

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

ICH HARMONISED GUIDELINE

ADAPTIVE DESIGNS FOR CLINICAL TRIALS
E20

Draft version

Endorsed on 25 June 2025

Currently under public consultation

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.

Explanatory Note for ICH E20: The draft guideline makes statements on adaptive design approaches for clinical trials. The draft guideline acknowledges the high potential for adaptive designs to accelerate the process of drug development and to allocate resources more efficiently without lowering scientific and regulatory standards. Some of the approaches may affect the nature and timing of interactions between industry and regulators at confirmatory trial planning and assessment. The final guideline will indicate key adaptive design principles and approaches for which discussion of adaptive design features, and the rationale for their use, are particularly critical at the planning stage. To inform guideline finalization, specific feedback is sought on adaptive design principles and approaches and their impact on industry-regulatory interactions. Until a final guideline is agreed under Step 5 of the ICH process, the draft guideline should not be understood as confirming full regulatory acceptance from ICH parties of its contents, nor superseding current regional guidance, which remains valid. Public consultation comments on the draft guideline are sought.

E20
Document History

Code	History	Date
E20	Endorsement by the Members of the ICH Assembly under <i>Step 2</i> and release for public consultation.	25 June 2025

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ICH Consensus Guideline

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1 **1. INTRODUCTION AND SCOPE**

2 This document provides guidance on confirmatory clinical trials with an adaptive design
3 intended to evaluate a treatment for a given medical condition within the context of its overall
4 development program. For the purpose of this guideline, an adaptive design is defined as a
5 clinical trial design that allows for prospectively planned modifications to one or more aspects
6 of the trial based on interim analysis of accumulating data from participants in the trial. The
7 term prospectively planned means that the potential trial adaptations are pre-specified in the
8 clinical trial protocol prior to initiation of the trial. The scope of this guideline does not include
9 trials with unplanned modifications to the design, such as a protocol amendment proposed by
10 an independent data monitoring committee (IDMC) based on unexpected interim results. It also
11 does not include design changes based entirely on emerging information from a source external
12 to the trial. Routine monitoring of operational aspects such as the enrollment rate, data quality,
13 or extent of participant withdrawal is also out of scope.

14 The focus of this guideline is on principles for the planning, conduct, analysis, and
15 interpretation of trials with an adaptive design intended to confirm the efficacy and support the
16 benefit-risk assessment of a treatment. The emphasis is on principles that are critical to ensuring
17 the trials produce reliable and interpretable information and that require specific considerations
18 with use of an adaptive design. This guideline does not discuss the use of specific statistical
19 methods. Although the guideline primarily focuses on confirmatory clinical trials, the
20 principles outlined are relevant to all phases of clinical development.

21 **2. ADVANTAGES AND CHALLENGES OF ADAPTIVE DESIGNS**

22 At the planning stage of confirmatory trials, uncertainty may remain regarding design aspects
23 such as the appropriate sample size, even after careful planning and conduct of earlier phases
24 of drug development. Yet, with a non-adaptive design, these aspects have to be determined
25 before the trial starts and cannot be changed during trial execution. Adaptive designs provide
26 flexibility and the ability to safeguard against inaccurate assumptions by taking advantage of
27 the accumulating information from trial participants and allowing pre-specified modifications
28 to design aspects during the trial.

29 This added flexibility can lead to a variety of advantages. First, adaptive designs can provide
30 ethical advantages. For example, a group sequential design with the potential for early trial
31 stopping if there is convincing evidence the treatment is efficacious and has a positive benefit-

32 risk profile can reduce the number of participants exposed to an inferior control. Second,
33 adaptive designs can improve the efficiency of a trial, for example, by increasing its power for
34 a given expected sample size. Third, adaptive designs can help improve understanding of
35 treatment effects and decision-making. For example, a confirmatory two-stage adaptive design
36 with selection between two doses at an interim analysis may reduce uncertainty about the dose
37 with the better benefit-risk profile while also allowing for confirmation of the efficacy of the
38 selected dose.

39 However, adaptive designs also present challenges, as they may add complexities and
40 uncertainty related to the key principles discussed in Section 3. For example, use of an adaptive
41 design may add logistical difficulties in maintaining confidentiality of interim results and
42 introduce risks to trial integrity which, if not properly addressed, may lead to unreliable results
43 and complications with their interpretation at trial end. In addition, appropriate planning for
44 and assessment of a trial with an adaptive design can be more complex and may require more
45 time than for a trial without an adaptive design. In particular, use of conventional analysis
46 methods that would apply in non-adaptive designs usually lead to an increased Type I error
47 probability and biased treatment effect estimate. For example, in a design with an interim
48 analysis to modify the target sample size based on the estimated treatment effect, the Type I
49 error probability can be more than doubled when using analysis methods that do not account
50 for the adaptation. As another example, the potential for early stopping for efficacy may lead
51 to biased treatment effect estimates because the trial will be stopped preferentially when
52 extreme data have been observed. Therefore, special analysis methods for hypothesis testing
53 and estimation that account for the adaptive design usually need to be used. In addition, some
54 trials with adaptive designs may provide less information about safety, potentially leading to
55 more uncertainty during benefit-risk assessments. Also, adaptive designs may not be beneficial
56 in all clinical trial settings. For example, adaptive designs may not be favored if there is fast
57 enrollment of participants relative to the assessment time of the endpoint on which the
58 adaptation is based, or if data cannot be made available quickly enough to facilitate reliable
59 adaptation decisions at an interim analysis.

60 The decision to use or not use a specific adaptive design in a clinical trial will depend on many
61 factors, including the ones described above. There can be a tension between the confirmatory
62 nature of a late-stage clinical trial and the proposal to adapt aspects of the trial while it is
63 ongoing. In planning an adaptive design, it is therefore essential to carefully justify the need to

64 adapt the trial and assess potential implications of the type, number, and complexity of the
65 adaptations involved. The justification should include both clinical and statistical
66 considerations. It should weigh the advantages of the design against the extent to which the
67 adaptations being considered add uncertainty about the trial's ability to produce reliable and
68 interpretable results. For example, the addition of a carefully planned interim analysis to
69 potentially stop a trial early for efficacy or futility using appropriate pre-specified stopping
70 rules and ensuring sufficient information for safety and benefit-risk assessment, along with use
71 of an IDMC to maintain trial integrity, may add minimal uncertainty. On the other hand, a
72 complex design involving adaptations to multiple trial features may add considerable
73 uncertainty related to maintaining trial integrity. This could include uncertainty about the
74 adequacy of information flow and data access specifications, or the potential impact of the
75 adaptation itself on trial conduct and the trial's ability to provide interpretable treatment effects.
76 This can lead to challenges in assessing results and in regulatory decision-making about the
77 efficacy and benefit-risk profile of a proposed dose of a treatment for a specific patient
78 population. A proposed adaptive design requires a clear and compelling justification. This
79 justification should discuss how the proposed design addresses inherent needs of the clinical
80 setting and should provide an evaluation of advantages and limitations as compared to
81 alternative designs (including non-adaptive designs), including a comparison of important trial
82 operating characteristics (e.g., power, expected sample size, reliability of adaptation decisions)
83 between candidate designs.

84 **3. KEY PRINCIPLES**

85 For the purpose of this guideline, a principle refers to a characteristic of a trial design that is
86 critical to ensure the reliability and interpretability of the results. This section describes
87 principles that require specific considerations with an adaptive design. The focus is on
88 proposals for confirmatory trials with an adaptive design. All of these principles should be
89 followed regardless of the type of adaptation and statistical approach (e.g., frequentist or
90 Bayesian methods).

91 **3.1 Adequacy Within the Development Program**

92 It is important that clinical trials are properly designed, conducted, and analyzed to address the
93 clinical research question(s) of interest within the context of an overall development program.
94 A stepwise program with careful analysis and evaluation of completed exploratory trials helps
95 inform the goals and design choices for subsequent confirmatory trials and ultimately generate

96 data necessary for regulatory decision-making. A complete development program should seek
97 to, among other aspects: characterize the dose-response relationship with respect to favorable
98 and unfavorable effects; identify an appropriate patient population for treatment; select
99 clinically meaningful and sensitive endpoints; and reliably confirm efficacy and support the
100 assessment of safety and benefit-risk in the intended patient population.

101 The number and complexity of adaptations at the confirmatory stage should generally be
102 limited. Increasing either of them, as a replacement for a sequence of multiple trials, can impair
103 the ability to answer important clinical questions and limit the opportunity to carefully reflect
104 on prior results to design a development program most effectively. Before planning a
105 confirmatory trial with multiple adaptations, sponsors should discuss whether additional
106 exploratory trials are necessary to investigate the question(s) addressed by the proposed
107 adaptation(s).

