mention of trial support for pregnant or lactating women – adapted conditions would be needed for visits, etc. The guidelines should outline what is required emotionally, informationally and practically to encourage these patients to participate/ stay in CTs.	n/a
K Richardson	458	458	4.3.2	"Reducing Burden and Harm on Pregnant Individuals in Clinical Trials"	"Harm" not defined or even mentioned in this section. Propose "Reducing Burden and Unacceptable Risks on Pregnant Individuals in Clinical Trials" to align with body text.
Prescrire	459	461	4.3.2	Despite the goal of reducing the burden of assessments, some of the recommendations (such as repeated evaluations and extended follow-up of the child) may considerably increase the burden on participants, and could jeopardise fully informed consent by further adding to day-to-day demands.	
EFPIA	467	467	4.3.2	"teratogenic rescue medications" are not assessments, they are rescue medications. Further, rescue medications are there to assist when there is a known potential risk or when there is no identified benefit from the patient. If these are the only medications that are available for rescue then the more appropriate guidance is that when they are teratogenic, pregnant females should not be recruited into the trial.	" ... ~~teratogenic rescue medications used in the protocol, or medication adjustments~~)"
EpiSafe Research Team	468	468	4.3.2	Acknowledging this possibility and planning sensitively for it supports emotional safety, and avoids retraumatising participants.	ADD "Protocols should outline how study procedures will be adapted in the event of pregnancy complications or loss, and this information should be shared with participants during consent and follow-up."
EFPIA	470	471	4.3.2	Trial investigators are expected to assess the ability of a potential study participant to be a "good" candidate for enrollment and that the candidate has the ability to comply with trial participation. It is unlikely that a pregnant female with a high-risk pregnancy (e.g., history of early fetal demise, history of eclampsia, multi-pregnancy (more than 1 fetus)) would be considered by many non-obstetric investigators to be appropriate for study participation. Suggest replacing this example as it is exceedingly blue-sky.	Replace high-risk pregnancy with something such as gestational diabetes.
EpiSafe Research Team	471	471	4.3.2	Participants and those with prior experience can highlight practical burdens researchers might overlook. Including them early improves the relevance, sensitivity, and acceptability of trial design (particularly important in pregnancy, where care pathways and life demands vary greatly). REF - Declaration of Helsinki (2024) - NIHR UK Standards for Public Involvement (2019)	ADD "Involving individuals with lived experience in designing the research and pathways may improve relevance and reduce unintentional burden."
EpiSafe Research Team	471	471	4.3.2	Reducing burden on participants should also include psychological burden. Explicit reference to mental health support would strengthen safeguards and improve participant experience.	Suggested new text: "Protocols should include measures to minimise stress and support maternal mental health during pregnancy and postpartum. Access to appropriate support services should be considered."
EpiSafe Research Team	474	474	4.3.2	Pregnancy is a time when existing social vulnerabilities (e.g. domestic abuse, housing insecurity, or financial hardship) can increase or become more visible. Clinical trial visits may be one of the few touchpoints where these issues are disclosed. Ensuring that trial teams are trained to identify and respond to safeguarding concerns appropriately helps protect participant wellbeing, uphold ethical standards, and prevent harm.	ADD "Research teams should receive appropriate training to identify potential safeguarding concerns and to follow local procedures for signposting or referral, recognising that pregnancy may be associated with increased vulnerability to social risk factors."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	475	475	4.4	There are no provisions for obtaining a consent from the second parent. The same applies for section 5.5	Please consider also taking into account the opinion of the second parent involved in the pregnancy besides the pregnant or breastfeeding individual, because it is the safety and wellbeing of their child as well
EFPIA	475	521	4.4	Does not mention biological father	Include need to assess consents for father in the event that there is a pregnancy
EFPIA	475	521	4.4	The section should clarify that local regulations is followed considering parental consent.	
EFPIA	476	521	4.4	It seems the role of the father is missing. To which extent this needs to be included in the consent. What if the father get´s custody and does not agree to the baby follow up. Suggest considering the role of the father (except situations of single mothers, children conceived via donors) in the consenting process	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	476	479	4	add that women consent should be enough for her own participation as well as child follow-up (see even above)	No second parent consent is needed for a pregenant woman to participate in a trial. Child follow-up after exposure during pregnancy should not require second parent consent, at least not for procedures that do not cause the child any harm or register-based follow-up.
spm² - safety projects & more GmbH	476	477	4.4	While adaptations to informed consent for pregnant and breastfeeding participants are discussed, more detail on minimum content requirements, especially regarding risks to fetuses or infants, and procedures for updating/reconsenting could provide additional clarity.	
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	476	479	4	add that women consent should be enough for her own participation as well as child follow-up (see even above)	No second parent consent is needed for a pregenant woman to participate in a trial. Child follow-up after exposure during pregnancy should not require second parent consent, at least not for procedures that do not cause the child any harm or register-based follow-up.
EpiSafe Research Team	481	481	4.4	Helps reduce confusion and supports informed decisions during what can be a sensitive and emotionally complex time.	Participants should be clearly informed what supplemental consent involves, how it differs from initial consent, and what changes to participation it may include.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	482	482	4	Are already pregnant	Are already pregnant and plan to continue the pregnancy.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	482	482	4	Are already pregnant	Are already pregnant and plan to continue the pregnancy.
Prescrire	483	486	4.4	The document refers to the need for supplemental consent, but does not specify what support individuals should be given to make an informed decision (independent consultation? reflection period?). It refers to potential post-trial follow-up without discussing the logistic and financial implications.	
EFPIA	487	492	4.4	The paragraph should be amended because the consent form should also include supplemental information on risks and benefits of breast-feeding immediately post-birth, as any woman dosed up to the end of pregnancy is likely to have drug present in the breast milk at birth, even if there is no intention to continue dosing post-birth.	
EpiSafe Research Team	488	488	4.4	Pregnant individuals may interpret risk differently depending on their circumstances and stage of pregnancy. Adding this language ensures consent materials reflect individualised needs, improving clarity and relevance.	This information should be contextualised (eg in terms of gestational age, maternal health status, the condition being studied) to support informed and personalised decision-making.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	492	494	4.4	The guidance provides for the following: "Local guidance on any additional consent requirements should be followed as well as requirements for informed consent for pregnant minors." Important to include that there might be particular situations where certain types of pregnant people should be excluded from study protocol for other reasons not having to do with general inclusion principles, like in the instance of minors or evaluation of someone with mental health issue where consent capacity is diminished; same comment for breastfeeding individuals.	Include language around assessing instances where specific populations of pregnant people should be considered for exclusion for other issues, such as instances where a minor is pregnant or instances where there are serious mental health issues that impact consent capacity.
EpiSafe Research Team	492	492	4.4	Being open about uncertainty builds trust and supports ethical informed consent.	Where evidence is lacking or outcomes are uncertain, this should be explicitly stated in the consent materials.
EpiSafe Research Team	492	492	4.4	Pregnancy is a time of increased vulnerability and responsibility. Communicating risks with sensitivity helps participants feel respected and reduces anxiety.	Consent materials should be in clear and accessible language and delivered in a supportive, non-judgemental manner that recognises the emotional weight of decision-making in pregnancy. Time should be given for questions and reflection.
EFPIA	493	494	4.4	Because it is the first mention of pregnant minors, the guideline should include any other special concerns regarding pregnancy minors and consider pregnant minors in other sections, as minors "bring" a lot other concerns, privacy, parents, etc.	
EFPIA	494	494	4.4	Correction	The consent process should include seeking consent on follow-up of the pregnancy/infant/child.
International Consortium for Innovation and Quality in Pharmaceutical Development	494	494		Recommend to include text ‘on consent on follow- up as needed’	The consent process should include seeking consent on follow-up of the pregnancy/infant/child.
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	496	505	4.4	There is no mention of paternal consent which is particularly important when clinical triallists wish to follow up the neonate and potentially collect samples or even continue treatment. I suggest this is added in as a consideration - it will likely depend on the laws of the country that the trials are being conducted in but consideration of this issue is useful to point out to those desigining clinical trials. Suggested text in bold in the next column	The consent process should seek consent on follow-up of the pregnancy/infant/child. There should be consideration of the potential requirement to seek paternal consent if the study will include interventions on the neonate after birth. This may include information on the planned duration of follow-up and any additional data sources that may be used.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	496	498		Add a strong recommendation on long-term follow-up of the child’s health and development. Add information on registerbased data.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	496	496	45751	"The consent process should seek consent on follow-up of the pregnancy/infant/child." Add information if any specific examinations may be needed in this follow-up.	"The consent process should seek consent on follow-up of the pregnancy/infant/child and specify whether any specific examinations are needed for this follow-up."
