E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials

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FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

INCLUSION OF PREGNANT AND BREASTFEEDING WOMEN IN CLINICAL TRIALS
E21

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E21
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ICH HARMONISED GUIDELINE

INCLUSION OF PREGNANT AND BREASTFEEDING WOMEN IN CLINICAL TRIALS

E21

ICH Consensus Guideline

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1. INTRODUCTION

1.1 Objective

The objective of this guideline is to provide recommendations for the appropriate inclusion and/or retention of pregnant and/or breastfeeding women in clinical trials and facilitate the generation of robust clinical data that allow for evidence-based decision making on the safe and effective use of medicinal products by these women and their healthcare providers (HCPs).

1.2 Scope

The scope of this guideline includes pre- and postmarketing clinical trials of investigational products (see ICH E6(R3)) for indications in the general population and indications specific to pregnant or breastfeeding women.

In principle, inclusion of pregnant and breastfeeding women in clinical trials should be considered for all products where women of childbearing potential are among the anticipated user population. It is especially important for conditions where there is high unmet medical need for treatment in pregnancy or while breastfeeding; however, the scope of this guideline is not limited to these scenarios.

1.3 Background

Many women who are pregnant or breastfeeding have acute or chronic medical conditions (including physical and/or mental health conditions that occur or may be exacerbated during pregnancy and the postpartum period) that require new, ongoing, or preventative treatment(s). 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 women.

Pregnant and breastfeeding women are often excluded from clinical trials and those who become pregnant while participating in a clinical trial are frequently discontinued from the clinical trial. As a result, pregnancy- as well as breastfeeding-specific information in the product labeling on benefits and risks of medicinal product use is, at best, sparse and treatment decisions need to be made in the absence of this information. This lack of data has the following potential consequences for pregnant and breastfeeding women:

- HCPs and/or patients avoiding or discontinuing indicated treatments leading to exacerbation of the condition or harm to the patient, pregnancy, or the child;

- HCPs and/or patients inadvertently choosing treatments harmful to the patient, pregnancy, or the child;

- Use of a dose or treatment regimen that is sub- or supra-therapeutic, leading to increased risk for under-treatment and/or adverse reactions;

- Avoidance or premature discontinuation of breastfeeding, or discontinuation of indicated treatment to allow for breastfeeding.

The potential magnitude of the public health impact of these negative consequences is considerable.

2. GENERAL PRINCIPLES

This guideline recommends that medicinal product use in pregnancy and/or breastfeeding receives careful consideration and is incorporated into planning throughout investigational product development from nonclinical studies through post-approval use of the product. Proactive planning for obtaining data related to use in pregnancy and/or breastfeeding through nonclinical and clinical studies (or the rationale for not obtaining data) should be done from the early stages of formulating the development strategy for the investigational product.

Sponsors of drug development programs and clinical trials are encouraged to consider strategies to generate data that support informed decision-making on the safety, dosing, and efficacy of the medicinal product’s use during pregnancy and breastfeeding. Sponsors are recommended to consult with regulatory authorities as early as possible and as needed throughout the investigational product development process regarding the plans for the participation of pregnant and/or breastfeeding women in clinical trials. 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 women are included or planned to be included in clinical trials. Early engagement with appropriate stakeholders, including patients, provides opportunities to address all relevant aspects of these clinical trials.

Assessing the safety in pregnant and breastfeeding women is complex as there are potential impacts on the fetus and breastfed child to consider. When considering including pregnant or breastfeeding women 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).

Collection of data pertinent to use of an investigational product in pregnant and breastfeeding women should continue into the postmarketing period. Ongoing safety monitoring of product use in these populations in the postmarketing period contributes 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 women.

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). Because pregnancy and breastfeeding present unique issues when gathering RWD, such as mother-child linkage, it is encouraged to proactively prepare platforms for post-approval data collection and to collect background information on population and disease-specific risks to assist with data interpretation.

Available data and assessment of investigational product benefits and risks during pregnancy and breastfeeding are expected to be included and updated as necessary in labeling documents. Any statements in the prescribing information regarding pregnancy outcomes should be based on and reflect the robustness and limitations of the data as well as consideration of baseline rates of the outcomes in the indicated population when known. Additional considerations for labeling are included in Appendix 1.

3. ETHICAL CONSIDERATIONS

Including pregnant and breastfeeding women in clinical trials to support safe and effective data-driven use of medicinal products is ethical and supported by the Declaration of Helsinki and ICH guidelines, specifically ICH E6(R3) and ICH E8(R1). In addition to the responsibilities of the sponsor and regulatory authorities, Institutional Review Boards (IRBs) or Ethics

Committees (ECs) have responsibility for evaluating whether the risks of conducting the trial are reasonable in relation to anticipated benefits. Consideration should be given to the use of IRBs or ECs experienced in working with pregnant and breastfeeding participants. For protocols involving pregnant or breastfeeding women, this responsibility involves considerations for the participant, for her pregnancy, and the fetus or breastfed infant. Ensuring ethical conduct of the trial therefore requires additional considerations regarding any need for appropriate safeguards related to pregnancy or breastfeeding (including risk mitigation measures implemented in the protocol and stopping criteria), as well as additional considerations regarding informed consent (Sections 4.4 and 5.5).

4. PREGNANCY

4.1 Development Strategy

Sponsors should anticipate that the approach to include pregnant women in clinical trials will require careful assessment of benefits and risks that may evolve depending on multiple factors, including the stage of clinical development, the duration of treatment, the indication being sought, and the strength of the available evidence. In addition, the approach may differ based on the anticipated trimester of pregnancy of participants to be included in the clinical trial. This section of the guideline lays out considerations for incorporating these complexities into the development strategy of an investigational product.

