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REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**INCLUSION OF PREGNANT AND BREASTFEEDING
INDIVIDUALS IN CLINICAL TRIALS
E21**

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ICH HARMONISED GUIDELINE
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E21

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1 **1. INTRODUCTION**

2 **1.1 Objective**

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

8 **1.2 Scope**

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

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

17 **1.3 Background**

18 Many individuals who are pregnant or breastfeeding have acute or chronic medical conditions
19 (including physical and/or mental health conditions that occur or may be exacerbated during
20 pregnancy and the postpartum period) that require new, ongoing, or preventative treatment(s).
21 Physiological changes during pregnancy can also have an impact on the pharmacokinetics (PK)
22 and/or pharmacodynamics (PD) of a medicinal product and there may be a need to modify the
23 dosage of medicinal products in pregnant individuals.

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

- 30 • HCPs and/or patients avoiding or discontinuing indicated treatments leading to
31 exacerbation of the condition or harm to the patient, pregnancy, or the child;
- 32 • HCPs and/or patients inadvertently choosing treatments harmful to the patient,
33 pregnancy, or the child;
- 34 • Use of a dose or treatment regimen that is sub- or supra-therapeutic, leading to
35 increased risk for under-treatment and/or adverse reactions;
- 36 • Avoidance or premature discontinuation of breastfeeding, or discontinuation of
37 indicated treatment to allow for breastfeeding.

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

40 **2. GENERAL PRINCIPLES**

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

47 Sponsors of drug development programs and clinical trials are encouraged to consider
48 strategies to generate data that support informed decision-making on the safety, dosing, and
49 efficacy of the medicinal product's use during pregnancy and breastfeeding. Sponsors are
50 recommended to consult with regulatory authorities as early as possible and as needed
51 throughout the investigational product development process regarding the plans for the
52 participation of pregnant and/or breastfeeding individuals in clinical trials. Every effort should
53 be made to reduce the burden of study procedures on pregnant and breastfeeding study
54 participants and it is essential to avoid any undue influence or coercion when pregnant or
55 breastfeeding individuals are included or planned to be included in clinical trials. Early
56 engagement with appropriate stakeholders, including patients, provides opportunities to
57 address all relevant aspects of these clinical trials.

58 Assessing the safety in pregnant and breastfeeding individuals is complex as there are potential
59 impacts on the fetus and breastfed child to consider. When considering including pregnant or
60 breastfeeding individuals in clinical trials, it is important to evaluate the risks and benefits
61 based on all available data, ensure that risks have been appropriately mitigated, and plan studies
62 that can yield scientifically robust data (see Sections 4.1.2 and 5.1.1).

63 Collection of data pertinent to use of an investigational product in pregnant and breastfeeding
64 individuals should continue into the postmarketing period. Ongoing safety monitoring of
65 product use in these populations in the postmarketing period contributes to the identification
66 of safety signals, especially for rare or delayed outcomes, that are unlikely to be thoroughly
67 addressed in pre-authorization clinical trials. Real-world data (RWD) used to generate
68 real-world evidence (RWE) can be helpful in assessing the usage and potential benefits or risks
69 of an investigational product in pregnant and breastfeeding individuals.

70 Ongoing assessment of an investigational product during pregnancy and breastfeeding may
71 draw from a variety of data sources, such as pharmacovigilance-generated data, electronic
72 health records, medical claims or health insurance databases, medicinal product or disease
73 registries, or other sources (such as digital health technologies). Because pregnancy and
74 breastfeeding present unique issues when gathering RWD, such as mother-child linkage, it is
75 encouraged to proactively prepare platforms for post-approval data collection and to collect
76 background information on population and disease-specific risks to assist with data
77 interpretation.

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

84 **3. ETHICAL CONSIDERATIONS**

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

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

98 **4. PREGNANCY**

99 **4.1 Development Strategy**

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

107 ***4.1.1 Factors to Consider When Planning for Pregnancy Data Collection***

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

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

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

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

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

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

139 Clinical trials of prenatal interventions intended to improve outcomes of the fetus/neonate are
140 not the focus of this guideline, however the principles discussed in this guideline may still
141 apply.

