ICH E20 Guideline on Adaptive Designs for Clinical Trials – Personal Reflections on the Version Recently Released for Public Consultation

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Disclaimer

- The views expressed in this presentation are the personal views of the presenter
- They do not express the views of Johnson & Johnson or EFSPI*

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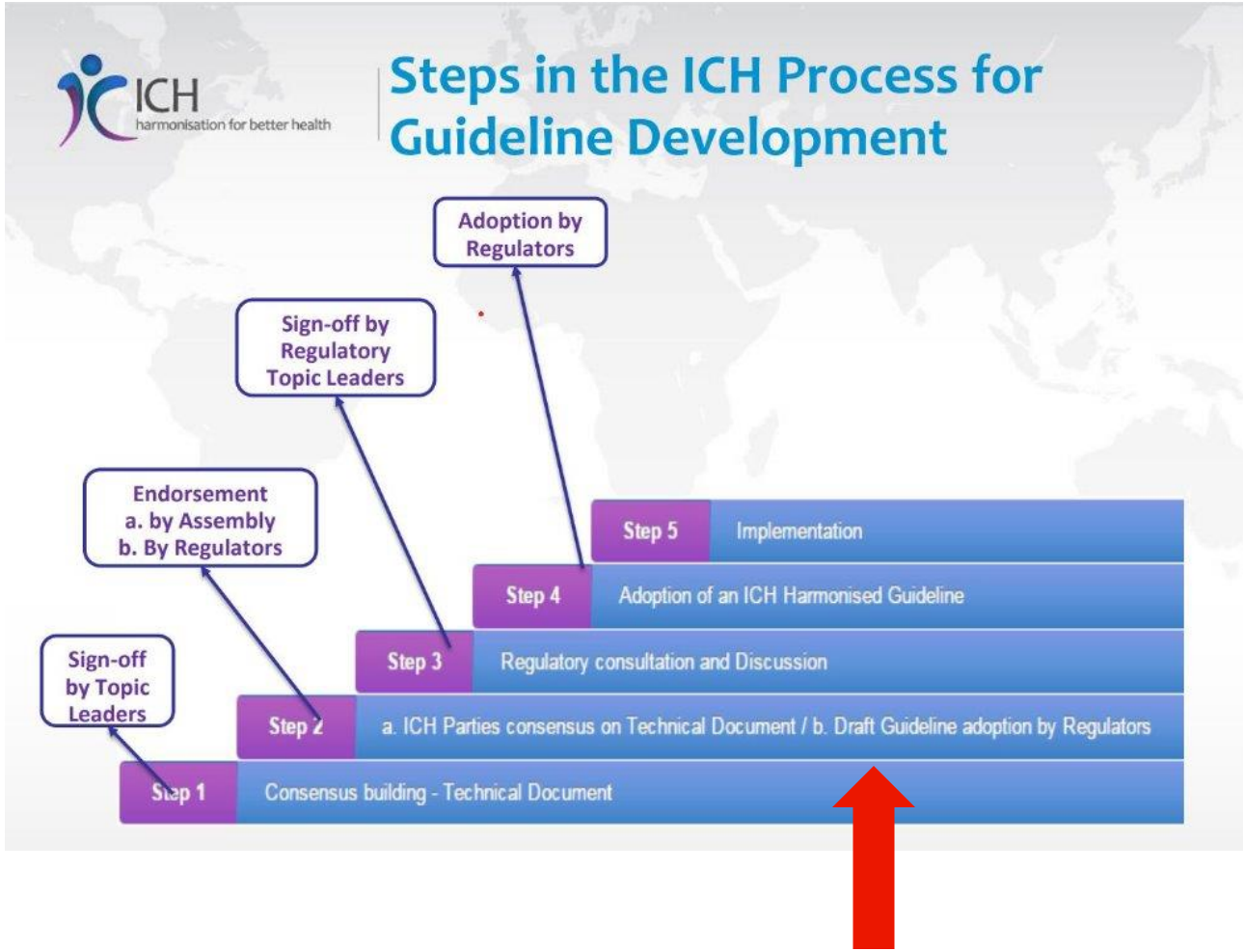
Acknowledgement

- This presentation has benefitted from the input of my colleague Vlad Dragalin at J&J, who has been a member of the ICH E20 Working group from the beginning

Some background about ICH

Who has heard of ICH and ICH E20?

- ICH=International Conference for Harmonisation
- Established in 1990, initial members from Europe, Japan and the US
- Goal to harmonise regulatory requirements worldwide



For ICH E20 we are now at step 2b

Selected ICH Guidelines

Only so-called ”efficacy guidelines” included below

- ICH E9: Statistical Principles for Clinical Trials
  - Recent addendum on estimands
- ICH E17: General principles for planning and design of Multi-Regional Clinical Trials
- ICH E3: Structure and content of clinical study reports
- ICH E4: Dose-response information to support drug registration
- ICH E20: Adaptive designs for clinical trials
  - Our focus today!