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	496	498		Add a strong recommendation on long-term follow-up of the child’s health and development. Add information on registerbased data.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	496	496	45751	"The consent process should seek consent on follow-up of the pregnancy/infant/child." Add information if any specific examinations may be needed in this follow-up.	"The consent process should seek consent on follow-up of the pregnancy/infant/child and specify whether any specific examinations are needed for this follow-up."
EFPIA	500	502	4.4	It should be clarified that the release of the medical records will only be on a need-to-know basis, so the patient doesn't erroneously think she is giving open access to her medical records and that such data will be protected by national data privacy regulations	"The informed consent should also include release of medical records on a need-to-know basis only, to allow the collection of relevant information…."
EFPIA	502	502	4.4	Suggest to add'/child' here as it may be that a longer follow-up period is required for some products	recommandation
EFPIA	502	502	4.4	Propose to change "follow-up information on the infant" to "follow-up information on the infant/child" as effects could last past infancy.	...follow-up information on the infant/child …
EFPIA	506	506	4.4	What test qualifies as a confirmed pregnancy? Home pregnancy test, blood test, or ultrasound?	State whether a home pregnancy test, blood test, or ultrasound is what qualifies as a confirmed pregnancy.
EFPIA	507	507	4.4	In the US for research that is federally funded (45 CFR) and for FDA regulated research (21 CFR), the IRB relies on the respective regulation: "45 CFR 46 Subpart D—Additional Protections for Children Involved as Subjects in Research" or "21 CFR 50 Subpart D–Additional Safeguards for Children in Clinical Investigations", in determining whether one or both parents are to sign the consent (permission) form. Is there a legal requirement for both parents to consent for a fetus?	This guidance should minimally include a statement that regional regulation dictates who (e.g., mother vs. mother and father, et cet) must sign a consent form when a fetus is a part of the research.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	509	509	45751	Add that there should be a plan/offer what to do in case of pregnancy discontinuation. Women should be allowed the decision to discontinue pregnancy and if applicable consent to the foster being examined for e.g. malformations.	
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	509	509	45751	Add that there should be a plan/offer what to do in case of pregnancy discontinuation. Women should be allowed the decision to discontinue pregnancy and if applicable consent to the foster being examined for e.g. malformations.	
EFPIA	514	514	4.4	….pregnant outcome and the health of their infants	Recommandation
EpiSafe Research Team	518	521	4.4	Pregnancy often involves complex care needs. Changes to the trial schedule or procedures may affect physical comfort, medical safety, or the participant's ability to remain engaged. Reconsent ensures the participant agrees to these new conditions with full understanding.	ADD A BULLET POINT AND TEXT "When trial procedures or schedules change in a way that may impact a pregnant participant's care, burden, or safety (e.g. additional visits, new procedures, changes to monitoring)"
EpiSafe Research Team	518	521	4.4	Pregnant participants must be informed if new data indicates increased risk to them or the fetus, even if the finding emerges externally. This empowers them to reassess participation with updated knowledge and reduces the chance of unintentional harm.	ADD A BULLET POINT AND TEXT "When a new pregnancy-specific safety signal emerges related to the investigational product, whether from the same trial or another source."
EpiSafe Research Team	518	521	4.4	Continuity of care is crucial in pregnancy. A change in care setting (eg bacause of access to specialist services, or patient choice) may alter communication or access to trial procedures. Reconsent helps maintain transparency and patient control when coordination across settings becomes more complex.	ADD A BULLET POINT AND TEXT "When a participant transitions to a new care provider or facility during pregnancy or birth, affecting how trial coordination will occur."
EFPIA	523	560	5.1	The composition of colostrum and foremilk are more fatty. Suggest to collect breastmilk samples after 2-3 minutes of lactation.	to ensure collection of breastmilk w more similar composition
EFPIA	523	560	5.1	There is no mentioning of sample size considerations for breastfeeding as opposed to pregnant individuals. Please consider samle size	suggestion. Please consider sample size

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	523	523	5.1	The known benefits of breastfeeding both for the mother and the infant should be considered in this section as part of the Benefit-Risk assessment.	
EFPIA	524	524	5	Proposal to rename the section heading to become "Lactation" rather than Breastfeeding as it discusses both breastfeeding as well as it gives consideration to breastmilk.	
Prescrire	524	560	5.1	This section treats breastfeeding primarily as a pharmacokinetic vector, and does not adequately acknowledge the nursing individual's own priorities, the importance they place on the expected benefits and potential risks, their choices and personal values, their lifestyle, and their lived experience if they have to temporarily stop breastfeeding due to the trial, etc. This approach is overly biomedical and insufficiently centred on the lived experience of breastfeeding individuals. Changes to breastfeeding can affect the mother-child bond and produce stress or feelings of guilt. This subjective experience must be taken into account in clinical trials.	
EFPIA	526	526	5.1	Clarification is requested if it is "child" or should be infant for consistency.	
EpiSafe Research Team	528	528	5.1	Women's feeding decisions are shaped by more than clinical pharmacology. Emotional, cultural, and practical factors — including feeding intentions, the ability to express milk or use formula, and the impact of treatment on maternal comfort — all influence real-world decision-making. Some medicines may reduce milk supply, or indirectly affect infant feeding (e.g. through effects on latch, oral development, or maternal pain), which in turn can compromise breastfeeding success. Ignoring these lived realities risks distress, early cessation of breastfeeding, non-adherence, or withdrawal from trials. Including these considerations ensures that benefit–risk decisions align with participants' values and practical realities, promoting both safety and trial retention.	ADD TEXT "These considerations should also include the values and preferences of breastfeeding individuals (e.g. feeding intentions, cultural context, and practical ability to implement alternatives), as well as potential effects of the investigational product on milk production or infant feeding."
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	529	529	45662	Add on consent, woman consent should be enough, it is her decision whether to breastfeed and take a medication/participate in a study. The child is already exposed.	
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	529	529	45662	Add on consent, woman consent should be enough, it is her decision whether to breastfeed and take a medication/participate in a study. The child is already exposed.	
EFPIA	530	535	5.1	These bullets read awkwardly	Consider alternatively: "· Obtaining information on how drugs the transfer of investigational product into breastmilk (either without or without investigational product drug exposure to the infant, as discussed in Sections 5.2.1 and 5.2.2, respectively); · Subsequently, inclusion of breastfeeding individuals in clinical trials in the general population after the investigational product's characteristics related to breastfeeding have been determined (as discussed in Section 5.3).
EFPIA	533	535	5.1	This does not necessarily need to be a 2-step approach, suggestion to rephrase.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ENTIS (European Network of Teratology Information Services)	536	540	5.1	Using permissive rather than restrictive language in clinical trial guidelines acknowledges clinical uncertainty without unnecessarily discouraging participation or treatment. In the context of breastfeeding, such language allows room for individualized decision-making and highlights the recognized health benefits of breastfeeding for both mother and child. Emphasizing these benefits ensures that guidance supports balanced risk–benefit considerations, rather than defaulting to avoidance in the absence of data.	The clinical development strategy for investigational product use in breastfeeding should be tailored to the stage of development and existing knowledge about the investigational product. In considering whether, and at what stage, to allow infant exposure through breastmilk, it is important to balance potential risks with the well-established benefits of breastfeeding for both mother and child. Whenever feasible, study designs should seek to preserve breastfeeding while ensuring adequate protection of the infan
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	536	536	45662	All women stop breast-feeding at a point. Many women who stopped medication due to lacking evidence during breastfeeding should be specifically offered to participate in a trial on measuring breatmilk concentration when they plan to stop breastfeeding for re-introduction of medication.	
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	536	536	45662	All women stop breast-feeding at a point. Many women who stopped medication due to lacking evidence during breastfeeding should be specifically offered to participate in a trial on measuring breatmilk concentration when they plan to stop breastfeeding for re-introduction of medication.	
EFPIA	538	540	5.1	If breastmilk is replaced with formula or other supplemental nutrition, the study may not accurately represent breastfeeding women. While postpartum women may still be included, those who are not breastfeeding will likely return to prepartum levels of exposure to the investigational product relatively quickly. This raises concerns about the validity of the data collected regarding the effects of the investigational product on breastfeeding individuals.	We recommend clarifying the intent of this statement. It would be beneficial to specify the implications of replacing breastmilk with formula in the context of studying breastfeeding women, as well as to address how this decision may impact the overall study design and outcomes.
EpiSafe Research Team	540	540	5.1	Involving individuals with lived experience in research design helps ensure study procedures are acceptable and contextually relevant, which supports recruitment, retention, and rellevance. REF Crocker JC, Ricci-Cabello I, Parker A, et al. (2018). Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis.	ADD TEXT "Engagement of individuals with lived experience of breastfeeding in the planning and design of research can help ensure that emotional, cultural, and practical factors are appropriately considered. Such involvement may improve protocol feasibility, enhance relevance to the target population, and help minimise unintentional participant burden."
