Opportunities and Challenges of using Bayesian Methods to support Regulatory Decision Making

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Views expressed are my own and do not necessarily reflect those of EFSPI or GSK

EFSPI
EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Why are there not more Bayesian Clinical Trials?

Perceived barriers to using Bayesian methods

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DIA

ANALYTICAL REPORT

Why are not There More Bayesian Clinical Trials? Perceived Barriers and Educational Preferences Among Medical Researchers Involved in Drug Development

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- Lack of familiarity among researchers
- Absence of clear regulatory guidance

1. **Knowledge**: Insufficient knowledge of Bayesian approaches
2. **Regulators**: Lack of clarity/guidance from regulators
3. **Clinical Team**: Reluctance from my internal clinical team
4. **NA**: The Bayesian approach is not applicable, and my organization sees no benefit
5. **Reg Team**: Reluctance from my internal regulatory team
6. **Stat Team**: Reluctance from my internal statistical team
7. **Mngmnt**: Reluctance from upper management
8. **Other**

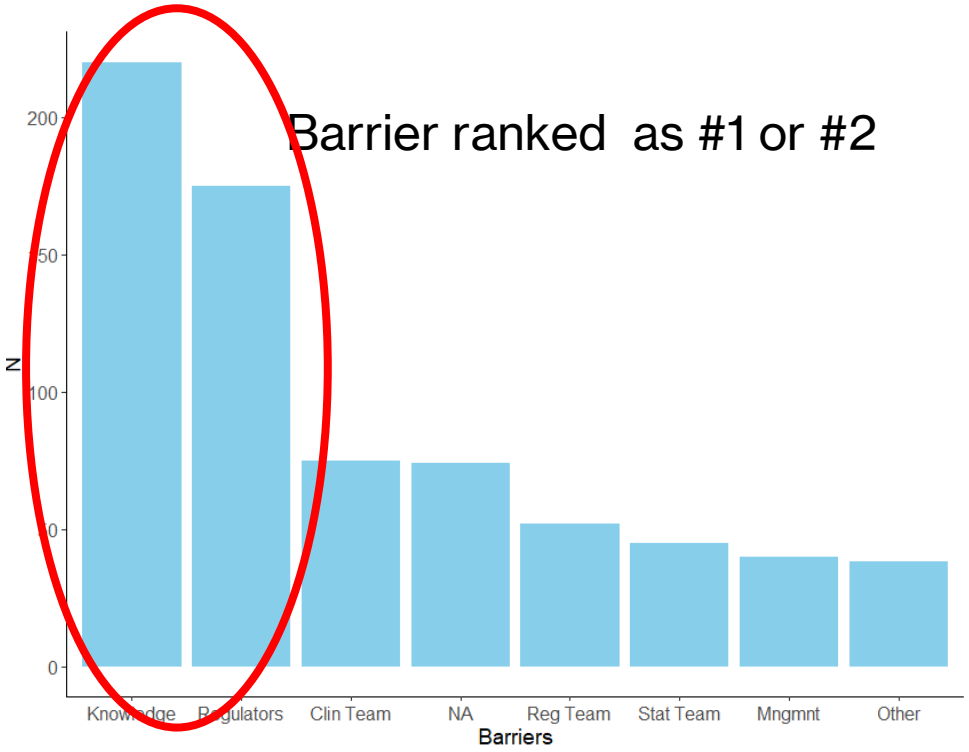

Figure adapted from Clark et al, 2023

Bayesian methods increasingly used for:

- Sponsor internal decision making
- Monitoring of safety data
- Informative priors in early-phase
- Medical device trials
- Long established use of Bayesian methods in pharmacometrics

Increased complexity of drug development:

- Rare diseases and unmet needs
- Treatment effect heterogeneity

Increased availability of high quality RWD

→ Need to move beyond traditional trial designs and analysis methods

Increased role for model-based methods and simulations to evaluate trial designs and facilitate regulatory decision-making