108 For example, consider a confirmatory two-stage adaptive clinical trial design with selection
109 between two doses at an interim analysis, and confirmation of efficacy of the selected dose. In
110 a setting where a dose-ranging trial has been conducted with remaining uncertainty about the
111 most appropriate of two candidate doses, such a design may help ensure identification of the
112 dose with the better benefit-risk profile in the intended patient population. However, if a proper
113 dose-ranging trial was not conducted in earlier stages of the development program, the
114 selection of two doses for the confirmatory trial(s) may not be well supported, adding risk that
115 the program may fail to identify an appropriate dose. An adaptive design should generally not
116 serve as a replacement for a proper dose-ranging trial. It is generally expected that the sponsor
117 has completed the necessary trials to evaluate a wider range and number of doses before
118 proceeding to the confirmatory trial(s) intended to confirm efficacy and assess benefit-risk.

119 **3.2 Adequacy of Trial Planning**

120 Adequate planning is important for all clinical trials to ensure the design is pre-specified,
121 conduct and analysis are appropriate, and results are reliable and interpretable. If a
122 confirmatory clinical trial is planned with an adaptive design, the number and complexity of
123 adaptations should generally be limited and there should be a justification for adapting aspects
124 of the trial at this stage of drug development. Prior to initiation of a trial with an adaptive
125 design, further aspects should be specified and justified in addition to the typical components
126 of trial planning. These include the number and timing of interim analyses, type of adaptation,
127 statistical methods for producing interim results, anticipated rule governing the adaptation

128 decision, statistical methods for the primary analysis aligned to each targeted estimand, and
129 approaches to maintain trial integrity. For adaptive designs with a planned selection of an
130 estimand at an interim analysis, such as treatment- or population-selection designs (Sections
131 4.3 and 4.4), all candidate estimands should be fully pre-specified and clinically relevant.

132 Some types of adaptive designs may require more planning than others. For example, a design
133 with unblinded sample size adaptation warrants additional approaches to maintain trial integrity
134 than one with blinded sample size adaptation. If simulations are critical to understand operating
135 characteristics of an adaptive design, the simulation study should be carefully planned,
136 conducted, and reported (Section 5.2). All relevant details pertinent to the planning of an
137 adaptive trial design should be appropriately documented (Section 6).

138 Adequate planning facilitates the evaluation of the appropriateness of the statistical approach
139 for many types of adaptations. For example, Type I error probability control requires the pre-
140 specification of criteria for early efficacy stopping or rules for combining evidence across
141 stages. As another example, specifying a blinded sample size adaptation in the protocol,
142 together with the adaptation rule, increases confidence that an adaptively selected sample size
143 was not influenced by unblinded data. Adequate planning also facilitates the evaluation of trial
144 operating characteristics and enables informed discussions with the IDMC (if involved in the
145 adaptations). Sponsors should discuss the type of adaptations and anticipated adaptation rules
146 in detail with the IDMC to confirm its understanding and support. This ensures the IDMC is
147 prepared to review interim results and make adaptation recommendations during the trial while
148 also protecting individual trial participants' safety.

149 There should always be a clear description of the anticipated rule on which the adaptation will
150 be based. The extent to which the anticipated rule governing the adaptation decision needs to
151 be adhered to at an interim analysis, however, can vary depending on the type of adaptation
152 and the statistical inferential methods being used. It is generally recommended to use analysis
153 methods that provide valid inference while allowing flexibility to deviate from the anticipated
154 adaptation rule based on the overall benefit-risk assessment at an interim analysis. For example,
155 consider a confirmatory two-stage adaptive clinical trial with selection between two doses at
156 an interim analysis, with the objective to confirm the efficacy and support the benefit-risk
157 assessment of the selected dose. At the trial planning stage, an efficacy-based rule for the
158 interim dose selection may be planned given that no meaningful safety issues are expected.
159 There is a chance, however, that interim data will suggest similar efficacy between the two

160 doses, with an unexpected safety concern for the higher dose. When using statistical methods
161 that allow for the flexibility to incorporate such benefit-risk considerations at the interim
162 analysis, the pre-specified plan should acknowledge the possibility of deviations from the rule
163 and outline factors that may lead to such deviations. If the planned statistical methods instead
164 require strict adherence to the rule governing the interim decision to ensure valid inference
165 (e.g., Type I error probability control), the importance of adhering to the rule should be
166 documented in the trial protocol.

167 **3.3 Limiting the Chances of Erroneous Conclusions**

168 It is important to limit the chances of erroneous conclusions about the efficacy, safety, and
169 benefit-risk profile of a proposed treatment. An essential element of regulatory decision-
170 making is controlling the chances of false positive efficacy conclusions (i.e., conclusions that
171 truly inefficacious treatments are efficacious). The common approach is to limit the probability
172 of false positive efficacy conclusions within a trial by using frequentist methods that control
173 the Type I error probability for a hypothesis test of the primary estimand at a pre-specified
174 threshold (ICH E9).

175 For most adaptive designs, it is necessary to use specific methods to control the Type I error
176 probability. For example, if a design includes an interim analysis with the potential for early
177 stopping for efficacy, appropriate pre-specified stopping rules are needed. When an adaptive
178 trial design includes multiple testing approaches to control the Type I error probability across
179 multiple primary and/or secondary endpoints, those approaches should additionally address the
180 potential for an increased Type I error probability due to the proposed adaptation.

181 Although the predominant approaches to the design and analysis of clinical trials have been
182 based on frequentist statistical methods, other approaches may be appropriate when the reasons
183 for their use are clear and when the resulting conclusions are sufficiently robust (ICH E9).
184 Section 5.3 describes important considerations for limiting the chances of false positive
185 efficacy conclusions in adaptive designs using Bayesian methods.

186 It is also important to understand how a proposed adaptive design may impact the potential for
187 other types of erroneous conclusions. This includes the need for the trial to provide sufficient
188 information on safety, important secondary efficacy endpoints, and relevant patient subgroups
189 to inform a reliable benefit-risk assessment. For example, when planning a trial with the
190 potential to stop early for an efficacy conclusion, it is important to justify that the sample size

191 and duration of follow-up at an interim analysis can adequately support a reliable benefit-risk
192 assessment. This also includes evaluation of the impact of adaptive designs on conclusions
193 made at interim analyses, and the risk that the adaptive design may be inadequate to fulfill the
194 trial objectives. For example, sponsors should evaluate the ability of an adaptive dose-selection
195 design to select the better out of two doses at an interim analysis based on efficacy and benefit-
196 risk considerations. Finally, adaptations can impact the chance of a false negative efficacy
197 conclusion (i.e., lack of evidence of an effect for a truly efficacious treatment) such that it is
198 important to evaluate whether the trial achieves adequate power.

199 **3.4 Reliability of Estimation**

200 Controlling the chances of false positive efficacy conclusions is expected in a confirmatory
201 clinical trial (Section 3.3). In addition, reliable estimation of treatment effects for the primary
202 efficacy endpoint and other key efficacy and safety outcomes is important to facilitate the
203 benefit-risk assessment and inform regulatory decision-making. The primary analysis of a trial
204 with an adaptive design should therefore provide an estimate of the treatment effect that is
205 reliable and aligned with the estimand of interest. Sponsors should evaluate bias and variability
206 of treatment effect estimates, including measures such as the mean squared error. In the trade-
207 off between bias and variance, the expectation is generally for limited to no bias in the primary
208 estimate of the treatment effect. The primary analysis should also support calculation of
209 accurate measures of uncertainty such as confidence intervals with targeted coverage
210 probabilities.

211 If a trial with an adaptive design uses approaches for estimation in the primary analysis that do
212 not account for the adaptive nature of the design, unreliable treatment effect estimates and
213 incorrect estimates of uncertainty (e.g., incorrect confidence interval coverage) may arise. For
214 example, selecting the treatment with the largest estimated effect from among several
215 treatments at an interim analysis will, on average, lead to an overestimation of that treatment's
216 effect. This holds true even if selection is based on an endpoint expected to be predictive of
217 efficacy rather than the primary endpoint itself. Similarly, treatment effect estimates for
218 secondary endpoints may be biased in the presence of adaptations. Adaptive design proposals
219 should therefore evaluate bias and variability of treatment effect estimates and provide support
220 of their reliability. In some cases, bias and variability can be calculated analytically. In other
221 cases, the evaluation has to rely on simulations. For some designs, specific estimation methods
222 have been derived with improved reliability, and these should be used. As one example,

223 methods are available in group sequential designs for adjusting estimates to reduce or remove
224 bias associated with the potential for early stopping and to improve performance on measures
225 such as the mean squared error.

