Regulatory considerations

on complex clinical trials and adaptive designs with Bayesian design elements

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

COMPLEX CLINICAL TRIALS

ADAPTIVE DESIGNS, PLATFORM TRIALS AND BEYOND

Adaptive designs

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- Adaptive designs—including group sequential designs—are **commonly used** in many clinical trials.
- Adaptive designs refer to trials with **pre-specified adaptation rules** based on information accruing in the trial (see CHMP/EWP/2459/02).
  - No discussion of Bayesian adaptive designs in the EMA Adaptive Designs Guideline
- The **upcoming ICH E20** will provide a harmonized regulatory view on these trials and to my knowledge will also **cover Bayesian methods**.
  - But adaptive designs do **not** make it **necessary** to use Bayesian methods!
  - A huge variety of **frequentist approaches** exists as well.

Platform trials

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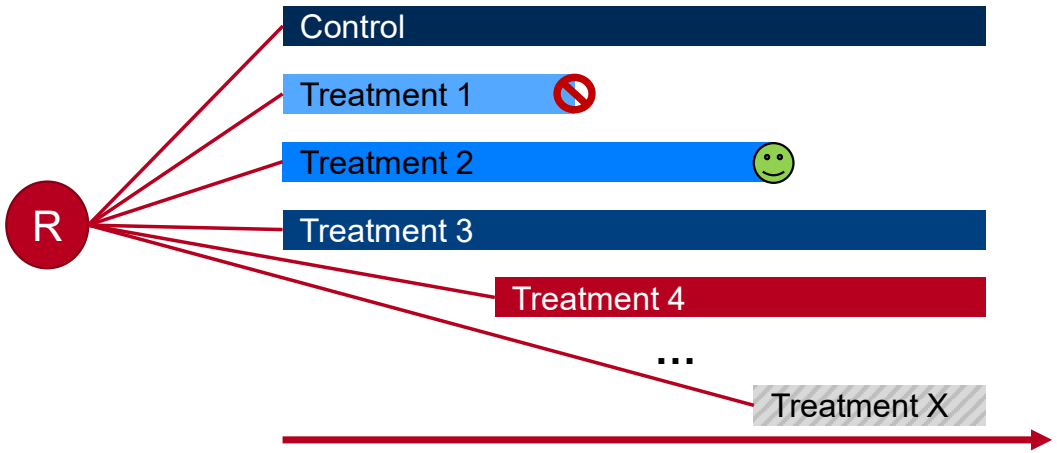
- Example of a platform trial



Some design aspects of platform trials

- **Controls:**
  - Designs can have a single common (shared) control, common controls per sub-study, or separate controls for all arms.
  - Non-concurrent controls are possible as well.
- **Adaptive features:**
  - Designs often include interim analyses for efficacy, futility or safety.
  - Further adaptive features such as RAR, SSR, … are possible.
  - Control treatment may be changed over time.
- **Further complexities:**
  - Further complexity can be added by treatment or sub-study specific IC/EC
  - Possibilities to opt-out from some arms / sub-studies, …

EU-PEARL

- Achievements of EU-PEARL
  - Discussions on T1E
  - Discussion on non-concurrent controls
  - Simulation software
  - Templates (e.g. protocol and SAP)
  - …
- See eu-pearl.eu for details

- But: No focus on Bayesian methods!

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

EU-PEARL has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853966-2. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Lessons learned from EU-PEARL