Motivation to use Bayesian methods

- Directly estimates probability of treatment effects in relevant ranges
- Facilitates interpretation for decision-making, e.g. interim futility / adaptations, dose selection
- Informing conditional approval in high-unmet need (criteria on risk/benefit)
- May offer operational advantages in settings where traditional asymptotic methods don’t apply (e.g. rare diseases, small populations, paediatrics)
- Allows consistency between missing data imputation (which is Bayesian) and the final analysis
- Framework for formal evidence synthesis and extrapolation
- Allows integration of prior knowledge

Additional complexities of Bayesian methods

- Subjective judgments have to be made when building Bayesian models
  - e.g. choice of priors, hyperparameters
  - Requires multidisciplinary discussion between sponsors and regulators
- Assumptions also needed for frequentist designs/analyses
  - E9 Addendum: “Statistical assumptions that underpin the main estimator should be documented” and “Sensitivity analysis should be planned for the main estimators of all estimands that will be important for regulatory decision making and labelling in the product information”

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- Strength of Bayesian Framework is that it encourages thoughtful cross-disciplinary discussion and transparency *up front*
- Could ICH-M15 and MIDD credibility assessment framework be helpful here?

Example

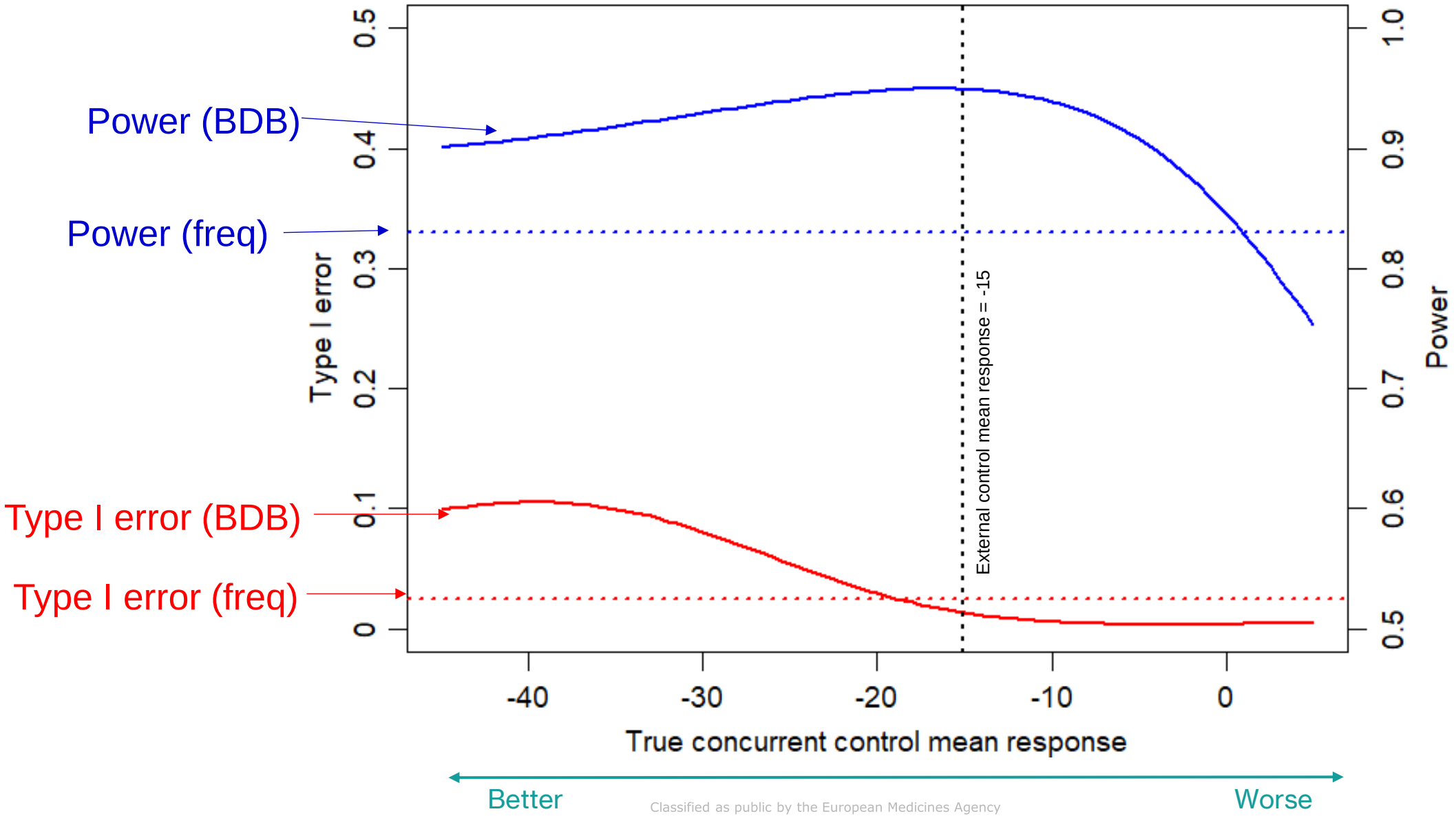
- Sponsor proposed use of Bayesian Dynamic Borrowing (BDB) in rare disease
  - Integration of clinical efficacy data from non-EU trial with planned multi-regional trial including EU
- Assessment of Ethnic Differences
  - Characterized comparability and evaluated potential impact on efficacy and safety of treatment
  - Included plans for real-world natural history and treatment patterns study
- Outlined planned *in silico* trial simulations to calibrate design and limit potential biases
- Regulatory Scientific Advice
  - "Bayesian approach may not guarantee extrapolatability to EU population"
- Need for Regulatory Guidance
  - What information is needed to enable up-front alignment on assumptions and parameter choices that would or would not support extrapolatability?

