

# Towards (long overdue) regulatory guidance on Bayesian statistics in clinical trials

BAYES 2025 Conference, Leiden

Juan Jose Abellan, European Medicines Agency

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# Disclaimer

The views expressed in this presentation are mine and should not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or its committees or working parties.

# At last!

- The **European Medicines Regulatory Network** is developing **guidance** on the use of **Bayesian statistics** in clinical trials
- A **Concept Paper** is **being developed**
  - Concept papers are short
  - Motivate the need for regulatory guidance on a specific topic
  - Outline the topics in scope of guidance
  - Recommend the development of a Reflection Paper or a Guideline
- Draft CP
  - is undergoing the (long) multi-layer review process by EMA Committees and Working Parties
  - considers feedback from EMA workshop on Bayesian statistics in clinical development
  - is **expected to be published for public consultation in Q1 2026**
- A **Guideline** on the use of Bayesian statistics in clinical trials **will follow**

Sorry it  
took so long!



# Regulatory guidance on statistical principles for CTs

- Provides stats methodological considerations on
  - Overall clinical development
  - Trial design, conduct, analysis and reporting
  - Evaluation of efficacy and safety
- Published in 1998
  - A lot has happened ever since...
- Approved by **EMEA's CPMP**
- The European Medicines Evaluation Agency (EMEA) was rebranded in 2004 to current EMA
- Approved by the extinct CPMP (Committee for Proprietary Medicinal Products), replaced by current CHMP in 2004



September 1998  
CPMP/ICH/363/96

**ICH Topic E 9  
Statistical Principles for Clinical Trials**

**Step 5**

**NOTE FOR GUIDANCE ON  
STATISTICAL PRINCIPLES FOR CLINICAL TRIALS  
(CPMP/ICH/363/96)**

TRANSMISSION TO CPMP	February 1997
RELEASE FOR CONSULTATION	February 1997
COMMENTS REQUESTED BEFORE	June 1997
FINAL APPROVAL BY CPMP	March 1998
DATE FOR COMING INTO OPERATION	September 1998

# What was written in ICH E9 on Bayesian statistics?

*Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate:*

*the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust.*

This is in the only instance where the word “Bayesian” appears (other than in the Glossary)

# Impact of ICH E9

- No use of Bayesian statistics in CTs because of high risk of regulatory rejection
- No perceived need from regulators world-wide for guidance development on the topic
- At least for CTs in medicine development
- But yes to Bayesian statistics in medical devices
- Why?
  - *“Good prior information is often available for medical devices because of their mechanism of action and evolutionary development. The mechanism of action of medical devices is typically physical. As a result, device effects are typically local, not systemic.”*

## Guidance for Industry and FDA Staff

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### Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials

**Document issued on: February 5, 2010**

**The draft of this document was issued on 5/23/2006**

# However,...

- Over the years, other regulatory documents have mentioned the use of Bayesian statistics
- The most notorious example: guidance on extrapolation
- EMA reflection paper: “**Examples of approaches could be using [...] Bayesian methods to explicitly borrow information (e.g. from adult trials, from control groups, from other paediatric clinical trials)**”
  - The word “Bayesian” appears 4 times
- ICH E11A: “**Bayesian and/or frequentist approaches can be used to combine data from the reference and target populations,...**”
  - The word “Bayesian” appears 19 times



7 October 2018  
EMA/189724/2018

## Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Final



27 August 2024  
EMA/CHMP/ICH/205218/2022  
Committee for Medicinal Products for Human Use

## ICH E11A Guideline on pediatric extrapolation

Step 5

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	06 April 2022
Deadline for comments	06 August 2022
Final adoption by CHMP	25 July 2024
Date for coming into effect	25 January 2025

# In other guidelines...

- ICH E17
  - The word “Bayesian” appears 0 times
- But, when discussing estimation of regional treatment effects:
  - *“If the sample size in a region is so small that the estimates of effect will likely be unreliable, the use of other methods should be considered, including [...] **borrowing information from other regions** or pooled regions using an appropriate statistical model”*
  - *“Methods using weighted averages of the overall effect estimate and the estimate using data from individual regions (**shrinkage estimates**) may be considered, particularly when regional sample sizes are small and outlying values may be overly influential.”*



