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

**ICH HARMONISED GUIDELINE**

**GENERAL CONSIDERATIONS FOR CLINICAL  
STUDIES**

**E8(R1)**

Draft version

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*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures*

## E8(R1)

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• **ICH HARMONISED GUIDELINE**

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**E8(R1)**

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# General Considerations for Clinical Studies

## 1 OBJECTIVES OF THIS DOCUMENT

Clinical studies of medical interventions are conducted to provide information that can ultimately improve access to safe and effective drugs with meaningful impact on patients, while protecting those participating in the studies. This document focuses on designing quality into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions.

The ICH document "General Considerations for Clinical Studies" is intended to:

1. Describe internationally accepted principles and practices in the design and conduct of clinical studies that will facilitate acceptance of data and results by regulatory authorities
2. Provide guidance on the consideration of quality in the design and conduct of clinical studies across the product lifecycle, including the identification during study planning of factors that are critical to the quality of the study, and the management of risks to those factors during study conduct
3. Provide an overview of the types of clinical studies performed during the product lifecycle, and describe the aspects of those studies that support the determination of which quality factors are critical to ensuring the protection of study subjects, the integrity of the data, the reliability of results, and the ability of the studies to meet their objectives
4. Provide a guide to the ICH efficacy documents to facilitate user's access (Annex 2 and 3)

General principles of clinical study design are described in Section 2 of this document, followed by a discussion of designing quality into clinical studies in Section 3. A broad overview of planning a clinical development programme, the types of studies and study objectives that are important at different points in the programme, and issues of study feasibility from the perspective of sponsors, investigators, regulatory authorities, and patients are

28 provided in Section 4. In Section 5, the elements composing study design are described. Section  
29 6 describes study conduct, ensuring the safety of human subjects, and study reporting. A  
30 general discussion of identifying critical to quality factors for a study is provided in Section 7.

31 For the purposes of this document, a clinical study is meant to refer to a study of a medicinal  
32 product in humans, conducted at any point in a product's lifecycle. The term "drug" should be  
33 considered synonymous with "medicinal product," including vaccines and biological products.  
34 The term "drug approval" refers to obtaining marketing authorization for the drug.

## 35 **2 GENERAL PRINCIPLES**

### 36 **2.1 Protection of Clinical Study Subjects**

37 Important principles of ethical conduct of clinical studies and the protection of subjects,  
38 including special populations, are stated in other ICH guidelines (ICH E6 Good Clinical  
39 Practice, ICH E7 Clinical Trials in Geriatric Populations, ICH E11 Clinical Trials in the  
40 Pediatric Population, and ICH E18 Genomic Sampling).

41 These principles have their origins in the Declaration of Helsinki and should be observed in  
42 the conduct of all human clinical investigations. The investigator and sponsor share  
43 responsibility for the protection of study subjects together with the Institutional Review  
44 Board/Independent Ethics Committee.

45 The confidentiality of information that could identify subjects should be protected in  
46 accordance with the applicable regulatory and legal requirement(s).

47 Before initiating a clinical study, sufficient information should be available to ensure that the  
48 drug is acceptably safe for the planned study in humans. Emerging clinical and non-clinical  
49 data should be reviewed and evaluated, as they become available, by qualified experts to assess  
50 the potential implications for the safety of study subjects. Ongoing and future studies should  
51 be appropriately adjusted as needed, to take new knowledge into consideration and to protect  
52 study subjects.

### 53 **2.2 Scientific Approach in Clinical Study Design, Conduct, and Analysis**

54 Clinical studies should be designed, conducted, and analysed according to sound scientific  
55 principles to achieve their objectives, and should be reported appropriately. The essence of



56 clinical research is to ask important questions and answer them with appropriate studies. The  
57 primary objective of any study should be clear and explicitly stated.

58 Quality of a clinical study is considered in this document as fitness for purpose. The purpose  
59 of a clinical study is to generate reliable information to answer key questions and support  
60 decision making while protecting study subjects. The quality of the information generated  
61 should therefore be sufficient to support good decision making.

62 Quality by design in clinical research sets out to ensure that the quality of a study is driven  
63 proactively by designing quality into the study protocol and processes. This involves the use  
64 of a prospective, multidisciplinary approach to promote the quality of protocol and process  
65 design, and clear communication of how this will be achieved.

66 Across the product lifecycle, different types of studies will be conducted with different  
67 objectives and designs. Depending on the study objectives and the position of the study in the  
68 overall development plan, the data sources may vary. For purposes of this guideline, the  
69 development plan is considered to cover the entire product lifecycle and include non-clinical,  
70 clinical, and post-approval studies (Section 4). Annex 1 provides a broad categorisation of  
71 study type by objective within the different stages of drug development.

72 The cardinal logic behind serially conducted studies is that the results of prior studies should  
73 inform the plan of later studies. Emerging data will frequently prompt a modification of the  
74 development strategy. For example, results of a confirmatory study may suggest a need for  
75 additional human pharmacology studies.

### 76 **2.3 Patient Input into Study Design**

77 Consulting with patients and/or patient organisations in the design, planning and conduct of  
78 clinical studies helps to ensure that all perspectives are captured. Patients' views can be  
79 requested on all phases of drug development. Involving patients at the early stage of study  
80 design is likely to increase trust in the study, facilitate recruitment, and promote adherence,  
81 which should continue throughout the duration of the study. Patients also provide their  
82 perspective of living with a condition, which contributes to the determination of endpoints that  
83 are meaningful to patients, selection of the right population, duration of the study, and use of

84 the right comparators. This ultimately supports the development of medicines that are better  
85 tailored to patients' needs.

### 86 **3 DESIGNING QUALITY INTO CLINICAL STUDIES**

87 The quality by design approach to clinical research (section 3.1) involves focusing on critical  
88 to quality factors to ensure the protection of study subjects, the generation of reliable and  
89 meaningful results, and the management of risks to those factors (section 3.2). The approach is  
90 supported by the establishment of an appropriate framework for the identification and review  
91 of critical to quality factors (section 3.3).

#### 92 **3.1 Quality by Design of Clinical Studies**

93 Quality is a primary consideration in the design, planning, conduct and analysis of clinical  
94 studies and a necessary component of clinical development programmes. The likelihood that a  
95 clinical study will answer the research questions posed in a reliable manner, meaningful for  
96 decision makers and patients, while preventing important errors, can be dramatically improved  
97 through prospective attention to the design of all components of the study protocol, procedures  
98 and associated operational plans.

99 Quality should rely on good design and its execution rather than overreliance on retrospective  
100 document checking, monitoring, auditing or inspection. These activities are an important part  
101 of a quality assurance process but are not sufficient to ensure quality of a clinical study.

102 Good planning and implementation of a clinical study derive from attention to well-established  
103 principles of clinical research, which include the protection of the rights, safety and wellbeing  
104 of study subjects and scientific criteria, such as:

- 105 • the need for clear pre-defined study objectives that address the primary scientific  
106 question(s);
- 107 • selection of appropriate subjects that have the disease, condition, or molecular/genetic  
108 profile that is being studied;
- 109 • use of approaches to minimize bias, such as randomisation, blinding or masking, and/or  
110 control of confounding;
- 111 • endpoints that are well-defined and measurable, and methods of assessment of those  
112 endpoints that are accurate and able to be implemented with minimal reporting or  
113 measurement bias.