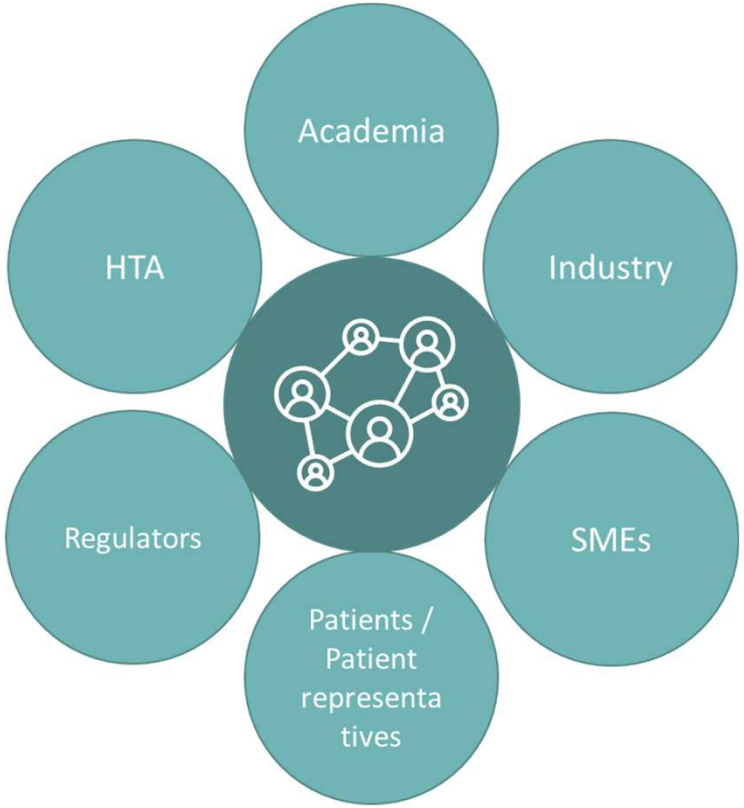
The value of collaboration in a trusted environment

- **Bringing** different expertise, different needs and different perspectives to the table
- **Understanding** the needs and perspectives of others
- **Finding** a common ground
- **Accepting** different views

- Real **interactive discussions** might help to overcome obstacles in CCTs

Suggested ways forward to address the challenges

- Collaborative and iterative multi-stakeholder dialogue exploring and defining the requirements for the design of a platform trial and facilitating early information sharing on lessons learned and acceptable design elements between various developers



Quote from: ACT EU multi-stakeholder workshop: A patient-centered approach to methodologies

GUIDANCE ON BAYESIAN METHODS

Reasons for using Bayesian methods

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- Bayesian methods may be used for **pragmatic reasons** to make it possible to estimate the effect in a given situation (e.g. with small sample size)
- In all other situations they are used to **leverage prior information**

- It is **common understanding** that the standard basis for approval is **self-standing evidence** usually generated by one (or even two) RCTs
  - However, no guideline seems to **specifically** requiring this!

Need for self-standing evidence

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- **Exceptions** are mentioned in multiple guidance documents, e.g.,
  - ICH E9 – Statistical principles for clinical trials (CPMP/ICH/363/96)
  - Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)
  - Points to consider on application with 1. meta-analyses; 2. one pivotal trial (CPMP/EWP/2330/99)
  - Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation (EMA/CHMP/564424/2021)
  - Draft ICH guideline E11A on pediatric extrapolation (EMA/CHMP/ICH/205218/2022)
  - Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018)
- Many refer to **Bayesian methods** as a possible approach ( )

ICH E9

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„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** and other **approaches may be considered** when the **reasons for their use are clear** and when the **resulting conclusions are sufficiently robust**.”

Guidance on Bayesian methods in complex clinical trials

- Complex clinical trials (CCTs) such as platform trials usually include adaptive designs as well and raised increasing attention over the last years.
- A Q&A on CCTs was released two years ago by ACT EU

Source: Complex clinical trials - Questions and answers (EMA/298712/2022)

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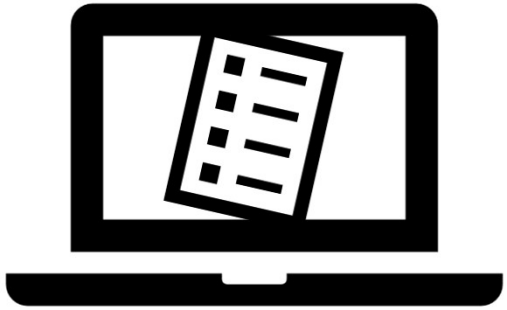
ACT EU Q&A

Complex clinical trials with Bayesian design

- Bayesian designs covered in Question 3:
  - “In complex clinical trials, Bayesian approaches are often used for specific trial activities such as, **interim** and final analyses (including for futility and for extrapolation), **adaptations**, **pooling** of data (active, control or external), or even using **external controls**, where any such activity needs a self-standing motivation (…)”
  - “Adjustment for multiple null-hypothesis significance testing (**type 1 error control**) is a central consideration in regulatory submissions for efficacy analyses (…). When using a Bayesian methodology, it is of importance that the methodology allows for an evaluation of corresponding issues, including via simulation.”
  - „Methodology needs to be **reasonably transparent** and its **results interpretable** (…). This is (...) 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.”
- **Documentation** is specifically highlighted (> next slide)