4.1.1 Factors to Consider When Planning for Pregnancy Data Collection

Incorporating evidence collection for pregnant women into the development strategy starts with considering the targeted condition, patient population, and existing treatments. In addition, sponsors should consider how pregnancy might affect the disease state (e.g., potential worsening of the disease/condition if under- or untreated), as well as how the patient's disease (and its treatment) could impact the pregnancy and its outcomes (e.g., the potential increase in risk of adverse pregnancy outcomes due to inadequate disease control). These considerations will influence the timing and the type of data to be collected (see Section 4.2).

When the investigational product is likely to be used by women of child-bearing potential, collecting data on safety, efficacy, PK during pregnancy, and predicted exposure to the fetus is important to support informed decision-making. Data should be collected as early as possible and appropriately timed in product development. Sponsors are encouraged to evaluate and update the development strategy as new information or data become available.

Situations that represent an especially high medical need for such data collection include but are not limited to:

- Public health emergencies;
- Diseases that, if left untreated, are likely to adversely affect the health of the pregnant woman, the outcome of the pregnancy, and/or the health of the fetus/child (e.g., certain autoimmune diseases such as systemic lupus erythematosus (SLE) or human immunodeficiency virus (HIV) infection);
- Diseases for which the available treatments are not satisfactory in pregnancy and/or are known to carry high risks for the pregnant woman and/or the fetus/child (e.g., known or suspected teratogenicity or increased risk of pregnancy loss).

In these scenarios, the development strategy should aim for early acquisition of data from pregnant women unless there exists justification for postponement. Sponsors should proceed proactively with activities to generate the data and evidence necessary to enable inclusion in clinical trials at a later stage.

Depending on the characteristics and pharmacology of the investigational product and/or the disease/condition and available data from other similar medicinal products, it may be considered appropriate to design studies that include participants for an entire pregnancy, any time during pregnancy, or certain pregnancy trimesters only (e.g., avoiding third trimester exposure for non-steroidal anti-inflammatory drugs).

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.

4.1.2 Evidence Needed to Support Inclusion of Pregnant Women in Clinical Trials

In alignment with the principles of ICH E8(R1), the approach to collecting data from pregnant women in clinical trials involves a systematic expansion of data collection across relevant sources and patient populations, guided by data-driven decisions to safeguard study participants. Development programs should aim to generate the nonclinical and clinical data necessary to enable the inclusion of pregnant women in clinical trials at the appropriate stage of clinical development.

The data and evidence needed to support the decision to include pregnant women in a clinical trial or to enable ongoing participation of women who become pregnant will depend on a weight of evidence approach and consideration of the following:

- The indication and the intended population;
- Nonclinical data;
- The prospect of benefit;
- The clinical pharmacology of the investigational product;
- Biological plausibility of harm due to pregnancy exposure;
- When during the pregnancy the investigational product would be administered;
- The novelty of the investigational product (i.e., the availability of data from molecular entities or treatments similar to the investigational product).

In the development strategy, the plan for collection of clinical data should be informed by an integrated assessment of these factors.

Prior to proceeding to studies including pregnant women, the results from relevant nonclinical studies need to be evaluated. These studies may include the standard Developmental and Reproductive Toxicology (DART) studies (see ICH M3 and ICH S5), the standard battery of genotoxicity studies if relevant (see ICH S2), appropriately qualified/validated alternative tests, and any relevant modeling. 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, the timing and/or necessity for DART studies may be influenced by the characteristics of the investigational product (such as biotechnology derived pharmaceuticals as outlined in ICH S6(R1)), the clinical indication (such as those covered by ICH S9), and/or the intended patient population (e.g., exposure during the third trimester or the first trimester). Nonclinical data evaluation should be further explored to understand any potential risk to a pregnancy. When risks are identified, further investigations may be warranted with modified reproductive toxicology studies to characterize them further (e.g., studies that investigate risks to the embryonic period vs. fetal period, duration of dosing).

In addition to gathering the nonclinical data needed to proceed to studies in pregnancy, acquiring clinical data in non-pregnant women will also usually be necessary. Generally, clinical data that support safety and prospect of benefit in non-pregnant study participants could reasonably be expected to be applicable for pregnant women. 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.

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. The objective of this assessment should be to determine whether the risks of proceeding with trials in pregnancy are reasonable given the anticipated benefits.

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. If the sponsor determines that proceeding with trials in pregnancy is appropriate, then the following approaches/actions (in no specific order) need to be considered and/or incorporated into the development strategy:

- Recruitment of pregnant women into ongoing and/or subsequent clinical trials;
- Removal of mandatory contraception requirements in ongoing and/or subsequent clinical trials;
- Ongoing participation of women who become pregnant during clinical trials;
- Implementation of study(ies) specifically designed to be conducted in pregnant women if needed.

4.1.3 When All the Data Necessary to Support a Favorable Benefit-risk Assessment are Not Yet Available

Before reaching the point where it may be appropriate to incorporate pregnant women into the clinical development program, clinical studies using the investigational product will typically have mandatory contraception requirements. Sponsors should recognize and plan for the fact that pregnancies can occur when the study population includes women of childbearing potential even when rigorous approaches to mandatory contraception are implemented. Implications for study design and implementation when an unintended pregnancy occurs are discussed in Section 4.2.11.

A decision will need to be made regarding potential continuation on the investigational product when pregnancies occur despite mandatory contraception. Such continuation may often be inappropriate, but there could be exceptions. Considerations in the decision making should include the following:

- Information obtained to date regarding the safety in pregnancy of the investigational product (nonclinical as well as any clinical findings);
- The participant's current health status, including the pregnancy and the underlying health condition;
- Risks of suspending study treatment (e.g., possible exacerbation of the treated disease, suitability or teratogenicity of alternative treatments, or impact of the disease on pregnancy);
- Any potential loss of the possible benefit (effectiveness) that might be obtained from the study treatment (e.g., through improvements in the underlying condition).

If the conclusion is for treatment with the investigational product to continue, then the participant should be reconsented as a pregnant participant.