114 Operational criteria are also important, such as ensuring a clear understanding of the feasibility  
115 of the study, selection of suitable investigator sites, quality of specialised analytical and testing  
116 facilities and procedures, and processes that ensure data integrity.

### 117 **3.2 Critical to Quality Factors**

118 A basic set of factors relevant to ensuring study quality should be identified for each study.  
119 Emphasis should be given to those factors that stand out as critical to study quality. These  
120 critical to quality factors are attributes of a study whose integrity is fundamental to the  
121 protection of study subjects, the reliability and interpretability of the study results, and the  
122 decisions made based on the study results. These quality factors are considered to be critical  
123 because, if their integrity were to be undermined by errors of design or conduct, the reliability  
124 or ethics of decision-making would also be undermined.

125 The design of a clinical study should reflect the state of knowledge and experience with the  
126 drug; the condition to be treated, diagnosed or prevented; the underlying biological mechanism  
127 (of both the condition and the treatment); and the population for which the drug is intended. As  
128 research progresses, knowledge increases and uncertainties about the safety and efficacy of a  
129 drug decrease.

130 This state of knowledge has a clear influence on the regulatory and ethical controls that apply  
131 to the authorisation, supervision, and conduct of clinical studies. Knowledge of the drug at the  
132 point in development when the study is designed or reviewed will therefore inform the  
133 identification of critical to quality factors and control processes used to manage them.

134 The sponsor and other parties designing quality into a clinical study should identify the critical  
135 to quality factors. Having identified those factors, it is important to determine the risks that  
136 threaten their integrity, the probability and impact of those risks and to decide whether they  
137 can be accepted or should be mitigated. Where it is decided that risks should be mitigated, the  
138 necessary control processes should be put in place and communicated, and the necessary action  
139 taken to mitigate the risks. The term risk is used here in the context of general risk management  
140 methodology to all factors of a study.

141 Proactive communication of the critical to quality factors and risk mitigation activities will  
142 support understanding of priorities and resource allocation by the sponsor and investigator

143 sites. Proactive support (e.g., broad training to all relevant site staff and description in the  
144 protocol or in the case report form) will enhance correct implementation of study protocol,  
145 procedures, and associated operational plans and process design.

146 Perfection in every aspect of an activity is rarely achievable or can only be achieved by use of  
147 resources that are out of proportion to the benefit obtained. The quality factors should be  
148 prioritized to identify those that are critical to the study, at the time of the study design, and  
149 study procedures should be proportionate to the risks inherent in the study and the importance  
150 of the information collected. The critical to quality factors should be clear and should not be  
151 cluttered with minor issues (e.g., due to extensive secondary objectives or processes/data  
152 collection not linked to the proper protection of the study subjects and/or primary study  
153 objectives).

### 154 **3.3 Approach to Identifying the Critical to Quality Factors**

155 A key aspect of a quality approach to study design is to ask whether the objectives being  
156 addressed by the study are clearly articulated; whether the study is designed to meet the need  
157 it sets out to address; whether these needs are meaningful to patients; and whether the study  
158 hypotheses are specific, timely and scientifically valid. The approach should consider whether  
159 those objectives can be met, well and most efficiently, by the chosen design and data sources.  
160 Study designs should be operationally feasible and avoid unnecessary complexity and  
161 unnecessary data collection. Patient consultation early in the study design process contributes  
162 to these factors and would be likely to result in fewer protocol amendments. Protocols and case  
163 report forms/data collection methods should enable the study to be conducted as designed.

164 Identification of critical to quality factors will be enhanced by approaches that include the  
165 following elements:

#### 166 **3.3.1 *Establishing a Culture that Supports Open Dialogue***

167 Create a culture that values and rewards critical thinking and open dialogue about quality and  
168 that goes beyond sole reliance on tools and checklists.

169 Choose quality measures and performance indicators that are aligned with a proactive approach  
170 to design. For example, an overemphasis on minimising the time to first patient enrolled may  
171 result in devoting too little time to identifying and preventing errors that matter through careful  
172 design.

173 Encourage proactive dialogue about what is critical to quality for a particular study or  
174 development programme and, when needed, the development of innovative methods for  
175 ensuring quality.

176 Discourage inflexible “one size fits all” approaches that undermine creation of specific  
177 strategies and actions intended to effectively and efficiently support quality in a given study.

178 Gather and synthesise evidence in a transparent manner, acknowledge gaps in data and  
179 conflicting data where present and known, and anticipate the possible emergence of such gaps  
180 or conflicts.

181 **3.3.2 *Focusing on Activities Essential to the Study***

182 Focus effort on activities that are essential to the reliability and meaningfulness of study  
183 outcomes for patients, and the safe, ethical conduct of the study for study subjects. Consider  
184 whether nonessential activities may be eliminated from the study to simplify conduct, improve  
185 study efficiency, and target resources to critical areas.

186 Rigorously evaluate the study design to verify that planned activities and choice of data to be  
187 collected are essential.

188 Deploy resources to identify and prevent or control errors that matter.

189 **3.3.3 *Engaging Stakeholders in Study Design***

190 Clinical study design is best informed by input from a broad range of stakeholders, including  
191 patients and treating physicians. It should be open to challenge by subject matter experts and  
192 stakeholders from outside, as well as within, the sponsor organisation.

193 The process of building quality into the study may be informed by participation of those  
194 directly involved in successful completion of the study such as clinical investigators, study  
195 coordinators and other site staff, and patients/patient organisations. Clinical investigators and  
196 potential study subjects have valuable insights into the feasibility of enrolling subjects who  
197 meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly  
198 burdensome and lead to early dropouts, and the general relevance of study endpoints and study  
199 settings to the targeted patient population (See Section 4.4). They may also provide insight into

200 the value of a treatment in the context of ethical issues, culture, region, demographics, and  
201 subgroups within a targeted patient population.

202 When a study has novel elements considered critical to quality (e.g., defining patient  
203 populations, procedures, or endpoints), early engagement with regulatory authorities should  
204 also be considered.

#### 205 **3.3.4 *Reviewing Critical to Quality Factors***

206 Build on accumulated experience and knowledge with periodic review of critical to quality  
207 factors to determine whether adjustments to risk control mechanisms are needed, since new or  
208 unanticipated issues may arise once the study has begun.

209 Pay special attention to studies designed to include adaptations and/or interim decision points  
210 during the study. These will require proactive planning and ongoing review and adjustment of  
211 critical to quality factors, and risk management.

## 212 **4 DRUG DEVELOPMENT PLANNING**

213 This section provides general principles to consider in planning a drug development  
214 programme. Efficient drug development usually requires appropriately planned interactions  
215 with regulatory authorities throughout development, both in relation to planning early as well  
216 as later studies including post-approval studies. This is particularly important for multiregional  
217 studies to ensure the study design is aligned with regional regulatory requirements.

218 A drug development plan describes all aspects of the development of a product from the target  
219 product profile through post-approval activities. The plan is usually prepared prospectively and  
220 updated as the development progresses and new information becomes available. The plan  
221 generally includes characterisation of formulation development, non-clinical studies required  
222 to support the evaluation of the product in human clinical studies and to support product  
223 approval, clinical studies designed to support the demonstration of efficacy and safety in the  
224 relevant patient population, studies in special populations (e.g., paediatric populations),  
225 regional considerations for product commercialisation (e.g., health technology assessments),  
226 and post-approval studies.

227 It is important to ensure that the experiences, perspectives, needs, and priorities of stakeholders  
228 relating to the development and evaluation of the drug throughout its lifecycle are captured and  
229 meaningfully incorporated into the development programme.

