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ICH E20: Adaptive Designs for Clinical Trials

Step 2 draft guideline – to be released for comments

25 June 2025

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

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Background

- This document has been signed off as a *Step 2a/b* draft guideline (25 June 2025) to be issued by the ICH Regulatory Members for public consultation
- This draft guideline was developed based on the MC-approved Concept Paper (18 November 2019) and Business Plan (18 November 2019)
- Anticipating finalisation as a *Step 4* final guideline to be implemented in the local regional regulatory system: 2026

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Introduction

- The objective is to provide guidance on clinical trials with an adaptive design;
- The focus is on principles for the planning, conduct, analysis, and interpretation of confirmatory trials with an adaptive design;
- The emphasis is on principles that are critical to ensuring the trials produce reliable and interpretable information and that require specific considerations with use of an adaptive design.

Definition and Scope

- Adaptive design: clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial
- The scope of the draft guideline does not include:
  - Trials with unplanned modifications to design;
  - Design changes based entirely on emerging external information;
  - Routine monitoring of operational aspects (e.g., enrollment rate, data quality, extent of withdrawal).

Advantages and Challenges

- Adaptive designs can provide advantages such as ethical advantages and improved efficiency;
- Adaptive designs present challenges such as by introducing risks to trial integrity or providing less information about safety;
- A proposed adaptive design requires a clear and compelling justification and should not lower scientific and regulatory standards.

Key Principles

- The draft guideline describes key principles for confirmatory trials with an adaptive design that should be followed to ensure the reliability and interpretability of results
- Five principles are discussed:
  - Adequacy within the development program;
  - Adequacy of trial planning;
  - Limiting the chances of erroneous conclusions;
  - Reliability of estimation;
  - Maintenance of trial integrity.

Adequacy Within the Development Program: A Few Considerations

- A trial with an adaptive design should be properly designed, conducted, and analyzed to address the clinical research question(s) of interest within the context of an overall development program;
- The number and complexity of adaptations should generally be limited at the confirmatory stage of development;
- Before planning a confirmatory trial with multiple adaptations, sponsors should discuss whether additional exploratory trials are necessary.

Adequacy of Trial Planning: A Few Considerations

- There should be a justification for adapting any aspect of a trial at the confirmatory stage
- Adequate planning also involves specification and justification of:
  - Number and timing of interim analyses;
  - Type of adaptation;
  - Statistical methods for producing interim results;
  - Anticipated adaptation rule;
  - Statistical methods for estimand-aligned primary analysis;
  - Approaches to maintain and assess trial integrity.

Limiting the Chances of Erroneous Conclusions: A Few Considerations

- An essential element of regulatory decision-making is controlling the chances of false positive efficacy conclusions;
- The common approach is to use frequentist methods to control the Type I error probability;
- It is necessary to use appropriate methods to control the Type I error probability for adaptive designs;
- Bayesian approaches may be appropriate when the reasons for use are clear and resulting conclusions are sufficiently robust;
- It is also important to understand the impact on other conclusions (e.g., safety, benefit-risk, adaptations, false negatives);

Reliability of Estimation: A Few Considerations

- Reliable estimation of treatment effects is important for benefit-risk assessment and regulatory decision-making;
- In the trade-off between bias and variance, the expectation is generally for limited to no bias;
- If a trial uses approaches for estimation that do not account for the adaptive design, estimates can be unreliable;
- Sponsors should evaluate the bias and variability of estimates and provide support of their reliability;
- For some designs, specific estimation methods have been derived with improved reliability, and these should be used.

Maintenance of Trial Integrity: A Few Considerations

- The integrity of a trial should be maintained such that it achieves its objectives in a reliable, ethical, and timely manner;
- It is recommended that participants, investigators, and the sponsor are blinded to individual treatment assignments and accumulating summary-level data by treatment group;
- An independent data monitoring committee (IDMC) should review unblinded interim data when such access is needed;
- Sponsors should discuss the potential impact of adaptations on trial integrity at the planning stage and justify it will be minimal;
- The assessment of results should consider the potential impact on integrity, including heterogeneity between stage-wise results.

Types of Adaptations

- The draft guideline discusses some common types of adaptations, with a focus on specific considerations relevant to the key principles for adaptive designs
- The discussion of specific types of adaptations also illustrates some of the advantages and challenges that adaptive designs can provide

Types of Adaptations Discussed in Guideline

- Early trial stopping
  - Potential for stopping when there is (1) compelling evidence of efficacy (stopping for efficacy) and sufficient information to evaluate safety and benefit-risk; or (2) when the trial is unlikely to demonstrate efficacy (stopping for futility)
- Sample size adaptation
  - Potential for modification of the sample size based on interim estimates of nuisance parameters (e.g., standard deviation of a continuous outcome) or interim treatment effect estimates

Types of Adaptations Discussed in Guideline

- Population selection
  - Potential for interim selection of the patient population to enroll in the rest of the trial (e.g., overall population or a targeted subpopulation)
- Treatment selection
  - Potential for interim selection of treatment arm(s) for continued randomization (e.g., selection of dose(s) of a drug)

Types of Adaptations Discussed in Guideline

- Adaptation to patient allocation
  - Potential for treatment assignment to depend on accumulating baseline covariate data (covariate-adaptive treatment assignment)
  - Potential for treatment assignment to depend on accumulating outcome data, such as response-adaptive randomization algorithms or changes to the randomization ratio at an interim analysis

Special Topics and Considerations

- Further considerations on data monitoring
  - Discusses the IDMC, independent statistical group supporting the IDMC, and related topics
- Planning, conduct, and reporting simulation studies
  - Discusses principles for the appropriate planning, conduct, and reporting of simulations when they are critical for understanding the operating characteristics of a trial with an adaptive design

Special Topics and Considerations

- Adaptive designs using Bayesian methods
  - Discusses considerations for different types of application of Bayesian methods to clinical trials with an adaptive design
- Adaptive designs in time-to-event settings
  - Discusses additional considerations specific to trials with an adaptive design in which the primary endpoint is the time to the occurrence of a certain event

Special Topics and Considerations

- Adaptive design in exploratory trials
  - Emphasizes that the principles in the guideline are relevant to exploratory trials early in drug development
  - Discusses additional considerations for exploratory trials with an adaptive design
- Operational considerations
  - Discusses challenges to the operational execution of a clinical trial with an adaptive design that should be addressed at the planning stage

Documentation Prior to Trial: Examples of Important Elements

- Rationale for proposed adaptive design;
- Description of adaptations being proposed;
- Description of statistical analysis methods;
- Description of how the adaptive design will be implemented;
- Description of steps to maintain confidentiality of interim results and protect trial integrity;
- Description of important operating characteristics of the design.

Documentation After Completed Trial: Examples of Important Elements

- All prospective plans;
- Information on how the adaptive design was implemented, e.g.,
  - The actual timing and number of interim analyses, interim results, and adaptation decisions made
  - Reporting of stage-wise trial results and any notable changes in trial conduct or heterogeneity in results across stages
- Information on compliance with the adaptation plan and processes for data access and maintaining trial integrity;
- Records of IDMC meetings;
- Results that appropriately account for the adaptive design.

Conclusions

- This draft guideline provides important principles for the planning, conduct, analysis, and interpretation of confirmatory clinical trials with an adaptive design;
- Global harmonisation can reduce barriers and make it possible to execute multi-regional confirmatory clinical trials with an adaptive design;
- This draft guideline will hopefully help support the appropriate use of adaptive designs in confirmatory clinical trials to accelerate the development and availability of safe and effective treatments.

Contact

- For any questions please contact the ICH Secretariat:

admin@ich.org