Previous Regulatory Guidelines on Adaptive Designs

- EMA reflection paper in 2007
- FDA Draft guideline on adaptive designs (AD) in 2010
- FDA final guideline in 2019
- NMPA draft guidance 2019
- Benefit of harmonizing requirements

Definitions of adaptive design

Adaptive Design is one that uses *accumulating data from the ongoing trial* to modify aspects of the study without undermining the validity and integrity of the trial
- PhRMA ADWG (2006)

*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*
– ICH E20 (2025)

Adaptive design is defined as a clinical trial design that allows for *prospectively planned modifications* to one or more aspects of the design *based on accumulating data from subjects in the trial*
– FDA Guidance on AD (2019)

A clinical trial design that will have adaptations based on the accumulating data from the trial and/or *external data.* Modifications based on the accumulating data from the trial should be pre-specified prior to initiation of the trial
– Draft NMPA (2019)

A study design is adaptive if statistical methodology allows the modification of a design element (e.g. sample-size, randomization ratio, number of treatment arms) at an IA *with full control of the type I error*
– EMA reflection paper (2007)

Adaptive designs in drug development

Harmonisation via ICH E20 very welcome

- COVID Vaccine Trials
- In particular group sequential designs routinely used in many areas
- “25 years of confirmatory adaptive designs” published >10 years ago

Featured Article | Open Access

Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls

Peter Bauer, Frank Bretz, Vladimir Dragalin, Franz König, Gernot Wassmer

First published: 16 March 2015 | https://doi.org/10.1002/sim.6472 | Citations: 167

My history with adaptive designs and ICH E20

- Started PhD on group sequential and adaptive designs 20 years ago
- Organized a session on ICH E20 at EFSPI Regulatory Workshop (Sep 2025)
  - Video recording+slides available on https://efspieurope.github.io/workshop/
- Collation of comments for PSI/EFSPI Regulatory SIG (deadline was Nov 6)
  - Comments will be submitted to EMA by Nov 30
- Colleagues on expert working group
  - I have greatly benefitted from their viewpoints
  - Views expressed today (including ones you may disagree with) are my own

So what is in ICH E20?

Released for public consultation in June 2025

https://www.ema.europa.eu/en/ich-e20-adaptive-designs-clinical-trials-scientific-guideline

Current effective version

ICH E20 guideline on adaptive designs for clinical trials - Step 2b

Draft: consultation open
Consultation dates: 30/06/2025 to 30/11/2025
Reference Number: EMA/CHMP/ICH/206586/2025
Summary: This document provides guidance on confirmatory clinical trials planned with an adaptive design within the context of its overall development programme, allowing pre-specified modifications of the trial design based on an interim analysis of the on-going trial.

Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

English (EN) (904.75 KB - PDF)
First published: 30/06/2025

View

Scope of ICH E20 Guideline per ICH webpage

Focus is on confirmatory trials with an adaptive design

This document provides guidance on confirmatory clinical trials planned with an adaptive design within the context of its overall development programme, allowing pre-specified modifications of the trial design based on an interim analysis of the on-going trial.

In addition, the guideline discusses opportunities for the application of Bayesian methodology. Input is sought whether there are further examples where Bayesian methodology can be employed in a way that it can be discussed within the clinical context of use.

Keywords: clinical trial design, adaptive design, interim analysis

In scope	Not in scope
Planned modifactions	Unplanned modifications
Adaptations based on within-trial data	Entirely exteral data
Adaptations that modify design or conduct	Monitoring of operational aspects only

Five core principles that should be adhered to

I will focus on the three the topics in red

1. Adequacy within the development program
2. Adequacy of trial planning
3. Limiting the chances of erroneous conclusions
4. Reliability of estimation
5. Maintenance of trial integrity

- Focus on “principles” makes it possible to move away from “less well understood AD” terminology used in previous regulatory guidance

Reflections on ”Reliability of estimation” principle

- General focus on “limited to no bias” in primary estimate of treatment effect
- Unbiased estimators not available for all complex adaptive designs
- Even for “vanilla” group sequential designs no consensus on best way to adjust
- Confidence Intervals may not be readily available in all situations
- Is “perfect” estimation always needed to support regulatory decision-making?
- On a positive note, more interesting research problems for statisticians?

Reflections on ”adequacy within development program”

- Important, but also for “non-adaptive” designs?
- Should “adaptive designs” have to be justified?
- It could be argued that some adaptive component should be the norm
  - Having no futility or efficacy boundary in a long trial could be less ethical?
- Speed versus robustness, speed may be a goal of adaptive designs?

Reflections on ”probability of erroneous conclusions”

- Limit probability of erroneous conclusions
  - Bayesian Borrowing would not control type I error across parameter space
- Differences of opinion within expert working group
  - Eg, Bayesian designs could be adaptive or non-adaptive
- Patient-level data always needed?
  - May want to build prior based on meta-analysis of summary level data
- Different HAs are currently developing guidelines on Bayes

Discussion

- Great resource for anyone designing and conducting adaptive designs
- Opportunity to improve document after public consultation
- Could/should requirement on estimation be softened?
- Further clarity on Bayesian section
- Do adaptive designs have to be “justified”?
- Principles are great, but do they mean “standard” AD will face undue scrutiny?
- Adaptive designs should (and will) become easier, not harder, with final ICH E20