142 ***4.1.2 Evidence Needed to Support Inclusion of Pregnant Individuals in Clinical Trials***

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

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

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

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

162 Prior to proceeding to studies including pregnant individuals, the results from relevant
163 nonclinical studies need to be evaluated. These studies may include the standard
164 Developmental and Reproductive Toxicology (DART) studies (see ICH M3 and ICH S5), the
165 standard battery of genotoxicity studies if relevant (see ICH S2), appropriately
166 qualified/validated alternative tests, and any relevant modeling. It is necessary to assess the
167 nonclinical studies on how informative these studies would be on the safety of the
168 investigational product for the intended patient population and make necessary adjustments to
169 the type of studies needed and/or the study design. For instance, the timing and/or necessity for
170 DART studies may be influenced by the characteristics of the investigational product (such as
171 biotechnology derived pharmaceuticals as outlined in ICH S6(R1)), the clinical indication
172 (such as those covered by ICH S9), and/or the intended patient population (e.g., exposure
173 during the third trimester or the first trimester). Nonclinical data evaluation should be further
174 explored to understand any potential risk to a pregnancy. When risks are identified, further
175 investigations may be warranted with modified reproductive toxicology studies to characterize

176 them further (e.g., studies that investigate risks to the embryonic period vs. fetal period,
177 duration of dosing).

178 In addition to gathering the nonclinical data needed to proceed to studies in pregnancy,
179 acquiring clinical data in non-pregnant individuals will also usually be necessary. Generally,
180 clinical data that support safety and prospect of benefit in non-pregnant study participants could
181 reasonably be expected to be applicable for pregnant individuals. The necessary quantity and
182 type of data from non-pregnant participants will typically be similar to the data needed for an
183 investigational product to proceed through clinical development.

184 When the necessary nonclinical and clinical data become available, the sponsor should perform
185 a benefit-risk assessment that incorporates all relevant information described above, using a
186 weight of evidence approach. The objective of this assessment should be to determine whether
187 the risks of proceeding with trials in pregnancy are reasonable given the anticipated benefits.

188 If the sponsor determines that proceeding with trials in pregnancy is not yet reasonable, they
189 should seek to obtain further data unless there is a rationale for not studying the investigational
190 product in pregnancy. If the sponsor determines that proceeding with trials in pregnancy is
191 appropriate, then the following approaches/actions (in no specific order) need to be considered
192 and/or incorporated into the development strategy:

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

199 **4.1.3 When All the Data Necessary to Support a Favorable Benefit-risk Assessment are Not Yet**
200 **Available**

201 Before reaching the point where it may be appropriate to incorporate pregnant individuals into
202 the clinical development program, clinical studies using the investigational product will
203 typically have mandatory contraception requirements. Sponsors should recognize and plan for
204 the fact that pregnancies can occur when the study population includes individuals of

205 childbearing potential even when rigorous approaches to mandatory contraception are
206 implemented. Implications for study design and implementation when an unintended
207 pregnancy occurs are discussed in Section 4.2.11.

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

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

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

223 ***4.1.4 When Existing Data Suggest a Safety Concern for Pregnancy***

224 If nonclinical and/or clinical data suggest that the investigational product is potentially harmful
225 to the pregnant individual and/or the fetus, the sponsor may conclude that inclusion of pregnant
226 individuals in clinical trials is initially not warranted. However, for some investigational
227 products, the benefits of use in pregnancy may still outweigh the potential risks. Examples
228 include situations where the target disease has a serious negative impact (e.g., diseases such as
229 malaria, which are known to have adverse effects on both the mother and the fetus) or where
230 available treatment(s) have a safety concern in pregnancy (e.g., methotrexate for SLE). In such
231 cases, including pregnant individuals in the trial may be considered on a case-by-case basis. In
232 determining whether that is appropriate, it is essential to consider what additional data are
233 needed to characterize the benefit-risk and to explore whether any potential risks can be

234 mitigated. Additionally, consideration should be given to the fact that medical needs and
235 potential risks associated with the product may differ depending on the trimester of exposure.

236 **4.1.5 *Strategies for Obstetric Conditions***

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

242 **4.2 Inclusion of Pregnant Individuals in Clinical Trials**

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

250 **4.2.1 *Study Design and Implementation***

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

257 **4.2.2 *Expertise Considerations***

258 Given the specialist knowledge required for investigational product and disease impacts on
259 pregnancy, embryo-fetal development, and neonatology, consultation with relevant specialist
260 (e.g., obstetrician or maternal fetal medicine specialist) should be available for study design
261 and safety monitoring (e.g., Data Monitoring Committee or other safety oversight body) to help
262 interpret any adverse events (AEs) reported during pregnancy.