Certara	545	547	5.1	"Of note, there may still be a need to understand how the product may affect lactation or the breastfed infant, even if the medicinal product is not to be used in pregnancy." This seems a bit strange and it does not become clear later on in the document in which cases this need to understand would prevail.	This statement should be clarified
EFPIA	545	547	5.1	A generic example on how such planning may optimize the clinical development strategy would be beneficial.	
EpiSafe Research Team	545	545	5.1	Lived experience can help anticipate burdens such as expressing milk under time pressure, feeding disruption, or practical logistics. Without this input, protocols may include avoidable demands or misjudge acceptability, leading to dropout or poor recruitment.	ADD TEXT "Such planning should be inclusive of input from individuals with lived experience of breastfeeding, to ensure protocols are feasible and minimise distress or disruption to feeding practices."
Pfizer Clinical Research Unit, Brussels	547	547	5.1	… even if the medicinal product is not to be used in pregnancy: please confirm that pregnancy and not breastfeeding period is meant in this sentence	it seems logical to adress product use during breasfeeding period when making reference to the need to understand how product may affect lactation or the breastfed infant
EFPIA	548	555	5.1	This paragraph recommends ways to collect data, but does this imply that ALL of the listed ways are required to be used or is it acceptable to use a few of them?	State whether all need to be used or it is acceptable to use a combination of a few of them.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	551	551	5.1	Prematurity is a relevant infant factor that should be considered and prepoerly discussed, keeping in mind the expected differences with full-term infants, not only with the general study population.	"...and infant factors, ~~such as~~ e.g., differences due to infant metabolic pathways, or gestational age/prematurity)"
EFPIA	556	556	5.1	What trials exactly are we talking about?	Clarify if Phase II and III are the ones refered to by "efficacy".
EFPIA	556	558	5.1	The safety profile in the child might be different if there was exposure during breastfeeding only or during both pregnancy and breastfeeding as overall exposure as well as time of exposure during ontogeny might have an effect.	
EFPIA	556	557	5.1	A risk to the interpretation of the lactation data because of potential exposure through placental transfer via late pregnancy exposure is seen and, thus, the proposed approach should not be encouraged.	
EFPIA	558	558	5.1	The immediate post partum period would give data on transfer to colostrum and would not reflect the entire breastfeeding period. The value of such data is questionable.	
EFPIA	559	560	5.1	Although we aknowledge the benefits of conducting lactation studies which permit to gather data on concentration in the breast milk without exposure to children, there is a burden for women to continuously express milk via pumping, with the level of tiredness this entails, in addition to having to take care of a newborn. In addition, the guideline states on lines 760-761 (section 5.4.2): 'Encourage participants to pump and store breastmilk prior to dosing such that the infant can be fed for several hours to a day or more with pre-study milk' - this is extremely burdensome for the mother as it is not always feasible, depending on the amounts the mother is able to produce, to pump breastmilk and also feed the child during the day.	The guidance should recognize the burden and the constraints and offer support whenever the mother has to pump and store breastmilk.
International Consortium for Innovation and Quality in Pharmaceutical Development	559	560		Although we acknowledge the benefits of conducting lactation studies that permit gathering data on concentration in the breast milk without exposure to children, there is a burden for women to continuously express milk via pumping, with the level of tiredness this entails, in addition to having to take care of a newborn. In addition, the guideline states on lines 760-761 (section 5.4.2): 'Encourage participants to pump and store breastmilk prior to dosing such that the infant can be fed for several hours to a day or more with pre-study milk' - this is extremely burdensome for the mother as it is not always feasible, depending on the amounts the mother is able to produce, to pump breastmilk and also feed the child during the day.	The guidance should acknowledge the burden of expressing breastmilk for the purposes of a clinical trial, and recommend that Sponsors provide appropriate support services to reduce the burden of trial participation on mothers and their children”
EFPIA	565	567	5.1.1	Given that this is an invasive method applied to the pediatric patient population, the study should be conducted in accordance with the specific obligations for pediatric development, when feasible.	(3) collect infant exposure, safety, and benefit data, ~~as applicable~~ as feasible~~–~~ (e.g. in a substudy in compliance with ICH E11(R1))
EFPIA	566	566	5.1.1	What would be considered benefit data in drug exposure over breast milk for newborns/ infants?	
EFPIA	566	566	5.1.1	Can the EWG please provide an e.g. to the text of what infant "benefit data" is? If there is none envisaged and this was an error, please delete.	
ACRO	573	577	5	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 would recommend 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.	Recommendation: inclusion of examples of participant-centric considerations such as the principle that, where possible, breastfeeding should be established before an individual is recruited into a trial.
EFPIA	573	573	5.1.1	Milk composition and quantity may also vary across individuals - some women produce more milk than others, some struggle with lactation whereas others overproduce. This should also be taken into account in the assessment.	Suggest rephrasing: 'Milk composition and quantity may vary during lactation and across individuals,...'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	573	576	5.1.1	There will also be inter-individual variability in the amount of milk produced adding to the variability. Please consider giving advice on gauging the daily output.	
International Consortium for Innovation and Quality in Pharmaceutical Development	573	573		Milk composition and quantity may also vary across individuals - some women produce more milk than others, some struggle with lactation whereas others overproduce. This should also be taken into account in the assessment.	Suggest rephrasing: 'Milk composition and quantity may vary during lactation and across individuals,...'
EFPIA	578	590	5.1.2	This section really only considers small molecule approachs that do not require the use of primates. Animal ethics should be considered here, as the conduct of a juvenile study in non-Human Primates (NHPs) requires removal of the infants from their mother at a very young age and may require them to be shipped with their mother, as well as being very long and costly studies. Some consideration of the benefit-risk of using juvenile NHPs to generate such data vs the risk of a Weight of Evidence approach to provide a rationale for why exposure via mother milk should not be adverse. It is also not standard practice to continue dosing the mother during lactation in NHP ePPND studies - if this is to be considered from now on, it should be very clear.	
EFPIA	581	583	5.1.2	The PPND study does not directly measure quality and quantity of milk, only indirectly through body weight development of the offspring.	delete mentioning of milk quantity and quality
EFPIA	581	582	5.1.2	The sentence is not complete as written. The study also provides information on the amount of transfer of the investigational product to breast milk.	This study provides information on the transfer of investigational product to the breastmilk and the effects of the investigational product on both the pups (e.g., adverse effects on pups) and lactation (e.g., milk quality and quantity) that can characterize the potential risk(s) to a neonate.
EFPIA	582	583	5.1.2	This section should be aligned with ICH S5(R3) discussion on animal milk levels significance for human milk levels of a pharmaceutical. Additional considerations on species differences in exposure and uptake from milk (e.g. IgG-containing FcRn uptake).	Clarify that a direct quantitative correlation cannot be made between animal and human milk drug levels.
Certara	588	590	5.1.2	This is the only time that PBPK modeling is cited - The gudance refers to ICM-M15, however it should be cited throughtout where PBPK modelling can be used. This is necessary because timing, milk composition, consideration of physicochemical parameters, etc can be assessed using PBPK i.e. (1) before any clinical data are collected; (2) Maternal sample only - using IDD to predict infant expsoures; (3) Maternal/infant study - using PBPK for untested scenarios to complement clinical lactation data. The tutorial presented by Pansari et al. 2024 could be used as reference. Link to such tutorial is provided in the Proposed changes/recommendations column (G24) Moreover, it recommnedations on the use of PopPK and QSP modelling should be included in the guidance.	A tutorial on physiologically based pharmacokinetic approaches in lactation research - PubMed
Certara	592	625	5.2	It is not clear when a lactation study is required and in which cases either "mother only" or paired (mother + infant)" study are expected to be conducted. Indications on how to measure the infant dose is missing	Clarify the situations where each type of lactation studies is required. A framework would be useful
EpiSafe Research Team	592	592	5.2.1	It is important to differentiate between levels in maternal milk and levels in the infant - these are not the same	Include distinction in section
EFPIA	596	596	5.2.1	For healthy volunteers, it should be noted that the participants should be exposed to the same drug levels as patients to appropriately inform milk data.	
EFPIA	597	598	5.2.1	There is some inconsistency in the document as here it states that lactation studies are a "prerequisite" for breastfeeding studies but nowhere in 5.3 does it indicate this. In fact, it states that these studies can be done under certain circumstances.	Please clarify.
EFPIA	597	598	5.2.1	This statement appears quite strong. Please clarify whether there are scenarios where infant exposure via breastfeeding could be assessed without conducting a dedicated lactation-only study. For example, if non-clinical data or data from similar compounds support a lack of risk to the infant, could that be considered sufficient?	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	604	605	5.2.1	As predictions especially in preterm and term neonates are still not reliable, see e.g. https://www.sciencedirect.com/science/article/abs/pii/S2468111319300222, has the ICH group any suggestions how this can be safely used?	