4.1.4 When Existing Data Suggest a Safety Concern for Pregnancy

If nonclinical and/or clinical data suggest that the investigational product is potentially harmful to the pregnant woman and/or the fetus, the sponsor may conclude that inclusion of pregnant women in clinical trials is initially not warranted. However, for some investigational products, the benefits of use in pregnancy may still outweigh the potential risks. Examples include situations where the target disease has a serious negative impact (e.g., diseases such as malaria, which are known to have adverse effects on both the mother and the fetus) or where available treatment(s) have a safety concern in pregnancy (e.g., methotrexate for SLE). In such cases, including pregnant women in the trial may be considered on a case-by-case basis. In determining whether that is appropriate, it is essential to consider what additional data are needed to characterize the benefit-risk and to explore whether any potential risks can be mitigated. Additionally, consideration should be given to the fact that medical needs and potential risks associated with the product may differ depending on the trimester of exposure.

4.1.5 Strategies for Obstetric Conditions

For the development of investigational products intended for obstetric conditions (e.g., pre-eclampsia or preterm birth), clinical trials in pregnant women are necessary to evaluate the investigational product's efficacy, safety, and dosing. In these scenarios, the data needed to proceed in clinical development and support a marketing application will be specific to the condition.

4.2 Inclusion of Pregnant Women in Clinical Trials

This section applies to trials that allow inclusion of pregnant women and those designed to be conducted as stand-alone trials in pregnant women. When a trial conducted in women of childbearing potential has no requirement for contraception, such a trial essentially enables inclusion of pregnant women. Acquiring data on medicinal products during early pregnancy is only likely to occur in trials that have no requirement for contraception. These trials will be important to help characterize the product’s safety profile in pregnancy unless there is a good rationale for not doing so.

4.2.1 Study Design and Implementation

While this guideline focuses mainly on the inclusion of pregnant women in interventional clinical trials, other trial types may be acceptable if they are appropriate for inclusion of pregnant women. The sponsor should carefully consider which study design would be most appropriate for the evaluation of an investigational product in pregnant women. Additionally, the safety impact on the pregnancy by all products used within the trial (i.e., test and comparator products) should be considered.

4.2.2 Expertise Considerations

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) should be available for study design and safety monitoring (e.g., Data Monitoring Committee or other safety oversight body) to help interpret any adverse events (AEs) reported during pregnancy.

4.2.3 Sample Size

Study designs should consider the number and proportion of pregnant women expected to be enrolled in trials, taking into consideration expected withdrawal rates based on the target population and trial conditions.

For clinical trials with non-obstetric indications, estimating the number of pregnant participants can help determine assessable endpoints. The PK data during pregnancy to enable appropriate dose estimates may be obtained in most cases. However, low participant numbers may limit safety conclusions, especially for rare adverse outcomes like specific birth defects.

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 women only.

4.2.4 Pharmacokinetics and Dosing Considerations

There may be a need to modify the dose or frequency of investigational product administration during pregnancy.

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. Depending on the duration of treatment, PK/PD measures should be assessed from the same participant wherever possible. The postpartum assessment period should be sufficiently long to understand PK/PD changes until the return to pre-pregnancy state.

For clinical trials that include pregnant participants, it is essential to include in the protocol whether pregnant participants should receive the same dose as non-pregnant participants or a different dose. 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. To initially estimate the dosage/dosing regimen for pregnant participants, clinical and dose-exposure data from non-pregnant participants could be considered. Modeling approaches, such as physiologically based pharmacokinetics (PBPK) modeling, which accounts for the PK alterations in pregnancy, may help to estimate the dosing strategy. Any observed PK alterations in pregnant participants, exposure-response analysis, and population PK analysis, all provide important information for proper dose selection for pregnant participants.

The dosing strategy for pregnant participants should be based on all the available evidence at the stage of the clinical development program. The proposed dosing strategy should be confirmed or further revised based on the findings of the clinical trial (e.g., safety concerns in the trial and the clinical impact of overexposure or underexposure).

4.2.5 Fetal Exposure Assessment

Before including pregnant women, predicting the extent of fetal exposure may be helpful for benefit-risk assessment. In the absence of data, risk assessments should assume a certain degree of fetal exposure. Currently, it is challenging to evaluate fetal exposure with available methods such as umbilical cord blood sampling. However, PBPK modeling could be a useful option for estimating fetal exposure. Despite the limitations, fetal exposure data could contribute to the overall pharmacologic and safety profile of the investigational product in fetuses and infants.

4.2.6 Endpoints and Outcomes

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 (for information on analysis, see Section 4.2.10). Additional endpoints may also be needed for pregnant participants (e.g., PK/PD data). When the planned method to measure the endpoint may present a risk in pregnancy (e.g., CT scans), the participant should be followed for safety or efficacy using alternative methods when available. Considerations regarding the type of data to be collected are similar whether the participant is enrolled while pregnant or becomes pregnant during trial participation.

4.2.7 Assessments and Data Collection for Pregnant Participants

Pregnancy-related assessments should be specified in the protocol and include those that are impacted by the disease.

Standard general recommendations on safety evaluation such as classification, assessment, and reporting of AEs (i.e., ICH E2A, ICH E2F, ICH E6(R3), ICH E8(R1)) apply to studies including pregnant participants. The safety assessment considerations in this section and in Appendix 2 apply in addition to standard assessments. Furthermore, 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, and depends on several factors, including but not limited to:

- The known properties of the investigational product;
- The known or potential safety risks of other investigational products in the same class, including emerging data;
- The timing and extent of exposure during gestation (see also Section 4.2.5);
- Availability and appropriateness of additional methodologies focused on assessment of gestational/fetal/infant/child health;
- The burden of additional assessments on the pregnant participant and the newborn/infant/child.

Where possible, additional information should be collected to aid in the interpretation of the safety profile. These data may provide context where risks to pregnancy associated with the underlying disease or other intrinsic or extrinsic factors are well-established (see Appendix 2). Outcomes and data parameters reported should include precise definitions, as well as their source(s).