226 In addition to ensuring reliable estimation of the treatment effect in the primary analysis, it is
227 also important to support that estimates at interim analyses can facilitate reliable adaptation
228 decisions. For example, conducting an interim analysis in an adaptive dose-selection design at
229 an early time point may result in highly variable estimates and the selection of an inferior dose.
230 Sponsors should therefore evaluate the overall operating characteristics of the design (e.g.,
231 probability of selecting the better dose) to inform careful selection of the timing of an interim
232 analysis and the adaptation rules.

233 **3.5 Maintenance of Trial Integrity**

234 It is important that the integrity of a trial is maintained such that it achieves its objectives in a
235 reliable, ethical, and timely manner. The impact of trial adaptations on the statistical validity
236 of trial results is discussed in Sections 3.3 and 3.4. Maintenance of trial integrity also relies on
237 appropriate execution of the trial and careful assessment of the potential impact of envisaged
238 adaptations on trial conduct, which is the focus of this section.

239 Knowledge by the sponsor, investigators, or trial participants about individual treatment
240 assignments, accumulating data, or certain trial changes can impact trial integrity by affecting
241 expectations and behaviors in ways that are difficult to predict and impossible to adjust for.
242 Such knowledge can introduce subtle changes in trial conduct, such as changes in the pace and
243 characteristics of participants enrolled, specific details of the administration of the study
244 treatment or other medications, or endpoint assessments, that may impact the interpretation of
245 trial results. For example, knowledge by investigators and trial participants of a small or
246 unfavorable estimated treatment effect based on accumulating data during an ongoing trial
247 could be misinterpreted as reliable evidence of no effect, causing decreased enrollment,
248 adherence, and retention of trial participants, ultimately leading to unreliable results and
249 difficulties with their interpretation at trial end. The recommended approach is to blind
250 participants, investigators, and the sponsor to individual treatment assignments and to
251 accumulating summary-level data in which treatment groups are identified (either with the
252 actual treatments or with labels such as A and B), therefore limiting the risk for occurrence of
253 conscious and unconscious changes in trial conduct arising from such knowledge.

254 A fundamental aspect of many types of adaptive designs is the need for some level of access to
255 unblinded interim results. Personnel having access to accumulating unblinded data should
256 generally be independent in the sense that they do not have conflicts of interest or any role in
257 trial activities and are external to the sponsor. To achieve this, an IDMC should be in place to
258 review unblinded interim data when such access is needed as part of the adaptive design. In
259 confirmatory trials, an IDMC will often already be planned to assure the safety of trial
260 participants and to protect the scientific integrity of the trial. In this case, the IDMC can have
261 an additional role of reviewing interim data for the purpose of implementing the planned
262 adaptations. If an IDMC is not already planned, one can be set up with objectives and member
263 expertise targeted toward implementing the adaptive design. Standard operating procedures
264 and confidentiality agreements should be put in place to limit access to unblinded interim
265 results beyond the IDMC. Additional discussion about the IDMC and other data monitoring
266 considerations is available in Section 5.1.

267 Even the knowledge of an adaptation itself can lead to unwanted changes in behavior on the
268 part of investigators or trial participants or can potentially reveal information about unblinded
269 interim results. For example, if an unblinded sample size adaptation is implemented, where the
270 revised sample size is a function of an interim treatment effect estimate, someone who
271 understands the adaptation rule and knows the revised sample size can infer the interim effect
272 estimate. Therefore, measures should be implemented to minimize the information that can be
273 inferred, while maintaining ethical standards (e.g., adequate informed consent forms) and
274 ensuring operational feasibility (e.g., adequate drug supply); see further discussion of
275 operational considerations in Section 5.6. One particular approach to limit the knowledge that
276 can be inferred during the trial is to use adaptation rules where a sufficiently large range of
277 interim estimates leads to the same change (e.g., with a sample size adaptation rule that includes
278 only a small number of potential adaptively selected sample sizes). Details of the adaptation
279 rule could be reserved for a specific document rather than the protocol, such as a confidential
280 appendix to the IDMC charter, that is only accessible to designated sponsor personnel separated
281 from the team managing and conducting any aspects of a clinical trial. Additionally, sponsor
282 personnel, investigators, and trial participants could be shielded from knowledge of specific
283 adaptive changes. For example, trial sites could be informed after a sample size adaptation that
284 the targeted enrollment has not been reached, or notified of site- or region-specific targets,
285 rather than notified of the overall sample size target.

286 Sponsors should discuss with regulators at the planning stage the potential implications of the
287 adaptations on trial conduct, including the type of participants enrolled, and on the
288 interpretation of the results at trial end. This should include a discussion of the sufficiency of
289 the size of the trial stages for assessing the impact of adaptations. Sponsors should implement
290 approaches for maintaining trial integrity. Processes should be documented to increase
291 adherence to these approaches and to provide transparency to relevant stakeholders (e.g.,
292 regulatory authorities and participating investigators). Appropriate training and careful
293 planning are needed to prevent compromises to the extent possible. Because even the most
294 rigorous processes may not fully guarantee trial integrity, the interpretation of results at trial
295 end should involve consideration of any heterogeneity between results from different stages of
296 the trial, the nature of the adaptive design (e.g., the number and type of adaptations and the size
297 of the stages of the trial), the processes in place and who had access to different kinds of data
298 and information during the trial, and any notable changes in trial conduct before and after an
299 interim analysis (e.g., changes in the types of participants enrolled). Unexpected heterogeneity
300 findings should be discussed by the sponsor and may impact the interpretation of the trial
301 results.

302 The principles for maintaining trial integrity discussed above are particularly critical in open-
303 label trials in which each participant's individual treatment assignment is known to the
304 participant and/or investigator. Notably, even though individual participant assignments are
305 known in such trials, it is feasible and strongly recommended to ensure that participants,
306 investigators, and the sponsor do not have access to accumulating summary-level data by
307 treatment group.

308 **4. TYPES OF ADAPTATIONS**

309 This section discusses common types of adaptations, with a focus on specific considerations
310 relevant to the principles in Section 3. This section also illustrates some of the advantages and
311 challenges of adaptive designs outlined in Section 2. The discussion focuses on designs using
312 frequentist approaches for statistical analysis. For special considerations related to adaptive
313 designs using Bayesian methods, see Section 5.3.

314 **4.1 Early Trial Stopping**

315 During the conduct of a clinical trial, accruing data can provide information that makes it no
316 longer appropriate to continue the trial. To address this, sponsors can consider a trial design

317 that includes prospectively planned sequential analyses of accumulating unblinded data with
318 anticipated rules for stopping when there is compelling evidence of efficacy (stopping for
319 efficacy) or when the trial is unlikely to demonstrate efficacy (stopping for futility). A clinical
320 trial design that allows such sequential analyses for early efficacy stopping based on
321 accumulating observations of groups of participants at pre-specified points throughout the trial
322 is called a group sequential design.

323 When planning a trial design that allows for early efficacy stopping, appropriate stopping
324 boundaries should be planned for the sequential analyses such that the Type I error probability
325 is controlled. The timing of interim analyses and specific stopping rules should be justified
326 based on factors such as the required persuasiveness of early results to stop the trial, the
327 probability of early stopping, and the expected and maximum sample sizes or numbers of
328 events that may be accrued. Approaches may be considered that allow deviation from the
329 anticipated timing of interim analyses. For example, this could help accommodate the
330 scheduling of IDMC meetings at specific calendar times, such that the actual sample size at an
331 interim analysis may differ slightly from the pre-specified target. In addition, methods for
332 calculating the primary treatment effect estimate and associated confidence interval that adjust
333 for the interim analyses should be planned to limit bias and improve performance on measures
334 such as the mean squared error (Section 3.4).