EFPIA	609	610	5.2.1	It is not clear from this sentence whether it is also required for participants to abstain from breastfeeding their infant. Clarification needs to be provided whether it refers to post-marketing and what is meant by "part of clinical care".	
EFPIA	609	610	5.2.1	We propose to amend the sentence by adding "and should take into consideration the long term benefits of breastfeeding for the mother and infant"	… Lactation studies that assess product levels in maternal milk only can also be conducted in breastfeeding individuals who are taking a medicinal product as part of clinical care and should take into consideration the long term benefits of breastfeeding for the mother and infant.
EFPIA	611	611	5.2.2	Breastmilk collection from nursing mothers should be restricted to only the necessary amount, with careful attention to how it might impact the infant’s ongoing milk supply	Please add
Prescrire	619	620	5.2.2	Or rather the overall benefit-risk profile, for the mother and infant, and monitoring of the infant (2).	
EFPIA	620	620	5.2.2	section talks about the need for a favorable benefit-risk for the infant in order to be included in the breastfeeding studies. Are there instances where the infant does not gain benefit from the drug but the risk is minimal and acceptable where the infant can be enrolled in trial?	
EFPIA	621	622	5.2.2	As predictions especially in preterm and term neonates are still not reliable, see e.g. https://www.sciencedirect.com/science/article/abs/pii/S2468111319300222, has the ICH group any suggestions how this can be safely used?	
EFPIA	621	622	5.2.2	Addition of mode of action of the product is proposed	
EFPIA	622	622	5.2.2	To provide an example of relevant modeling	and modeling to predict absorption in the infant *(including Pharmacokinetic/Pharmacodynamic relationship in non pregnant and pregnant species for nonclinical studies)*
Gedeon Richter plc.	622	624	5.2.2	Can you please clarify what methods of blood collection should be used to avoid excessive blood sampling in infants?	
ACRO	626	626	5	ACRO welcomes the inclusion of subsection 4.2.2 describing the expertise needed to support study design and safety monitoring for studies in pregnancy. ACRO would recommend a similar subsection is included in section 5, reflecting the need for expertise to support the studies involving breastfeeding individuals.	Recommendation: inclusion of a similar subsection to 4.2.2 within section 5, reflecting the need for expertise to support the studies involving breastfeeding individuals.
EFPIA	626	626	5.3	In section 5.2.1 the guideline states that for these inclusions the sponsor need as pre-requesite to have lactation studies (maternal exposure only), but in section 5.2.2 these are cited as possible with exposure of breastfed infant provided that data support a favorable benefit-risk profile, such data may include lactation data but doesn't seem mandatory. Clairification is required.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Prescrire	627	634	5.3	The inclusion of breastfeeding individuals should be restricted to situations in which the disease studied is directly related to breastfeeding (e.g. mastitis or breast pain), since the breastfed child is exposed to the investigational product without receiving any direct benefit. In trials that include nursing individuals, the breastfed child becomes jointly exposed without being able to give consent. The mother gives consent on the child's behalf, without necessarily being able to fully assess the implications (the effects may be delayed or impossible to measure in the short term). Restricting trials to cases in which the treatment is intended to directly improve the breastfeeding individual's health makes the consent more ethical. Even low concentrations may be problematic for a preterm or unwell breastfed child. (Restricting inclusion to situations where it is strictly justified prevents dangerous exposure from becoming the norm) Pumping breastmilk, discarding it and subjecting a breastfed child to testing all put a considerable mental and emotional burden on the mother. (Participation should be considered only in situations where this burden may be outweighed by a direct benefit) For a benign condition unrelated to breastfeeding, the burden may become disproportionate.	
EFPIA	630	632	5.3	Guidelines states, "…trial if they demonstrate no clinically relevant transfer of the investigational product into breastmilk or when there is no clinically relevant absorption in the infant." Testing the absorption in the infant is not ethically appropriate (absent the exception noted above) if there is a clinical relevant amount of the investigational product in the breastmilk. The phrasing does not capture the ethical ordering of these studies.	
EFPIA	631	632	5.3	The term "clinically relevant" is a vague term and could be taken as requiring data using the agreed primary endpoint parameter(s). Clarification is requested on what is needed here. The term "pharmacologically relevant" is considered more useful, as this then would allow Sponsors to define the concentrations at which the drug can no longer induce the expected pharmacology in vitro.	
EFPIA	632	634	5.3	Please consider adding the following sentence	and/or if benefits to the mother form the drug outweigh the risks without a significant effect on an infant
EFPIA	633	634	5.3	Guidelines states, "…when the infant has a potential benefit from investigational product exposure that outweighs the potential risks." This statement is unclear and potentially harmful. The infant NEVER benefits from exposure to the investigational product. The benefit is from the breast milk.	
EFPIA	633	633	5.3	section talks about the need for a favorable benefit-risk for the infant in order to be included in the breastfeeding studies. Are there instances where the infant does not gain benefit from the drug but the risk is minimal and acceptable where the infant can be enrolled in trial?	
EFPIA	635	638	5.3	Is the EWG expectation that there is a minimum number of participants that is required?	Please clarify in the text
EFPIA	636	636	5.3	It is proposed to add "PK/exposure" following "dose".	...trials may allow for evaluations of whether dose, PK/exposure, efficacy, …
EFPIA	639	639	5.3.1	Request for clarification in this section about the possibility to consider use of milk supplement for the baby during the study (versus exclusive breastfeeding).	
EFPIA	640	641	5.3.1	Please provide guidance on what to "assess" for safety in exposed infants. Is there a set of relevant endpoints that have been identified (provide reference) that are generalizeable or is additional text required to denote that you are talking about the known profile of the IMP (e.g., B-cell depletion and the ability of the infant to mount an adequate response to a pathogen).	Please clarify in the text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	641	644	5.3.1	Guidelines states, "When there is reasonable scientific assumption that the investigational product may not be meaningfully absorbed from breastmilk or the potential benefits for mother and infant outweigh any potential risk to the infant, the protocol could allow a choice for participants to keep breastfeeding." The issue in this statement is the lack of ethical clarity. The lack of the investigational product in the breastmilk should be tested, not assumed, prior to the infant exposure. Absent these data, a risk/benefit assessment of continued breastfeeding cannot be determined.	
EFPIA	641	644	5.3.1	How is 'reasonable scientific assumption' determined? What sources of information (gestault, theoretical, nonclinical, clinical, other)?	Please clarify
EFPIA	642	642	5.3.1	Proposal to change 'absorbed from breastmilk' to 'absorbed following breastmilk intake'	… be meaningfully absorbed following breastmilk intake or the …
EFPIA	647	651	5.3.1	This comment is specific to the safety monitoring aspect of the sentence, not the design aspect. A typical DMC typically includes a statistical expert, disease experts and experts in the therapeutic area(s) to advise on issues related to known/identified/emerging risks. It would be unusual to include other specialists unless there is an identifiable reason to do so. Breastfeeding specialists are not typically the experts who would be suited to weigh in on pediatric growth and maturation milestones in the exposed breastfed infant? Given this, this paragraph should be revised to use language such as "when necessary", "where appropriate", et cet.	
EFPIA	649		5.3.1	(e.g., specialists in breastfeeding and breastfeeding support)	We recommend considering adding: such as neonatalogist and pediatrician
EFPIA	649	649	5.3.1	Guideline states, "…(e.g., specialists in breastfeeding and breastfeeding support)…" Notably absent here are specialists who can assess the impact on the neonate of the potential exposure to the investigational product.	
EFPIA	649	649	5.3.1	Who are "specialists in breastfeeding and breastfeeding support" - MDs, nurse lactation specialists, other?	Clarify or list the credentials required for these specialists.
EFPIA	652	653	5.3.1	This guideline has now added a request for an obstetric expert, a lactation expert, a breastfeeding specialist and a neonatal/pediatrician to the study team. The EWG should revisit all of these recommendations and draft a more pragmatic recommendation as to what is essential for a trial that is inclusive of pregnant and/or lactating women. It is highly unrealistic to expect that every trial will bring in the full complement of experts on the program team level (the number of available experts are low) AND at the level of the site investigators research team (the number of available experts is low and the additional cost to the site overhead is high).	
EFPIA	661	663	5.3.2	Guideline states, "In addition, studies to assess alterations to the breastfeeding strategy (e.g., timing of breastfeeding the child), in relation to dose regimen should be considered, if applicable." Such alterations would only be possible if we have an understanding of the variation of the product to be found in breastmilk through well-designed milk only studies. In addition, such studies would only be necessary (or even reasonable to consider) if product is found in the breastmilk in any appreciable amount.	