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, ultrasound scans, and blood and urine tests.

When feasible, appropriate, and allowed by local regulations, it may improve clinical accessibility for the study participant to align and/or combine study visits with regular pregnancy-related clinical visits, employ mobile study visits, or virtual (telemedicine) study visits.

4.2.8 Assessments and Data Collection for Infants

The duration of follow-up should be considered on a case-by-case basis and will depend on the investigational product’s half-life, indication, nonclinical data, mechanism of action, timing and duration of exposure, and time to manifestation of outcomes of interest, taking into consideration that birth defects and functional or neurodevelopmental disorders may be diagnosed beyond birth. Infant characteristics at birth and outcomes in the neonatal period to be considered are included in Appendix 2. It is recognized that the follow-up may extend until past the clinical trial completion date. Sponsors should ensure a mechanism for such follow-up is in place. 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.

4.2.9 Safety Monitoring

Participants should be closely monitored for pregnancy-related AEs, with appropriate management plans if required. The impact of the investigational product on the health of the pregnancy and infant may not be fully revealed during a clinical trial. Depending on the investigational product and trial design, follow-up may be needed beyond the duration of the trial. Appropriate mechanisms for such follow-up should be considered.

Provision for suspending or discontinuing investigational product for pregnant participants should be considered in the event of an emerging pregnancy-related safety signal. 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.

4.2.10 Analysis and Interpretation

Data on efficacy, PK, and safety for pregnant women can help inform conclusions regarding whether the efficacy, dosing, and safety of the investigational product in pregnant women are similar to the general population. Clinical trial data even from a small sample size may contribute important information for product labeling. 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. However, care should be taken when analyzing clinical trial results in small subpopulations, such as pregnant women, as this may lead to difficulty with interpreting adverse pregnancy outcomes.

Given that the indication for treatment (i.e., the underlying disease or condition) may be harmful to the pregnancy or embryo-fetal development, the pregnancy-related outcomes to be measured should be assessed in the context of known impacts of the disease on pregnancy and the fetus (e.g., congenital malformation in diabetes). Insight into the efficacy of the product in treating the underlying health condition in that case will be accompanied by insight into whether and how treating the underlying health condition with the investigational product benefits the pregnancy.

Interpretation of the causality of AEs in the infant exposed to investigational product *in utero* should be made with caution in instances where the sample size is small or if there is no control arm. Possible confounders should also be considered. Additionally, the pregnancy trimester of exposure should be considered when evaluating any associations between exposure and outcome, (e.g., neural tube defects are unlikely to result from third trimester exposures).

External reference rates of adverse pregnancy outcomes in the general population may be helpful to provide context. However, disease-specific pregnancy registries or observational studies may be more informative.

4.2.11 Considerations for Pregnancies Occurring During a Clinical Trial With Mandatory Contraception

In trials with mandatory contraception, as noted in Section 4.1.3, pregnancies do still occur. In view of this, sponsors are encouraged to design protocols which:

1. Allow as appropriate, the option of remaining in the trial with suspension of investigational product for the duration of the pregnancy, or earlier resumption once data to support resumption of investigational product are available;

2. In some cases where pregnancy occurred, allow the option of continuing on treatment after reconsenting (see Section 4.1.3 for considerations as to when this might be appropriate);

3. For both situations above, provide for additional data collection (e.g., PK, PD, and additional safety monitoring, see Appendix 2);

4. Specify whether and when unblinding would be expected. A participant becoming pregnant should not automatically lead to the unblinding of the participant’s treatment assignment.

4.3 Recruitment and Retention of Pregnant Women in Clinical Trials

The general principles for recruitment outlined in ICH E6(R3) apply for clinical trials including pregnant women.

Pregnancy is a time when social and/or family interests are enhanced compared to the health of a non-pregnant woman. Such interests may influence a pregnant woman's autonomy and either unduly encourage or deter her participation in a clinical trial.

Increasing wider awareness of opportunities and considerations around participating in clinical trials while pregnant is recommended. Providing detailed information on the proposed study and its potential impact on future pregnant women with the same condition can help address concerns and improve recruitment for these trials.

Engaging with patients' advocacy groups, organizations managing disease specific registries, and clinicians experienced in conducting research in pregnant women before clinical trial initiation may help reduce challenges to recruitment or barriers to participation for specific disease areas and/or identify opportunities for reducing burden for pregnant participants. Early engagement with relevant stakeholders may help recruitment in several ways:

- 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-orientated outcomes of interest and/or reducing burdens for inclusion of pregnant women in clinical trials (see Section 4.3.2);

- Consideration of cultural differences regarding aspects of the birth, cord blood, and placenta (and use of placental samples) may identify important aspects;

- Engaging HCPs familiar with the community (e.g., midwives, community [home health] nurses, or prenatal care providers) may help recruitment (e.g., introducing trial information or asking for contact information to follow-up);

- Involving healthcare teams relevant to pregnancy could enable education of HCPs about the value of their patients participating in research on conditions which may affect pregnancy and health of the future child, to address any concerns and to encourage participation;

- Early consideration of how and when to engage with potential participants may enhance the ability to recruit pregnant women (including those at a particular trimester of pregnancy) to relevant clinical trials and may enable best use of sponsor resources.

The additional time required for follow-up of pregnancy and infant outcomes, may mean that additional efforts are needed to support retention of participants such as: maintaining contact information, discussing potential barriers and facilitators to study participation at every visit (e.g., time constraints, financial burden, or availability of study personnel to answer questions).

4.3.1 Recruitment of Pregnant Women for Clinical Trials

Where available, local clinical research networks for obstetric care may help identify potential study centers with expertise in the conditions under investigation, including ongoing care during pregnancy. Appropriate use of electronic health records may help to identify patients, but sponsors/investigators may need to consider possible issues regarding confidentiality (see ICH E6(R3)) and misidentification (e.g., due to pregnancy loss). If recruited through obstetric clinics or electronic healthcare records, consideration should be given to local privacy laws regarding disclosing pregnancy status.