335 A trial that is stopped early for efficacy will provide less information (e.g., because of a smaller
336 sample size and/or shorter duration of follow-up) for the evaluation of safety, important
337 secondary efficacy endpoints, and relevant patient subgroups, which are important for the
338 overall benefit-risk assessment. Therefore, the timing of interim analyses should be selected
339 such that the sample size is large enough and the duration of follow-up is long enough to ensure
340 sufficient information is available for decision-making. There usually is a limit on how early
341 interim analyses should occur or whether they should occur at all because a minimum sample
342 size and/or duration of follow-up is expected for a sufficient evaluation of safety. This is often
343 a relevant criterion, for example, in preventive vaccine trials and to meet regulatory standards
344 for the extent of population exposure for treatments intended for long-term treatment of non-
345 life-threatening conditions (ICH E1). Furthermore, interim analyses with the potential for early
346 stopping are more often considered in circumstances where there are compelling ethical
347 reasons (e.g., the primary endpoint is survival), and efficacy stopping rules typically require

348 highly persuasive results in terms of both the magnitude of the estimated treatment effect and
349 the strength of evidence of an effect.

350 In the case that a stopping rule at an interim analysis is met and a decision is made to stop the
351 trial for efficacy, additional data beyond those included in the interim analysis may continue to
352 accumulate on participants in the trial prior to the final database lock. This can occur as a result
353 of a time lag between data collection and interim analysis during which data adjudication and
354 cleaning are carried out. Sponsors should ensure this additional information is appropriately
355 documented and should report results from the interim analysis and from the analysis based on
356 all available data, which are both important for regulatory decision-making. For example, a
357 change in the estimated treatment effect between these two analyses that may affect the benefit-
358 risk assessment would warrant investigation of potential explanations and may make
359 interpretation of the trial results challenging.

360 When a trial design incorporates the potential for futility stopping, while anticipated futility
361 rules should be pre-specified and justified, it is generally recommended to use nonbinding
362 futility rules. This means that the futility stopping criteria serve as guidelines that can be
363 deviated from based on the interim results without increasing the Type I error probability. This
364 flexibility is important because decision-making about whether to stop for futility or continue
365 is usually not an algorithmic process and may need to incorporate additional information
366 beyond the primary efficacy endpoint, such as safety or other efficacy data. In contrast, there
367 have been proposals to use binding futility rules and adjust the efficacy decision criteria for the
368 planned futility criteria. These approaches have the disadvantage of requiring that sponsors
369 adhere to the pre-specified futility stopping criteria, as otherwise the Type I error probability is
370 not controlled and the interpretation of trial results can be compromised.

371 **4.2 Sample Size Adaptation**

372 Even after a carefully planned and conducted early-phase development program, a considerable
373 degree of uncertainty might exist in the parameter assumptions that affect the sample size
374 calculations for a clinical trial. One source of uncertainty are assumptions about the nuisance
375 parameters that are not of primary interest but may affect the sample size of a trial. Examples
376 of nuisance parameters include the standard deviation of a continuous outcome and the
377 probability of response of the control arm for a binary outcome, which can be highly variable
378 across trials in certain disease settings. In such cases where a sound rationale exists, sponsors
379 may consider incorporating the potential for modification of the initial sample size based on

380 interim estimates of nuisance parameter values to ensure the trial is adequately powered.
381 Another source of uncertainty at the planning stage are assumptions about the anticipated
382 treatment effect size. In cases where there is justification based on residual uncertainty (e.g.,
383 after appropriate exploratory trials; see Section 3.1), sponsors may consider a sample size
384 adaptation based on an interim treatment effect estimate. The goal would be to ensure sufficient
385 power under a range of plausible and clinically meaningful treatment effect sizes.

386 Appropriate planning of any design incorporating sample size adaptation should include pre-
387 specification and justification of the minimum and maximum potential sample sizes, the
388 anticipated sample size adaptation rule, and the statistical analysis method. It is important that
389 the minimum sample size still provides sufficient information for benefit-risk assessments
390 (e.g., for evaluating safety, secondary endpoints, and subgroup analyses), similar to
391 considerations for early stopping (Section 4.1).

392 Adaptations to the sample size based on nuisance parameter estimates should be carried out
393 using blinded data as this approach does not incorporate information about treatment
394 assignment, thus minimizing risks for trial integrity. The anticipated sample size adaptation
395 rule should be pre-specified to increase confidence that an adaptively selected sample size was
396 not influenced by unblinded data. Such pre-specification also facilitates evaluation of trial
397 operating characteristics (e.g., power and expected sample size). Sponsors should propose and
398 justify a testing approach that controls the Type I error probability. In some cases, conventional
399 analysis methods that would apply in non-adaptive designs can be used for the primary analysis
400 if there is justification (e.g., in a reasonably sized two-arm superiority trial with a continuous
401 endpoint). In other cases (e.g., a two-arm non-inferiority trial with a continuous endpoint), the
402 use of these conventional methods may lead to an increase in the Type I error probability and
403 different approaches are needed.

404 Trials with sample size adaptations based on interim effect estimates should use an IDMC and
405 adequate processes to maintain trial integrity, given that the adaptations are based on unblinded
406 data. This should include steps to minimize the information that can be inferred from the
407 interim sample size selection (Section 3.5). Given that such designs typically allow for an
408 increase in sample size compared to the initially planned sample size, statistical significance
409 can be achieved with weaker observed effects than initially planned. When planning such a
410 design, it is therefore important to judge the magnitudes of effects that would be clinically

411 meaningful, justify the added participant exposure, and ensure that the potential sample sizes
412 under the adaptive design are sensible from a clinical perspective.

413 It is generally recommended to use sample size adaptation methods that do not require
414 adherence to the anticipated adaptation rule, such as hypothesis testing based on pre-specified
415 weights for combining the information across trial stages. Still, the anticipated adaptation rule
416 should be pre-specified to facilitate the evaluation of trial operating characteristics (e.g.,
417 expected sample size and power) and ensure that the IDMC understands and is in agreement
418 with the anticipated adaptation rule.

419 For most designs involving adaptations to the sample size based on interim treatment effect
420 estimates, conventional testing methods for non-adaptive designs are not appropriate and
421 specific statistical methodology needs to be used to ensure Type I error probability control. In
422 addition, conventional point estimates of the effect size may be biased, and conventional
423 confidence intervals may have incorrect coverage probabilities. Therefore, it is recommended
424 to evaluate the reliability of these estimates at the trial planning stage. This evaluation may
425 inform the acceptability of the proposed adaptive design or the interpretation of trial results. In
426 some cases, methods are available that adjust estimates to reduce or remove bias associated
427 with the adaptation and these are preferred.

428 **4.3 Population Selection**

429 In certain settings, there may be remaining uncertainty about the patient population who should
430 be treated with a new treatment. For example, a treatment may be expected to benefit a certain
431 targeted subset of the overall population, while the benefit in the non-targeted (complementary)
432 subset may be unclear. This targeted subpopulation could be defined, for example, by
433 demographic characteristics or by a genetic or pathophysiologic marker that is assumed to be
434 related to the treatment's mechanism of action. If the treatment were truly efficacious in the
435 targeted subpopulation but not efficacious or minimally efficacious in the complementary
436 subpopulation, conducting a trial in the overall population might have insufficient power to
437 establish a treatment effect and might unnecessarily expose participants to a treatment from
438 which they will not receive benefit. On the other hand, if the treatment were truly efficacious
439 in the overall population, a trial in only the targeted subpopulation would not provide data on
440 the effects of the treatment in the complementary subpopulation and would result in restricting
441 the indication for the treatment to only a subset of the overall population that would benefit.

442 Such uncertainty would usually be investigated in an exploratory trial. However, in some cases
443 there also may be consideration to conducting a confirmatory trial in the overall population,
444 with an analysis plan that includes evaluation of efficacy in a targeted subpopulation (e.g., with
445 a multiple testing approach to control the Type I error probability across analyses in the overall
446 population and in the subpopulation). Alternatively, it may be more efficient to consider a
447 design for a confirmatory trial with the option for adaptations to the patient population based
448 on unblinded interim results. A trial might enroll participants from the overall population up
449 through an interim analysis, at which time a decision would be made whether to continue
450 enrollment in the overall population or to restrict future enrollment to a targeted subpopulation.
451 If enrollment continues in the overall population, a decision would then need to be made
452 whether to evaluate in the analysis at trial end the treatment effect in only the overall
453 population, or in both the overall population and the targeted subpopulation. If enrollment is
454 restricted to the targeted subpopulation, the analysis at the end of the trial would focus on the
455 treatment effect in that subpopulation. In such settings, data accumulated both before and after
456 the interim analysis should be appropriately combined to draw inference on the treatment effect
457 in the selected population(s).