EFPIA	661	663	5.3.2	Breastfeeding is usually recommended ad libidum according to infant needs, so we assume this means alterations to the dose regimen in relation to breastfeeding and not the other way around?	
EFPIA	664	0	5.3.2	When assessing outcomes related to lactation, fluid intake may need to be monitored or specified when evaluating breastmilk production/ quantity. May also need to prohibit or monitor for herbs/ other substances known to impact breast milk production.	
EFPIA	668	671	5.3.3	This paragraph should be presented as an example of a case where the evaluation/endpoints have to be adjusted due to breastfeeding.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Prescrire	668	671	5.3.3	This paragraph approaches breastfeeding from a technical perspective, failing to acknowledge the physical, emotional and relational impact of interrupting breastfeeding. There is no reference to support measures or specific precautions to be taken when considering interruption of breastfeeding. There is no recognition of the fact that pumping and discarding breastmilk may be physically uncomfortable, or that interrupting breastfeeding may result in lower milk production or disrupt the mother-child bond. ➡ This violates the principle of doing no harm to a practice (breastfeeding) that is recognised as beneficial. The breastfeeding individual is asked to make a disproportionate sacrifice for protocol-planned assessments that could be postponed or avoided altogether. This raises doubts about whether participation is ethical.	
EFPIA	672	673	5.3.3	Sponsor should select relevant outcomes of interest related to breastfeeding: guidance not specific enough	Recommend standardizing maternal and infant endpoints for lactation/PK studies. E.g. Breastmilk PK, infant PK, relative infant dose, infant feeding behaviour...
EFPIA	672	672	5.3.3	What are the ICH defined relevant "outcomes of interest related to breastfeeding"? As this section is not about breastfeeding or milk lactation studies but rather about when including breastfeeding females as part of a larger study population, the EWG should strive to define why breastfeeding outcomes should be captured in a non-obstetric study (e.g., hypertension, hypercholesterolemia, asthma, rheumatoid arthritis). It would seem that this paragraph does not belong here and should be deleted, or (a) should be moved to the relevant section of the guideline or (b) at a minimum requires more explicit guidance on what the EWG wants studied and why the EWG believes that these assessments can and should be accurately/adequately conducted by non-obstetricians.	Provide examples of "...outcomes of interest (e.g., XXX, XXX, and/or XXX) ..."
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	672	677	5.3.3	Please note there is now a specific AE terminology available to define and grade the impact of IMPs on lactation: the Lactation and Breastfeeding Adverse Events Terminology (LABAET). This was developed with definitions and newly developed terms mapped to MedDRA. Grading was done through internatational consensus and a Delphi process. https://internationalbreastfeedingjournal.biomedcentral.com/articles/10.1186/s13006-025-00743-3 Maksym, K.M., Kalita-Kurzyńska, K., Spatz, D. et al. Development of lactation and breast/chestfeeding adverse event terminology (LaBAET) through a Delphi consensus approach. Int Breastfeed J 20, 53 (2025). https://doi.org/10.1186/s13006-025-00743-3 The terminology includes 3 new definitions to describe delayed secretory activation, primary lactation insufficiency, and secondary lactation insufficiency. Please add in the amended text as per next column	"Impact on lactation itself should be evaluated (e.g., effects on breastmilk production, delayed secretion and oversupply)." Add in specific mention of the LABAET terminology
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	675	675	5.3.3	Prematurity is proposed to be specifically mentiond as a relevant infant condition	"...other medical conditions of the mother or infant (e.g., prematurity), …"
Certara	678	682	5.3.3	It is not clear ow the PK data are expected to be analysed and what does the sentence about collecting data from "other breastfeeding study participants to enanche the dataset" means.	Clarify the paragraph meaning and the Regulators' expectations
EFPIA	678	682	5.3.3	This paragraph is presumptively about how to utilize PK data, that may have been collected from a breastfeeding subset included in a confirmatory trial, to complement specific PK data captured in a trial specific to breastfeeding females. If so, please revise to succinctly relay your message.	
EFPIA	678	679	5.3.3	Suggest to include modelling in addition to sparse PK as approaches that could enhance the dataset.	Sparse PK sampling as well as modelling approaches can be useful to supplment detailed PK data to enlarge the patient population studied.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Prescrire	678	682	5.3.3	The breastfed child is treated as an experimental model. There is no reference to their well-being, biological rhythm or attachment, or to the parent's decision to pursue exclusive breastfeeding. ➞ This runs counter to the patient-centric approach (or an approach centred on the mother-child bond).	
EFPIA	681	682	5.3.3	The necessity of this data collection is questioned and if done, it could bring discrepancies into the dataset.	
Prescrire	684	703	5.3.4	The monitoring of adverse effects in breastfed children exposed through breast milk is not clearly defined. If the evaluation criteria, frequency and duration are not defined, there is a risk of inconsistent data collection and ethical uncertainty for the families concerned. Propose a framework for monitoring adverse effects (e.g. short-term and long-term evaluation criteria, minimum monitoring period) and procedures for obtaining supplemental consent as the breastfed child grows up. The guideline refers to follow-up of breastfed children exposed through breast milk, but without setting out a clear framework, for example regarding its duration, the nature of the data collected and long-term consent. This is important, since long-term effects can occur, and poorly managed follow-up may lead to overmedicalisation or an invasion of the child's privacy.	
EFPIA	693	693	5.3.4	Here we believe the EWG means infant and not child as this is a breastfeeding section. How does one measure the "general well-being" of an infant?	Either delete or provide guidance/examples of what is meant by "general well-being" in an infant.
Gedeon Richter plc.	693	698	5.3.4	Duration and type of pediatric follow-up remain vague in the guidance. Is there a minimum follow-up duration recommended for exposed children in case of potentially long-term effects?	
EFPIA	697	698	5.3.4	The practice of monitoring the effect on lactation and the child beyond the duration of the trial should be encouraged.	No requested change to text
EFPIA	697	698	5.3.4	The safety profile in the child might be different if there was exposure during breastfeeding only or during both pregnancy and breastfeeding as overall exposure as well as time of exposure during ontogeny might have an effect.	
EFPIA	699	703	5.3.4	Interpretation of the causality of AEs in the infant exposed to investigational product during breastfeeding should be made with caution and take into consideration any medical condition of the infant and other confounding factors (e.g., maternal diet, concomitant medicinal products or need for supplemental nutrition with formula or other supplement), and any prior in utero exposure	Suggest emphasizing the importance of using robust epi methods & external control data since in most cases, direct trial data will be limited: "Interpretation of the causality of AEs in the infant…… or need for supplemental nutrition with formula or other supplement), and any prior in utero exposure. Where direct trial data are limited, robust epidemiological methods, the judicious use of external control data, and use of real-world evidence if and when applicable are essential to strengthen causal inference regarding infant outcomes."
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	700	701	5.3.4	Prematurity is proposed to be specifically mentiond as a relevant infant condition	"…take into consideration any medical condition of the infant (e.g., prematurity)
EFPIA	701	701	5.3.4	Guideline states, "(…concomitant medicinal products…" Unclear if this is referring to medication taken by the breastfeeding parent, or also in case the infant is taken medication for a specific condition.	Suggestion to clarify if concomitant medicinal products refer to medication the breastfeeding parent and/or the infant is taken.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	702	703	5.3.4	Guideline states, "…and any prior in utero exposure." Generally, it can be assumed that an infant who is exposed during breastfeeding has also been exposed in utero.	
EFPIA	704	704	5.3.5	Is this header accurate? There is no discussion of the 'Discontinuation and Suspension of Treatment' - the discussion of discontinuation is in reference to breastfeeding.	
EFPIA	706	709	5.3.5	Breastfeeding is usually recommended ad libidum according to infant needs, so we assume this means alterations to the dose regimen in relation to breastfeeding and not the other way around?	
EFPIA	713	713	5.3.5	Clarification is requested if "exposed child" should be "exposed infant".	
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	714	799	5.4.1	There is no mention about lactation trials for preterm neonates, or the possibility of enrollment on a lactation trial and then having a preterm baby. It is important to consider the practicalities, for example the exclusion criteria or the possibility of breastfeeding of a surviving twin or triplet from a multiple pregnancy.	Please add in suitable wording to address this issue thank you.
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	714	799	5.4.1	There is a gap around processes and guidelines for communicating with pregnant or lactating women, birthing people and parents when a pregnancy loss or death of a baby happens during a trial/study. This can happen to seemingly low-risk women as our obstetric tools to predict late miscarriage, preterm birth and stillbirth are poor. This includes speaking to participants about their ongoing involvement and what might happen to their data etc. Please add this in. Having clear communication processes around this difficult time is vital to ensure that the clinical trial is conducted in a supportive and thoughtful way for participants.	Please add in suitable wording to address this issue thank you.