263 **4.2.3 *Sample Size***

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

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

271 The number of participants required to determine an efficacy endpoint should be achieved by
272 design for clinical trials of investigational products used for obstetric indications or in trials
273 designed for pregnant individuals only.

274 **4.2.4 *Pharmacokinetics and Dosing Considerations***

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

277 The physiological changes that occur during pregnancy may affect absorption, distribution,
278 metabolism, and elimination of the product potentially leading to an altered PK/PD profile of
279 the investigational product. In addition, the extent of these physiological changes can vary over
280 the course of pregnancy, so PK/PD should be assessed during the different trimesters and
281 postpartum. Depending on the duration of treatment, PK/PD measures should be assessed from
282 the same participant wherever possible. The postpartum assessment period should be
283 sufficiently long to understand PK/PD changes until the return to pre-pregnancy state.

284 For clinical trials that include pregnant participants, it is essential to include in the protocol
285 whether pregnant participants should receive the same dose as non-pregnant participants or a
286 different dose. Dose adjustments may be needed for pregnant participants in cases where
287 efficacy becomes suboptimal because of insufficient systemic exposure, or where the
288 therapeutic index or safety margins are narrow. To initially estimate the dosage/dosing regimen
289 for pregnant participants, clinical and dose-exposure data from non-pregnant participants could
290 be considered. Modeling approaches, such as physiologically based pharmacokinetics (PBPK)
291 modeling, which accounts for the PK alterations in pregnancy, may help to estimate the dosing
292 strategy. Any observed PK alterations in pregnant participants, exposure-response analysis, and

293 population PK analysis, all provide important information for proper dose selection for
294 pregnant participants.

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

299 **4.2.5 Fetal Exposure Assessment**

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

307 **4.2.6 Endpoints and Outcomes**

308 Pregnant participants should be evaluated with the same efficacy, safety, PK, and PD endpoints
309 as those in the general study population, with the same frequency of evaluation whenever
310 feasible (for information on analysis, see Section 4.2.10). Additional endpoints may also be
311 needed for pregnant participants (e.g., PK/PD data). When the planned method to measure the
312 endpoint may present a risk in pregnancy (e.g., CT scans), the participant should be followed
313 for safety or efficacy using alternative methods when available. Considerations regarding the
314 type of data to be collected are similar whether the participant is enrolled while pregnant or
315 becomes pregnant during trial participation.

316 **4.2.7 Assessments and Data Collection for Pregnant Participants**

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

319 Standard general recommendations on safety evaluation such as classification, assessment, and
320 reporting of AEs (i.e., ICH E2A, ICH E2F, ICH E6(R3), ICH E8(R1)) apply to studies
321 including pregnant participants. The safety assessment considerations in this section and in
322 Appendix 2 apply in addition to standard assessments. Furthermore, a plan to follow and collect

323 pregnancy-specific outcome data systematically is needed to evaluate the impact of the
324 investigational product on maternal and fetal/infant/child health. How this is best achieved will
325 need to be considered on a study specific basis, and depends on several factors, including but
326 not limited to:

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

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

340 Local routine pregnancy monitoring for trial participants may be part of study-specific
341 assessments. These may include prenatal and postpartum follow-up visits, neonatal
342 consultations, ultrasound scans, and blood and urine tests.

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

347 **4.2.8 Assessments and Data Collection for Infants**

348 The duration of follow-up should be considered on a case-by-case basis and will depend on the
349 investigational product's half-life, indication, nonclinical data, mechanism of action, timing
350 and duration of exposure, and time to manifestation of outcomes of interest, taking into

351 consideration that birth defects and functional or neurodevelopmental disorders may be
352 diagnosed beyond birth. Infant characteristics at birth and outcomes in the neonatal period to
353 be considered are included in Appendix 2. It is recognized that the follow-up may extend until
354 past the clinical trial completion date. Sponsors should ensure a mechanism for such follow-up
355 is in place. Options may include subgroup-specific safety follow-up studies, enrollment in
356 existing programs such as pregnancy registries, or other appropriate methods to ensure longer-
357 term data collection on infant outcomes.

358 **4.2.9 Safety Monitoring**

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

364 Provision for suspending or discontinuing investigational product for pregnant participants
365 should be considered in the event of an emerging pregnancy-related safety signal. Sources for
366 the detection of a signal could include clinical trials and post-trial follow-up, from clinical use
367 during pregnancy or pediatric use, or published data, if applicable.