ACT EU Q&A
Complex clinical trials with Bayesian design

- Documentation needed on
  - Sound rationale including
    - Pre-specification of inferential plan (metrics)
    - Discussion of alternatives, which were considered
  - Details of model
    - Special focus is given to choice and specification of priors
    - Type of Bayesian model matters
  - Operating characteristics
    - Prior predictive simulations and posterior probabilities
    - Use a wide range of possible scenarios
    - Plan for sensitivity analysis (at analysis time)



➢ Requires good communication and early interaction

Further guidance mentioning Bayesian methods

- Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)
- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017)

MWP Workplan (2022-2024)

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2. Tactical goals: activities/projects to deliver the strategic goals

2.1. Guideline activities

2.1.3. Clinical Trial Modernisation (including ICH E9 implementation)

- RP on bayesian methods in clinical development.

- **High priority / short-term goal**
- The need is justified by an **increasing number** of such proposals.
- “New guidance in these areas [is needed] to ensure these novel approaches meet the required **evidentiary standards** and facilitate their evaluation”

Source: https://www.ema.europa.eu/en/documents/work-programme/consolidated-3-year-work-plan-methodology-working-party-mwp_en.pdf

RECENT EXAMPLES

Analysis of MAA examples

- Based on publicly available documents
  - EPARs – European Public Assessment Reports [1]
  - Search for „Bayes“ using an internal tool

Some limitations

- Covered EPARs
  - Restriction to **initial MAAs**
  - Variations not covered (> hardly any extrapolation cases)
  - Only **successful MAAs**
- Search tool & depth of search
  - AI based search tool[2]
  - **No systematic search**
  - 13 hits under first 20 search results on Bayes
- Reporting bias
  - Bayesian methods **not always flagged** in EPAR (especially in popPK analyses and supportive efficacy/safety analyses)
  - Methods not **always properly described** in the EPAR, hence sometimes methods or methodological details remain unclear
- Assessment/endorsement
  - **Not always explicitly assessed**

- [1] List of products see EMA Search page
- [2] see Bergman et al. (2023), DOI 10.1371/journal.pone.0294560

Examples of iMAAs with Bayesian methods

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Product	Context of use	Assessment		Source
Breyanzi (lisocabtagene maraleucel)	**Supportive analysis** to help ruling out differences between studies; Exploratory bridging analysis of ORR results with small sample size	No specific comments on Bayesian methods; Methods and results overall endorsed	+	EPAR (2022)
Calquence (acalabrutinib)	**PopPK model** with Empirical Bayes analysis	No specific comment on empirical Bayes method, overall models were endorsed	+	EPAR (2020)
Comirnaty (COVID-19 mRNA vaccine)	**Primary analysis** based on Bayesian credible intervals to conclude on efficacy and to allow for interim analyses	Usually not accepted as confirmatory evidence, but given the observed effects not of concern here; Clopper-Pearson CIs presented in SmPC	−	EPAR (2021)
Ervebo (Ebola Zaire Vaccine)	**Primary analysis** of cluster-randomized efficacy trial; Beta-binomial model with frequentist 95% CIs	Underlying assumptions and consequences of model were considered „uncertain“	~ −	EPAR (2019)
Finlee (dabrafenib)	**Paediatric PopPK model** utilizing also adult data	Bayesian approach was not considered necessary here and FOCE would have been preferred, but in principle acceptable if fit-for-purpose	~	EPAR (2023)
Lumykras (sotorasib)	**Futility interim analyses** based on Bayesian predictive probability (cMA based on partial data [for NSCLC] from a phase 2 *basket trial*)	No comment on futility interim analysis and Bayesian methodology	+	EPAR (2021)
Nexviadyme (avalglucosidase alfa)	**Post-hoc Bayesian analysis** to rescue a failed trial (only one of multiple analyses)	Considered helpful for interpretation purposes but not considered to provide any new information; Added issues as not pre-specified	~	EPAR (2021)