Type 1 error control

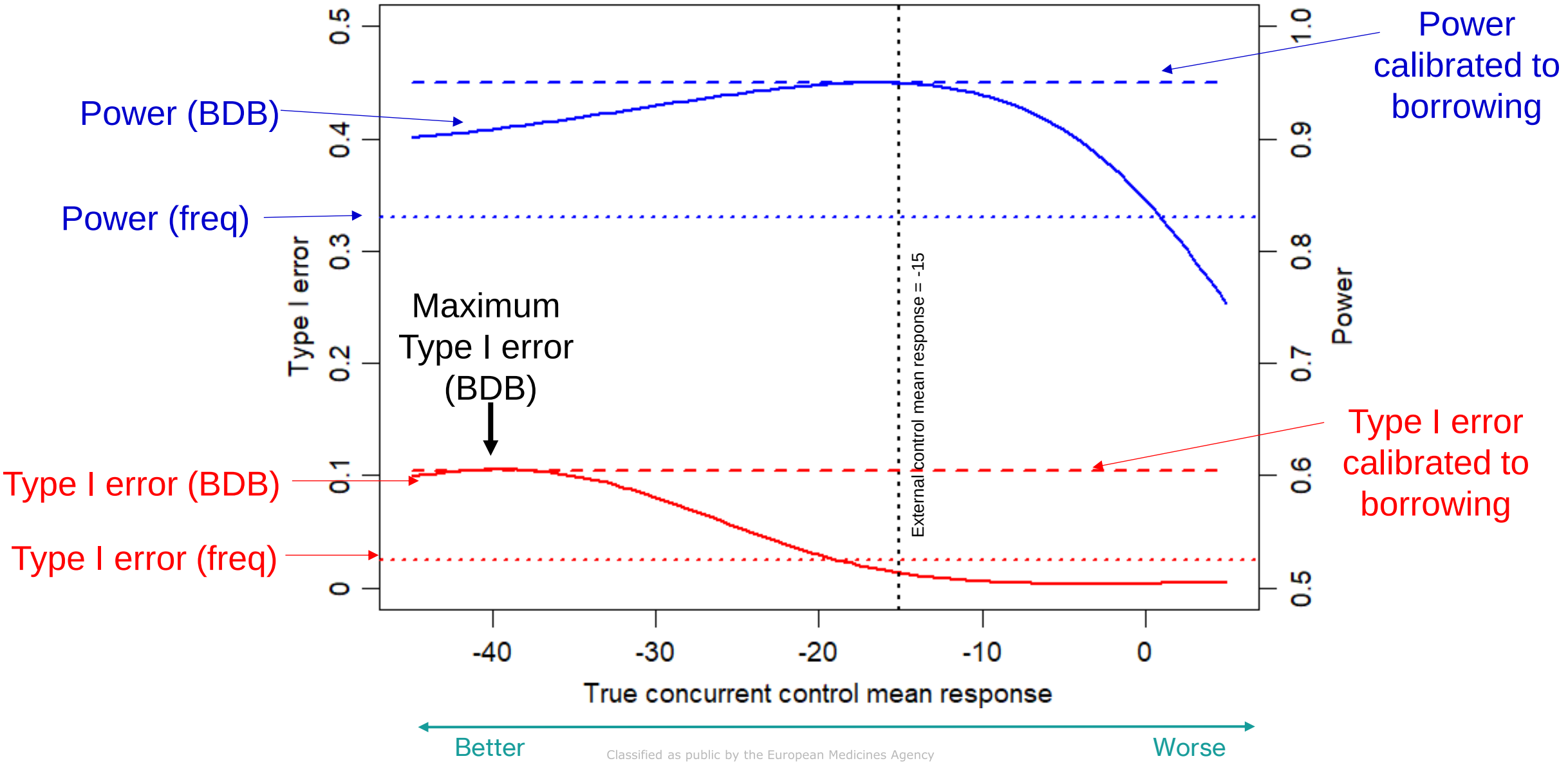
- Type 1 error can be evaluated and controlled for Bayesian designs **without borrowing**
- Type I error of **Bayesian borrowing** designs → area of active research
- If type 1 error is strictly controlled
  - ➢No power gains possible (Kopp-Schneider et al (2020) and others)
- Kopp-Schneider et al (2024): framework for calibrating (frequentist) test without borrowing to maximum type 1 error of a borrowing design
  - ➢No power gains are possible
  - ➢Assumes all possible values of the parameter space are equally important
  - ➢Power gains from borrowing are possible if we are willing to consider some regions of the parameter space as more important than others and restrict (or weight) operating characteristics to that region