Recruitment at earlier timepoints of pregnancy may require different approaches as first trimester pregnancies may be difficult to identify through electronic health records or obstetric/antenatal care units. Reaching out to specialized care physicians with educational material about a potential clinical trial in this target population may help recruitment of participants early in pregnancy. Studies in early pregnancy could include women who have been exposed to an investigational product in routine clinical care or who become pregnant in a trial (see Section 4.1.3).

4.3.2 Reducing Burden and Harm on Pregnant Women in Clinical Trials

Every effort should be made to assess the potential impact of study procedures to reduce burden on pregnant participants, which supports retention in the clinical trial and may minimize missing data. The impact of study procedures on the birth plan and delivery should be minimized.

Early identification of study procedures that are not applicable or could pose unacceptable risks during pregnancy may enable use of alternative monitoring procedures and/or flexibility in trial protocols. For instance, the protocol may need to allow for pregnant women to reduce or suspend study assessments that are not necessary (e.g., pregnancy testing), or assessments associated with additional risks to the fetus (e.g., X-rays, teratogenic rescue medications used in the protocol, or medication adjustments) until her pregnancy outcome has occurred.

Allowing some flexibility in timing of trial procedures may help address additional considerations specific to pregnancy (e.g., nausea and vomiting in early pregnancy, additional monitoring requirements with high-risk pregnancies) and may enhance adherence to protocols.

The rationale for any extra visits in the context of the study should be explained to the participant along with how the investigator and her other medical care specialists will work together to deliver the participant's care plan.

4.4 Informed Consent for Studies with Pregnant Participants

Informed consent of all participants should follow the usual process (see ICH E6(R3)), with appropriate adaptations for pregnant participants. The primary consent for participation in clinical trials should clearly state whether ongoing participation will be allowed during pregnancy and, if so, under what conditions.

Depending on the study design, informed consent could include focusing on the pregnancy aspects in the form of supplemental informed consent for participants who:

- Are already pregnant;
- Could become pregnant during clinical trials in which contraception is not mandated;
- Have a pregnancy during a trial requiring mandatory contraception and need to reconsent regarding pregnancy-related information if they wish to remain in the trial on treatment during the pregnancy.

The consent form should reflect the potential benefits and risks of the investigational product as applicable in the intended pregnancy trimester(s) of exposure. This may be especially pertinent if recruitment of participants at various stages of pregnancy is part of the study design.

Information should be provided to participants in terms of the potential benefits and risks to the woman and the fetus/infant/child of taking or not taking study medication and assessments performed during the study. Local guidance on any additional consent requirements should be followed as well as requirements for informed consent for pregnant minors. IRBs and ECs experienced in this patient population may also advise regarding the appropriateness of any proposed compensation for study participants.

The consent process should seek consent on follow-up of the pregnancy/infant/child. This may include information on the planned duration of follow-up and any additional data sources that may be used. The information provided to the patient and HCPs should make it clear how study procedures will be handled in the case of uncomplicated and complicated deliveries and that clinical care takes precedence over the study protocol. The informed consent should also include release of medical records to obtain relevant information on the course of the medical condition, the pregnancy, obstetric history, and follow-up information on the infant. It should also explain confidentiality of the study data and possible implications of participation (e.g., revealing of underlying genetic conditions that otherwise would not have been identified or follow-up of the exposed child may disclose underlying maternal conditions).

Participants who have a confirmed pregnancy while enrolled in a clinical trial should be provided with information to make an informed decision for both themselves and their fetus regarding options as per protocol for (1) staying on study investigational product, (2) suspending investigational product until later in or after pregnancy (3) discontinuing the investigational product and moving to pregnancy follow-up or (4) withdrawing from the study. The information provided to participants should clearly explain any changes to the protocol that are needed to allow for these women to reduce or suspend relevant study assessments until their pregnancy outcome occurs. Participants who withdraw from the study should understand the importance of follow-up of their pregnancy outcome and be encouraged to consent to collection of this data.

Additional circumstances related to clinical trials in pregnancy where participants should be reconsented include:

- When mandatory contraceptive requirements of the trial have been removed while the trial is ongoing (see Sections 4.1.2 and 4.2.11);

- When new information changes the assessment between benefits and risks for the pregnant participant or her fetus.

5. BREASTFEEDING

5.1 Development Strategy

The benefit-risk considerations for medicinal product use during breastfeeding involve multiple factors, such as the amount of investigational product present in breastmilk, the extent of absorption by the child, the potential benefits and risks of the medicine for the patient and the breastfed child, available treatment alternatives, the benefits of breastfeeding, and available alternatives to breastfeeding.

Sections 5.2 and 5.3 of this guideline discuss the following:

- Obtaining information on the transfer of investigational product into breastmilk (either without or with investigational product exposure to the infant as discussed in Sections 5.2.1 and 5.2.2, respectively);
- Subsequently, inclusion of breastfeeding women 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).

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. Since investigational product exposure to the infant can be avoided by replacing breastmilk with formula or other supplemental nutrition, whether and, if so, when to allow such exposure during development must be carefully considered.

Sponsors should anticipate if, and when, clinical trials involving breastfeeding women may be initiated and plan to conduct studies to gather information on exposure levels and effects on a breastfed child if needed as early as possible in development. Early planning for when and how to obtain the relevant data may enable optimizing the clinical development strategy of the investigational product. 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.

The approach to collecting data related to breastfeeding should consider the level of information available on the investigational product (e.g., physicochemical characteristics, mechanism of entry into breastmilk, data from nonclinical studies such as pre- and postnatal development and juvenile toxicology studies, and infant factors, such as differences due to infant metabolic pathways). In addition, there could be other data sources to consider such as use of the investigational product in pediatric patients. Early identification of available data and knowledge gaps should be addressed to establish the safe and effective use of medicinal products for breastfeeding women.