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

14 December 2017  
EMA/CHMP/ICH/453276/2016 Rev.1  
Committee for Medicinal Products for Human Use

## ICH guideline E17 on general principles for planning and design of multi-regional clinical trials

### Step 5

Transmission to CHMP	21 July 2016
Transmission to interested parties	28 July 2016
Deadline for comments	28 January 2017
Final adoption by CHMP	14 December 2017
Date for coming into effect	14 June 2018

# More recently...



18 June 2025  
EMA/CHMP/ICH/206586/2025  
Committee for Human Medicinal Products

- ICH E20, currently open for consultation
  - The word “Bayesian” appears 19 times
- Includes a section on *Adaptive Designs using Bayesian Methods*:
  - **“Bayesian methods can be used to inform adaptations in a trial where decision criteria for the primary analysis are chosen to ensure that the Type I error probability is controlled.”**
- Section header includes a footnote:
  - **“This section on Bayesian methods for adaptive designs is not fully harmonized. [...] 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.”**

## ICH E20 Guideline on adaptive designs for clinical trials

### Step 2b

Transmission to CHMP	18 June 2025
Adoption by CHMP	19 June 2025
Release for public consultation	30 June 2025
Deadline for comments	30 November 2025

<b>5. SPECIAL TOPICS AND CONSIDERATIONS .....</b>	<b>18</b>
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# 'Acceptability' of Bayesian stats in the EU

## Example: scientific advice in respiratory paediatric study

### Scientific Advice request

- *Would the Agency consider acceptable, the potential use of Bayesian techniques (in addition to within study comparisons) to incorporate historical <endpoint> data into the analysis in order to increase the precision of the estimated treatment difference in <endpoint> between treatment A+B vs treatment A*
- *The historical data will be summarized in the form of a Bayesian prior distribution... and a method which incorporates dynamic borrowing from the prior will be used so that inference from the study is not dominated by historical data if there is a discrepancy between current and past trials.*

### CHMP response

- *CHMP is willing to explore the use of Bayesian methodology in the clinical extrapolation from adults to adolescents and there is a particular rationale in clinical settings where previously adolescents and adults have been studied together.*
- *The proposed metric is agreeable: historical adult information should not be allowed to dominate the outcome of the paediatric trial and limits need to be fixed in advance and justified from where onwards one would be willing to extrapolate to the adolescent population. The chosen strategy to use 'dynamic borrowing' could be acceptable*

# 'Acceptability' of Bayesian stats in other jurisdictions

- **In the US**, FDA Complex Innovative Designs (CID) under PDUFA VI, continued under PDUFA VII
- All 5 use cases published so far used Bayesian statistics in some fashion, e.g.
  - **A Study in Patients with Epilepsy with Myoclonic-Atonic Seizures.** FDA considers innovative:
    - Borrowing of treatment effect information from historical studies of the same drug for different indications.
    - Goldilocks methodology using Bayesian predictive probabilities to make sample size decisions.
  - **Master Protocol to Study Chronic Pain.** FDA considered innovative:
    - Borrowing of placebo information from sub-studies of different investigational products for the same type of chronic pain.
    - Borrowing of treatment effect information from sub-studies for the same treatment for different types of chronic pain.
- In the context of paediatric development, Bayesian analyses have played a critical role in the approval of several medicines in the recent years
  - Use of Bayesian stats discussed first at FDA workshop in 2004, but use in actual CDER regulatory review took until 2019
- **In China**, the CDE has also approved medicines where the evidence package relied on Bayesian analyses

# Bayesian methods in light of current EU strategy (1/3)

- The **European Medicines Agencies Network Strategy** (EMANS) to 2028 focuses on 6 topics
- One of those relates to leveraging data
  - *“As part of its strategy, the network also aims to **maximise the use of data** and evidence generation to support decision making.”*
- Arguably, Bayesian statistics provides a formal and scientifically rigorous framework to leverage existing data

