Bayesian Approaches in Confirmatory Clinical Trials: A Discussion on Regulatory Expectations.

Katharina Hees (SBD5 Data Science & Methods)
Florian Krach (Haematology, Cell & Gene Therapy)

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

Paul-Ehrlich-Institut

Disclaimer

Views are our own and **do not** necessarily represent the views of

- the Paul-Ehrlich-Institut (PEI),
- the European Medicines Agency (EMA), or
- any other European regulatory agency (NCA).

“The clinical drug development process, however, with its accumulation of data over time, can be well suited for the use of Bayesian statistical approaches that explicitly incorporate existing data into clinical trial design, analysis and decision-making.” (Ruberg et. al., 2023)

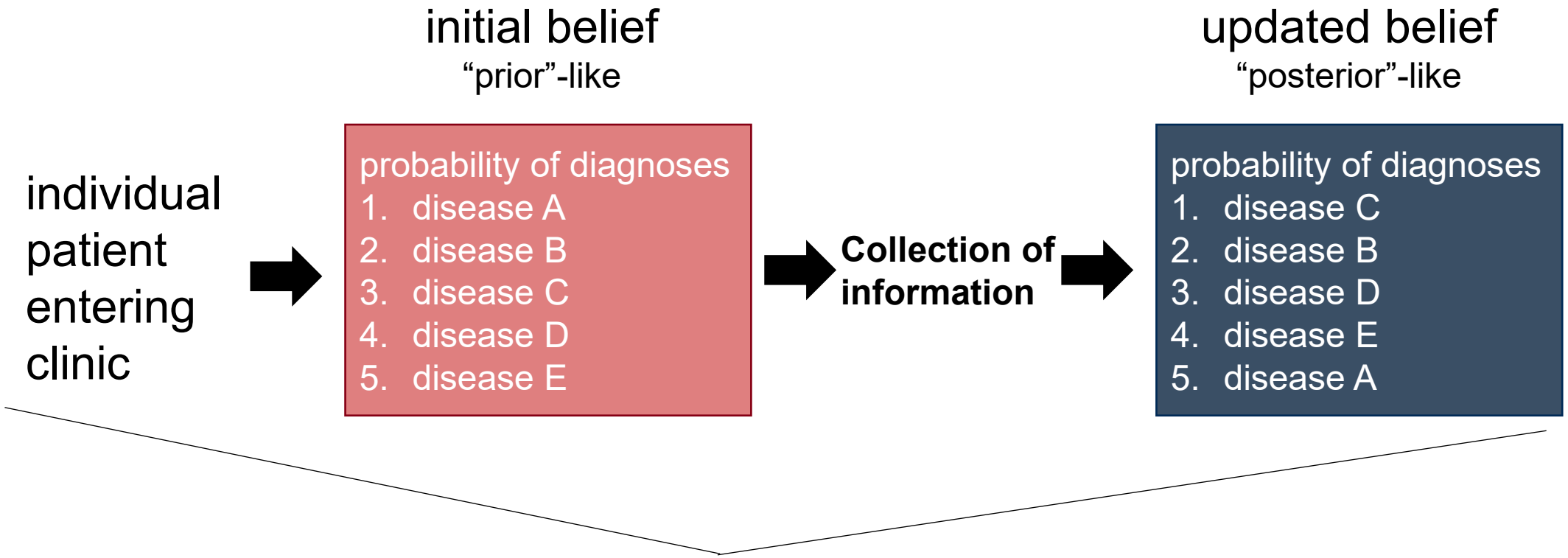
Why clinicians are natural bayesians

Christopher J Gill, Lora Sabin, Christopher H Schmid

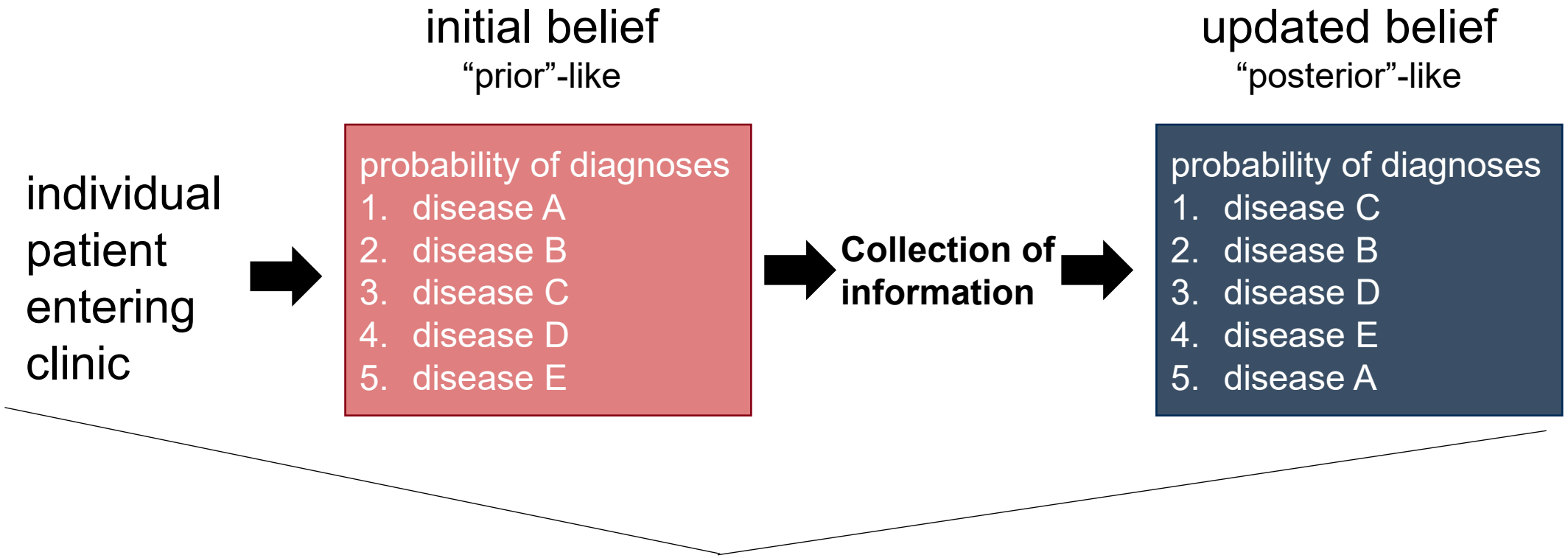
Thought you didn't understand bayesian statistics? Read on and find out why doctors are expert in applying the theory, whether they realise it or not

Gill, C. J., Sabin, L., & Schmid, C. H. (2005). Bmj, 330(7499), 1080-1083.

Aspects of Bayesian thinking reflect decision making in normal clinical practice



Aspects of Bayesian thinking reflect decision making in normal clinical practice



- Clinicians can understand Bayesian thinking
- Explaining and good communication is key

Bayesian learning **seems** to perfectly fit to the clinical development process

- Why is Bayes not the standard?
- Is this just a communication and/or education issue?

INTRODUCTION

EXPERIENCE AND GUIDANCE

Experience on regulatory side

- Still not many (confirmatory) clinical trial applications with Bayesian approaches
- More Bayesian approaches seen in Phase 1 trials
- Probably due to
  - the expectation that frequentist approaches are the (only) acceptable standard for regulatory side
  - insufficient practice and undereducation on both sides

Guidelines mentioning Bayesian methods….

Guideline title	Overarching topic/domain
ICH E9 – **Statistical principles** for clinical trials	Statistical methods in general
E11A on **paediatric extrapolation**	Paediatric extrapolation
ICH E20 Guideline on **adaptive designs** for clinical trials (draft)	Adaptive designs
Reflection paper on the use of **extrapolation** in the development of medicines for **paediatrics**	Paediatric extrapolation
Guideline on clinical trials in **small populations**	Small populations
Guideline on reporting the results of **Pop-PK analyses**	Pop-PK analyses
Reflection paper on statistical methodology for the comparative assessment of **quality attributes** in drug development	Statistical methods for quality
Q&A on **complex clinical trials**	Complex clinical trials