Type I error and Bayesian dynamic borrowing (BDB)

Illustrative example using BDB for hybrid control arm in 2-arm trial

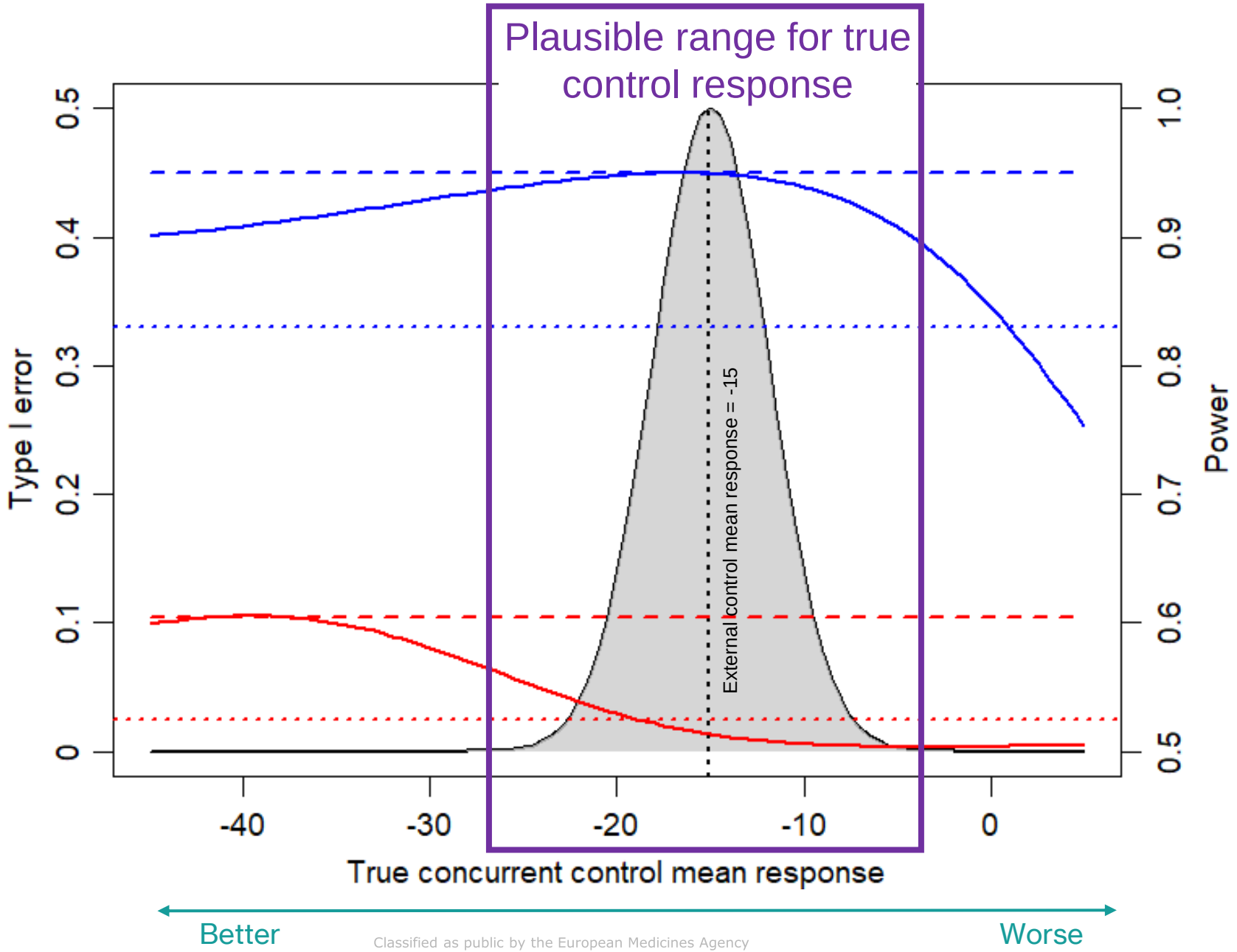