368 **4.2.10 Analysis and Interpretation**

369 Data on efficacy, PK, and safety for pregnant individuals can help inform conclusions regarding
370 whether the efficacy, dosing, and safety of the investigational product in pregnant individuals
371 are similar to the general population. Clinical trial data even from a small sample size may
372 contribute important information for product labeling. In addition, PK data from a small set of
373 pregnant participants can help to reinforce data from models approximating exposure in the
374 pregnant population at large. However, care should be taken when analyzing clinical trial
375 results in small subpopulations, such as pregnant individuals, as this may lead to difficulty with
376 interpreting adverse pregnancy outcomes.

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

382 whether and how treating the underlying health condition with the investigational product
383 benefits the pregnancy.

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

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

392 ***4.2.11 Considerations for Pregnancies Occurring During a Clinical Trial With Mandatory***
393 ***Contraception***

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

- 396 1. Allow as appropriate, the option of remaining in the trial with suspension of
397 investigational product for the duration of the pregnancy, or earlier resumption once
398 data to support resumption of investigational product are available;
- 399 2. In some cases where pregnancy occurred, allow the option of continuing on treatment
400 after consenting (see Section 4.1.3 for considerations as to when this might be
401 appropriate);
- 402 3. For both situations above, provide for additional data collection (e.g., PK, PD, and
403 additional safety monitoring, see Appendix 2);
- 404 4. Specify whether and when unblinding would be expected. A participant becoming
405 pregnant should not automatically lead to the unblinding of the participant's treatment
406 assignment.

407 **4.3 Recruitment and Retention of Pregnant Individuals in Clinical Trials**

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

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

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

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

- 422 • Involving potential participants and other stakeholders such as relevant healthcare
423 teams (e.g., obstetric and maternal-fetal medicine professionals) early in the study
424 design stages, could provide input on patient-orientated outcomes of interest and/or
425 reducing burdens for inclusion of pregnant individuals in clinical trials (see
426 Section 4.3.2);
- 427 • Consideration of cultural differences regarding aspects of the birth, cord blood, and
428 placenta (and use of placental samples) may identify important aspects;
- 429 • Engaging HCPs familiar with the community (e.g., midwives, community [home
430 health] nurses, or prenatal care providers) may help recruitment (e.g., introducing trial
431 information or asking for contact information to follow-up);
- 432 • Involving healthcare teams relevant to pregnancy could enable education of HCPs
433 about the value of their patients participating in research on conditions which may affect
434 pregnancy and health of the future child, to address any concerns and to encourage
435 participation;
- 436 • Early consideration of how and when to engage with potential participants may enhance
437 the ability to recruit pregnant individuals (including those at a particular trimester of
438 pregnancy) to relevant clinical trials and may enable best use of sponsor resources.

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

443 **4.3.1 Recruitment of Pregnant Individuals for Clinical Trials**

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

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

458 **4.3.2 Reducing Burden and Harm on Pregnant Individuals in Clinical Trials**

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

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

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

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

475 **4.4 Informed Consent for Studies with Pregnant Participants**

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

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

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

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

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

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

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

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

- 518 • When mandatory contraceptive requirements of the trial have been removed while the
519 trial is ongoing (see Sections 4.1.2 and 4.2.11);
- 520 • When new information changes the assessment between benefits and risks for the
521 pregnant participant or their fetus.

522 **5. BREASTFEEDING**

523 **5.1 Development Strategy**

524 The benefit-risk considerations for medicinal product use during breastfeeding involve
525 multiple factors, such as the amount of investigational product present in breastmilk, the extent

526 of absorption by the child, the potential benefits and risks of the medicine for the patient and
527 the breastfed child, available treatment alternatives, the benefits of breastfeeding, and available
528 alternatives to breastfeeding.

529 Sections 5.2 and 5.3 of this guideline discuss the following:

- 530 • Obtaining information on the transfer of investigational product into breastmilk (either
531 without or with investigational product exposure to the infant as discussed in
532 Sections 5.2.1 and 5.2.2, respectively);
- 533 • Subsequently, inclusion of breastfeeding individuals in clinical trials in the general
534 population after the investigational product's characteristics related to breastfeeding
535 have been determined (as discussed in Section 5.3).

536 The clinical development strategy for investigational product use in breastfeeding should be
537 tailored to the stage of development and existing knowledge about the investigational product.
538 Since investigational product exposure to the infant can be avoided by replacing breastmilk
539 with formula or other supplemental nutrition, whether and, if so, when to allow such exposure
540 during development must be carefully considered.

