Moving towards harmonisation for (confirmatory) trials with an adaptive design

Frank Petavy (FP), and Khadija Rerhou Rantell (KR)
On behalf of the ICH E20 EWG

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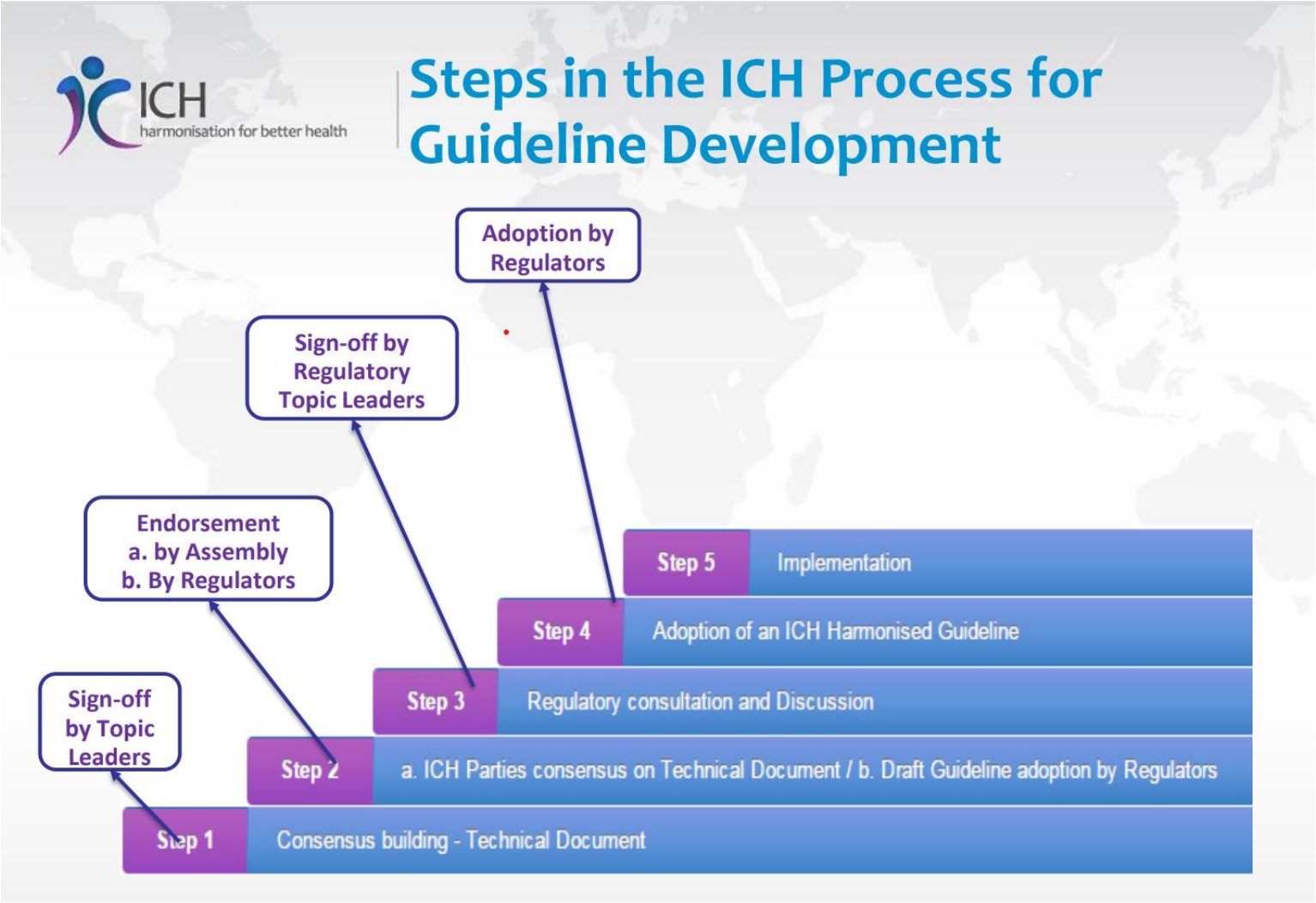
About ICH

- 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
    - Without a harmonised perspective among the different ICH regions, **sponsors and regulators would be limited** in their ability to build an efficient multi-regional prospective plan for drug development which incorporates these innovative designs.
- 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

ICH E20 harmonisation process



Source: ICH Official web site : ICH

Development of ICH20 guidelines occurs through a **transparent standardised operating procedure**

This document was developed based on a **Concept Paper** (Nov 2019)

This document was signed off as a Step 2b **'draft'** document (May 2025) to be issued by the ICH **Regulatory** Members for public consultation.

Scope of ICH E20

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.*"

Focus is on confirmatory trials with an adaptive design.

In vs out of scope:

- Trials with planned vs unplanned modifications to the design.
- Design changes based on *interim analysis of accumulating data from participants in the trial* vs entirely on emerging information from a source external to the trial.
- Modifications of the design or study conduct (stopping for efficacy or futility) vs routine monitoring of operational aspects.

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)*."

Consensus – Examples

Easily reached

- In general, **Section 4** about types of adaptation
  - Frequentist approaches for early trial stopping
  - Sample size adaptation (reassessment)
  - Population selection
  - Treatment selection
  - Adaptation to patient allocation

Challenging

- General requirement for Bayes in confirmatory trials vs specific to adaptive designs
- Focus of simulation studies on ‘erroneous conclusion or better experimental design?
- As a principle, should we aim for simpler designs by breaking down the research question, or can any complex design be envisaged?
- Focus on experimental issues (e.g. placebo response in depression) and improving knowledge (e.g. better dose)?
- Efficiency of drug development coupled with efficiency of assessment?

Expectation from Public Consultation

All comments will be considered by the Expert Working Group

- **Please focus on**
  - content (principles, any ambiguity in the 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 avoid** editorial comments *unless you think they obscure the meaning*
- **Please feel free to flag** anything that would benefit from inclusion in training materials for implementation
- **Specific for Bayesian methods:** do you see other applications beyond borrowing where Bayesian methods can be beneficially used with a metric to guarantee interpretability of trial outcome?

Note: Deadline for comment is 30 November 2025 (EMA and MHRA)

Thank You.
Any Questions?