230 With increased globalisation of drug development programmes there is a need to consider  
231 factors that impact quality of a protocol when it is conducted in more than one region (see ICH  
232 E17 Multi-Region Clinical Trials). Early engagement with regulatory authorities to understand  
233 local/regional requirements is encouraged and will facilitate the ability to design quality into  
234 the study protocol. The results of a study are often used in regulatory submissions in multiple  
235 regions, and the design should also consider the relevance of the study results for regions other  
236 than the one(s) in which the study is conducted.

237 Clinical development programmes may also feature requirements for co-development of  
238 validated biomarkers, diagnostic testing, or devices that facilitate the safe and effective use of  
239 a drug.

240 An overview of the types of studies that may contribute to a development programme is  
241 provided in the table in Annex 1.

#### 242 **4.1 Non-Clinical Studies**

243 In preparing a development plan, the non-clinical information that is required for the drug  
244 should be addressed. Non-clinical information may include toxicology, carcinogenicity,  
245 pharmacology, and pharmacokinetics to support clinical trials (e.g., ICH Safety (S) Guidelines  
246 and M3 Nonclinical Safety Studies). Important considerations for determining the necessary  
247 non-clinical studies, and their timing with respect to clinical studies, depend on the  
248 physiological and toxicological characteristics of the drug. These characteristics can include  
249 the drug's chemical or molecular properties (e.g., small-molecule, biologic/cellular/gene  
250 therapy, complex drug, and vaccine); pharmacological basis of principal effects (mechanism  
251 of action); route(s) of administration; absorption, distribution, metabolism, and excretion  
252 (ADME); physiological effects on organ systems; dose/concentration-response relationships;  
253 half-life; duration of action; and indication. Use of the drug in special populations (e.g.,  
254 pregnant or breast-feeding women, children, elderly) may require additional toxicological  
255 assessments.

256 Before proceeding to studies in humans, there should be sufficient information to support  
257 selection of the initial human dose and safe duration of exposure, and to provide a preliminary  
258 assessment of physiological and toxicological effects of the drug.

#### 259 **4.2 Quality and Formulations of Investigational Medicinal Products**

260 Quality of investigational medicinal products is an important consideration in planning a drug  
261 development programme and is addressed in the ICH quality guidelines. Of particular  
262 importance in transitioning from non-clinical to clinical studies is the quality of the product  
263 formulation to be taken into clinical development. Formulations should be well characterised  
264 in the drug development plan, including information on bioavailability. The formulation should  
265 be appropriate for the stage of drug development. Ideally, the supply of a formulation will be  
266 adequate to allow testing in a series of studies that examine a range of doses. During drug  
267 development, different formulations of a drug may be tested. Links between formulations,  
268 established by bioequivalence studies or other means, are important in interpreting clinical  
269 study results across the development programme. Age-appropriate formulation development is  
270 a consideration when clinical studies are anticipated in paediatric populations (ICH E11).

#### 271 **4.3 Clinical Studies**

272 Clinical drug development, defined as studying the drug in humans, is conducted in a sequence  
273 that builds on knowledge accumulated from previous studies. Although clinical drug  
274 development is often described as consisting of four temporal phases (Phase 1-4), it is  
275 important to appreciate that the phase concept is a description, not a set of requirements. Studies  
276 may be better categorized by other design elements such as study objective (see Annex I and  
277 Section 5). It is also important to realise that the temporal phases do not imply a fixed order of  
278 studies. Drug development is ideally a logical, step-wise process in which information from  
279 small early studies is used to support and plan later larger, more definitive studies. To develop  
280 new drugs efficiently, it is essential to identify characteristics of the investigational medicine  
281 in the early stages of development and to plan an appropriate development based on this profile.

282 Initial studies provide an early evaluation of short-term safety and tolerability and can provide  
283 pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range  
284 and administration schedule for initial exploratory studies. Later confirmatory studies are  
285 generally larger and longer and include a more diverse study population. Dose response  
286 information may be obtained at any stage of development, from early tolerance studies, to



287 studies of short-term pharmacodynamic effect, to large efficacy studies (ICH E4 Dose-  
288 Response Studies). Throughout development, new data may suggest the need for additional  
289 studies.

290 **4.3.1 Human Pharmacology (usually referred to as Phase I)**

291 Clinical development begins with human pharmacology studies and includes the initial  
292 administration of an investigational new drug to humans.

293 Studies in this phase of development may be conducted in healthy volunteer subjects or in a  
294 selected population of patients who have the condition or the disease, depending on drug  
295 properties and the objectives of the development programme.

296 Studies typically address one or a combination of the following aspects:

297 **4.3.1.1 Estimation of Initial Safety and Tolerability**

298 The initial and subsequent administration of an investigational new drug to humans is usually  
299 intended to determine the tolerability of the dose range expected to be evaluated in later clinical  
300 studies and to determine the nature of adverse reactions that can be expected. These studies  
301 typically include both single and multiple dose administration.

302 **4.3.1.2 Pharmacokinetics**

303 Characterisation of a drug's absorption, distribution, metabolism, and excretion continues  
304 throughout the development plan, but the preliminary characterisation is often a goal of Phase  
305 1. Pharmacokinetic studies are particularly important to assess the clearance of the drug and to  
306 anticipate possible accumulation of parent drug or metabolites, and potential drug-drug  
307 interactions. Some pharmacokinetic studies are commonly conducted in later phases to answer  
308 more specialised questions. For many orally administered drugs, especially modified release  
309 products, the study of food effects on bioavailability is important. Obtaining pharmacokinetic  
310 information in sub-populations such as patients with impaired elimination (renal or hepatic  
311 impairment), the elderly, children, and ethnic subgroups should be considered (ICH E5 Ethnic  
312 Factors in the Acceptability of Foreign Clinical Data, E7, E11).

313 If a potential for drug-drug interaction is suggested by metabolic profile, by the results of non-  
314 clinical studies, or by information on similar drugs, studies on drug interaction during clinical  
315 development are highly recommended and may be required to inform safe use and drug

316 labelling, especially for drugs that are frequently co-administered. This is particularly true for  
317 drugs that are known to alter the absorption or metabolism of other drugs, or whose metabolism  
318 or excretion can be altered by effects of other drugs. Drug-drug interaction studies are generally  
319 performed at later phases of development, but studies in animals and in vitro studies of  
320 metabolism and potential interactions may inform the need for earlier studies.

#### 321 **4.3.1.3 Pharmacodynamics & Early Measurement of Drug Activity**

322 Depending on the drug and the endpoint studied, pharmacodynamic studies and studies relating  
323 drug levels to response (PK/PD studies) may be conducted in healthy volunteer subjects or in  
324 patients with the target disease. If there is an appropriate measure, pharmacodynamic data can  
325 provide early estimates of activity and potential efficacy and may guide the dosage and dose  
326 regimen in later studies.

327 Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase 1 as  
328 a secondary objective. Such studies are generally performed in later phases but may be  
329 appropriate when drug activity is readily measurable with a short duration of drug exposure in  
330 patients at this early stage.