458 Adequate planning of such designs should include pre-specification of the candidate
459 population(s) that may be selected at the interim analysis to be the target of future enrollment,
460 the decisions to be made at the interim analysis regarding the population(s) for statistical
461 inference and how they will be analyzed at the end of the trial, and the anticipated adaptation
462 rules. There should also be a plan for managing participants from a population for which further
463 enrollment and evaluation is stopped based on an interim analysis. In designs that select
464 population(s) for enrollment and analysis based on interim treatment effect estimates, specific
465 statistical methodology is typically needed to control the Type I error probability. Methods are
466 generally recommended that allow flexibility in deviating from the anticipated adaptation rule,
467 as considering the totality of information available at the interim analysis helps ensure
468 appropriate population selection. Sponsors should also ensure that interim estimates can
469 facilitate reliable population selection, including planning the interim analysis at an appropriate
470 time point. Furthermore, given that such a design tends to select population(s) with more
471 favorable interim results, conventional treatment effect estimates at trial end may be biased.
472 The reliability of the treatment effect estimates in the different populations should be evaluated,
473 and adjusted estimates that reduce or remove bias should be considered.

474 It is important that a trial with population adaptation has a sound scientific rationale. For
475 example, a trial in the overall population that includes an interim analysis to potentially focus
476 future enrollment and analysis on a particular subpopulation should be motivated by results
477 from previous trials and/or biologic evidence that the benefit-risk profile may be meaningfully
478 more favorable in the targeted subpopulation. With such a trial, it is also important to ensure
479 that the design facilitates reliable decision-making in the scenario in which enrollment in the
480 overall population continues after the interim analysis. This includes ensuring that the trial will
481 provide adequate information on the benefit-risk profile in the complementary subpopulation.
482 It also includes specifying criteria, including criteria for the estimated treatment effect in the
483 complementary subpopulation, that would justify a conclusion of benefit in the overall
484 population. If the baseline characteristic that may be used to define subpopulations is not binary
485 in nature, justification should be provided at the planning stage for any threshold(s) used to
486 define the subpopulations.

487 **4.4 Treatment Selection**

488 Some trials are conducted with the intent to evaluate more than one treatment. The multiple
489 treatments might be different drugs or different doses of a single drug. For example, there might
490 be uncertainty remaining at the end of the exploratory development phase about the benefit-
491 risk profile of two likely efficacious doses of a certain drug. A confirmatory trial might then
492 compare these two doses against control with the objective to confirm their efficacy and to
493 select the most appropriate dose(s) at trial end. In such a setting, it may be conceivable to design
494 a trial with the option for dose selection based on an interim analysis of accumulating unblinded
495 data. Participants would initially be randomized to either of the two doses or control. At the
496 interim analysis, one or both doses would be selected for continued randomization in the second
497 stage. The analysis at the end of the trial would then aim to confirm efficacy and assess benefit-
498 risk of the selected dose(s) based on data across both trial stages.

499 Adequate planning of a trial with adaptive treatment selection should involve specification of
500 the treatments that will be evaluated, the decisions to be made at the interim analysis, and the
501 anticipated rules for the selection process, including any implications for the randomization
502 scheme and overall sample size. There should also be a plan for managing participants who are
503 receiving a treatment for which further evaluation is stopped based on an interim analysis. In a
504 design that potentially selects one (or more) treatments based on interim effect estimates,
505 specific statistical methodology is needed to control the Type I error probability. It is generally

506 recommended to use methods that allow for flexibility in deviating from the anticipated
507 adaptation rule. Such flexibility enables consideration of the full scope of information available
508 at the interim analysis, helping to support more informed and appropriate treatment selection
509 decisions. Sponsors should also ensure that interim estimates can facilitate reliable treatment
510 selection, including planning the interim analysis at an appropriate time point. Given that such
511 a design tends to select treatment(s) with more favorable interim results, conventional treatment
512 effect estimates at trial end may be biased. The reliability of estimates should be evaluated, and
513 adjusted estimates that reduce or remove bias should be considered.

514 **4.5 Adaptation to Participant Allocation**

515 In a randomized trial, participants are typically allocated to treatment arms according to fixed
516 randomization probabilities. Alternatively, there are different approaches that can be
517 considered to incorporate adaptations to the allocation scheme, where the assignment of
518 participants to treatment arms depends on the data of earlier trial participants. These include
519 covariate-adaptive approaches where assignment depends on accumulating baseline covariate
520 data and response-adaptive approaches where assignment depends on accumulating outcome
521 data. This section focuses on response-adaptive randomization (RAR) approaches where
522 incoming participants are randomized to treatments according to probabilities that depend on
523 previous unblinded outcome data. The key idea is to assign new participants with greater
524 probability to treatment arms that have had, to that point, more positive outcomes than to other
525 treatment arms.

526 RAR is sometimes valued for advantages to trial participants such as exposure of fewer
527 participants to an inferior treatment or reduction in the expected number of participant
528 treatment failures in a trial with a binary response endpoint. However, RAR procedures also
529 bring challenges in ensuring valid statistical inference. Perhaps most concerning, RAR designs
530 are susceptible to bias and inflation of the Type I error probability in the presence of overall
531 time trends. For example, a RAR design would more likely show a false positive treatment
532 effect if earlier-enrolled participants are both more likely to be assigned to control and to have
533 a poor prognosis (e.g., because of changes in background care or participant characteristics
534 over time) than later-enrolled participants. In addition, the use of efficacy-based algorithmic
535 modifications to the randomization scheme could lead to an insufficient sample size to support
536 decision-making on a treatment that may have lesser efficacy but a better benefit-risk profile.

537 Any proposal to use RAR should address these potential issues. The specific RAR procedure
538 should be pre-specified and justified. There should be careful specification of analysis methods
539 that provide Type I error probability control and reliable estimates. The proposal should address
540 the potential for confounding due to time trends. The degree of such confounding may depend
541 on factors such as the expected duration of the trial and the likelihood of changes in background
542 care or prognostic factors over time (e.g., such changes may be likely in a rapidly evolving
543 infectious disease setting). One approach that controls the Type I error probability is to allow
544 randomization ratio adaptation at only a single or small number of interim analyses, while
545 utilizing adaptive hypothesis testing based on pre-specified weights for combining the
546 information across trial stages. Time trends may also be addressed by using specific
547 methodology (e.g. re-randomization tests), but an RAR design using such tests might be less
548 powerful than a design with a fixed randomization scheme.

549 An approach that implements the changes to the randomization scheme over time without
550 sponsor involvement should be planned to reduce the risk to trial integrity. Given that
551 knowledge of the RAR procedure and the adaptively selected randomization ratio could reveal
552 information about the interim treatment effect estimate, steps should be taken to minimize what
553 can be inferred from the adaptations (Section 3.5). Finally, there can be additional challenges
554 such as ensuring the timely availability of high-quality interim data on an ongoing basis and
555 integrating the algorithm into the randomization system.

556 There are also non-randomized, deterministic adaptations to participant allocation such as in a
557 two-arm trial where a response results in assigning the next participant to the same treatment,
558 while a non-response leads to assigning the next participant to the alternative treatment. Such
559 deterministic procedures are discouraged (ICH E9) due to the high risk of bias and the potential
560 for predicting the next treatment allocation.

561 **5. SPECIAL TOPICS AND CONSIDERATIONS**

562 This section expands on some special topics for adaptive designs, including data monitoring,
563 simulations, use of Bayesian methods, time-to-event endpoints, exploratory trials, and
564 operational execution.

565 **5.1 Further Considerations on Data Monitoring**

566 This section discusses further considerations related to data monitoring in confirmatory trials
567 with adaptive designs that include interim analyses based on accumulating unblinded data. An

568 IDMC for a trial with an adaptive design should contain, as a group, all expertise needed for
569 making adaptation recommendations in addition to meeting its usual responsibilities (i.e.,
570 protecting individual participants' safety while maintaining trial integrity). It should include at
571 least one statistician knowledgeable and experienced in interim monitoring and in statistical
572 methodologies relevant to the proposed adaptive design and analysis. The IDMC should
573 generally have access to unblinded efficacy and safety data. Operational aspects should be
574 outlined in a designated charter to document details such as content and frequency of reports
575 to be prepared, meeting schedule and logistics, procedures to maintain confidentiality,
576 statistical aspects of the monitoring plan, and processes for making recommendations. It is
577 important that sponsors align upfront with the IDMC on the trial objectives and design,
578 expectations for the IDMC (including those that go beyond the usual responsibilities), type and
579 implications of adaptations, and anticipated adaptation rules.

