

Development of the ICH E20 guideline on adaptive designs in clinical trials: current status and future work

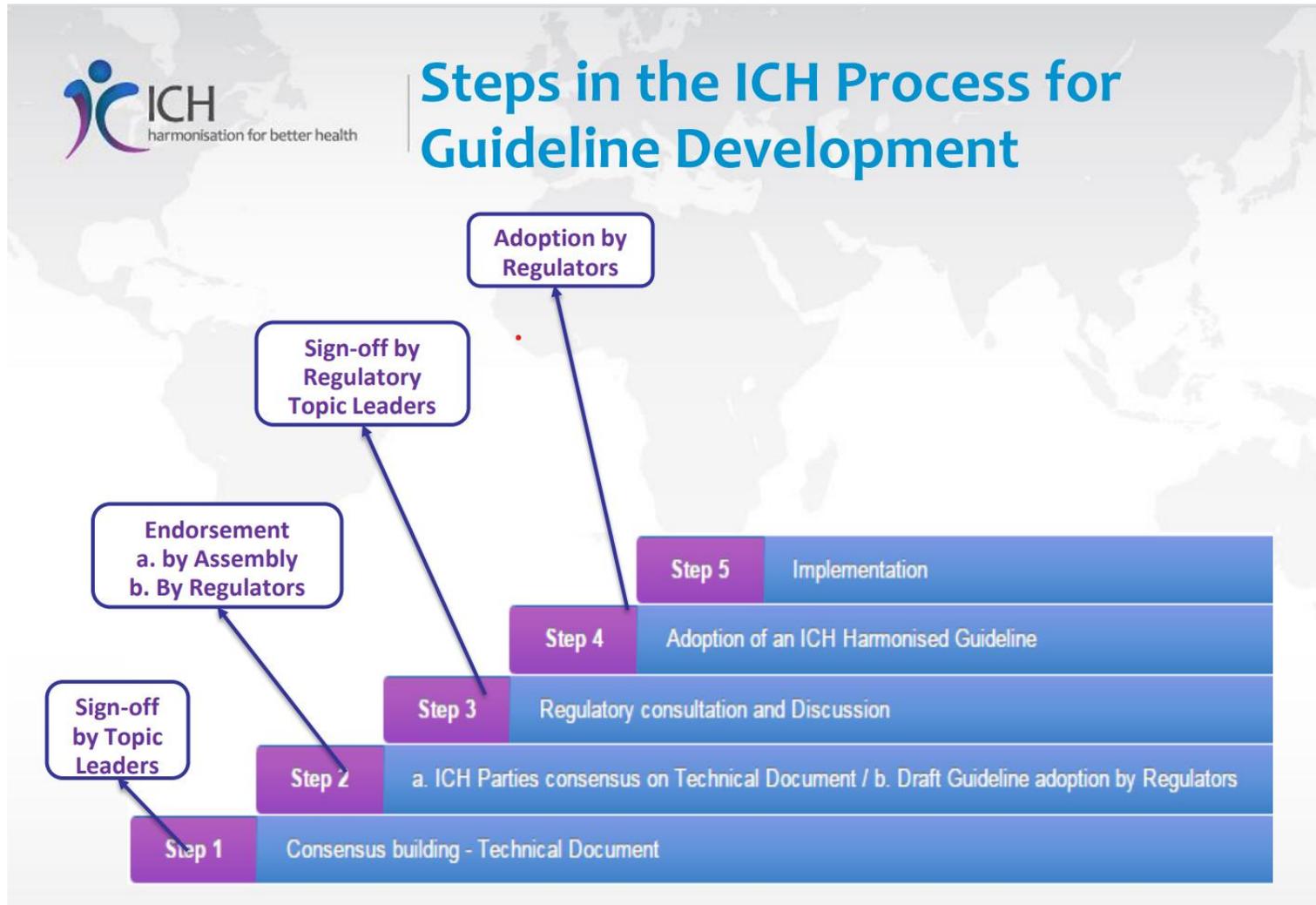
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On behalf of the ICH E20 EWG

About ICH

- Established in 1990, ICH aims to **harmonise the regulatory requirements** for pharmaceutical products around the globe. Initially constituted by members from Europe, Japan, and the US
- New topic proposed by an **ICH Member or Observer** for endorsement by the ICH Assembly
- Informal **Working Group** established that **develops a Concept Paper** to provide further context and define the objectives
- **Expert Working Group (EWG)** or Implementation Working Group established that develops a detailed Work Plan to constitute milestones and deadlines

Introduction to ICH harmonization process



Development of new ICH guidelines occurs through a **transparent standardised operating procedure**

The ICH guidelines are categorised into four main areas:

Quality, Safety, Efficacy, and Multidisciplinary guidelines.