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Product	Context of use	Assessment		Source
Omjjara (momelotinib)	**Post-hoc Bayesian dynamic borrowing analysis** to support the clinical relevance of observed effects	Considered partially supportive	~ +	EPAR (2023)
Rezzayo (rezafungin)	**PopPK model** was used for Bayesian probability of target attainment analyses	No specific comment on Bayesian methodology; Some issues with respect to the clinical relevance of the derived results	+	EPAR (2023)
Spevigo (spesolimab)	**PopPK model** for exposure response analysis for safety based on empirical Bayes	No specific comment on Bayesian methodology; Analysis considered exploratory given clinical data on posology exists	+	EPAR (2022)
Tremelimumab AstraZeneca (tremelimumab)	**PopPK model** based on empirical Bayes estimates; Simulation of serum concentrations for dose rationale	No specific comment on Bayesian methodology; No discussion of analysis results	+	EPAR (2022)
Vitrakvi (larotrectinib)	**Supportive efficacy data** promised as SOB in a CMA to confirm treatment activity; CMA based on a *basket trial*; Response in all tumour subtypes will be evaluated using Bayesian methods	No specific comment on Bayesian methodology	~ +	EPAR (2019)
Zilbrysq (Zilucoplan)	**Bayesian meta-analysis** using external, historical placebo data as prior to combine clinical trials	Approach was considered appropriate and model diagnostics as well as transparency and pre-specification were acknowledged	+	EPAR (2023)

Quick overview of examples

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➢ Overall acceptance of Bayesian approaches in many cases

Summary of examples

- Most identified use cases are **PopPK** models were **empirical Bayes** estimates are very common and covered extensively in guidance
  - See e.g. Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)
- Additionally, many cases were Bayesian analyses were used to derive **supportive evidence** via exploratory analyses e.g. applying
  - Bayesian dynamic borrowing approaches
  - Bayesian meta-analyses
- Only two cases of **Bayesian adaptive designs (incl. 1 basket trial)**
  - Acceptability might depend on justification and role of analysis (cf. futility vs. efficacy interim analysis)
- One further case of **complex clinical trial** with Bayesian design
  - Not an adaptive Bayesian design
  - Bayesian methods suggested by Applicant to combine data across baskets

➢ Bayesian approaches are **endorsed in many situations** if well justified and fit for purpose.
➢ Bayesian designs for **primary (efficacy) analyses more challenging**.

CONCLUSION

Conclusions (I)

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- Bayesian designs drastically **change the current standard paradigm**
  - Self-standing evidence is replaced with complex combination of data sources / data plus prior information.
- Good **communication (and justification)** of model and its properties is key
  - Usually / often not the case
  - Thorough coverage of all relevant aspects in dossiers needed
  - Interactive tools (e.g. R Shiny apps) might support communication

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Conclusions (II)

- Assessment of CTAs and MAAs becomes much **more complicated**
  - Planning assumptions gain more weight: Choice of prior crucial
    - Bayesian designs may rely on specific expert opinion
    - Raises the question if the prior is plausible in the context of current scientific knowledge and if results from historical data are transportable
    - Self-standing evidence essentially relies on randomization only
    - Assessment requires interdisciplinary expertise and discussions
  - Potential prior-data conflict (a posteriori)
    - Added value of collected data over prior
  - Type 1 error control (and other operational characteristics) only via simulation
    - Not exhaustive! No proof!
    - Power gain only possible with additional assumptions, hence no strict type 1 error control[(1)]
    - BUT: Regulators need to guarantee a level playing field for all applicants

Source: Wikimedia, Modified version of picture in Public Domain

➢ Increasing **need for resources** on all ends

➢ Increasing the **risk for the Applicant**

[(1)] Kopp-Schneider A, Calderazzo S, Wiesenfarth M. Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control. Biom J. 2020; 62(2): 361-374.

Conclusion (III)

- Bayesian methods **can be used** already now (if well justified)
- Standard situations are
  - PopPK models
  - Dose finding
  - Other early phase clinical trials (including platform trials in that area)
  - Paediatric developments & extrapolation
  - Rare diseases

✓ Use these situations to **gain more experience and show utility** of the models

➢Seek early interaction with regulators if you plan to use a Bayesian design (especially in a confirmatory trial)