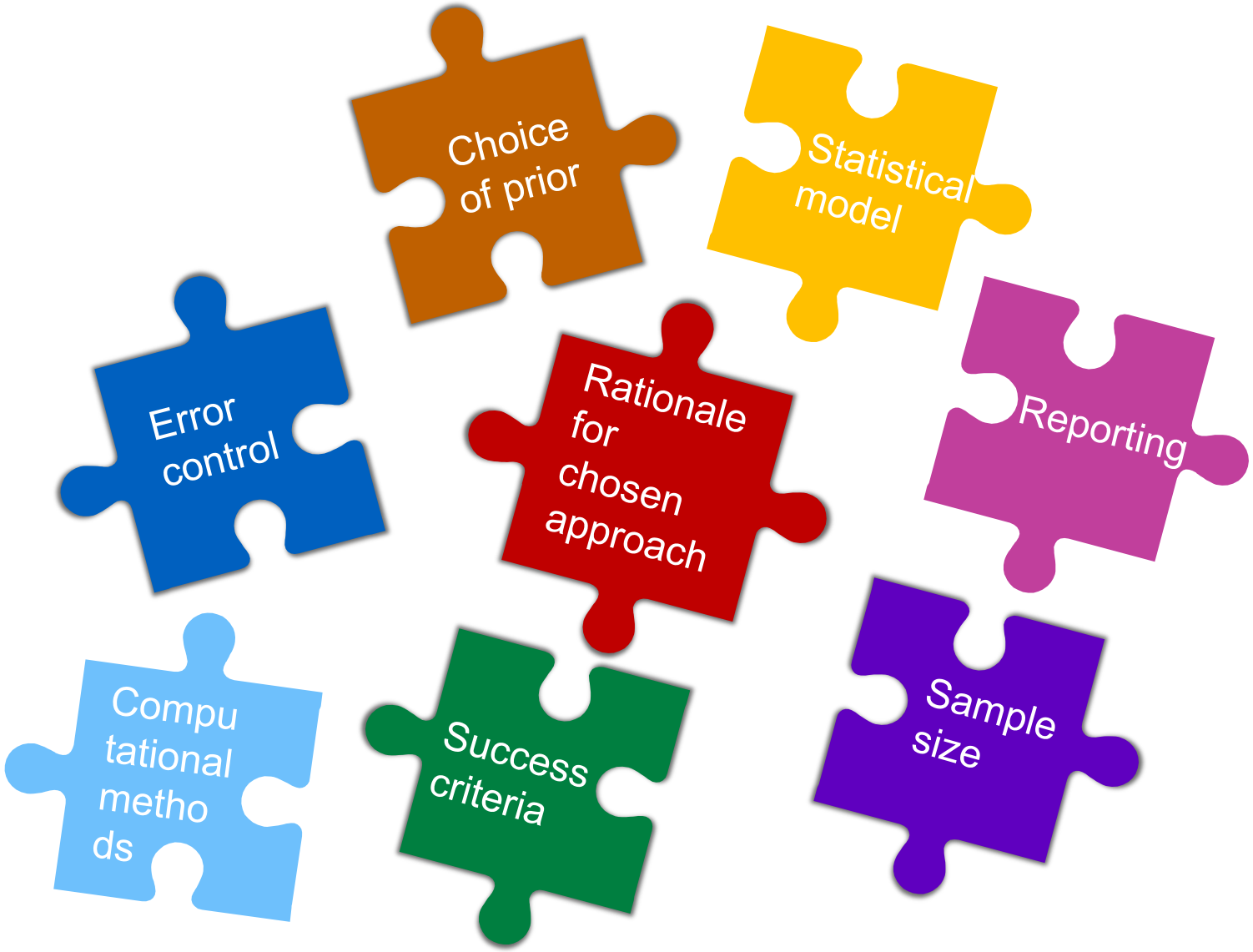
Guidelines mentioning Bayesian methods….

Guideline title	Overarching topic/domain
ICH E9 – **Statistical principles** for clinical trials	Statistical methods in general
E11A on **paediatric extrapolation**	Paediatric extrapolation
ICH E20 Guideline on **adaptive designs** for clinical trials (draft)	Adaptive designs
Reflection paper on the use of **extrapolation** in the development of medicines for **paediatrics**	Paediatric extrapolation
Guideline on clinical trials in **small populations**	Small populations
Guideline on reporting the results of **Pop-PK analyses**	Pop-PK analyses
Reflection paper on statistical methodology for the comparative assessment of **quality attributes** in drug development	Statistical methods for quality
Q&A on **complex clinical trials**	Complex clinical trials