#### 331 **4.3.2 Exploratory and Confirmatory Studies (usually referred to as Phase 2 or Phase 3)**

332 Exploratory studies (Phase 2) support clinical proof of concept for the drug in a selected  
333 population of patients who have the condition or disease for which the drug is intended. If the  
334 data are promising, then further clinical evaluation follows to confirm the early findings. These  
335 evaluations may aim to refine the effective dose(s) and therapeutic regimens (including  
336 concomitant medication) for subsequent studies, refine the definition of the target population,  
337 provide a more robust safety profile for the drug, and may include evaluation of potential study  
338 endpoints for further study. Initial exploratory studies may use a variety of study designs,  
339 including concurrent controls, comparisons with baseline status, and adaptive dose-finding.  
340 Other studies may involve modelling early or intermediate outcome data to predict clinical  
341 outcomes and thereby inform the design of the follow-on, larger confirmatory studies.

342 Confirmatory studies (Phase 3) are designed to confirm the preliminary evidence accumulated  
343 in earlier phases that a drug is safe and effective for use for the intended indication and recipient  
344 population. These studies are often intended to provide an adequate basis for marketing  
345 approval, and to support adequate instructions for use of the drug and official product  
346 information. They aim to evaluate the drug in a larger population of patients with or at risk of

347 the condition or disease. These subjects more accurately represent the population of patients  
348 who will receive the drug once approved and may include subgroups of patients with frequently  
349 occurring or potentially relevant co-morbidities (e.g., cardiovascular disease, diabetes, hepatic  
350 and renal impairment) to characterise the safe and effective use of the drug in patients with  
351 these baseline conditions.

352 Confirmatory studies may further explore the dose-response relationship or explore the drug's  
353 use in different stages of disease or in combination with one or more drugs. If the intent is to  
354 administer a drug for a long period, studies involving extended exposure to the drug should be  
355 conducted (ICH E1 Clinical Safety for Drugs used in Long-Term Treatment). Irrespective of  
356 the duration of administration, the duration of effect of the drug will usually guide the demand  
357 for understanding long-term effects and therefore the duration of follow-up in the study.

358 Confirmatory studies often use randomised parallel designs. They may use complex adaptive  
359 or innovative designs to realize efficiencies or test assumptions as data accumulate during the  
360 study.

#### 361 **4.3.3 Post Approval Studies (usually referred to as Phase 4)**

362 Post approval studies are studies conducted following drug approval. They may be performed  
363 for a variety of reasons, including providing additional information on the efficacy, safety, and  
364 use of the drug. For example, in certain circumstances, a drug may be approved based on  
365 surrogate endpoints likely to predict clinical outcomes. After such an approval, studies would  
366 be conducted to demonstrate effects on clinical endpoints. Studies in special populations, such  
367 as paediatric and elderly populations, may be conducted to understand the drug effects in these  
368 populations. Safety studies may be conducted after authorization to refine the understanding of  
369 potential risks. Studies with long-term follow-up or with comparisons among authorized drugs  
370 may provide important information on safety and efficacy to the medical community. Post-  
371 approval studies encompass a range of designs and data sources (See Section 5).

#### 372 **4.3.4 Additional Development**

373 After initial approval, drug development may continue with studies of new or modified  
374 indications, new dosage regimens, new routes of administration, or additional patient  
375 populations. If a new dose, formulation or combination is studied, additional non-clinical

376 and/or human pharmacology studies may be indicated. Data from previous studies or from  
377 clinical experience with the approved drug may inform these programmes.

378 **4.3.5 Consideration in Special Populations**

379 Some groups in the general population may require special study because they have unique  
380 risk/benefit considerations that need to be taken into account during drug development, or  
381 because they can be anticipated to need modification of the dose or schedule of a drug. ICH E5  
382 provides a framework for evaluating the impact of ethnic factors on a drug's effect. Non-  
383 clinical safety studies to support human clinical studies in special populations may be needed  
384 (see, e.g., ICH S5 Reproductive Toxicology, S11 Nonclinical Paediatric Safety, and M3).  
385 Following are examples of special populations to be considered during development planning.

- 386 • Investigations in pregnant women

387 If a pregnant woman is enrolled in a clinical study, or a woman becomes pregnant while  
388 participating in a clinical study, evaluation of the pregnancy, foetus, and child, and reporting  
389 of all outcomes in the clinical study report, is often necessary. The same applies for clinical  
390 studies that include pregnant women, where the medicinal product is intended for use during  
391 pregnancy.

- 392 • Investigations in nursing women

393 Excretion of the drug or its metabolites into human milk should be examined where applicable  
394 and feasible. When nursing mothers are enrolled in clinical studies their babies are usually also  
395 monitored for the effects of the drug.

- 396 • Investigations in children

397 ICH E11 provides an outline of critical issues in paediatric drug development and approaches  
398 to the safe, efficient, and ethical study of drugs in paediatric populations.

- 399 • Investigations in geriatric populations

400 ICH E7 provides an outline of critical issues in geriatric drug development and approaches to  
401 the safe, efficient, and ethical study of drugs in geriatric populations.

- 402 • Investigations in renal and hepatic impaired populations

403 Pharmacokinetic studies in patients with renal and hepatic impairment are important to assess  
404 the impact of potentially altered drug metabolism or excretion.

405 Particular attention should be paid to the ethical considerations related to informed consent in  
406 vulnerable populations (ICH E6 and E11).

407 **4.4 Feasibility**

408 During drug development, the feasibility of the individual studies should be assessed. The  
409 foundation of a successful study is a protocol that is both scientifically sound and operationally  
410 viable. A detailed feasibility assessment includes consideration of study design and  
411 implementation elements that could impact the successful completion of a clinical development  
412 programme or study from an operational perspective in a particular geographical region.

413 Consideration of critical to quality factors relating to study feasibility can inform study design  
414 and enhance quality implementation. Feasibility considerations include but are not limited to  
415 the availability of qualified investigators/site personnel with experience in conducting a clinical  
416 study; availability of equipment and facilities required to successfully conduct the clinical  
417 study; availability of the desired patient population; ability to enrol sufficient numbers of  
418 participants as determined by the study's power analysis; the ethical and regulatory  
419 considerations, which include informed consent, parental/caregiver consent and patient assent  
420 for paediatric studies; and regional standards of care.

421 An important aspect of study feasibility is understanding the view of potential study subjects  
422 about protocol elements that could impact their willingness to enrol or continue participation  
423 in the study (e.g., impact of study procedures, meaningfulness of the study  
424 objectives/outcomes). The retention of study subjects and the follow-up of subjects who have  
425 withdrawn from treatment are key critical to quality factors. It is important to not underestimate  
426 the value that appropriate and early consultation with patients will have on the feasibility of  
427 the study, adherence to the protocol, and, more essentially, relevance (or suitability) for patients  
428 of the drug approval based on the accumulated knowledge and experience from the clinical  
429 studies.

## 430 **5 DESIGN ELEMENTS FOR CLINICAL STUDIES**

431 Study objectives impact the choice of study design and data sources, which in turn impact the  
432 strength of a study to support regulatory decisions and clinical practice. This section presents  
433 important elements that define the design of a clinical study. It is intended to assist in  
434 identifying the critical to quality factors necessary to achieve the study objectives and the  
435 protection of study subjects, while also enabling flexibility in study design and promoting  
436 efficiency in study conduct. This document does not discuss all possible study types that may  
437 be included within the drug lifecycle. The elements outlined here are expected to be relevant  
438 to study types and data sources in use in clinical studies now, and that may be developed in the  
439 future.

440 Clear objectives will help to determine the study design and conversely, the process of  
441 specifying the design may help to further clarify the objectives. Objectives may need to be  
442 modified as practical considerations and limitations are revealed.