580 An independent statistical group that conducts analyses of accumulating unblinded data and
581 produces interim reports for the IDMC should be in place. It should not include members of
582 the monitoring committee and should not support other trial activities. Trial integrity will be
583 best protected when this statistical group having access to unblinded data is external to and
584 independent from the sponsor. The statisticians and programmers that comprise this group
585 should have the appropriate expertise to carry out the analyses needed to implement the
586 adaptive design and to support the IDMC. They should have access to all trial data needed to
587 carry out their responsibilities. It is strongly recommended that the independent statistical
588 group and IDMC have sole access to unblinded interim data and results. Appropriate processes
589 for maintaining confidentiality (e.g., standard operating procedures and confidentiality
590 agreements) should be in place.

591 Upon reviewing the unblinded interim results, the IDMC should provide adaptation
592 recommendations to designated sponsor personnel separated from the trial team. In the specific
593 case that the IDMC has made a recommendation to stop a trial early, sufficient information
594 may then be communicated to the sponsor (e.g., key efficacy and safety results) to allow
595 sponsor decision-making about whether to stop the trial. In general, however, the adaptations
596 should be planned such that the sponsor can implement the IDMC recommendations regarding
597 trial adaptations without having access to any unblinded interim results. For example, this
598 would be the case when the IDMC recommends continuing the trial in a group sequential
599 design or when it selects a specific sample size in a sample size adaptation design. This requires

600 extensive planning and discussion between the sponsor and the IDMC at the planning stage to
601 ensure a common understanding of the monitoring processes and anticipated adaptation rule.

602 Risks to trial integrity are most easily minimized by completely restricting sponsor access to
603 unblinded interim results. However, sponsors may propose some degree of access to unblinded
604 data in certain circumstances. This should be made explicit at the planning stage. Any proposal
605 for sponsor access needs to be supported by a compelling rationale. In this case, there also
606 should be planned steps to protect trial integrity such as minimizing the number of individuals
607 with access, ensuring individuals with access are independent from those involved in trial
608 conduct, and implementing processes to maintain confidentiality. All information regarding
609 who accessed what data should be recorded in detail so that regulators assessing trial results
610 before and after the adaptation can be reassured at the end of the trial that trial integrity was
611 not compromised.

612 **5.2 Planning, Conducting, and Reporting Simulation Studies**

613 Simulation studies often play an important role in the planning of a trial with an adaptive
614 design. A simulation is the repeated execution of a large number of hypothetical clinical trials
615 to understand operating characteristics of a trial design under a series of specific configurations
616 of assumptions (scenarios). Simulations can be used to investigate operating characteristics of
617 a proposed adaptive design in different scenarios, such as under different treatment effect and
618 nuisance parameter assumptions, in the presence of varying dropout or enrollment rates, or
619 with a specific sample size when analytical properties of an analysis approach rely on large
620 sample sizes. For example, the probability of a false positive conclusion can be estimated by
621 calculating the proportion of simulated clinical trials that would lead to a false positive
622 conclusion that a treatment is effective when data have been simulated under the assumption
623 of no beneficial treatment effect. Simulations can facilitate comparisons of adaptive and non-
624 adaptive designs, comparisons of different adaptive design options, and comparisons of
625 different drug development programs (i.e., a comparison of a sequence of trials). Simulations
626 can also inform internal sponsor decision-making on trial logistics such as site selection and
627 drug supply. This section focuses on principles for the appropriate planning, conduct, and
628 reporting of simulations when they are critical for understanding the operating characteristics
629 of a trial with an adaptive design.

630 It is important to clearly define and focus on the key objectives the simulation study is designed
631 to address. These should be specific, relevant, and directly related to the decisions that will be

632 made as a result of the simulation study. To address the objectives, a range of clinical trial
633 designs and analysis options should be carefully selected. These should include a benchmark
634 design and analysis approach, i.e., a design with well-understood operating characteristics such
635 as a non-adaptive or group sequential design. This range of designs may also include, for
636 example, different choices for the number and timing of interim analyses, stagewise sample
637 sizes, types of adaptations, stopping and adaptation rules, and statistical methods for testing
638 and estimation. The choice of design options may be an iterative process as operating
639 characteristics are explored and should be sufficiently broad to allow a comprehensive
640 assessment of the selected adaptive design. The evaluation of the advantages and limitations of
641 all design options included in the simulation study is critical to understand the tradeoffs in the
642 selection of the proposed design.

643 It is also important to define and assess key operating characteristics that align with the
644 questions the simulation study is designed to address. These operating characteristics should
645 generally include the Type I error probability, expected sample size, expected trial duration,
646 power, coverage of confidence intervals, and bias and mean squared error of treatment effect
647 estimates. Other operating characteristics such as the probability of stopping for futility or
648 efficacy at an interim analysis may also be of interest, depending on the trial design and setting.
649 Considerations around operating characteristics for adaptive designs using Bayesian methods
650 are discussed in Section 5.3. Sometimes, operating characteristics beyond a single trial may be
651 of interest, such as the probability of selecting an appropriate dose and subsequently confirming
652 its efficacy. While it is relevant to summarize the average of the results across the simulated
653 trials (repetitions), it may also be important to evaluate the variability, minimum and maximum,
654 or other aspects of the distribution of results (e.g., the sample size distribution in a trial with
655 the potential for early stopping or sample size adaptation).

656 The scenarios included in the simulation study should cover the plausible range of assumptions
657 to ensure a robust assessment of the performance of the proposed adaptive design. This includes
658 assumptions about the treatment effects and nuisance parameters, such as the standard
659 deviation for a continuous outcome, and operational assumptions for which a sponsor may have
660 greater control (e.g., enrollment or dropout rates). The adequacy of the assumptions should be
661 justified based on clinical and statistical considerations, with documentation of the supporting
662 knowledge. This information can come from a variety of sources, including data from previous
663 trials, publications, results from extrapolations, and expert input. All relevant sources of

664 information available to the sponsor should be used, and attempts should be made to quantify
665 uncertainty and identify potential biases. Using a grid of assumptions (e.g., discrete set of
666 assumptions across a specific range) should be supported by justification based on existing
667 clinical knowledge that the range evaluated in the grid covers all plausible scenarios. It is also
668 important to justify (e.g., based on monotonicity arguments) that the grid is fine enough (i.e.,
669 that a sufficient number of different assumptions are included within the range) to provide a
670 reliable estimate of the operating characteristics of interest. Sources of information based on
671 robust evidence and understandable from a clinical perspective will make the simulation study
672 results more interpretable and convincing.

673 It is essential that the simulated scenarios comprehensively cover the plausible range of
674 nuisance parameter configurations. For example, in using simulations to investigate the Type I
675 error probability, it is impossible to simulate under every nuisance parameter configuration
676 consistent with no beneficial treatment effect, even in the simplest trial designs. Thus, there is
677 additional uncertainty for designs in which simulations are critical to understand the Type I
678 error probability. Given the additional uncertainty, additional justification is expected to
679 support such designs.

680 Implementation details of the simulation study should be described and justified. This includes
681 clear specification of the data-generating process. In many cases, a simple statistical model,
682 such as a normal distribution with mean and variance obtained from previous trials, may be
683 appropriate. In other cases, a more complex model fit based on earlier trial results (e.g.,
684 longitudinal patient profiles) may be considered. This also includes determining the number of
685 repetitions needed to get sufficient precision in the estimation of important operating
686 characteristics. More precision may be needed for certain operating characteristics or scenarios.
687 For example, it may be important to use 100,000 or more repetitions per scenario to ensure
688 sufficient precision for estimating the Type I error probability, whereas fewer repetitions may
689 suffice for other operating characteristics such as power. Algorithms should be documented
690 and random numbers should be generated in a reproducible way, such as using a documented
691 seed.

692 Finally, it is important to document the design, results, and conclusions of the simulation study.
693 A comprehensive and structured report of the simulations should be included in regulatory
694 submissions prior to conducting the trial (Section 6.1). There should be explicit links between

695 clinical and statistical assumptions and results of the simulations. The report should align with
696 the considerations outlined in this section and include the following:

- 697 1. Key questions the simulation study is designed to address.
- 698 2. The clinical trial design and analysis options evaluated in the simulation study.
- 699 3. The choice of operating characteristics assessed in the simulation study.
- 700 4. Existing knowledge, and any supporting data or references, to inform the simulation
701 scenarios.
- 702 5. The set of parameter configurations used for the simulation scenarios, along with a
703 clinical justification based on existing knowledge that the set adequately covers the
704 plausible range of values for the different parameters.
- 705 6. Implementation details, including the data-generating process and the number of
706 repetitions for each scenario, along with justifications for these choices.
- 707 7. Software package used for simulations and, if custom software was used, the simulation
708 code. When code is provided, it should have adequate comments with detailed
709 instructions on how to execute the code (e.g., an example call and the starting seed).
- 710 8. A summary providing overall results, interpretations, and conclusions. This should
711 include a detailed discussion of the proposed adaptive design and its estimated
712 operating characteristics under the various scenarios. Summarizing results in interactive
713 graphs, where possible, can help make the results more accessible.
- 714 9. A description of relevant examples of single simulated clinical trials with different
715 adaptations and conclusions. For example, in a design with sample size adaptation, this
716 might include trials with different sample size modifications at the interim analysis and
717 with positive or negative primary analysis results to facilitate a better understanding of
718 potential interim decisions and their impact on the trial results.
- 719 10. A description of any aspects that limit the interpretation of the simulation results (e.g.,
720 uncertainty in assumptions or extrapolations).