541 Sponsors should anticipate if, and when, clinical trials involving breastfeeding individuals may
542 be initiated and plan to conduct studies to gather information on exposure levels and effects on
543 a breastfed child if needed as early as possible in development. Early planning for when and
544 how to obtain the relevant data may enable optimizing the clinical development strategy of the
545 investigational product. Of note, there may still be a need to understand how the product may
546 affect lactation or the breastfed infant, even if the medicinal product is not to be used in
547 pregnancy.

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

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

561 **5.1.1 Evidence Generation Planning Related to Investigational Product Use and Breastfeeding**

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

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

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

578 **5.1.2 Nonclinical Considerations**

579 Nonclinical studies may be used to generate data on lactational exposure to an investigational
580 product. The standard pre- and postnatal development (PPND) study (see ICH S5) exposes the
581 pups both during gestation and lactation. This study provides information on the effects of the
582 investigational product on both the pups (e.g., adverse effects on pups) and lactation (e.g., milk
583 quality and quantity) that can characterize the potential risk(s) to a neonate. A challenge of this
584 study is understanding whether any neonatal effects observed were related to the gestational or
585 lactational exposure. To distinguish this, a juvenile toxicology study with direct dosing of
586 juvenile animals can be used to further characterize potential risks (see ICH S11).

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

591 **5.2 Lactation Studies**

592 **5.2.1 *Lactation Studies Assessing Investigational Product Levels in Maternal Milk***

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

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

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

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

611 **5.2.2 *Lactation Studies Assessing Exposure in Breastfed Infants***

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

617 lactation studies, and lactation studies conducted within clinical trials where breastfeeding
618 individuals are enrolled along with the general population.

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

626 **5.3 Inclusion of Breastfeeding Individuals in Clinical Trials**

627 The inclusion of breastfeeding individuals in clinical trials for indications in the general
628 population may be permissible with the appropriate data available and considerations for
629 benefit-risk for both the mother and the child. Lactation studies can support the benefit-risk
630 profile of breastfeeding to the infant while participants are in the trial if they demonstrate no
631 clinically relevant transfer of the investigational product into breastmilk or when there is no
632 clinically relevant absorption in the infant. Inclusion of breastfeeding individuals in clinical
633 trials may also be permissible when the infant has a potential benefit from investigational
634 product exposure that outweighs the potential risks.

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

639 **5.3.1 Study Design**

640 Clinical trials that enroll breastfeeding individuals should minimize the potential risks to the
641 breastfed infant and assess safety in exposed infants. When there is reasonable scientific
642 assumption that the investigational product may not be meaningfully absorbed from breastmilk
643 or the potential benefits for mother and infant outweigh any potential risk to the infant, the
644 protocol could allow a choice for participants to keep breastfeeding. Data collection should be
645 planned such that the burden of trial participation remains manageable for trial participants (see
646 Section 5.4.2).

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

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

654 **5.3.2 *Pharmacokinetics and Dosing Considerations***

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

659 In general, changes in dosing regimen during breastfeeding are not expected to be necessary.
660 However, if dosages have been adjusted due to pregnancy, time to readjust to pre-pregnancy
661 doses may need to be considered. In addition, studies to assess alterations to the breastfeeding
662 strategy (e.g., timing of breastfeeding the child), in relation to dose regimen should be
663 considered, if applicable.

664 **5.3.3 *General Outcomes Related to Breastfeeding***

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

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

672 Outcomes of interest related to breastfeeding should be selected with relevance for
673 investigational product labeling and health outcomes of mother and infant. Impact on lactation
674 itself should be evaluated (e.g., effects on breastmilk production). Data on lactation stage or
675 the schedule of breastfeeding, child age, other medical conditions of the mother or infant, and

676 concomitant therapies that could affect breastfeeding or have an impact on the infant should be
677 recorded.

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

683 **5.3.4 Safety Monitoring Related to Breastfeeding**

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

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

699 Interpretation of the causality of AEs in the infant exposed to investigational product during
700 breastfeeding should be made with caution and take into consideration any medical condition
701 of the infant and other confounding factors (e.g., maternal diet, concomitant medicinal products
702 or need for supplemental nutrition with formula or other supplement), and any prior *in utero*
703 exposure.