## The six themes in EMANS 2028



Accessibility



**Leveraging data**, digitalisation and artificial intelligence



Regulatory science, innovation and competitiveness



Antimicrobial resistance and other health threats



Availability and supply



Sustainability of the network

# Bayesian methods in light of current EU strategy (2/3)

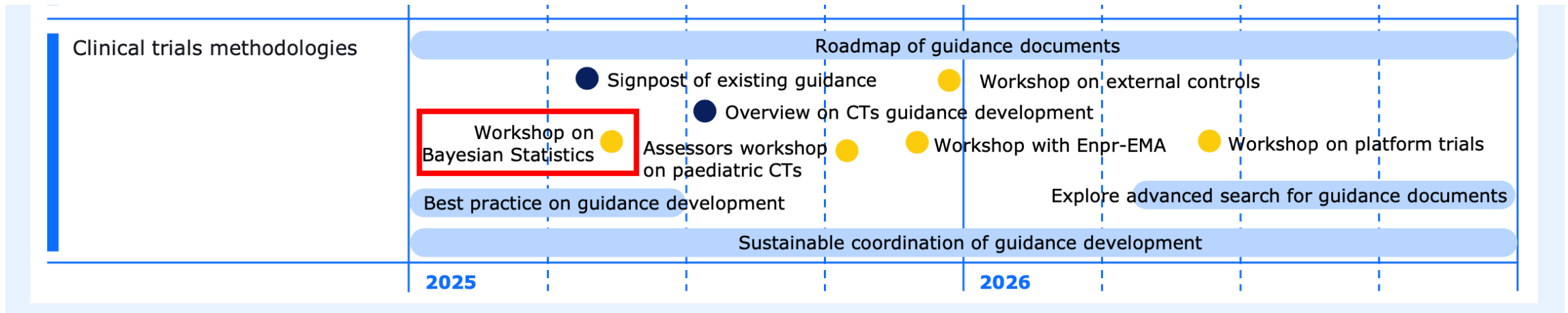
- ACT EU includes 10 Priority Actions:

8. **Develop and publish key methodologies guidance** e.g. on ..., complex trials, ... (to strengthen links between innovation and scientific advice fora.)



- Includes activities related to **design and conduct of excellent clinical trials**

## Accelerating Clinical Trials in the EU (ACT EU) Delivering an EU clinical trials transformation initiative



# Bayesian methods in light of current EU strategy (3/3)

- Workplan of the EMA Methodology Working Party 2022-2024
- Updated workplan of the MWP 2025-2027

## 2.1.3. Clinical Trial Modernisation (including ICH E9 implementation)

- Revision of guideline on multiplicity issues in clinical trials.
- RP on the use of single arm trials.
- Revision of guideline on the non-inferiority margin, and possibly the guideline on switching between superiority and non-inferiority.
- Revision of guideline on missing data.
- RP on bayesian methods in clinical development.
- Revision of small population guideline.
- RP on platform trials.

- In Subsection Tactical Goals > Biostatistics:

- *“Across the clinical research landscape, how trials are designed and conducted is changing with an increasing number of proposals utilising tools such as master protocols and **Bayesian methods**. [...]. **There is a need for new guidance in these areas** to ensure these novel approaches meet the required evidentiary standards and facilitate their evaluation as well as improve quality and efficiency of drug development.”*

# Workshop on Bayesian statistics in clinical trials

- Organised by MWP and ACT EU at EMA premises on 17 June 2025
- Hybrid format: 50 attendees onsite, 466 online
- Speakers: Statisticians and clinicians from industry, academia and regulatory agencies
- Structure
  - Morning sessions:
    - Introductory principles of Bayesian designs
    - Upcoming guidance: Concept Paper; ICH E20
  - Afternoon sessions:
    - Use cases without borrowing from external information
    - Use cases borrowing from external information:
    - Other use cases
- Context of application of Bayesian stats
  - Trials in rare and ultra-rare diseases, oncology and in paediatric conditions where feasibility of standard clinical trial designs is challenging.
  - Trials with rare outcomes, e.g. large cardiovascular outcome trials with thousands of participants followed up for several years.
- Motivation to use Bayesian statistics
  - External information borrowing
    - External controls to supplement current controls
    - Treatment effects in the context of extrapolation
  - Adaptive designs with Bayesian predictive probabilities to support decision making at the interim analysis
  - ‘shrinkage’ estimation in subgroup analysis

# Workshop Discussion and outcomes

- Concerns related to borrowing from external information include:
  - Added complexity and assumptions
  - Lack of strict control of a wrong positive conclusion
  - Risk of bias introduced by borrowing external information
- Transparency
  - Context of use, which external data, methods to construct the prior distribution
  - Simulations to understand operating characteristics of Bayesian designs under different scenarios
- Education and Communication
  - Training for statisticians, clinicians, and regulators is needed
  - Visual tools and clear documentation can aid understanding and acceptance