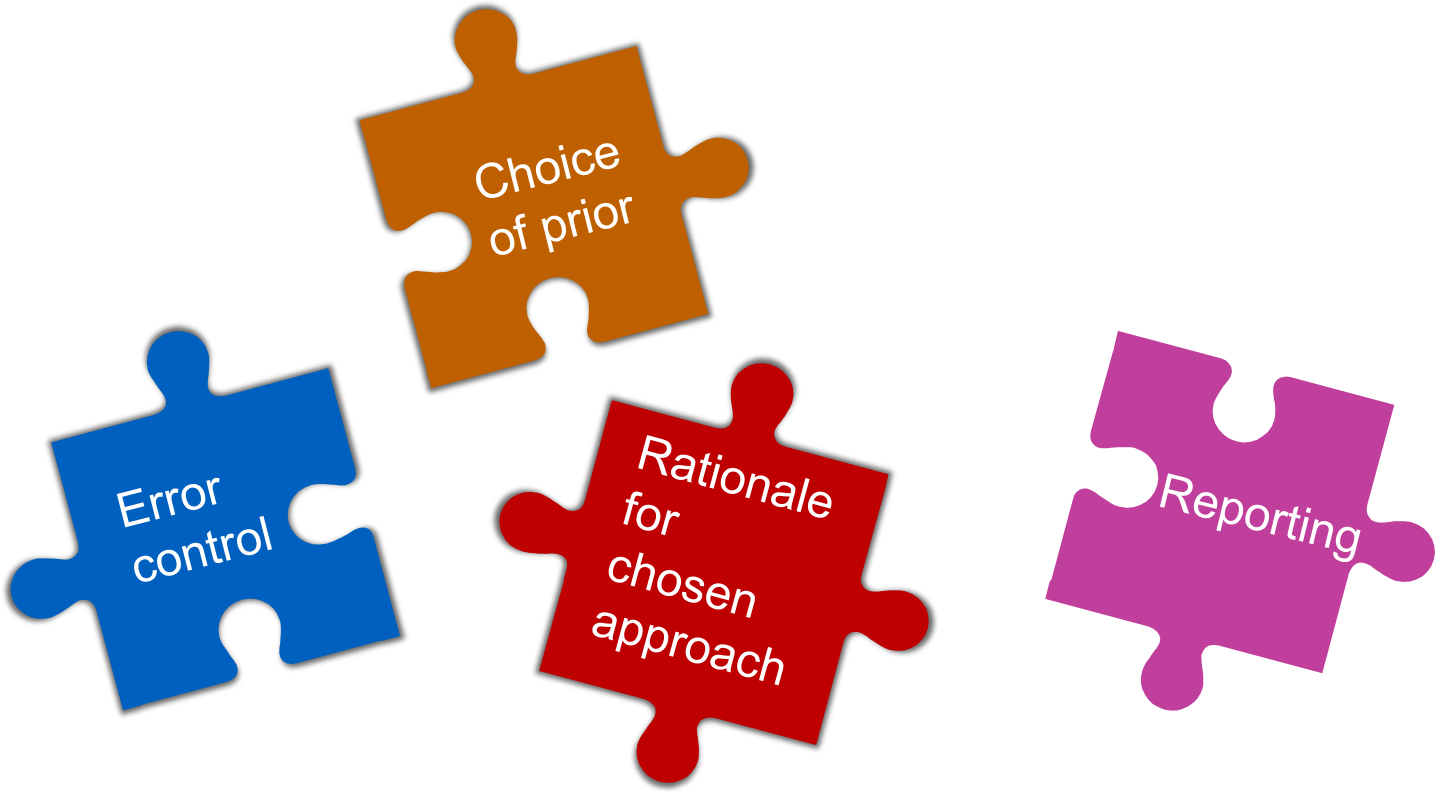
- Concrete guidance is still rare
- Upcoming Concept Paper (followed by a Reflection Paper) on Bayesian methods

WHICH INFORMATION NEEDS TO BE INCLUDED IN A PROPOSAL?

Which information to include into a study proposal?



Which information to include into a study proposal?



➢ In the following we will dive deeper into these puzzle pieces

RATIONALE

WHICH INFORMATION TO INCLUDE INTO A PROPOSAL

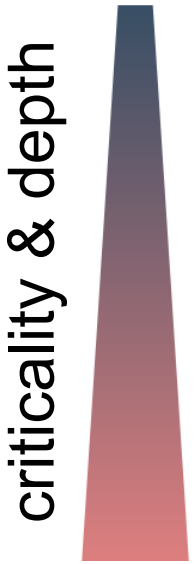
Presentation of a rationale is required

ICH E9 : „The use of **Bayesian** and other **approaches may be considered** when the **reasons for their use are clear** and when the **resulting conclusions are sufficiently robust**."