704 **5.3.5 *Discontinuation and Suspension of Treatment***

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

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

714 **5.4 Recruitment and Retention of Study Participants**

715 **5.4.1 *Recruitment of Study Participants***

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

721 The following points should also be considered:

- 722 • Engaging patients and stakeholders in advance of recruitment to provide accurate,
723 relevant information on a specific trial may reduce concerns of potential participants
724 and their close family and/or social group, if applicable, about participating in research;
- 725 • Involving patients and other stakeholders such as relevant healthcare teams early in the
726 study design stages, could provide insights into how to better monitor and collect timely
727 information to enable any risk mitigation during the study to support recruitment and
728 retention of participants during the study;
- 729 • Providing education to HCPs about study participation for their patients and address
730 any concerns in order to encourage participation;
- 731 • Cultural differences regarding breastfeeding.

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

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

742 **5.4.2 Reducing Burden on Participants**

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

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

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

- 760 • Encourage participants to pump and store breastmilk prior to dosing such that the infant
761 can be fed for several hours to a day or more with pre-study milk;
- 762 • Lactation consultants (or their equivalent) can be used to help the participants continue
763 to express sufficient quantities of milk during the clinical trial.

764 **5.5 Informed Consent for Studies with Breastfeeding Participants**

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

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

773 Participants enrolling in a lactation study should be informed that the primary purpose is to
774 investigate the investigational product levels in the blood (i.e., maternal and may include
775 infant) and breastmilk and the correlation between them. In a lactation study where the infant
776 is not exposed to the investigational product, the participant should be advised about the
777 duration that the investigational product will be present in breastmilk to avoid inadvertently
778 exposing the breastfed child to the investigational product. The following should also be
779 considered: timing of sampling and testing, duration of interruption of breastfeeding, the
780 availability of nutritional alternatives to mother's milk, and conditions of their infant (e.g.,
781 prematurity) that may affect prioritizing breastmilk provision vs. research participation.

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

- 784 • Up-to-date information about the investigational product and its clinical and nonclinical
785 development should be made available, to support decisions regarding breastfeeding,
786 especially in relation to investigational product transfer through breastmilk.
- 787 • Local guidance on any additional consent requirements should be followed if an infant
788 would be exposed to the investigational product through breastmilk.

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

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

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

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

800 **6. APPENDICES**

801 **APPENDIX 1: CONSIDERATIONS FOR LABELING**

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

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

- 808 • Recommended dose during pregnancy and any dosage adjustments during pregnancy,
809 breastfeeding, and/or the postpartum period;
- 810 • The product's effects on the pregnancy (such as risk of miscarriage or pregnancy
811 complications);
- 812 • Risks of disease progression during pregnancy (e.g., potential worsening of the
813 disease/condition if under- or untreated);
- 814 • The potential for the product to cross the placenta;
- 815 • Effects on the fetus (such as risks of congenital malformation, effect on fetal growth,
816 and potential for long-term effects on the infant and the child);
- 817 • Extent of the product's presence in breastmilk and exposure of the breastfed infant;
- 818 • Effects of the product on lactation and on the breastfed child;
- 819 • Any adverse drug reactions or withdrawal symptoms in the neonate;
- 820 • Any recommended measures to minimize a product's risk to pregnant and breastfeeding
821 individuals and to the fetus or the infant;
- 822 • Any monitoring recommendations for pregnant and breastfeeding individuals and the
823 fetus or the infant;
- 824 • Any differences identified for the above items based on demographic, disease state, or
825 other subpopulations.

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

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

832 **Maternal and Gestational Outcomes of Interest:**

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

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

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

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

856 **Infant Characteristics at Birth:**

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

860 Additional postnatal infant outcomes to be considered when relevant include:

- 861 • Cardiovascular and respiratory examinations, including need for supplemental oxygen
862 or resuscitation;
- 863 • Developmental and functional assessments (e.g., APGAR or neurological assessment
864 (muscle tone, spontaneous activity)).

865 **Outcomes in the Neonatal Period and Infant Follow-up:**

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

- 867 • Size- and growth-related assessments;
- 868 • Developmental (including neurologic) assessments;
- 869 • Feeding characteristics including use of breastmilk and/or formula, occurrence of
870 feeding difficulties, and gastrointestinal intolerances;
- 871 • Congenital malformations diagnosed in the neonatal period;
- 872 • Health of major organ systems (e.g., kidney or liver function);
- 873 • Postnatal infections or other health issues arising in the neonatal period including
874 hospitalizations.

875 Infant follow-up outcomes of interest will differ based on the maternal disease or disorder,
876 investigational product type, and gestational exposure. It should be considered that some

877 neurological and physical developmental delays or conditions may not be visible until later in
878 life.