721 11. A clinical discussion about if and to what extent the simulation results address the key
722 questions.

723 The careful documentation of simulation studies is also critical because the validity of the
724 simulations and associated conclusions will be part of the regulatory review of results at the
725 end of the trial.

726 **5.3 Adaptive Designs Using Bayesian Methods¹**

727 ICH E9 notes that the use of Bayesian methods in clinical trials may be considered when the
728 reasons for their use are clear and when the resulting conclusions are sufficiently robust.
729 Bayesian methods refer to a wide range of statistical approaches that combine a prior
730 probability distribution with current trial data to obtain a posterior probability distribution for
731 a quantity of interest (e.g., the treatment effect or estimand). Bayesian methods are potentially
732 applicable to a variety of adaptive designs. The principles outlined in Section 3 should be
733 followed regardless of the specific statistical approach. There are different types of application
734 of Bayesian methods to clinical trials with an adaptive design, each with different
735 considerations.

736 Bayesian methods can be used to inform adaptations in a trial where decision criteria for the
737 primary analysis are chosen to ensure that the Type I error probability is controlled. For
738 example, a trial might include interim analyses with pre-specified non-binding futility stopping
739 rules based on a scale such as the posterior probability that the treatment is inefficacious or the
740 predictive probability of rejecting the null hypothesis at trial end, where the primary efficacy
741 analysis is performed with a frequentist hypothesis test at a pre-specified significance level.
742 For such designs, expectations for operating characteristics are the same as for adaptive designs
743 that do not involve Bayesian methods. Sponsors should justify that the prior distribution,
744 decision criteria, and adaptive design elements (e.g., number and timing of interim analyses
745 and adaptation rules) can achieve targeted operating characteristics (e.g., power, expected
746 sample size, reliability of adaptation decisions) while maintaining Type I error probability
747 control.

¹ This section on Bayesian methods for adaptive designs is not fully harmonized. The broad use of Bayesian methods may not be justified in all situations for regulatory decision-making. As noted in ICH E9 and in this draft guideline, the use of Bayesian methods in clinical trials may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust. Public consultation comments are sought on the topic, and on situations in which Bayesian methods satisfy the core adaptive design principles, and in which the use of Bayesian methods could be considered.

748 A special case is the use of adaptive design elements in the context of clinical trials that use
749 Bayesian methods to borrow external information based on an informative prior distribution,
750 with decision criteria for the primary analysis based on the posterior distribution for the
751 estimand of interest (i.e., a threshold on the posterior probability for efficacy). Borrowing of
752 external data to inform inference requires a thorough scientific justification that addresses the
753 feasibility of alternative approaches not involving borrowing (e.g., design and conduct of a
754 fully powered trial without using external data) and supports the relevance and quality of the
755 external data. Misspecification of the prior distribution can lead to lack of control of the
756 probability of false positive conclusions. Ensuring that a prior accurately reflects relevant
757 available information and addressing the potential for conflict between prior and current trial
758 data introduce additional uncertainties that are not present when using frequentist inference
759 with no borrowing.

760 For such designs, sponsors should discuss and document in the protocol the source of the
761 external information used to generate the prior, the relevance of the external information to the
762 trial design (e.g., whether the populations and concomitant care are sufficiently similar, and the
763 endpoints are the same), the list of all potentially relevant sources of information, and why
764 selected information sources were used and other potentially relevant sources were discarded.
765 Input from clinical subject matter experts is crucial for evaluating the relevance of external
766 information. When considering the source of external information, data from randomized
767 controlled trials and recent data are generally preferred. Patient-level data are generally
768 expected because they allow a thorough evaluation at the planning stage of the relevance of the
769 external information and may facilitate strategies to address potential conflict between the prior
770 and current trial data at the assessment stage.

771 Sponsors should pre-specify and justify the details of a proposed prior distribution, including
772 the amount of borrowing from the external data, as well as the criteria for defining trial success.
773 The prior and decision criteria should ensure the design fulfills the principles in Section 3.3,
774 including control of the chances of false positive conclusions. The justification for the prior
775 should include a discussion of the balance between the prior and trial data and strategies to
776 mitigate the risk that observed trial data may conflict with the prior. There should be a sufficient
777 amount of current trial data to support benefit-risk assessment. Simulations should be
778 performed to evaluate the chances of erroneous conclusions, including the chances of false
779 positive conclusions, under various scenarios of prior-data conflict. There should be a

780 discussion at the planning stage about the maximum amount of borrowing and the relationship
781 between observed conflict and the degree of borrowing, including circumstances that would
782 question the relevance of the external data and lead to no borrowing. Sensitivity analyses
783 should also be planned to investigate the robustness of the trial conclusions against alternative
784 reasonable choices for the prior distribution. It is also important to evaluate the current trial
785 data with no borrowing.

786 **5.4 Adaptive Designs in Time-to-Event Settings**

787 There are additional considerations specific to trials in which the primary endpoint is the time
788 to occurrence of a certain event. In such time-to-event trials, the statistical power of the trial
789 depends on the number of events rather than the number of participants. It is therefore common
790 for such trials to target a fixed number of events when calculating the sample size at the trial
791 planning stage. In addition, the follow-up time of participants is often unspecified, meaning
792 that the trial does not have a fixed observation period, and all participants are followed until a
793 certain number of events have occurred. For trials with adaptive designs in time-to-event
794 settings, interim analyses are therefore often planned at target numbers of events rather than
795 target sample sizes. Furthermore, a sample size adaptation based on an interim treatment effect
796 estimate in a time-to-event trial may entail modification of the initially planned number of
797 events. For example, targeting a larger number of events than originally planned could be
798 achieved by simply waiting longer for events to occur (i.e., allowing for longer follow-up
799 times) with the originally planned number of trial participants. Alternatively, the number of
800 trial participants could be increased, or both approaches could be applied. In considering
801 increases in the number of trial participants relative to the number of events, sponsors should
802 ensure that sufficient data will be available for the benefit-risk assessment (e.g., to understand
803 longer term treatment effects and to evaluate relevant subgroups of the patient population,
804 including those with lower background risk of the event).

805 Adaptive designs are most straightforward when each trial participant only takes part in one
806 stage of the trial. If the data collected prior to an interim analysis are completely independent
807 of the data collected afterwards, a statistical analysis combining all information can proceed in
808 a relatively simple way. In a time-to-event setting, however, some trial participants may be
809 enrolled and remain event-free in one stage, but may contribute an event in a later stage. Using
810 information (e.g., on secondary endpoints) from participants who have been enrolled in the
811 trial but not yet experienced the event of interest at an interim analysis to inform potential

812 adaptations violates the independence assumption and can inflate the Type I error probability
813 (even when using adaptive test statistics). Therefore, it is important to define plans with specific
814 methodology for maintaining the Type I error probability. One option is to fully pre-specify an
815 adaptation rule that relies on only the primary endpoint, without the possibility of deviations
816 from such a rule. Another option is to use special methods that involve defining stages based
817 on the sets of participants enrolled before and after the interim analysis, while also setting in
818 advance either a fixed follow-up time or a fixed number of events for each stage. Alternatively,
819 rather than incorporating adaptations to the number of events, sponsors can consider a design
820 that targets a larger number of events and includes the option to stop the trial early at an interim
821 analysis. Similar conceptual problems and respective considerations also apply to adaptive
822 designs with longitudinal outcomes, as using surrogate or intermediate outcome information
823 on participants who have not completed all follow-up visits at the interim analysis can increase
824 the Type I error probability unless appropriate analysis methods are used.