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	714	799	5.4.1	Please include wording that makes it clearer that 'stakeholder organisations' like charities and parent/patient groups specifically should not only be involved at early stages of trial design (to help with recruitment and retention strategies), but also continue to be involved during trial to support with potential / unforeseen recruitment and retention challenges that may occur. They are also key in raising awareness especially for the pregnancy trials where many people are understandably likely to have concerns about participation. Stakeholder organisations should be included on signposting for advice on how best to involve people in Patient Public Inclusion for trials, and participation renumeration etc, not just IRBs and ethics committees who may not have the relevant knowledge.	Please add in suitable wording to address this issue thank you.
Prescrire	716	741	5.4.1	This section does not take into account the possible influence of family members or social norms on the decision of nursing individuals to take part in a clinical trial. In many contexts, decisions concerning breastfeeding or participation in a clinical trial are also influenced by friends and family, which can restrict the patient's ability to decide freely.	
EFPIA	717	717	5.4.1	"enrollment in lactation studies...." does this include breastfeeding studies?	
EFPIA	737	737	5.4.1	Guideline states, "For clinical trials in which infants are exposed to investigational product through breastmilk, …" This risk to the infant is not solved by a more robust informed consent process.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
K Richardson	740	741	5.4.1	"The purpose and types of study procedures should be clearly explained to participants."	Propose "The purpose and types of study procedures should be clearly explained to participants, including those intended to be performed on infants."
EFPIA	742	763	5.4.2	If participating in a lactation study in which some amount of breastmilk cannot be used for feeding, add provision of supplementary infant formula as part of the actions to reduce burden on study participants.	
Global Heart Hub	743	744	5.4.2	Incorporating flexiblity, as well as adequate compensation and other support mechanisms (e.g., childcare, facilitation of transportation, etc.), are key to reduce the burden on participants	n/a
Prescrire	743	763	5.4.2	The guideline acknowledges the burden on participants, but does not set out ways to compensate for it or to provide practical support. Taking part in a trial in the postpartum period may be challenging (for example due to transport arrangements, fatigue, and logistics concerning the breastfed child). Recommend practical support measures: reimbursing transport costs, childcare, home visits, breastfeeding support.	
EFPIA	746	748	5.4.2	Challenges are that if a study investigator is a gynecologist or an adult specialist (e.g. rheumatologist, cardiologist) he/she will not have access to the pediatricians notes and records, and therefore no infant source information may be available.	Address the need to consider the importance of adding relevant sub-Investigators to facilitate provision of infant outcomes data.
EFPIA	751	751	5.4.2	Please indicate safety issues with respect to infant burden.	Please clearly specify burden on infant with regard to safety.
EFPIA	751	751	5.4.2	Sampling infant blood requires phlebotomy experts proficient in infant sampling (not typically part of a study team for adult medicinal trials). Therefore, sampling is not likely to be feasible without relevant sub-Investigators (pediatric).	Address the need to consider the importance of adding relevant sub-Investigators to facilitate infant blood sampling.
International Consortium for Innovation and Quality in Pharmaceutical Development	751	751		Please indicate safety issues with respect to infant burden.	Please clearly specify burden on infants with regard to safety.
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	752	753	5.4.2	Sponsors should be encouraged to provide the breastmilk pumps (not only to consider providing). Prompt and afordable access to brestmilk pumps may vary across countries, therefopre, providing them will not only reduce participants' burden but also facilitate study recruitment.	~~Consideration should be given to providing~~ Sponsors are encouraged to provide breastmilk pumps for efficient milk expression or use of alternative methods for sampling;
EFPIA	752	753	5.4.2	Would add other breast feeding supplies here like lactation bags, pads and ointments to reduce excoriation, 24/7 phone access to lacation consultants	
EFPIA	752	753	5.4.2	Suggest specification on timing of milk sampling (time to drug intake; and first ml or more in the middle milk sampling)	Suggest specification on timing of milk sampling (time to drug intake; and first ml or more in the middle milk sampling)
EFPIA	754	754	5.4.2	Recommend we attempt to remove this. If a sponsor were to make available child care/activities (which would almost certainly be via a third party service provider), the sponsor could be held liable for that provision.	
EFPIA	754	754	5.4.2	Can consider providing funds/vouchers for childcare during study visits	
Global Heart Hub	754	754	5.4.2	Other siblings and/or people dependant on the trial participant should also be considered to reduce the logistical and psychological burden on trial participants	Provision of care/activities for the child and other siblings;
EFPIA	758	759	5.4.2	We welcome the considerations to the use of mobile study visits, virtual telemedicine study visits and home health nurses to aleviate the burden of pregnant individuals after birth, especially considering the post-partum follow-up could take a long time.	No requested change to text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Global Heart Hub	763	763	5.4.2	There is no mention of trial support for pregnant or lactating women – adapted conditions would be needed for visits, etc. The guidelines should outline what is required emotionally, informationally and practically to encourage these patients to participate/ stay in CTs.	n/a
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	764	794	45782	This section needs clarification that the consent should only be needed from the mother, not the other parent.	Clarify that consent is only needed from the mother.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	764	794	45782	This section needs clarification that the consent should only be needed from the mother, not the other parent.	Clarify that consent is only needed from the mother.
TRT-5 CHV	770	771		Some clinical trialson HIV already applied this recommandation in France. More detailed guidance on this drafting could be developed in the framework of these recommendations. We remain available and are in contact with researchers who may be interested.	Add : "The drafting of the informed consent form should, as far as possible, preserve the confidentiality of the participant's health status with respect to the other parent of the unborn child."
EFPIA	773	781	5.5	Information to participants in lactation study - instructions about planning interruption of breastfeeding incl. milk storage and potentially other elements could be useful	consider adding.
EFPIA	773	775	5.5	Guideline states, "Participants enrolling in a lactation study should be informed that the primary purpose is to investigate the investigational product levels in the blood (i.e., maternal and may include infant) and breastmilk and the correlation between them." Overall, the document is very vague about the ethical conditions under which it is appropriate to expose an infant to an investigational product that does not offer any clinical benefit to the infant. Because of this lack of clarity, the recommendations are muddled. This ambiguity throughout the discussion of clinical lactation studies creates the real risk of unethical studies being conducted.	
ACRO	780	781	5	Given the importance of breastfeeding for infant health, ACRO would recommend that the guideline includes further examples of considerations of prioritization of participant and infant needs. For example line 780-781 could be expanded to include reference to the potential impact of intercurrent illness on prioritization of research participation.	Recommendation: inclusion of additional text in lines 780-781 such as "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, and conditions of their infant (e.g., prematurity) that may affect prioritizing breastmilk provision vs. research participation, *intercurrent illness which could affect the individual's ability to breastfeed (e.g. reduced volume)* ."
EFPIA	782	783	5.5	Guideline states, "…studies that permit breastfeeding during exposure to the investigational product:…" This is unclear - why would this be allowed absent data on the level of investigational product in breastmilk other than limited circumstances where discontinuing breastfeeding would be dangerous?	
"Sociedad Española de Farmacología Clínica" and "European Association for Clinical Pharmacology and Therapeutics"	798	799	5.5	The sentence "IRB/EC experienced in this patient population" is vague. It would be better to indicate theat those IRB/EC with expertise in the treatment/management of lactating mother-child pairs, such as those with obstetitric, pediatric, neonatologist members or capability to consult them ad hoc.	"IRBs and ECs ~~experienced in this patient population~~ with expertise in the treatment/management of lactating mother-child pairs (e.g., such as those with obstetitric, pediatric, neonatologist members or capability to consult them ad hoc)…"

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Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	800	800	6	Add that not-labeling products at all could be an option for certain trials when a product is used in an academic trial on e.g. the setting, surveillance etc where a drug/medical technical product is involved that has indication or is used off-label but with sound scientific evidence from cochrane/HO etc (e.g. many products used during induction of labour). Here it should be enough to register the batch number and follow clinical routine.	
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	800	800	6	Add that not-labeling products at all could be an option for certain trials when a product is used in an academic trial on e.g. the setting, surveillance etc where a drug/medical technical product is involved that has indication or is used off-label but with sound scientific evidence from cochrane/HO etc (e.g. many products used during induction of labour). Here it should be enough to register the batch number and follow clinical routine.	
EFPIA	801	825	6	Data from pregnancies occurring in a clinical study which is not specifically designed to evaluate pregnancy and outcomes is unlikely to be sufficient to clearly inform benefit-risk in this population. Include a discussion of the limitations of such data when considering presentation and guidance in labeling.	