Journey since ICH E20 Concept Paper

- This document was developed based on a Concept Paper (Nov 2019)
 - Reflection paper and draft guidance for adaptive clinical trials have been issued by regulatory agencies (eg EMA and FDA), these **documents themselves are not fully harmonised**
- This document has been signed off as a **Step 2** document (expected June 2025) to be issued by the ICH Regulatory Members for public consultation
- Anticipating finalisation as **Step 4** document to be implemented in the local regional regulatory system: date not yet finalised

Role of Guidance: Status in the EU system

- ICH Guidelines are implemented in the European System as **Scientific Guidelines**. ICH-E9 (e.g.) is CPMP/ICH/363/96
- The role of guidelines is defined in [EMEA/42371/2008](#) directly referencing the Introduction of [Annex I of Directive 2001/83/EC](#)

"(4) In assembling the dossier for application for marketing authorisation, **applicants** shall also **take into account the scientific guidelines** relating to the quality, safety and efficacy of medicinal products for human use as adopted by the [CPMP] ..."
- Relevant statements include:
 - “scientific guidelines do not have legal force”,
 - “alternative approaches may be taken, provided that these are appropriately justified”,
 - “scientific guidelines are to be considered as harmonised Community positions”,
 - “which if they are followed by relevant parties such as the applicants, marketing authorisation holders, sponsors, manufacturers **and regulators** will facilitate assessment, approval and control of medicinal products”

Role of Guidance: Efficient guidelines

EMA Website:

“The Agency strongly encourages applicants and marketing authorisation holders to follow these guidelines. Applicants need to justify **deviations from guidelines** fully in their applications at the time of submission. Before that, they should seek [scientific advice](#), to discuss any proposed deviations during medicine development.”

In other words, a guidance is efficient if

- ... it states accepted standards (the agreed positions),
 - ... it is clear about conditions for accepting a certain design aspect,
 - ... it explains, how to argue, if you want to deviate,
- ... in a transparent way to enable efficient stakeholder discussions.

EMA Reflection paper: (CHMP/EWP/2459/02, 2007)

What are assessment needs in confirmatory trials?

- Pre-planning + clear justification why adaptation is needed in Phase III.
- Limited number of adaptations: too many make the trial exploratory.
- Control of the pre-specified T1E (see EMA multiplicity guideline: CPMP/EWP/908/99).
- A mere presentation of P-values is not sufficient.
- Pre-plan how to assure that results from different stages can be justifiably combined.
- The justification should include consideration of the impact of the modification on patient population, schedule of assessments, patient management and other features of the trial, which, if affected, would complicate the interpretation of the trial.
- Depending on the nature of the design modification, the simple rejection of a global null hypothesis across all stages of the trial may not be sufficient to establish a convincing treatment effect.
- No small steps: after a design modification, re-assurance is needed, that the treatment effect refers to the same patient population treated under similar conditions.

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Definition of an Adaptive Design

*"For the purpose of this guideline, an adaptive design is defined as a 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."*

Scope

Focus is on confirmatory trials with an adaptive design

Out of scope:

- Trials with unplanned modifications to the design
- Design changes based entirely on emerging information from a source external to the trial
- Routine monitoring of operational aspects

Advantages and Challenges

*"In planning an adaptive design, it is therefore **essential to carefully justify the need to adapt** the trial and assess potential implications of the type, number, and complexity of the adaptations involved. [...] It should **weigh the advantages of the design against the extent to which the adaptations being considered add uncertainty about the trial's ability to produce reliable and interpretable results.**"*

Key Principles

- Adequacy within the development program
- Adequacy of trial planning
- Limiting the chances of erroneous conclusions
- Reliability of estimation
- Maintenance of trial integrity

"All of these principles should be followed regardless of the type of adaptation and statistical approach (e.g., frequentist or Bayesian methods)."