825 **5.5 Adaptive Designs in Exploratory Trials**

826 This guideline focuses on the use of adaptive designs in confirmatory clinical trials. If a trial
827 may be intended to confirm efficacy and support benefit-risk assessment, it is critical that the
828 principles in Section 3 are followed. Adaptive designs may also be used in exploratory trials
829 early in drug development that are intended to obtain information on a wide range of aspects
830 of treatment use (e.g., choices of dose, regimen, population, endpoints). Trials at this stage of
831 the development program may include a larger number of adaptations to generate information
832 that support important decisions about subsequent development phases. The principles in this
833 guideline are also relevant in these settings to ensure the reliability and interpretability of the
834 results and subsequent decision-making based on such trials.

835 Additional considerations may apply, however, for exploratory trials because independent
836 confirmation of findings will usually follow in one or more separate trials. For example, it may
837 be sufficient that the protocol describes general principles for trial adaptations rather than the
838 specific adaptation rule. This may be appropriate in, for example, dose-escalation trials where
839 model-based dose recommendations are to be considered in the context of other emerging
840 information (e.g., about toxicities that do not qualify for a dose-limiting toxicity). In addition,
841 it is critical that exploratory trials with an adaptive design can reliably inform the decisions
842 they are intended to support. For example, providing a convincing basis for decision-making
843 about the appropriate target dose to be investigated in a confirmatory trial is critical as a

844 suboptimal conclusion can have serious consequences for the subsequent development
845 program. Maintaining the integrity of exploratory trials with an adaptive design is also
846 important, but there may be additional considerations for the sponsor's role in interim decision-
847 making. For example, monitoring of an adaptive dose-ranging trial intended to inform the
848 adequate dose for subsequent confirmatory trials may entail multidimensional adaptation
849 decisions that require considerable input from various disciplines within the sponsor. Sponsors
850 should then take into account the questions a trial intends to answer and its position within the
851 development program, as well as the tradeoffs for sponsor involvement in the monitoring
852 process versus limitation of access to unblinded results to maintain trial integrity. Any
853 monitoring plan should ensure the protection of trial participants' safety.

854 **5.6 Operational Considerations**

855 Use of an adaptive design can add challenges to the operational execution of a clinical trial and
856 these should be addressed at the trial planning stage. For example, measures should be
857 implemented to minimize the information that can be inferred from an interim analysis to
858 maintain trial integrity (Section 3.5). As another example, informed consent forms should cover
859 the possibility of adaptive changes in the trial. Participants should understand the reasons for
860 such changes (e.g., the goal of selecting the dose with the best benefit-risk profile from among
861 multiple doses at an interim analysis), that these changes reflect improved knowledge about
862 the treatment under investigation, and that their rights and safety remain protected. As yet
863 another example, the infrastructure needed for trials with an adaptive design, such as data
864 management systems, may differ from that of trials with a non-adaptive design. Clinical trials
865 with an adaptive design typically use an interactive voice or web randomization system to
866 manage randomization and assignment of participants to treatment arms. Such systems should
867 be fully integrated into clinical trial operational processes and drug supply chain mechanisms.
868 Pre-specified algorithms should be built into the system to ensure it is capable of handling the
869 foreseeable scenarios (e.g., a change in the treatment arms or randomization ratio) with
870 minimum sponsor involvement. Also, adaptations to the sample size, treatment arms, or
871 participant allocation can lead to drug supply challenges. One such challenge is lead times for
872 manufacturing drugs, as rapid adaptations can strain drug supply chains and lead to delays in
873 participant treatment if sufficient drug supply is not readily available. These challenges may be
874 increased when a clinical trial with an adaptive design spans multiple countries or even regions,
875 as drugs need to be distributed to these locations in a timely manner. Simulations may help
876 support supply-related decisions at planning and execution stages of the trial. Finally, processes

877 should be established at the planning stage to ensure relevant interim data can be appropriately
878 validated and cleaned in a timely manner to ensure quality interim data informing the
879 adaptation decision. This may include requiring a formal interim database lock to ensure
880 completion of data validation and cleaning activities.

881 **6. DOCUMENTATION**

882 **6.1 Documentation Prior to Conducting a Confirmatory Trial with an Adaptive Design**

883 Documentation is a critical part of adequate planning of a confirmatory trial and allows a
884 rigorous evaluation of the proposed adaptive design. In addition to the information typically
885 included in a clinical trial protocol or in other documents, where suitable, documentation
886 should include the following:

- 887 1. A rationale for the proposed adaptive design: The rationale should include both clinical
888 and statistical considerations, justifying the proposal to adapt in a confirmatory trial and
889 the adequacy of the proposed trial design within the clinical development program. A
890 discussion of advantages and limitations as compared to alternative designs (including
891 non-adaptive designs) will help regulators evaluate the acceptability of any additional
892 uncertainty attributable to proposed adaptive elements.
- 893 2. A description of the adaptations being proposed: This should include the aspects of the
894 trial that may be modified, the number and timing of interim analyses, and the
895 anticipated rule governing the adaptation decision (e.g., the formula for determining the
896 target sample size as a function of the interim treatment effect estimate, including the
897 minimum and maximum potential sample size, in a design with sample size adaptation).
898 If the design involves selection of an estimand at an interim analysis (e.g., through
899 treatment or population selection), this should include precise definitions of all
900 candidate estimands.
- 901 3. A description of the statistical analysis methods: This should include the methods for
902 producing interim results and guiding adaptations decisions, the statistical approach for
903 primary and secondary analyses (e.g., for hypothesis testing and for estimating
904 treatment effects and corresponding measures of uncertainty), and important sensitivity
905 and supplementary analyses.
- 906 4. A description of how the adaptive design will be implemented: This should include who

907 will carry out interim analyses; who will be responsible for reviewing interim analysis
908 results and making adaptation recommendations and/or decisions; and membership,
909 roles, responsibilities, and operational aspects of any relevant committees.

910 5. A description of steps to maintain confidentiality of interim results and protect trial
911 integrity, among other details of the operational execution: This should include
912 processes for information transfer and access; who will have access to unblinded
913 interim results; how access to unblinded interim results will be controlled, what type of
914 information will be disseminated following adaptive decisions, from whom, and to
915 whom; and where records about information access and dissemination will be saved.

916 6. A description of important operating characteristics of the design. In cases where
917 simulations are critical for understanding operating characteristics, this should include
918 a report that describes the objective, design, implementation, and results of the
919 simulation study (Section 5.2).

920 This information should be documented and included in regulatory submissions prior to
921 initiation of the trial, in accordance with applicable national and regional regulatory
922 requirements and practices. The protocol should contain the core elements, including the trial
923 objectives and corresponding estimand(s), and the principal features of the trial design,
924 conduct, and statistical analysis, including all adaptive design elements and their rationale.
925 Some information, such as details on operation of an IDMC and data access processes, may
926 instead be included in a separate document such as an IDMC charter. In some cases, details of
927 the anticipated adaptation rule should be reserved for specific documents with access
928 restrictions, rather than the protocol, to maintain trial integrity (Section 3.5).

929 **6.2 Documentation to Include in a Marketing Application After a Completed Confirmatory Trial**
930 **with an Adaptive Design**

931 A marketing application for a treatment that relies on a confirmatory clinical trial with an
932 adaptive design should include sufficient documentation to allow a comprehensive review of
933 the trial results. In addition to its typical components, a marketing application should include:

- 934 1. All prospective plans described in Section 6.1.
- 935 2. Information on how the adaptive design was implemented, including the actual number
936 and timing of interim analyses, an evaluation of whether aspects of trial conduct (e.g.,

937 baseline characteristics, enrollment rate, adherence, retention) varied notably before
938 and after the interim analysis, the results of interim analyses used for adaptation
939 decisions, any notable heterogeneity between results from different stages of the trial,
940 the adaptation decisions that were made, whether anticipated adaptation rules were
941 followed, and the date of sponsor unblinding. If there was any deviation from the
942 anticipated plan (e.g., in terms of the number or timing of interim analyses or adherence
943 to the anticipated adaptation rule), this should include a discussion of the reasons for
944 the deviation, any measures taken to minimize impact on trial integrity, and any other
945 potential impact on the interpretation of trial results.

946 3. Any information on compliance with planned processes for data access and maintaining
947 trial integrity, such as results of any audits and reporting of any known deviations from
948 the processes, along with a discussion of potential implications.

949 4. Records of deliberations by the IDMC (e.g., all closed and open IDMC meeting
950 minutes), including records of discussions related to any adaptation decisions.

951 5. Reporting of results that appropriately account for the adaptive design (e.g.,
952 appropriately adjusted estimates, confidence intervals, and p-values).