Q&A on CCTs: „This is one of the reasons **why simpler analyses may be preferred over complex ones**, and, for example, why external data may be more readily useful in a text discussion of a trial's context than when included in modelling."

Bayesian methods can be used in a confirmatory trial …

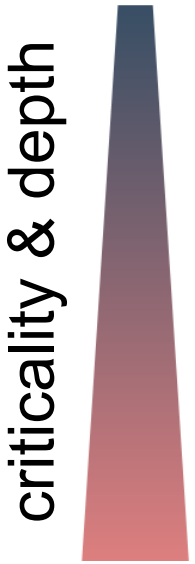
- for the **primary efficacy analysis**, with the use of
  - a **weakly-informative prior**
  - of an **informative prior**
    - **with** calibration of decision criteria to control the **Type I error** probability
    - **without** calibration for **Type I error** probability control



Bayesian methods can be used in a confirmatory trial …

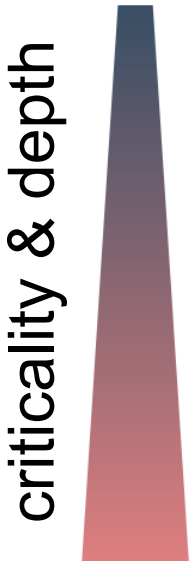
- for the **primary efficacy analysis**, with the use of
  - a **weakly-informative prior**
  - of an **informative prior**
    - **with** calibration of decision criteria to control the **Type I error** probability
    - **without** calibration for **Type I error** probability control

- for an interim analysis, to inform **adaptations** in a trial



Bayesian methods can be used in a confirmatory trial …

- for the **primary efficacy analysis**, with the use of
  - a **weakly-informative prior**
  - of an **informative prior**
    - **with** calibration of decision criteria to control the **Type I error** probability
    - **without** calibration for **Type I error** probability control



- for an interim analysis, to inform **adaptations** in a trial

➢ Depth of presentation of rational depends on criticality of use of Bayes in the trial

Informative vs non-informative prior

- In many discussions, the topic of **“Bayesian vs. frequentist approaches”** is often mixed with the topic **“external data vs. internal data”**.
- Bayes is first of all another definition of probability, based on a different philosophy

Informative vs non-informative prior

- In many discussions, the topic of **“Bayesian vs. frequentist approaches”** is often mixed with the topic **“external data vs. internal data”**.
- Bayes is first of all another definition of probability, based on a different philosophy

➢Same requirements apply if external data is used - regardless of the chosen statistical approach

Need for self-standing evidence

- It is **common understanding** that the standard basis for approval is **self-standing evidence** usually generated by two confirmatory RCTs with (strong) Type I error control
  - However, no guideline seems to **specifically** requiring this!
- Bayesian trials with an **informative prior** would no longer adhere to the paradigm of self-standing evidence
- Power gains **& Control of Type I error** with an informative prior not possible (Kopp-Schneider et. al. 2019)
- **Exceptions** from the self-standing evidence paradigm are mentioned in multiple EMA/ICH guidance documents
- Many of them refer to **Bayesian methods** as a possible approach

Possible use-cases for Bayes in confirmatory clinical trials
(esp. with informative prior)

- Estimate the effect in a situation with small sample sizes (**rare diseases / small populations**)
- **Extrapolate results** (e.g. specific populations)
- Use of an **external control arm** when a concurrent control arm has no clear clinical equipoise
- (Ultra-)personalized medicinal products?

Possible use-cases for Bayes in confirmatory clinical trials
(esp. with informative prior)

- Estimate the effect in a situation with small sample sizes (**rare diseases / small populations**)
- **Extrapolate results** (e.g. specific populations)
- Use of an **external control arm** when a concurrent control arm has no clear clinical equipoise
- (Ultra-)personalized medicinal products?