Key Principles

Statistical Principles

Limiting the chances of erroneous conclusions

- *"The common approach is to limit the probability of false positive efficacy conclusions within a trial by using frequentist methods that control the Type I error probability (ICH E9)."*
- *"For most adaptive designs, it is necessary to use specific methods to control the Type I error probability."*
- *In adaptive designs using Bayesian methods, "important considerations for limiting the chances of false positive efficacy conclusions" apply*

Reliability of Estimation

- *"... provide an estimate of the treatment effect that is reliable and aligned with the estimand of interest."*
- *"In the trade-off between bias and variance, the expectation is generally for limited to no bias in the primary estimate of the treatment effect."*

Key Principles

Other Principles

Adequacy within the development program

- An adaptive clinical trial is not meant to be a *"replacement for a sequence of multiple trials"*
- *"Number and complexity of adaptations ... should generally be limited."*

Adequacy of trial planning

- *"... to ensure the design is pre-specified, conduct and analysis are appropriate, and results are reliable and interpretable."*

Maintenance of trial integrity

- *"... blind participants, investigators, and sponsor to individual treatment assignments and to accumulating summary-level data in which treatment groups are identified ..."*

Examples of consensus reached easily

Specific considerations for common types of adaptations when using frequentist approaches for statistical analysis, such as:

- **Early trial stopping** for
 - Futility: use nonbinding rules
 - Efficacy: select timing of interim analyses such that sample size / follow-up provides sufficient information for benefit-risk decision-making
- **Sample size adaptation** based on estimates of
 - Nuisance parameter: use blinded data to minimize risks to trial integrity
 - Treatment effect size: use
 - IDMC and adequate processes to maintain trial integrity
 - Methods that preserve Type I error probability control but do not require adherence to the anticipated adaptation rule

Examples of consensus reached easily (cont'd)

- **Population selection** to provide
 - Justification and pre-specification of candidate population(s), decisions to be made at interim, analysis at trial end, and anticipated adaptation rules
 - Reliable treatment effect estimates in the different populations and adequate information on the benefit-risk profile in complementary subpopulation(s)
- **Treatment selection**
 - For dose selection, ensure completion of necessary trials to evaluate a wider range and number of doses before proceeding to confirmatory trial(s)
- **Adaptation to patient allocation**
 - Deterministic adaptations to participant allocation are discouraged

More challenging ...

... and maybe somewhat exaggerated ...

<p>Definition: „... a 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.”</p>	<ul style="list-style-type: none"> • Interim analysis, • Interim analysis with adaptation / modification of the further conduct, • Type-1-error control as part of the definition.
<p>Need to adapt contradicts „confirmation“?</p> <ul style="list-style-type: none"> • ... each adaptation should be well justified... 	<ul style="list-style-type: none"> • “... a limited number of ...” • ... preferably to address obstacles to experimentation (e.g. PBO-response in depression), • ... or improve knowledge (e.g. dropping dose-groups).
<p>Benefit/Risk-discussion for study design:</p> <ul style="list-style-type: none"> • ... can higher efficiency justify higher risks to trial interpretation? 	<ul style="list-style-type: none"> • ... without lowering scientific or regulatory standards...
<p>The role of simulation:</p> <ul style="list-style-type: none"> • “... to assure no relevant impact on T1E .” 	<ul style="list-style-type: none"> • ... better understand design alternatives, impact of ICEs, power.
<p>Bayes:</p> <ul style="list-style-type: none"> • E20 as the place to discuss general requirements for Bayes in confirmatory clinical trials. 	<ul style="list-style-type: none"> • E20 to discuss Bayes for specific applications (e.g. borrowing external information), where the regulatory metrics is clear.

Expectation from Public Consultation

Once consultation is open you can submit comment through e.g. EMA (see link below)

<https://www.ema.europa.eu/en/news-events/open-consultations>

All comments will be considered by the WG.

- **The speakers will particularly find it helpful if consideration is given to**
 - content (principles, any ambiguity in message, or gaps)
 - whether this matches your expectations from the agreed concept paper
 - whether the recommendations and level of detail are pitched at the right level
- **Please feel free to flag** anything that would benefit from inclusion in training materials for implementation
- **Only send comments once**
- **Specific for Bayes:** do you see other applications beyond borrowing, where Bayes can be beneficially used with a metric to guarantee interpretability of trial outcome?

**Thank You.
Any Questions?**