Women participating in efficacy clinical trials of the investigational product during pregnancy may be willing to participate in lactation studies. Data from such participants can provide important information for breastfeeding in the immediate postpartum period. Participants who are not intending to breastfeed could participate in lactation studies with no planned infant exposure.

5.1.1 Evidence Generation Planning Related to Investigational Product Use and Breastfeeding

Developing a strategy to collect data relevant to breastfeeding can be broadly categorized into the following steps: (1) determine the concentration of investigational product in breastmilk (relative to maternal therapeutic blood levels), (2) use breastmilk concentration data for estimation of the daily infant dose and relative infant dose, and (3) collect infant exposure, safety, and benefit data, as applicable. Together this information is important in determining the appropriate breastfeeding and/or treatment advice.

Lactation studies (see Section 5.2) which evaluate investigational product levels in breastmilk can contribute to an understanding of any potential effects on the breastfed infant and may be appropriate to be conducted as a clinical pharmacology trial. Studies which allow exposure of the child to the investigational product through breastmilk enable evaluation of whether the presence of the investigational product in milk has any impact on the breastfed infant.

Milk composition and quantity may vary during lactation, with different patterns of breastfeeding and age of the child, which may affect the amount of investigational product to which the infant is exposed. Therefore, inclusion of women at different stages of breastfeeding is encouraged. Additionally, colostrum, foremilk, and hindmilk vary in composition, which should be considered when PK analysis of breastmilk is being planned.

5.1.2 Nonclinical Considerations

Nonclinical studies may be used to generate data on lactational exposure to an investigational product. The standard pre- and postnatal development (PPND) study (see ICH S5) exposes the pups both during gestation and lactation. This study provides information on 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. A challenge of this study is understanding whether any neonatal effects observed were related to the gestational or lactational exposure. To distinguish this, a juvenile toxicology study with direct dosing of juvenile animals can be used to further characterize potential risks (see ICH S11).

Qualified/validated alternative assays (ICH S5) may also be used to generate lactational exposure data. In addition, appropriate use of modeling techniques, such as PBPK modeling, may provide insights into likely levels of an investigational product in breast milk, and subsequent infant exposure, absorption, and metabolism (see ICH M15).

5.2 Lactation Studies

5.2.1 Lactation Studies Assessing Investigational Product Levels in Maternal Milk

This section discusses lactation studies that assess product levels in maternal milk with no infant exposure to investigational product through breastmilk (i.e., maternal-only studies). These studies are usually conducted in breastfeeding patients but, when necessary, can be conducted in breastfeeding healthy volunteers. In both cases, the participant must pump and discard the breastmilk. The data collected from these studies are considered a prerequisite for the planning of the studies described in Section 5.3.

Women could be enrolled once they have decided to stop breastfeeding their child or are willing to interrupt breastfeeding during the study and until all investigational product would be expected to be cleared from the breastmilk and maternal blood.

Lactation studies evaluating investigational product levels in breastmilk provide detailed information about the amount/concentration and duration of an investigational product in breastmilk. The data can also be used to model the likely exposure levels in the infant (e.g., amount of investigational product in milk and predicted absorption in the infant). As they are usually short in duration, these studies could be designed as stand-alone studies or as an initial sub-study of a larger trial that at some later point intends to enroll or include breastfeeding participants.

Lactation studies that assess product levels in maternal milk only can also be conducted in breastfeeding women who are taking a medicinal product as part of clinical care.

5.2.2 Lactation Studies Assessing Exposure in Breastfed Infants

This section discusses lactation studies that assess investigational product levels in the maternal milk as well as in the infant exposed through breastmilk. These studies include both mother and infant as part of the study population (i.e., mother-infant pair studies). This scenario includes opportunistic studies which recruit patients who are already on a marketed medication based on clinical need and choose to continue treatment during breastfeeding, stand-alone lactation studies, and lactation studies conducted within clinical trials where breastfeeding women are enrolled along with the general population.

For lactation studies in which the infant is exposed to the investigational product, that are not opportunistic in design, data are needed to support a favorable benefit-risk profile in the infant. Such data may include nonclinical data, lactation data on the amount of investigational product in milk, and modeling to predict absorption in the infant. Uptake of the investigational product in the infant needs to be evaluated, using paired sampling from mothers and their breastfed infant. The study should evaluate whether the amount absorbed may have short and/or long-term implications for the infant as appropriate.

5.3 Inclusion of Breastfeeding Women in Clinical Trials

The inclusion of breastfeeding women in clinical trials for indications in the general population may be permissible with the appropriate data available and considerations for benefit-risk for both the mother and the child. Lactation studies can support the benefit-risk profile of breastfeeding to the infant while participants are in the 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. Inclusion of breastfeeding women in clinical trials may also be permissible when the infant has a potential benefit from investigational product exposure that outweighs the potential risks.

Depending on the numbers of participants, the inclusion of breastfeeding women in clinical trials may allow for evaluations of whether dose, efficacy, and safety are similar to the non-breastfeeding population. Additionally, it could be evaluated whether the investigational product affects breastfeeding.

5.3.1 Study Design

Clinical trials that enroll breastfeeding women should minimize the potential risks to the breastfed infant and assess safety in exposed infants. 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. Data collection should be planned such that the burden of trial participation remains manageable for trial participants (see Section 5.4.2).

Given the specialist knowledge required for investigational product and disease impacts on breastfeeding, postpartum physiology, and child health, consultation with relevant specialists (e.g., specialists in breastfeeding and breastfeeding support) should be available for study design and safety monitoring (e.g., Data Monitoring Committee or other safety oversight body) to help interpret any AEs reported during the study.

As evaluation of the child's well-being and adequate development is crucial in these situations, the presence of neonatologist/pediatricians in the study teams is also recommended.