➢ **Note:** Always a case-by-case decision and depends on many individual factors and specifics of the study design and the applied Bayesian method(s)

CHOICE OF PRIOR

WHICH INFORMATION TO INCLUDE INTO A PROPOSAL

General considerations regarding choice of prior

- Prior distribution must be **pre-defined** and **justified** in the protocol
- Description on **used sources** for the derivation of the prior
- Discussion on **balance between prior and trial data**, including maximum amount of borrowing (prior effective sample size)
- **Methods** used **to construct** the prior
- Strategies to **mitigate the risk** that observed **trial data may conflict with the prior**
- Simulations to understand (frequentist) **operating characteristics** under a **wide range** of different scenarios (e.g. prior data conflict)
- **Sensitivity analyses** with different priors & hyperparameters
- Provide **programming code**, maybe even shiny app

Considerations for informative priors

- Possible sources of prior information
  - other (historical) clinical trials
  - pilot studies
  - challenging / not endorsed: data on very similar products (case-by-case decision), patient registries, expert opinion
- Studies used to construct the prior should be similar in the following aspects:
  - protocol (endpoints, target population, etc.)
  - time frame of the data collection (e.g., to ensure that the practice of medicine and the study populations are comparable)
  - sometimes even in investigators and sites
- Bias should be evaluated
  - Representativeness of the studies that are included
  - Reasons for including or excluding each study
  - Publication bias: non-favorable/negative studies unlikely to be published
  - Comparability of study phase (e.g. Phase 2 trial effects are often larger)
  - Considerations of endpoint – population interactions

Considerations for informative priors

- Possible sources of prior information
  - other (historical) clinical trials
  - pilot studies
  - challenging / not endorsed: data on very similar products (case-by-case decision), patient registries, expert opinion
- Studies used to construct the prior should be similar in the following aspects:
  - protocol (endpoints, target population, etc.)
  - time frame of the data collection (e.g., to ensure that the practice of medicine and the study populations are comparable)
  - sometimes even in investigators and sites
- Bias should be evaluated
  - Representativeness of the studies that are included
  - Reasons for including or excluding each study
  - Publication bias: non-favorable/negative studies unlikely to be published
  - Comparability of study phase (e.g. Phase 2 trial effects are often larger)
  - Considerations of endpoint – population interactions

➢ Critical and holistic, statistical and clinical review of informative priors needed

ERROR CONTROL

WHICH INFORMATION TO INCLUDE INTO A PROPOSAL

Error control

- Plots of Type I error under different scenarios
- Other error measures? Average type one error with different design priors?
- Multiplicity: Description of the strategy to control Type I error, despite multiple endpoints and/or interim analyses.

REPORTING OF RESULTS

WHICH INFORMATION TO INCLUDE INTO A PROPOSAL

Reporting of results

- Credible intervals (including definition of it)
- Measure of central tendency (e.g. posterior mean/median)
- Posterior probability of alternative
- Plot of prior, likelihood & posterior distribution
  (also for different prior distributions, maybe even with shiny apps)
- Sensitivity analyses with different prior distributions
  (also non- or weakly informative prior(s) or with frequentist methods)

CONCLUSIONS

Why is Bayes not an alternative?
Just a communication and/or education issue?

- **To some extent: yes**. There is a lot room for improvement, **on all sides!**

Regulators:

- harmonization and clarity regarding requirements
  (→ reflection paper upcoming)

- promote communication between statistical and clinical experts

Sponsors:

- thorough and transparent presentation and reporting of approach (→ regulators can learn from good proposals)

- promote communication between statistical and clinical experts

But not only a communication issue:

- Generation of self-standing evidence is important
- Upon closer inspection and when making case-by-case decisions, the difficulty of generating a trustworthy prior becomes apparent.
- Bayesian study proposals with non-informative priors may not be regarded as that advantageous by applicants?

But not only a communication issue:

- Generation of self-standing evidence is important
- Upon closer inspection and when making case-by-case decisions, the difficulty of generating a trustworthy prior becomes apparent.
- Bayesian study proposals with non-informative priors may not be regarded as that advantageous by applicants?

➢ **Seek early interaction with regulators** if you plan to use a Bayesian design

References & Resources

- ICH (1998), ICH E9: statistical principles for clinical trials
- ACTEU (2023), Complex clinical trials – Questions and answers
- ICH (2025), ICH E20 guideline on adaptive designs for clinical trials (draft)
- FDA (2010), Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials
- Kopp-Schneider et. al. (2020). Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control. Biometrical Journal, 62(2), 361-374.
- Ruberg, S. J et. al. (2023). Application of Bayesian approaches in drug development: starting a virtuous cycle. Nature Reviews Drug Discovery, 22(3), 235-250.
- Liu, S. et. al. (2025). Is Repeated Bayesian Interim Analysis Consequence-Free?. arXiv:2508.07403.
- Gill, C. J. et. al. (2005). Why clinicians are natural bayesians. Bmj, 330(7499), 1080-1083.