Type I error and Bayesian dynamic borrowing (BDB)



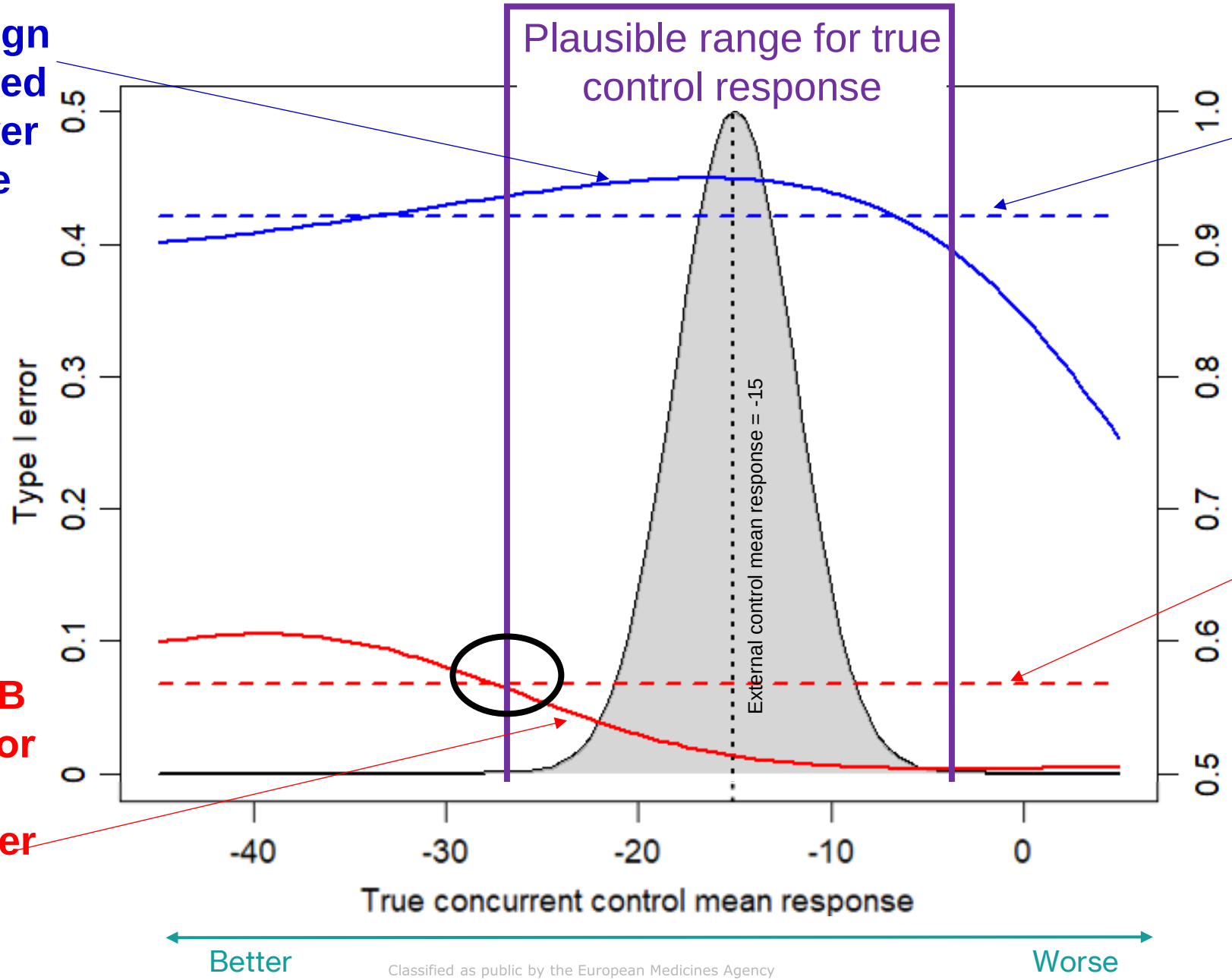
Type I error and Bayesian dynamic borrowing (BDB)