### 443 **5.1 Study Design**

444 The fundamental design elements of a clinical study include population, intervention, control  
445 group, response variable, methods to reduce or assess bias, and statistical analysis. The protocol  
446 brings these elements together with the study objectives, study type, and data sources (see  
447 Section 5.2), and should be finalised before the start of the study (see ICH E6).

#### 448 **5.1.1 Study Population**

449 The population to be studied should be chosen to support the study objectives and is defined  
450 through the inclusion and exclusion criteria for the study. In practice, the study population is  
451 limited to subjects available to participate and for whom consent is available (see ICH E6).  
452 Recruitment efforts should ensure that the study subjects reflect the planned population for the  
453 study. If objectives include obtaining information on certain subgroups, then efforts should be  
454 made to ensure adequate representation of these subgroups.

455 The study population might be narrowly defined to reduce heterogeneity and maximize the  
456 sensitivity of the study for detecting a certain effect. Conversely, it may be broadly defined to  
457 more closely represent the population for which the drug is intended. In general, studies  
458 conducted early in a development programme, when little is known about the safety of the  
459 drug, tend to be more homogeneous in study population definitions, and those conducted in the

460 later phases of drug development or post-approval tend to be more heterogeneous. Recruitment  
461 for a precision medicine study, for example, may target the subgroup of diseased patients with  
462 a particular phenotype or genotype, either exclusively or through an enrichment study design.  
463 The choice of study population will depend on the study objectives, and the degree to which a  
464 study succeeds in recruiting and enrolling the desired population will impact the ability of the  
465 study to meet those objectives.

466 For example, a study population representative of clinical practice may be the target of a  
467 pragmatic trial conducted within an existing healthcare system. In such a study, recruitment  
468 procedures may differ from other types of studies, in that the inclusion and exclusion criteria  
469 may be assessed based on existing medical records.

470 Because of the study objectives or because of feasibility or efficiency, there may be situations  
471 in which the population unit is not an individual but a group of subjects (known as a cluster).  
472 For example, some vaccine studies make use of cluster randomisation to measure their  
473 protective effects on communities. The use of a cluster unit has implications for multiple design  
474 elements and quality factors (e.g., intervention, analysis, consent).

475 The study should plan to have a sufficient number of subjects to make statistical conclusions  
476 based on the findings either by obtaining a certain precision or by controlling the probabilities  
477 of making false conclusions (see ICH E9 Statistical Principles for Clinical Trials). A larger  
478 database may be needed to establish the safety of a drug (see ICH E1).

#### 479 **5.1.2 Intervention**

480 An important distinction between studies is whether the choice of the study drug and the health  
481 management of the subjects are controlled by the study (with proper regard to human subject  
482 protection and regulatory requirements) or merely observed in the study. The former case is  
483 referred to as an interventional study and the latter case is referred to as an observational study.

484 Interventional studies often have the potential to control biases better than observational studies  
485 (see Section 5.1.5). Factors such as study objectives, feasibility, data sources, and anticipated  
486 biases and uncertainty play a role in the choice between interventional and observational  
487 studies. Observational studies are usually conducted in the post-approval period.

488 There is varying overlap between interventional and observational studies. For example, a  
489 pragmatic trial is a mix of the two types in that the intervention is controlled by the study, but  
490 health management is controlled to a lesser degree than in other study types.

### 491 *5.1.3 Control Group*

492 The drug effect of interest may be the effect relative to not receiving the drug or the effect  
493 relative to receiving other therapies. For example, comparisons may be made with placebo, no  
494 treatment, active controls or different doses of the drug under investigation. To derive these  
495 comparisons, information on a group of subjects not receiving the drug or receiving other  
496 therapies is usually needed. This group is known as the control group (see ICH E10). The  
497 choice of a control group may be influenced by the study objectives, ethical considerations,  
498 and study feasibility.

499 The source of control group data may be internal or external to the study. With use of an internal  
500 control group, all subjects in the study are selected by the same processes, and data are acquired  
501 by the same procedures at the same time, with the intent that the only differences observed  
502 among subjects in the study are due to the treatment they receive. With use of an external  
503 control group, subjects are selected from an external source, and the control group subjects  
504 may be treated at an earlier time (historical control group) or during the same time but in  
505 another setting than subjects in the study.

506 External control subjects may differ from subjects participating in the study with respect to  
507 follow-up and measurement of study outcomes and other data elements. In addition, external  
508 control subjects may differ from study subjects with respect to some demographic and  
509 background characteristics (e.g., medical history, concurrent diseases, etc.), possibly reflecting  
510 a somewhat different subject population, which should be taken into account in the design and  
511 analysis of the study.

512 It may be possible for a single clinical study to use both internal and external control subjects.  
513 For example, conduct of the study may be facilitated by supplementing the internal control  
514 group with additional data on an external control group.

515 In some circumstances, rather than using a separate group of control subjects, subjects may  
516 function as their own control receiving the drug and control at different points of time. Both  
517 interventional and non-interventional studies may make use of such an approach. Examples of



518 this approach include crossover designs for interventional studies and case-crossover designs  
519 for non-interventional studies.

520 There are critical to quality factors that are associated with the choice and use of the control  
521 group, including study objective, availability and quality of control data, feasibility of  
522 conducting the study, ethical considerations, comparability between treatment and control  
523 populations, and comparability of outcome ascertainment.

524 Subject level data may not be available for some choices of external control groups, but if  
525 summary measures are available from the external source, they may be used to form the basis  
526 of comparisons with treated subjects to estimate and test hypotheses about drug effects. In this  
527 case, however, the critical to quality factor of comparability between treatment groups is unable  
528 to be addressed through adjustment for subject-level covariates.

529 When control data considered adequate to support comparisons are not available, responses to  
530 treatment observed in the study may be compared to a relevant and justified target value for  
531 the control response rate (e.g., tumour response rate in oncology; cure rate for anti-infectives).  
532 Even in cases where comparable control data are available, an external target value may still  
533 be useful in evaluating the response rate observed in the study.

#### 534 **5.1.4 Response Variables**

535 A response variable is a subject-level attribute of interest that may be affected by the drug. The  
536 response variable may relate to the pharmacokinetics, pharmacodynamics, efficacy, safety, or  
537 use of the drug post-approval including compliance with risk minimisation measures. Study  
538 endpoints are the response variables that are chosen to assess drug effects.

539 The choice of primary endpoint is critical to the quality of the study. The primary endpoint  
540 should be the variable capable of providing the most clinically relevant and convincing  
541 evidence directly related to the primary objective of the study, taking into account feasibility  
542 considerations (ICH E9). Secondary variables are either supportive measurements related to  
543 the primary objective or measurements of effects related to the secondary objectives. The  
544 choice of endpoints should be meaningful for the intended population and take into account the  
545 views of patients.

546 The definition of each study endpoint should be specific. The specificity should include how it  
547 is ascertained and at what time point in a subject's treatment course of the drug and follow-up  
548 it is ascertained. The methods used to ascertain endpoints should be of sufficient accuracy,  
549 precision, responsiveness (sensitivity to change), reproducibility, reliability, and validity.

550 Pragmatic trials may make use of existing data from healthcare systems to obtain response  
551 variables rather than through study specific data collection, similar to the way healthcare data  
552 can be used to select the study population as described above (See Sec 5.1.1).