International Consortium for Innovation and Quality in Pharmaceutical Development	801	825	Appendix 1	Differences should also be identified depending on the pregnancy period (i.e., trimester)	Suggest rephrasing: 'Any differences identified for the above items based on demographic, disease state, other subpopulations or pregnancy period (trimester)'
Prescrire	802	825	6.1	Appendix 1 does not mention animal data; it does not mention the adverse effect profile in adults as being useful for predicting disorders in infants exposed in utero during the second or third trimesters of pregnancy or via breastfeeding; there is no explicit link to pregnancy registries, mother-child cohorts or health databases. There is no encouragement to cross-reference the data produced from trials with day-to-day pharmacovigilance data. This prevents signal detection in the long term, or in relation to uncommon but serious cases. There is no mechanism for providing rapid updates in the event of an emerging signal. This undermines the responsiveness of the system for protecting pregnant or breastfeeding individuals and their children. There is no guidance in the appendix concerning management of pregnancies that occur during treatment, or cases in which nursing is mistakenly pursued with a product that is not recommended in this situation. In the absence of clear guidance, this may lead to decisions with major consequences (such as elective abortion, therapeutic abortion, sudden weaning or hospitalisation of the nursing infant), without supporting justification. No hierarchisation of the types of risks or quality of evidence. The text does not offer a framework for interpreting the level of risk: malformation, functional impairment, etc. It does not explain how the quality of evidence (e.g. a few case reports vs clinical trials) should influence the labelling. This limits the clinical utility of package leaflets as a protective tool.	
EFPIA	803	803	6	Proposed edit for clarity.	Suggest to replace "dose data" by "data on the effect of dose" in following sentence: "Sources for information in product labeling include nonclinical data and clinical data such as PK, PD, and dose data on the effect of dose obtained through relevant studies and/or (…)
EFPIA	806	807	6	Consider broadly including the source of the data in the product labeling to provide context and allow some transparency on the weight of evidence/ relevance to clinical use (e.g., non-clinical data, PKPD modelling, clinical, epidemiological studies).	Consider including the following text ior similar: "When available, and depending on regional labeling guidances and subject to regulatory review, the following information, along with the source of the data (e.g, non-clinical, PK modelling studies), should be considered for inclusion in labeling

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EFPIA	806	806	Appendix 1	It is proposed to add "compassionate use" to the list.	
EFPIA	808	809	Appendix 1	Trimester-specific data for labeling, where relevant.	consider adding.
EFPIA	808	825	6	A new bullet should be added to the existing list to mention the inclusion in labeling of pharmacokinetic data in pregnant women during each trimester and post-partum (i.e. exposure parameters).	Add new bullet: • Pharmacokinetic data in pregnant women during each trimester and post-partum (exposure parameters)
ENTIS (European Network of Teratology Information Services)	810	811	6	Expansion of the list of adverse pregnancy outcomes	The product's effects on the pregnancy (such as risk of miscarriage or pregnancy complications); Pregnancy complication: preterm birth, (Postpartum Hemorrhage), growth restriction, NICU admission
EFPIA	812	813	Appendix 1	Depending on the condition, consideration should be given when there is sufficient control of the disease symptoms for a pregnancy being safe to occur.	
EFPIA	814	814	Appendix 1	Consider reference to (IgG) mABs and their potential to cross the placenta (see ICH S6(R1)) and excretion in breastmilk	consider adding.
EFPIA	814	814	Appendix 1	Suggest adding during specific trimesters/weeks of pregnancy.	Suggest adding during specific trimesters/weeks of pregnancy.
ENTIS (European Network of Teratology Information Services)	815	816	6	Expansion of the effects on the fetus	Effects on the fetus (such as risks of congenital malformation, effect on fetal growth,neurodevelopmental impairment, and potential for long-term effects on the infant and the child);
EFPIA	818		6	The term "child" in this context may imply individuals beyond the age of one year. It is important to clarify whether this definition is intended. Additionally, there are concerns regarding the feasibility of studying this population, as it may not be practical or necessary to include them in such studies.	We recommend considering the removal of references to "child" from the guideline altogether. This adjustment would help streamline the focus of the labeling information and address the challenges associated with studying this demographic.
EFPIA	819	819	Appendix 1	Proposal to change "" as only use neonate 3 times in the document. It is considered more appropriate to use the term "infant".	….Any adverse drug reaction or withdrawal sympltoms in an infant;
EFPIA	824	825	Appendix 1	Differences should also be identified depending on the pregnancy period (i.e., trimester)	Suggest rephrasing: 'Any differences identified for the above items based on demographic, disease state, other subpopulations or pregnancy period (trimester)'
EFPIA	825	825	Appendix 1	It is proposed to add a bullet point: "Effect of untreated disease on pregnancy"	proposed addition: "Effect of untreated disease on pregnancy"
Gedeon Richter plc.	826	878	Appendix 2	Outcomes are listed but without standardization. Should stratification by gestational age be added?	
International Consortium for Innovation and Quality in Pharmaceutical Development	826	878	Appendix 2	Maternal and Gestational Outcomes of Interest is not harmonized with other sources and does not provide standard terminology	We suggest this be harmonized with outcome requirements/ definitions used in post-marketing observational pregnancy studies: e.g.: distinguish between major congenital malformation (MCM) vs pattern of minor congenital malformation. We would suggest including a table of standardized definitions for key outcomes (e.g., preterm birth, small for gestational age) to ensure consistency globally.

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Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	826	855	APPENDIX 2	The MFAET terminology provides a systematic way to assess maternal and fetal adverse events in a way that each can be graded to indicate the degree of impact of an intervention on them independently. This allows for much more granularity and nuance in assessing adverse events. Please would you update this whole section to mention the AEs that are defined and graded in MFAET to indicate the comprehensive coverage of events that can be achieved. A number of significant AEs are not currently mentioned, for example, amniotic fluid embolism, retained placenta, antepartum haemorrhage, abnormal fetal movements, abnormal fetal heart rates.	MFAET version 1.1 includes these: Maternal AEs graded in both mother and fetus:: Haemorrhage in pregnancy; Preterm premature rupture of membranes; Chorioamnionitis; Anaemia of pregnancy; Maternal only AEs: Gestational hypertension; Pre-eclampsia; Eclampsia; Premature labour; Puerperal infection; Postpartum haemorrhage (primary); Retained placenta or membranes; Amniotic fluid embolism. Fetal only AEs: Fetal fluid collection; Fetal bradycardia: non-labour; Fetal tachyarrhythmia; Cardiac function abnormalities; Fetal brain scan abnormal; Fetal gastrointestinal tract imaging abnormal; Fetal musculoskeletal imaging abnormal; Fetal renal imaging abnormal; Fetal movement disorders; Fetal neoplasm; Fetal structural abnormalities: not otherwise classified; Abnormal fetal growth; Fetal intraoperative injury; Procedural haemorrhage; Post-procedural haemorrhage.
International Advisory Committee on Clinical Trials in Multiple Sclerosis, National Multiple Sclerosis Society, and European Committee for Treatment and Research in Multiple Sclerosis	826	878	Appendix II	We appreciate the provision of Appendix II which identifies maternal and gestational outcomes of interest. More specific guidance about how to measure and report these outcomes could enable prospective harmonization across clinical trials, enabling comparisons across trials. Prospective harmonization of maternal, fetal, and neonatal outcome measures across trials is critical. We encourage the EMA to endorse core outcome sets for pregnancy-related endpoints in neurology and MS specifically. These core outcome sets should include the minimum duration of follow-up and temporality of these outcomes to treatment exposure, delivery, and breastfeeding status and duration. We also encourage the EMA to consider recommending global registries, possibly disease-specific, to support capturing outcomes related to maternal and child health in a consistent, cost-efficient manner across clinical trials.	
spm² - safety projects & more GmbH	826	878	Appendix 2	While Appendix 2 lists possible outcomes, the guideline could clarify which endpoints are essential versus optional depending on trial type, design, or investigational product risk profile. This would help to clearly identiy which information is essential.	
EFPIA	832	878	Appendix 2	Maternal and Gestational Outcomes of Interest is not harmonized with other sources and does not provide standard terminology.	We suggest this be harmonized with outcome requirements/definitions used in post-marketing observational pregnancy studies: e.g.: distinguish between major congenital malformation (MCM) vs pattern of minor congenital malformation. We would suggest including a table of standardized definitions for key outcomes (e.g., preterm birth, small for gestational age) to ensure consistency globally.
EFPIA	832	855	Appendix 2	Fetal information in abortion (spontaneous or induced) missing. Among maternal conditions, the status of underlying disease (indication) at the time of drug exposure during pregnancy is missing.	consider adding.
EFPIA	833	833	APPENDIX 2	Current wording "Standard maternal and gestational measures of interest" is prone to different interpretation , thus leading to non-harmonized reporting across different products of the same class and /or geographies	Suggest addition of references, e.g. to IMI ConcePTION WP2: Core data elements for pregnancy pharmacovigilance
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	836	836	6	Refer to relevant core outcome sets, crown initiative	If available, outcome registration should follow published core outcome sets as e.g. from the crown initiative.