Our best information on the control response based on historical data



Type I error and Bayesian dynamic borrowing (BDB)

Power of BDB design > power of calibrated frequentist test over most of plausible range



Power calibrated to borrowing **on plausible range**

Type I error of BDB design ≤ type I error of calibrated frequentist test over entire plausible range

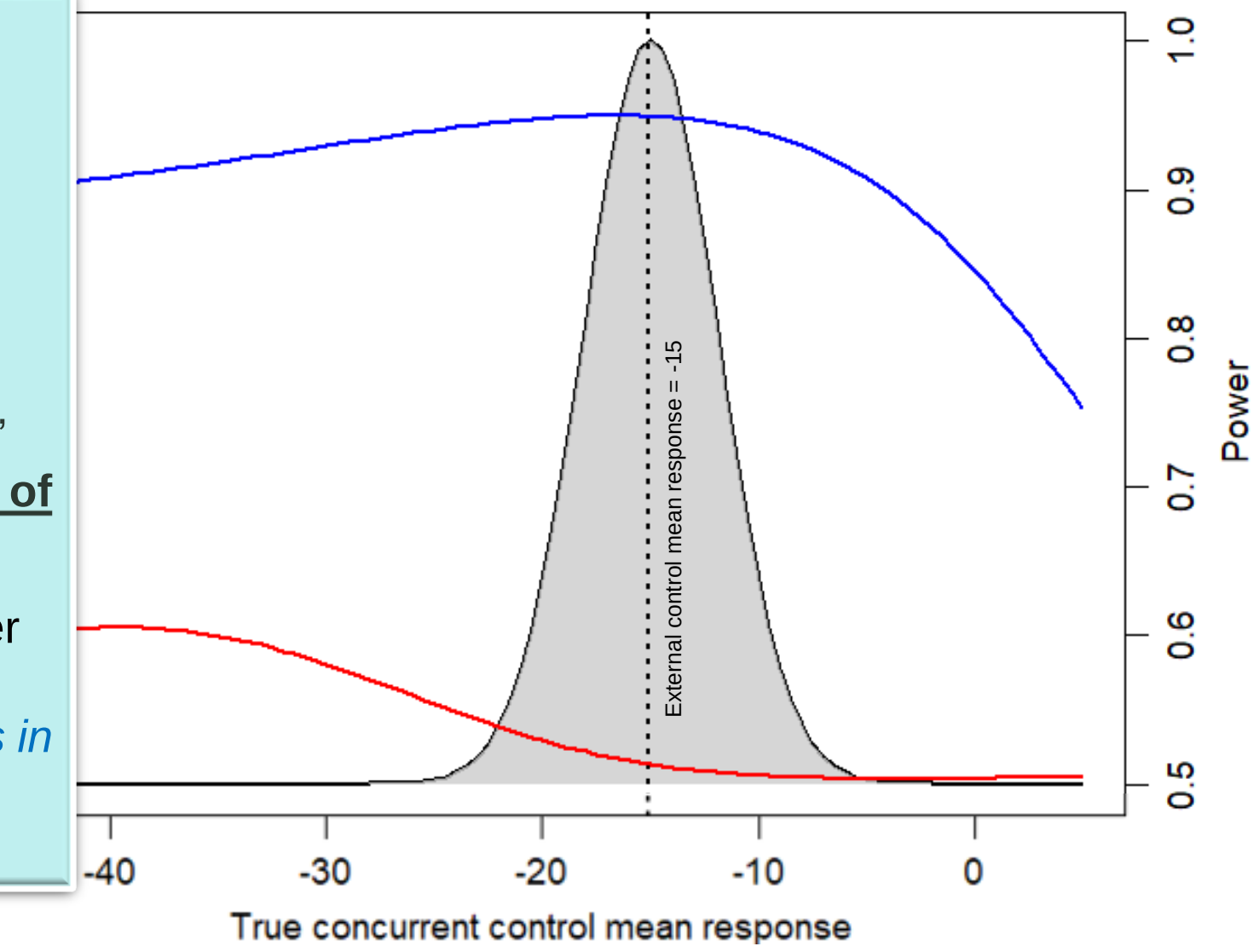
Type I error calibrated to borrowing **on plausible range**