553 The knowledge of the drug, the clinical context, and the purpose of a given study affect what  
554 response variables should be collected. For example, a proof-of-concept study may employ  
555 short-term surrogates rather than objective clinical outcomes. Clinical outcomes would then be  
556 used to confirm a clinically meaningful effect in a large-scale confirmatory study. In other  
557 cases, for example, a post-approval study where the safety profile of the drug is well  
558 characterised, the extent of safety data collection may be tailored to the objectives of the study.

#### 559 **5.1.5 Methods to Reduce or Assess Bias**

560 The study design should address sources of bias that can undermine the reliability of results.  
561 Although different types of studies are subject to different sources of bias, this section  
562 addresses the more common sources. ICH E9 discusses principles for controlling and reducing  
563 bias mainly in the context of interventional studies.

564 In conducting a controlled study, randomised allocation is the preferred means of assuring  
565 comparability of test groups, thereby minimising the possibility of bias in treatment  
566 assignment.

567 Randomisation addresses differences between the groups at the time of randomisation but does  
568 not prevent differences arising after randomisation. Events after randomisation (intercurrent  
569 events) may also affect the comparability of the groups. For example, there may be differences  
570 in the follow-up patterns between the groups, such as subjects in one group dropping out of the  
571 study because of adverse events or lack of efficacy. Careful consideration of the potential  
572 impact of intercurrent events will help with the identification of critical to quality factors, such  
573 as preventing dropouts, retrieving data for dropouts, and definition of treatment effect in the  
574 presence of dropouts.

575 Concealing the treatment assignments (blinding or masking) limits the occurrence of conscious  
576 or unconscious bias in the conduct and interpretation of a clinical study that may affect the  
577 course of treatment, monitoring, endpoint ascertainment, and subject responses. A study where  
578 the treatment assignment is not known by the study participant is referred to as a single-blind  
579 study. When the investigator and sponsor staff who are involved in the treatment or clinical  
580 evaluation of the subjects are also unaware of the treatment assignments, the study is double-  
581 blind. Maintaining confidentiality of interim study results also can help to reduce bias.

582 In an open-label study (either single-arm or unblinded comparative), the consequences of the  
583 lack of blinding may be reduced through the use of pre-specified decision rules for aspects of  
584 study conduct, such as treatment assignment, subject management, safety reporting, and  
585 response variable ascertainment.

586 Observational studies pose unique challenges to the control of bias. Multiple design elements  
587 are often necessary to address these challenges, including methods to address biases associated  
588 with the (1) selection of subjects, (2) differences in prognostic factors associated with the  
589 choice of therapies (confounding), and (3) ascertainment of response variables and other  
590 important study variables.

#### 591 **5.1.6 Statistical Analysis**

592 The statistical analysis of a study encompasses important elements necessary to achieving the  
593 study objectives. The study protocol should include a statistical methods section that is  
594 appropriate for the objectives and study design (ICH E6 and E9). A separate statistical analysis  
595 plan may be used to provide the necessary details for implementation. The protocol should be  
596 finalised before the conduct of the study, and the statistical analysis plan should be finalised  
597 before the unblinding of study data, or in the case of an open-label study, before the conduct  
598 of the study. These steps will increase confidence that important aspects of analysis planning  
599 were not based on accumulating data in the study or inappropriate use of external data, both of  
600 which can negatively impact the reliability of study results. For example, the choice of analysis  
601 methods in a randomised clinical trial should not change after examining unblinded study data,  
602 and external control subjects should not be selected based on outcomes to be used in  
603 comparative analyses with treated study subjects.

604 Statistical analyses of primary and secondary endpoints to achieve study objectives with  
605 respect to both efficacy and safety should be described, as well as any interim analyses and/or  
606 planned design adaptations (E9). The analysis plan should describe the analytical methods for  
607 the estimation and tests of hypotheses about the drug effect, addressing the method of treatment  
608 allocation, the measurement methods of response variables, the analysis population, and other  
609 critical to quality factors relating to the planned analysis strategy appropriate for the study  
610 design. The plan should address the handling of intercurrent events, such as treatment  
611 discontinuations, use of rescue medication, missed visits, and other protocol violations.

612 The statistical analysis plan should describe how the various sources of bias discussed above  
613 will be addressed in the context of the particular study design and data sources (see Section  
614 5.1.5).

615 Pre-specification is particularly important for studies that make use of existing data sources  
616 rather than primary data collection (see Section 5.2), not only for the statistical analysis planned  
617 for the study but also for any feasibility analysis to assess the applicability of the existing data.  
618 For example, for a single arm interventional study with an external control, the specifics of the  
619 external control should be specified prior to the conduct of the interventional aspect of the  
620 study. Assurances and procedures should be in place so that any review of the data prior to the  
621 design of the study does not threaten the study integrity.

622 Sensitivity analyses should be planned to test the impact of the assumptions made for the  
623 primary analyses on the results of the study. For example, if the primary analysis relies on a  
624 particular assumption about the reasons data are missing, sensitivity analyses should be planned  
625 to assess the impact of those assumptions on the study results. An example for observational  
626 studies might be consideration of additional confounders.

## 627 **5.2 Study Data**

628 The study data should reliably contain the necessary information to conduct, monitor, and  
629 analyse the study. The study data may be acquired through a variety of methods, including  
630 paper-based and electronic capture. Data from the use of technologies (e.g., digital health  
631 tools), electronic health record databases and patient registries may contribute to the  
632 development of a new investigational drug or for further evaluation of an approved drug.

633 Study data can be broadly classified into two types: (1) data generated specifically for the  
634 present study and (2) data obtained from sources external to the present study. The distinction  
635 between the two types may not always be clear. For example, clinical study data may be  
636 collected during scheduled study visits via case report forms, laboratory measurements, and  
637 other mechanisms, while also including information obtained from existing medical records.  
638 Data from both types of data sources comprise the clinical database in this case.

639 The term primary data collection, refers to data collected for study purposes using processes  
640 that ensure a sufficient level of quality. The term secondary data use, refers to the use of data  
641 that were collected for other purposes and are not collected just for the study. Note that  
642 secondary data themselves may have had careful quality control processes implemented during  
643 their acquisition, but those processes were not designed with the objectives of the present study  
644 in mind. Examples of secondary data sources that might be used in clinical studies include  
645 national death databases, disease and drug registries, claims data, and medical and  
646 administrative records from routine medical practice.

647 With secondary data use, the appropriateness of the available data should be considered. For  
648 example, when using existing electronic health record data to ascertain the study endpoint  
649 rather than through primary data collection, information in the health record about outcomes  
650 would need to be converted to the study endpoint. The sensitivity, specificity, and timing of  
651 the outcomes in the record should be considered. In some cases, secondary data use may not  
652 be sufficient for all aspects of the study and may need to be supplemented with primary data.

653 There are several additional considerations when using secondary data. Concealing the drug  
654 name in the measurement and recording of data is typically not present in secondary data use.  
655 Absence of affirmative information on a condition or event does not necessarily mean the  
656 condition is not present. For example, absence of smoking status in a medical record may not  
657 mean the patient is not a smoker. There also may be a delay between events and their presence  
658 in existing data sources.

659 The use of data standards for the terminology, storage, exchange, and access of study data  
660 promotes the reliability and the proper interpretation of the data. Data standards also facilitate  
661 the ease and correctness of the data analysis. International data standards exist for many sources  
662 of study data. Data standards should be developed for emerging sources of study data.