# ICH E9:... *when the reasons for use are clear...*

- Written in 1998. Is this still needed?
- Regulators are aware of the scientific rigour of the Bayesian paradigm
  - Have provided clear reasons for use over the years (e.g. extrapolation, shrinkage, adaptive designs), either through guidance or *de facto* by granting approvals based on evidence generated using Bayesian statistics
- One can also think of additional philosophical and technical arguments for the use of Bayesian statistics
  - The true treatment effect will never be known. Why not using probability to quantify its uncertainty?
    - When testing  $H_0: \theta \leq \theta_0$  vs  $H_1: \theta > \theta_0$ , shouldn't we care about  $\Pr(H_1 | \text{Data})$ ? What does  $p < 0.025$  say about  $H_1$ ?
  - The likelihood principle: all relevant experimental information for inference about a parameter is contained entirely within the likelihood function of the observed data
    - If we observe  $y = 8$  responders in 10 subjects, to test say  $H_0: \theta \leq 0.6$  vs  $H_1: \theta > 0.6$ , the p-value calculation involves  $\Pr(Y = 8 | \theta = 0.6) + \Pr(Y = 9 | \theta = 0.6) + \Pr(Y = 10 | \theta = 0.6)$ , but we did not observe 9 or 10 responders
  - A frequentist analysis can be mapped to a Bayesian one with non-informative priors
  - One-sided test p-values are similar to the posterior probability of the null in settings using non-informative priors

# ICH E9: ...and when the resulting conclusions are sufficiently robust

- This is critical (as it would be for any approach)
- **Regulators need to understand the risks associated with a trial design using Bayesian methods**
- Risk of a wrong positive conclusion in a clinical trial?
  - The job of regulators is to ensure that risk is minimal
    - There will always be some uncertainty on the efficacy of a drug. The goal of a medicine development program is to reduce that uncertainty to low limits
  - Regulatory principle implemented in frequentist setting with strict control of type 1 error in hypothesis testing
  - With Bayesian methods using informative priors, ‘frequentist type I error’ cannot be controlled
    - In the context of extrapolation, there’s some belief in relevance of external data to inform *target* population, so we expect the risk of a wrong conclusion to be low, but no zero!
- Risk of bias?
  - Biased treatment effects in the SmPC will mislead clinicians and patients

# Considerations – pre-specification is key

## Design



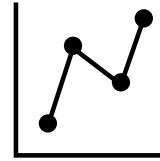
Characterise your prior:

- Prior mean/median of treatment effect and 95%CrI?
- Prior probability of  $H_1$ ?

OC's under different drift scenarios:

- Frequentist type 1 error and power
- Bias, precision,...
- How much info brings the prior to the posterior?

## Primary analysis



- Interpretability of parameters
- Transparency. How does the prior update with the paediatric data?
- Analytical calculation of the posterior?
- MCMC needed to obtain a sample of the posterior? Convergence?
- Posterior summaries, including posterior probability statements
- Info coming from the prior (ESS)

## Sensitivity analysis



- Those that could also be expected for a frequentist primary analysis
- 'Credibility analyses', to contextualise the results with respect to choices made to construct the prior

# Summary

- Despite what was written in ICH E9, regulators world-wide have acknowledged over the years the potential of Bayesian statistics in evidence generation for regulatory purposes
- EU regulators are developing guidance on the use of Bayesian statistics in CTs
  - Concept Paper expected to be published for public consultation in Q1 2026
  - A Guideline will follow, which will also be published for public consultation
- This guidance serves to strategic goals of the EU regulatory network (EMANS 2028, ACT EU)
- In the meantime, when planning CT designs with Bayesian methods to leverage external information, please engage early with regulators and be mindful of
  - External data not randomised/blinded in the current trial -> risks of bias
  - Risk of a wrong positive conclusion not controlled over the whole parameter space. Even if it's controlled on average over some design prior, it is critical to understand type 1 error vs drift
  - Be transparent and provide exhaustive characterisation of your design, and details of planned analyses



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# Thank you

[juanjose.abellan@ema.europa.eu](mailto:juanjose.abellan@ema.europa.eu)

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