Type I error and Bayesian dynamic borrowing (BDB)

Other potential metrics include:

- Maximum Type I error **with** corresponding probability of occurance
- "Averaged" Type I error
- Maximum or "Averaged" Type I error **over range of interest**
- Similar metrics for power

Best et al (2024) *Statistics in Biopharmaceutical Research*



Bayesian results in product labels

PFIZER-BIONTECH COVID-19 VACCINE

FACT SHEET FOR HEALTHCARE PROVIDERS

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, vaccine efficacy against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.3, 97.6), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the COMIRNATY group compared to 162 COVID-19 cases in the placebo group.

Food and Drug Administration (.gov)
https://www.fda.gov › vaccines-blood ...

BOOSTRIX | FDA - U.S. Food and Drug Administration

Oct 27, 2023 · BOOSTRIX is a vaccine indicated for: immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age.

the third trimester of pregnancy. This preliminary effectiveness estimate was updated using a Bayesian meta-analysis with an informative prior constructed from four observational studies that provided estimates of the vaccine effectiveness of the non-U.S. formulation of BOOSTRIX against pertussis in infants whose mothers were immunized during pregnancy.[5, 6, 7, 8] To account for potential publication bias, this informative prior was downweighted by combining it with an uninformative prior. When the informative prior has 20% weight, the Bayesian update resulted in estimates of effectiveness of vaccination during the third trimester of pregnancy of 81.5% (95% credible interval:12.9, 94.5). When the informative prior has 90% weight, the Bayesian update resulted in estimates of effectiveness of vaccination during the third trimester of pregnancy of 83.4% (95% credible interval: 55.7, 92.5). The vaccine effectiveness point estimates were consistent, regardless of the weight applied to the informative prior.

Nucala approved for use in China

Jan 16, 2024

*The primary endpoint was the frequency of clinically significant exacerbations of asthma and the **Bayesian Dynamic Borrowing (BDB) analysis showed a clinically meaningful and statistically significant reduction** in the rate of clinically significant exacerbations of asthma for Nucala 100 mg SC compared with placebo over the 52week treatment period. The **frequentist analysis provides further support for the treatment benefit** of Nucala in Chinese participants, with an identified **rate ratio of 0.35 (95% CI [0.24,0.50])**. The frequency of exacerbation in this study was reduced by 65% among participants treated with SC Nucala compared with placebo.*

Concluding remarks

Bayesian methods are mathematically & scientifically rigorous and have a track record of practical application in all areas of science and society

Bayes is not a magic bullet

- but it is an essential tool for drug developers and regulators/decision makers

Requires investment in education & understanding of Bayes for both statisticians and clinicians

Requires commitment to rigorous upfront multi-disciplinary discussions to align on key assumptions, choice of design elements, applicability of prior data etc.