663 For all data sources, procedures to ensure the confidentiality of personal data should be  
664 implemented. The study design should explicitly address the protection of personal data. Local  
665 regulations related to privacy of participants' data should be followed.

## 666 **6 CONDUCT AND REPORTING**

### 667 **6.1 Study Conduct**

668 The principles and approaches set out in this guideline, including those of quality by design,  
669 should inform the approach taken to the conduct and reporting of clinical studies and the  
670 proportionality of control measures employed to ensure the integrity of the critical to quality  
671 factors. The study should be conducted according to the principles described in this guideline  
672 and in accordance with ICH E6 and other relevant ICH guidelines (see Annex 2 and Annex 3).

#### 673 **6.1.1 Protocol Adherence**

674 Adherence to the study protocol is essential, and many aspects of adherence should be  
675 considered among the study's critical to quality factors. If modification of the protocol becomes  
676 necessary, a clear description of the rationale for the modification should be provided in a  
677 protocol amendment (ICH E6).

#### 678 **6.1.2 Training**

679 Study stakeholders, such as sponsors; investigators, coordinators, and other local site staff; site  
680 monitors; adjudicators and members of the data monitoring committee; and third-party service  
681 providers (e.g., central laboratory or reading centre personnel) should receive thorough training  
682 prior to enrolment of the first study subject. Updated training should occur during the conduct  
683 of the study to reinforce the importance of adherence to study procedures and to address issues  
684 related to critical to quality factors observed during the course of the study.

#### 685 **6.1.3 Data Management**

686 As discussed in ICH E6, the manner and timelines in which study data are collected and  
687 managed are critical contributors to overall study quality. Operational checks and statistical  
688 surveillance can identify important data quality issues at a point at which corrective action is  
689 feasible. Data management procedures should account for the diversity of data sources in use  
690 for clinical studies (see Section 5.2).

691 **6.1.4 Access to Interim Data**

692 Inappropriate access to data during the conduct of the study may compromise study integrity.  
693 In studies with planned interim analyses, special attention should be given to which individuals  
694 have access to the data and results. Even in studies without planned interim analyses, special  
695 attention should be paid to any ongoing monitoring of data to avoid inappropriate access.

696 **6.2 Subject Safety**

697 Important standards of ethical conduct and the protection of subjects in clinical studies are  
698 described in Section 2.1. This section describes safety related considerations during the conduct  
699 of the study.

700 **6.2.1 Safety Monitoring**

701 The goals of safety monitoring are to protect study subjects and to characterize the safety  
702 profile of the drug. Procedures and systems for the identification, monitoring, and reporting of  
703 safety concerns including the timing of reporting during the study should be clearly specified.  
704 The approach should reflect the risks to the study subjects and what is known about the drug  
705 and the study population. Guidance is available on reporting of safety data to appropriate  
706 authorities and on the content of safety reports [ICH E2 Pharmacovigilance (A, B, and D), and  
707 ICH E6].

708 **6.2.2 Withdrawal Criteria**

709 Clear criteria for stopping study treatment while remaining in the study or withdrawing from  
710 the study altogether are necessary to ensure the protection of the subjects; however,  
711 consideration could be given to methods that will preserve subjects' safety and rights while  
712 still minimising loss of critical data, if possible.

713 **6.2.3 Data Monitoring Committee**

714 An important component of safety monitoring in many clinical studies is the use of a data  
715 monitoring committee (DMC). A DMC monitors accumulating data while the study is being  
716 conducted to make determinations on whether to continue, modify, or terminate a study.

717 During programme planning, the need for an external safety monitoring committee to monitor  
718 safety data across studies in a development programme may also be assessed. If a data  
719 monitoring committee is needed for either an individual study or the entire development

720 programme, procedures governing its operation and, in particular, the review of unblinded data  
721 while preserving study integrity (ICH E9) should be established.

### 722 **6.3 Study Reporting**

723 Clinical study reports should be adequately documented following the approaches outlined in  
724 other ICH guidelines. ICH E3 focuses particularly on the report format for interventional  
725 clinical studies. Other types of studies (e.g., observational studies) should use reporting formats  
726 appropriate for the type of study and information being reported.

727 The transparency of clinical research in drug development includes the registration of clinical  
728 trials on publicly accessible and recognised databases, and the public posting of clinical trial  
729 results. Adopting such practices for observational studies also promotes transparency. Making  
730 objective and unbiased information publicly available can benefit public health in general, as  
731 well as individual patient populations, through enhancing clinical research, reducing  
732 unnecessary clinical studies and informing decisions in clinical practice.

## 733 **7 CONSIDERATIONS IN IDENTIFYING CRITICAL TO QUALITY FACTORS**

734 The identification of critical to quality factors should be supported by proactive, cross-  
735 functional discussions and decision making at the time of study planning, as described in  
736 Section 3. Different factors will stand out as critical for different types of studies, following  
737 the concepts introduced in Sections 4 through 6.

738 In designing a study, applicable aspects such as the following should be considered to support  
739 the identification of critical to quality factors:

- 740 • Engagement of all relevant stakeholders, including patients, is considered during  
741 study planning and design.
- 742 • The prerequisite non-clinical studies, and where applicable, clinical studies, are  
743 complete and adequate to support the study being designed.
- 744 • The study objectives address relevant scientific questions appropriate for a given  
745 study's role in the development programme, taking into account the accumulated  
746 knowledge about the product.
- 747 • The clinical study design supports a meaningful comparison of the effects of the  
748 drug when compared to the chosen internal or external control groups.



- 749 • Adequate measures are used to protect subjects' rights, safety, and welfare  
750 (informed consent process, Institutional Review Board/Ethics Committee review,  
751 investigator and clinical study site training, pseudonymisation, etc.).
- 752 • A feasibility assessment is conducted to ensure the study is operationally viable.
- 753 • The number of subjects included, the duration of the study, and the frequency of  
754 study visits are sufficient to support the study objective.
- 755 • The eligibility criteria should be reflective of the study objectives and be well  
756 documented in the clinical study protocol.
- 757 • Information about study subjects that may be important to understanding the  
758 benefit/risk of the drug (e.g., age, weight, sex, co-morbidities, concomitant  
759 therapies) is specified in the protocol, captured and incorporated in the design,  
760 conduct, and analysis, as appropriate.
- 761 • The choice of response variables and the methods to assess them are well-defined  
762 and support evaluation of the effects of the drug.
- 763 • Clinical study procedures include adequate measures to minimise bias (e.g.,  
764 randomisation, blinding).
- 765 • The statistical analysis plan is pre-specified and defines the analysis methods  
766 appropriate for the endpoints and the populations of interest.
- 767 • Systems and processes are in place to ensure the integrity of critical study data.
- 768 • The extent and nature of study monitoring are tailored to the specific study design  
769 and objectives and the need to ensure subject safety.
- 770 • The need for a data monitoring committee is assessed.

771 These considerations are not exhaustive and may not apply to all studies. Other aspects may  
772 need to be considered to identify the critical to quality factors for each individual study.

773 **ANNEX 1: TYPES OF STUDIES**

774 Drug development is ideally a logical, step-wise process in which information from small early  
 775 studies is used to support and plan later larger, more definitive studies. In the table below, types  
 776 of studies are categorized by objectives. Illustrative examples, not intended to be exhaustive,  
 777 are provided. Examples appearing under one type may also occur under another.