5.3.2 Pharmacokinetics and Dosing Considerations

As there are physiological changes in the postpartum period (e.g., reduced plasma volume during lactation), albeit to a lesser extent than during pregnancy and which progressively normalize over time, the collection of PK data from the breastfeeding participant at various stages of breastfeeding should be considered at least until return to pre-pregnancy status.

In general, changes in dosing regimen during breastfeeding are not expected to be necessary. However, if dosages have been adjusted due to pregnancy, time to readjust to pre-pregnancy doses may need to be considered. 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.

5.3.3 General Outcomes Related to Breastfeeding

When enrolled in clinical trials along with the general population, study participants who are breastfeeding should, wherever possible, be evaluated with the same efficacy outcomes as those in the general study population, with the same endpoints and frequency of evaluation.

If the planned assessment may expose a breastfed child to a specific risk (e.g., effect of radiological contrast dye on the milk) alternative assessments or endpoints should be considered or the breastmilk could be temporarily discarded for the required time to avoid exposing the child to a specific risk.

Outcomes of interest related to breastfeeding should be selected with relevance for investigational product labeling and health outcomes of mother and infant. Impact on lactation itself should be evaluated (e.g., effects on breastmilk production). Data on lactation stage or the schedule of breastfeeding, child age, other medical conditions of the mother or infant, and concomitant therapies that could affect breastfeeding or have an impact on the infant should be recorded.

Sparse PK sampling approaches can be useful to supplement detailed PK data to enlarge the patient population studied. Even when some trial data are available on the effects of the investigational product on breastmilk production, the levels in the breastmilk, and the absorption by the breastfed infant (when appropriate), it may be useful to collect data from other breastfeeding study participants to enhance the dataset.

5.3.4 Safety Monitoring Related to Breastfeeding

Standard general recommendations on safety evaluation such as classification, assessment, and reporting of AEs (i.e., ICH E2A, ICH E2F, ICH E6(R3), ICH E8(R1)) apply to studies including breastfeeding women. In addition, the safety assessment considerations in this section apply. When both the mother and the infant are exposed to the investigational product, uptake of the product in the infant needs to be understood (or evaluated, if necessary), at relevant timepoints. Where present, the study should evaluate whether the amount absorbed may have short and/or long-term implications for the breastfed child (e.g., severity/frequency of AEs or impact on growth and/or development, as appropriate). Depending on the specific impact, a safety follow-up plan should be implemented.

The planned follow-up assessments should consider the general well-being of the child, as well as any outcomes predicted from the pharmacologic effects and the safety profile of the investigational product. Information from investigational products within the same class or experience with use of the investigational product in pediatric populations may be helpful for setting the safety follow-up plan. It should be considered whether monitoring of the effect on lactation and the child may be needed beyond the duration of the trial.

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.

5.3.5 Discontinuation and Suspension of Treatment

The protocol should outline criteria for discontinuing breastfeeding in case of emerging safety concerns to the breastfed child. Additionally, consideration should be given whether adjustments to the breastfeeding strategy (e.g., timing or pump and discard) could serve as effective measures to ensure infant safety, allowing the mother to continue participating in the trial.

For studies involving breastfeeding participants, in addition to standard sources, any new safety signal emerging from pediatric exposures should be considered (e.g., other or ongoing clinical trials with the study investigational product(s)) as these might provide information relevant for the exposed child.

5.4 Recruitment and Retention of Study Participants

5.4.1 Recruitment of Study Participants

Recruitment strategies for inclusion of breastfeeding women may differ depending on whether enrollment is for lactation studies or for clinical trials. Early consideration of how and when to engage with potential participants may enhance the ability to recruit participants to relevant studies to obtain clinically relevant information on investigational products in a timely manner.

The following points should also be considered:

- Engaging patients and stakeholders in advance of recruitment to provide accurate, relevant information on a specific trial may reduce concerns of potential participants and their close family and/or social group, if applicable, about participating in research;

- Involving patients and other stakeholders such as relevant healthcare teams early in the study design stages, could provide insights into how to better monitor and collect timely information to enable any risk mitigation during the study to support recruitment and retention of participants during the study;

- Providing education to HCPs about study participation for their patients and address any concerns in order to encourage participation;

- Cultural differences regarding breastfeeding.

When an investigational product is to be used from the very early postpartum period, it could be preferable to start screening procedures for patient enrollment during the pregnancy period to be ready to potentially include the patient in the trial immediately after delivery. If screening is started during pregnancy, some screening procedures may need to be repeated to confirm eligibility before enrollment.

For clinical trials in which infants are exposed to investigational product through breastmilk, recruitment efforts will need to include facilitating the understanding of benefits and risks through educational materials for the mother and their families when appropriate and the impact of trial participation on breastfeeding intentions. The purpose and types of study procedures should be clearly explained to participants.

5.4.2 Reducing Burden on Participants

Flexibility can be incorporated into several aspects of the study to reduce the burden on participants.

Early and avoidable discontinuation of participants can be mitigated by recognition and support of the challenges of this period. To lessen the burden for participants, assessments required as part of a study protocol may be integrated with information contained in records from standard pediatric care visits where appropriate and feasible. Additional considerations to reduce burden to study participation include:

- Quantities of breastmilk required for sample analysis should be minimized;
- Where appropriate, interventions for sampling infant blood should be minimized;
- Consideration should be given to providing breastmilk pumps for efficient milk expression or use of alternative methods for sampling;
- Provision of care/activities for the child;
- If possible, and without compromising study integrity, provide real-time results to participants in lactation studies evaluating investigational product levels in breastmilk, to allow restarting of breastfeeding (if appropriate);
- It is recommended that participants collect and store samples or utilize home health nurses, when appropriate;

- 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;

- Lactation consultants (or their equivalent) can be used to help the participants continue to express sufficient quantities of milk during the clinical trial.

5.5 Informed Consent for Studies with Breastfeeding Participants

For informed consent the principles of ICH E6(R3) apply, and additional considerations for breastfeeding and lactation are outlined below.