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Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	836	836	6	Refer to relevant core outcome sets, crown initiative	If available, outcome registration should follow published core outcome sets as e.g. from the crown initiative.
EFPIA	839	839	Appendix 2	Identification of congenital malformation prenatally. Suggest adding that, if possible, identification of such malformations should be conducted pre-dosing.	
Ethics Committee UZ Leuven	849	849		Not all centers have a placental pathologist so second opinions or second readings may be needed	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	855	855	6	Add that in countries with existing registers, potential effects for coming pregnancies should be considered as well.	In countries with existing registers, outcomes in future pregnancies and longterm foloow-up of mother and child should be conidered.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	855	855	6	Add that in countries with existing registers, potential effects for coming pregnancies should be considered as well.	In countries with existing registers, outcomes in future pregnancies and longterm foloow-up of mother and child should be conidered.
EFPIA	856	856	Appendix 2	infant to be changed to newborn	Recommandation
EFPIA	856	864	Appendix 2	Newborn outcome; Sex, GA at birth, weight, length, small for GA/ large for GA, head circumference (HC)	Recommandation
Maternal Fetal Adverse Event Terminology (MFAET) International Steering Committee: MembersEMA/CHMP/ICH/149462/2025 from Spain, Germany, Belgium, UK and USA. https://tinyurl.com/mtzh3dd7	856	874	APPENDIX 2	Please also mention the validated Neonatal Adverse Event Severity Scale (NAESS) which grades and defined AEs in neonates. This has also been mapped to MedDRA. Salaets T, Turner MA, Short M, Ward RM, Hokuto I, Ariagno RL, Klein A, Beauman S, Wade K, Thomson M, Roberts E, Harrison J, Quinn T, Baer G, Davis J, Allegaert K; International Neonatal Consortium. Development of a neonatal adverse event severity scale through a Delphi consensus approach. Arch Dis Child. 2019 Dec;104(12):1167-1173. doi: 10.1136/archdischild-2019-317399. Epub 2019 Sep 19. PMID: 31537552; PMCID: PMC6943241.	Add in detail of NAESS: https://evs.nci.nih.gov/ftp1/Pediatric_Terminologies/INC/About.html
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	857	864	6	The infant outcomes are few.	I suggest they are recommended to use an obstetrical core outcome set.
Swedish network for national clinical studies in Obstetrics and Gynecology (SNAKS, www.snaks.se)	857	864	6	The infant outcomes are few.	I suggest they are recommended to use an obstetrical core outcome set.
EFPIA	863	864	Appendix 2	The Apgar score was designed to assess the need for intervention such as respiratory support or other resuscitative measures, not as a gauge for outcomes. Literature would suggest that the change in score from 1 to 5 minutes and an individual score at 5 and 10 minutes is more predictive of certain outcomes.	The statement as written suggesting collection of Apgar score and linkage to developmental and functional assessments is a poor suggestion, in particular when the EWG has provided no relevant context on which measures to collect and how they do or do not predict outcomes.

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Ethics Committee UZ Leuven	863	863		fe Bailey scale of infant development at 18 months of age	
EFPIA	865	878	Appendix 2	Outcomes in the neonatal and infant follow-up - more detail could be provided naming any specific developmental delays or congenital malformations. May also want to discuss preferred time of follow up 1 yr or 5yrs if developmental issue.	
EFPIA	865	874	Appendix 2	Standardized assessments (incl HC) with nurse 28 days, 3 months, 6 months - OR timed with the countries Childhood immunization Programme	
EFPIA	875	876	APPENDIX 2	Provision of some examples could be beneficial to illustrate the following statement : "Infant follow-up outcomes of interest will differ based on the maternal disease or disorder, investigational product type, and gestational exposure"	Suggest referring to some references with examples. E.g. example for neurodevelopmental outcomes - Bromley R. L. et al. Expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies. Front Pharmacol. 2023 Jun 1;14:1094698. doi: 10.3389/fphar.2023.1094698. PMID: 37332344; PMCID: PMC10270323.
EFPIA	875	878	Appendix 2	if investigational product is neurotropic there should be a Late assessment of developement/neurological status. This assesment should be performed by a peadiatric doctor at 9-12 months of age	Recommandation
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	875	876	6	Add existing registers	...gestational exposure and the availability of existing health and quality registers.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	875	878	6.2	Lack of clarity regarding the duration and nature of follow-up The guideline refers to follow-up "on a case-by-case basis", but does not provide clear guidance (follow-up to 6 months, 1 year, 5 years or adolescence?). It is important to note that certain effects (e.g. on neurodevelopment, puberty and metabolic function) cannot be identified for several years. ➞ Risk: underestimation of long-term effects.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	875	878	6.2	Paediatric follow-up involves: Coordination between the study team and paediatricians (Evolving) parental consent on behalf of the child Processing of sensitive medical information about a minor ➞ Risks: Children being lost to follow-up (incomplete follow-up, biased data) Evolving parental consent, in particular if the mother leaves the trial or no longer wants to take part Risk of invasion of the child's privacy, particularly if genetic or cognitive testing is performed	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	875	878	6.2	Potential stigmatisation of exposed children Children may be perceived (or perceive themselves) as being "at risk" or as "guinea pigs", particularly if the trial involves frequent or intrusive examinations.	

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Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	875	878	6.2	Suggestions for improvement - Provide guidance on the minimum duration of follow-up, based on the anticipated risk (with long follow-up periods for psychotropic drugs, hormonal therapies, immunosuppressants, etc.). - Introduce a dedicated ethics committee for child follow-up, independent from pharmaceutical companies and made up of patients, pharmacovigilance experts, paediatricians, psychologists, etc. - Strengthen the procedures for informing parents and securing their consent, with documents appropriate for paediatric follow-up. - Guarantee families the right to simply withdraw from the trial completely, with no negative consequences. - Look ahead to the transition to children giving consent for themselves once they reach a certain age (12 years? 15 years?).	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	875	876	6	Add existing registers	...gestational exposure and the availability of existing health and quality registers.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	877	877	App 2		"may not manifest" suggested instead of "may not be visible"
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	0	0	0	We welcome the increasing attention to the inclusion of pregnant patients in clinical research. In analogy to the regulatory requirement for a Pediatric Investigation Plan (PIP) — or waiver — as part of the marketing authorization dossier, we suggest that a similar mechanism be established for pregnancy. Specifically, the creation of a Pregnancy Investigation Plan (PregIP) — or waiver — could serve as a structured regulatory tool to ensure systematic consideration of pregnant patients during drug development. At present, there is no legal framework to mandate such a requirement. However, we consider it important that regulators review existing legislation and explore the development of the necessary legal instruments to implement this obligation. Such an approach would represent a concrete step toward addressing the current gap in evidence for the use of medicines in pregnant patients, thereby strengthening patient safety and public health.	No specific text changes are proposed.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	0	0	4.1.1	Guidance should take alternative conception methods into consideration along with their differential risks like Assisted Reproductive Technologies(ART)	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	0	0	4.2.4	Consideration should be given to modeling and artificial intelligence solutions that may help reduce burden on human participants.	
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	142	159	4.1.2	Chapter developed around CTs. Whats about evidence form RWD and not CTs? Line 153 mentions non-clinical data. What is meant to be considered here?	Please clarify.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	194	195	4.1.2	Removal of mandatory contraception requirements in ongoing trials will provide very limited scientific data	Please clarify the intention of this statement
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	3	5	1.1	"appropriate inclusion" and "robust clinical data"	Propose to delete Appropriate and Robust. Not appropriate.

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Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	358	367	4.2.9	Safety monitoring for pregnancy related AEs how does that relate with the aim to have information on infants? I do not think both should be mixed under pregnancy.	Please reflect the comment.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	47	47	2	"clinical trials"	IS the intention to consider the CTs the SOC. IF so please add this information alog the lines.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	640	641	5.3.1	In case of an exposed infant, which parameters should be avaluated ?	Please clarify in the guidance. We need more clear guidance on how to copnduct such studies.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	70	77	2	Although this is well structured and very important, it is missing information on the difficulties to gather data on pregnancy, recruit pregant patients and most likely find bread-feeding data	Missing mentioning to sample size and difficulties associated to the specific populations being mentioned.
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)	9	10	1.2	"postmarketing" clinical trials	I would caustiously leave the postmarketing clinical trials out as they pose different understanding. Would you unintentionally mean post-approval use?
Nordic Alliance of Clinical Trials in Obstetrics and Gyneology (NORD-ACT)			5.3.1	The guidelines should spell out the need to include patient organisations and pregnant and lactating patients in protocol design – particularly given that patients at this important life juncture may not wish to participate in CTs – safety concerns/ new baby taking priority	n/a