<i>Type of Study</i>	<i>Objective(s) of Study</i>	<i>Study Examples</i>
Non-clinical testing to support and supplement clinical investigations	<ul style="list-style-type: none"> <li>• Assess non-clinical PK<sup>4</sup> /PD<sup>5</sup></li> <li>• Assess toxicity</li> <li>• Assess developmental toxicity</li> <li>• Assess mutagenicity, carcinogenicity</li> <li>• Assess immunogenicity and cross-reactivity</li> <li>• Understand target and mechanism of action</li> </ul>	<ul style="list-style-type: none"> <li>• AMES<sup>1</sup> test</li> <li>• ADME<sup>2</sup> studies</li> <li>• Animal carcinogenicity</li> <li>• Mechanism of action investigations in animal disease models</li> <li>• Animal toxicology</li> <li>• Animal PK/PD</li> </ul>
Human Pharmacology	<ul style="list-style-type: none"> <li>• Assess tolerance and safety</li> <li>• Define/describe clinical PK and PD</li> <li>• Explore drug metabolism and drug interactions</li> <li>• Estimate activity, immunogenicity</li> <li>• Assess renal/hepatic tolerance</li> <li>• Assess cardiac toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• BA/BE<sup>3</sup> studies under fasted/fed conditions</li> <li>• Dose-tolerance studies</li> <li>• Single and multiple-rising dose PK and/or PD studies</li> <li>• Drug-drug interaction studies</li> <li>• QTc prolongation study</li> </ul>
Exploratory	<ul style="list-style-type: none"> <li>• Explore use for the targeted indication</li> <li>• Estimate dose/dosing regimen for subsequent studies</li> <li>• Explore dose-response/exposure-response relationship</li> <li>• Provide basis for confirmatory study design (e.g., clinical endpoints, patient reported outcome measures, effect modifiers, target population, etc.)</li> </ul>	<ul style="list-style-type: none"> <li>• Randomized controlled clinical trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures</li> <li>• Dose finding studies</li> <li>• Biomarker exploration studies</li> <li>• Studies to validate patient reported outcomes</li> </ul>
Confirmatory	<ul style="list-style-type: none"> <li>• Demonstrate/confirm efficacy</li> <li>• Establish safety profile in larger, more representative patient populations</li> <li>• Provide an adequate basis for assessing the benefit/risk relationship to support licensing</li> <li>• Establish dose-response/exposure-response relationship</li> </ul>	<ul style="list-style-type: none"> <li>• Randomized controlled clinical trials to establish efficacy in larger, more representative patient populations, commonly employing clinical endpoints but may also use surrogate or pharmacological endpoints</li> <li>• Dose-response studies</li> <li>• Clinical safety studies</li> <li>• Studies of mortality/morbidity outcomes</li> </ul>

## ICH E8(R1) Guideline

	<ul style="list-style-type: none"> <li>• Establish safety profile and confirm efficacy in specific populations (e.g., paediatrics, elderly)</li> </ul>	<ul style="list-style-type: none"> <li>• Studies in special populations</li> </ul>
Post-Approval	<ul style="list-style-type: none"> <li>• Refine understanding of benefit/risk relationship in general or special populations and/or environments</li> <li>• Identify less common adverse reactions</li> <li>• Refine dosing recommendations</li> </ul>	<ul style="list-style-type: none"> <li>• Comparative effectiveness studies</li> <li>• Long-term follow-up studies</li> <li>• Studies of additional endpoints</li> <li>• Large, simple trials</li> <li>• Pragmatic trials</li> <li>• Pharmacoeconomic studies</li> <li>• Observational studies</li> </ul>
<p><sup>1</sup> AMES: mutagenicity test  <sup>2</sup> ADME : Absorption, Distribution, Metabolism, Excretion  <sup>3</sup> BA studies - <i>Bioavailability</i> means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.  <sup>3</sup> BE studies - <i>Bioequivalence</i> means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.  <sup>4</sup> Pharmacokinetics  <sup>5</sup> Pharmacodynamics</p>		

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779 **ANNEX 2: ICH E FAMILY OF GUIDELINES**

780 The ICH Efficacy guidelines are an integrated set of guidance covering the design, conduct, analysis and reporting of clinical studies. ICH E8  
781 provides an overall introduction to clinical development, designing quality into clinical studies and focusing on those factors critical to the quality  
782 of the studies. The guidelines should be considered and used in an integrated, holistic way rather than one or other guideline or subsection being  
783 focussed on in isolation of the others.

**E8 General Considerations for Clinical Trials**

**Design and analysis:**

E4 Dose-Response Studies  
E9 Statistical Principles for Clinical Trials  
E10 Choice of Control Group in Clinical Trials  
E17 Multi-Regional Clinical Trials

**Conduct and reporting:**

E3 Clinical Study Reports  
E6 Good Clinical Practice

**Safety reporting:**

E1 Clinical Safety for Drugs used in Long-Term Treatment  
E2A - E2F Pharmacovigilance  
E14 Clinical Evaluation of QT  
E19 Safety Data Collection

**Populations:**

E5 Ethnic Factors  
E7 Clinical Trials in Geriatric Population  
E11 - E11A Clinical Trials in Pediatric Population  
E12 Clinical Evaluation by Therapeutic Category

**Genetics/genomics:**

E15 Definitions in Pharmacogenetics / Pharmacogenomics  
E16 Qualification of Genomic Biomarkers  
E18 Genomic Sampling

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785 \*This diagram will be updated as new ICH guidelines are finalized or updated.

786 ANNEX 3: SELECTED EXAMPLES OF CRITICAL TO QUALITY FACTORS

Selected Examples of Critical to Quality Factors	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
<b>Protocol Design</b>																	
<b>Eligibility Criteria</b>						√	√	√	√		√	√	√	√		√	
<b>Randomisation</b>				√		√		√	√	√		√	√			√	
<b>Blinding/Masking</b>						√		√	√	√							
<b>Types of Controls</b>	√			√				√		√			√			√	
<b>Data Quality</b>	√						√	√	√					√			
<b>Endpoints</b>				√	√			√	√	√	√	√				√	
<b>Procedures Supporting Study Endpoints and Data Integrity</b>					√	√		√	√	√	√	√				√	
<b>Investigational Product (IP) Handling and Administration</b>						√							√				
<b>Feasibility</b>																	
<b>Study and Site Feasibility</b>																√	√
<b>Accrual</b>									√		√		√				
<b>Patient Safety</b>																	
<b>Informed Consent</b>						√					√						√
<b>Withdrawal Criteria and Trial Participant Retention</b>			√			√					√		√				

ICH E8(R1) Guideline

<u>Selected Examples of Critical to Quality Factors</u>	E1	E2A-E2F	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E14	E15	E16	E17	E18
<b>Signal Detection and Safety Reporting</b>		√ (B)	√			√						√	√				
<b>Data Monitoring Committee (DMC)/Stopping Rules</b>						√			√	√			√				
<b>Study Conduct</b>																	
<b>Training</b>						√							√			√	√
<b>Data Recording and Reporting</b>		√ (B,C,F)	√	√					√		√		√		√	√	√
<b>Data Monitoring and Management</b>		√ (A,B,D)	√						√						√	√	√
<b>Statistical Analysis</b>			√	√	√				√				√			√	
<b>Study Reporting</b>																	
<b>Dissemination of Study Results</b>		√ (D,F)															√
<b>Third-Party Engagement</b>																	
<b>Delegation of Sponsor Responsibilities</b>						√											
<b>Collaborations</b>						√											

787 \*This chart will be updated as ICH guidelines are finalized or updated.