Depending on the study design, informed consent may need to consider the potential benefit and exposure risk to the mother and the infant, and risks related to study procedures for the mother and the infant (e.g., breastmilk sampling or blood draws). Consent should follow regional guidance related to parental consent. The consent should also include information on how clinical trial processes and procedures may impact breastfeeding and prioritizing participant and infant safety.

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. In a lactation study where the infant is not exposed to the investigational product, the participant should be advised about the duration that the investigational product will be present in breastmilk to avoid inadvertently exposing the breastfed child to the investigational product. 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 her infant (e.g., prematurity) that may affect prioritizing breastmilk provision vs. research participation.

Additionally, depending on the study design, for studies that permit breastfeeding during exposure to the investigational product:

- Up-to-date information about the investigational product and its clinical and nonclinical development should be made available, to support decisions regarding breastfeeding, especially in relation to investigational product transfer through breastmilk.

- Local guidance on any additional consent requirements should be followed if an infant would be exposed to the investigational product through breastmilk.

- The informed consent should include follow-up plans for the infant, including the frequency and type of safety assessments conducted, and access to infant medical records, if appropriate.

- It may be appropriate for the informed consent to include release of information from maternal medical records to obtain relevant information on the course of the medical condition and the pregnancy.

There may be circumstances where participants should be reconsented (e.g., new information that changes the assessment of benefits and/or risks of the investigational product for the breastfeeding participant or the breastfed child).

IRBs and ECs experienced in this patient population may also advise regarding the appropriateness of any proposed compensation for study participants.

6. APPENDICES

APPENDIX 1: CONSIDERATIONS FOR LABELING

Sources for information in product labeling include nonclinical data and clinical data such as PK, PD, and dose data obtained through relevant studies and/or modeling and simulations, clinical efficacy and safety trials, epidemiological studies, pregnancy registries, and pharmacovigilance pertaining to pregnant and breastfeeding women.

When available, and depending on regional labeling guidances and subject to regulatory review, the following information should be considered for inclusion in labeling:

- Recommended dose during pregnancy and any dosage adjustments during pregnancy, breastfeeding, and/or the postpartum period;
- The product’s effects on the pregnancy (such as risk of miscarriage or pregnancy complications);
- Risks of disease progression during pregnancy (e.g., potential worsening of the disease/condition if under- or untreated);
- The potential for the product to cross the placenta;
- Effects on the fetus (such as risks of congenital malformation, effect on fetal growth, and potential for long-term effects on the infant and the child);
- Extent of the product’s presence in breastmilk and exposure of the breastfed infant;
- Effects of the product on lactation and on the breastfed child;
- Any adverse drug reactions or withdrawal symptoms in the neonate;
- Any recommended measures to minimize a product’s risk to pregnant and breastfeeding women and to the fetus or the infant;
- Any monitoring recommendations for pregnant and breastfeeding women and the fetus or the infant;
- Any differences identified for the above items based on demographic, disease state, or other subpopulations.

APPENDIX 2: ADDITIONAL OUTCOMES TO BE CONSIDERED IN CLINICAL TRIALS INCLUDING PREGNANT PARTICIPANTS

In addition to standard reporting requirements and Good Clinical Practice (GCP) (see ICH E6(R3)), the following outcome parameters are to be considered, with attention to the disease/condition being treated by the investigational product, investigational product properties, duration of use, and therapeutic context.

Maternal and Gestational Outcomes of Interest:

Standard maternal and gestational measures of interest include pregnancy outcome, including timing and underlying circumstances of pregnancy losses, (particularly if due to congenital malformation), characteristics and gestational age at birth (e.g., cesarean section delivery or preterm), and infant measurements at birth (e.g., weight).

In addition to these standard measures and where relevant, consideration should be given to the following:

- Identification of congenital malformation prenatally (e.g., fetal cardiac ultrasound);
- Gestational/prenatal assessments and findings, including complications of pregnancy (e.g., chorioamnionitis or intrauterine growth restriction);
- Maternal conditions affecting gestational health (e.g., gestational diabetes, disease flares, or opportunistic infections);
- Obstetric history (e.g., miscarriages along with previous history of preeclampsia/eclampsia, postpartum hemorrhage, caesarean section, or allergies to specific medicinal products);
- Characteristics of childbirth including complications of labor (e.g., premature rupture of membranes, method of delivery, stillbirth, or asphyxia);
- Placental pathology or notable placental abnormalities;
- Endpoints specific to multiple pregnancies, including chorionicity, zygosity, loss of one or more fetuses in a higher-order multiple pregnancy, and conditions such as twin-twin transfusion syndrome;

- Other relevant factors, e.g., use of folic acid, relevant paternal health factors, access to and quality of prenatal care, or use of assisted reproduction (including donor gametes/embryos).

Infant Characteristics at Birth:

Infant outcomes should include sex, gestational age at birth, infant weight at birth (e.g., small for gestational age) and congenital malformations or other functional or morphological abnormalities apparent at or immediately following birth.

Additional postnatal infant outcomes to be considered when relevant include:

- Cardiovascular and respiratory examinations, including need for supplemental oxygen or resuscitation;

- Developmental and functional assessments (e.g., APGAR or neurological assessment (muscle tone, spontaneous activity)).

Outcomes in the Neonatal Period and Infant Follow-up:

Neonatal outcomes to consider when relevant within the first 28 days after birth include:

- Size- and growth-related assessments;

- Developmental (including neurologic) assessments;

- Feeding characteristics including use of breastmilk and/or formula, occurrence of feeding difficulties, and gastrointestinal intolerances;

- Congenital malformations diagnosed in the neonatal period;

- Health of major organ systems (e.g., kidney or liver function);

- Postnatal infections or other health issues arising in the neonatal period including hospitalizations.

Infant follow-up outcomes of interest will differ based on the maternal disease or disorder, investigational product type, and gestational exposure. It should be considered that some neurological and physical developmental delays or conditions may not be visible until later in life.