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Bayesian techniques in paediatric development

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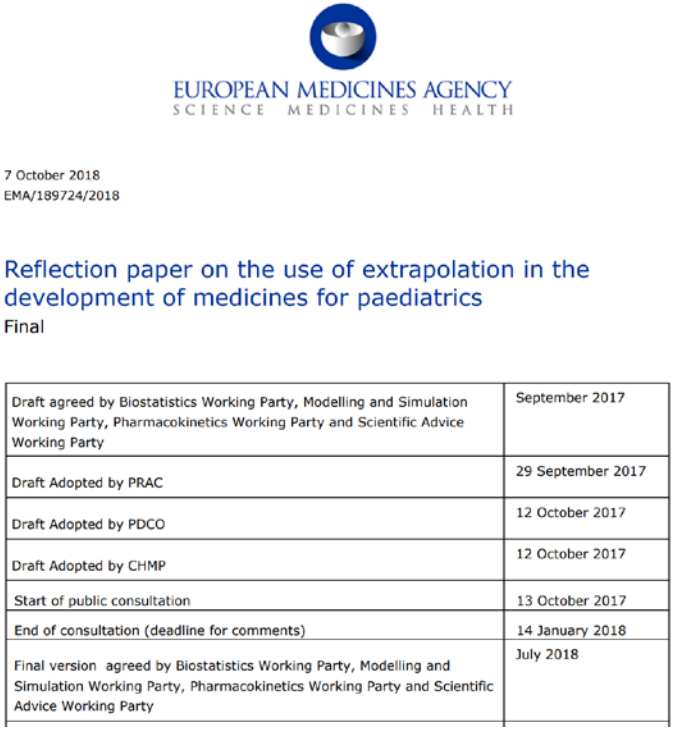
Advancing the Development of Pediatric Therapeutics (ADEPT 7)

An agency of the European Union

EMA Extrapolation Reflection Paper

- Multidisciplinary approach
- Opens door to Bayesian methods
- *“the exercise should identify if there is already sufficient evidence to support paediatric extrapolation, i.e. if effects can be reliably predicted in the target population, or if additional clinical information is needed”*



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

Draft agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	September 2017
Draft Adopted by PRAC	29 September 2017
Draft Adopted by PDCO	12 October 2017
Draft Adopted by CHMP	12 October 2017
Start of public consultation	13 October 2017
End of consultation (deadline for comments)	14 January 2018
Final version agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	July 2018

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Why do an RCT in children?

To generate efficacy data

- Gaps identified such that we cannot rely on PK / PD alone – pivotal evidence
- Possibly at raised level of alpha
- P-value declares positive result

To confirm the predicted efficacy

- Sufficient uncertainty such that controlled data is needed
- Purpose is to confirm predicted efficacy
- Interested in consistency between observed and predicted results

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Generating Efficacy

- Bayesian methods that borrow information raise the Type 1 Error
  - And that is OK!
- Regulators should encourage the most powerful statistical methods for a given acceptable level of “consumer risk”
- For Bayesian methods this is not fixed – see later slides
- Unclear whether we are just buying power with raised Type 1 Error
  - And if so, whether the Bayesian method is optimal to do this

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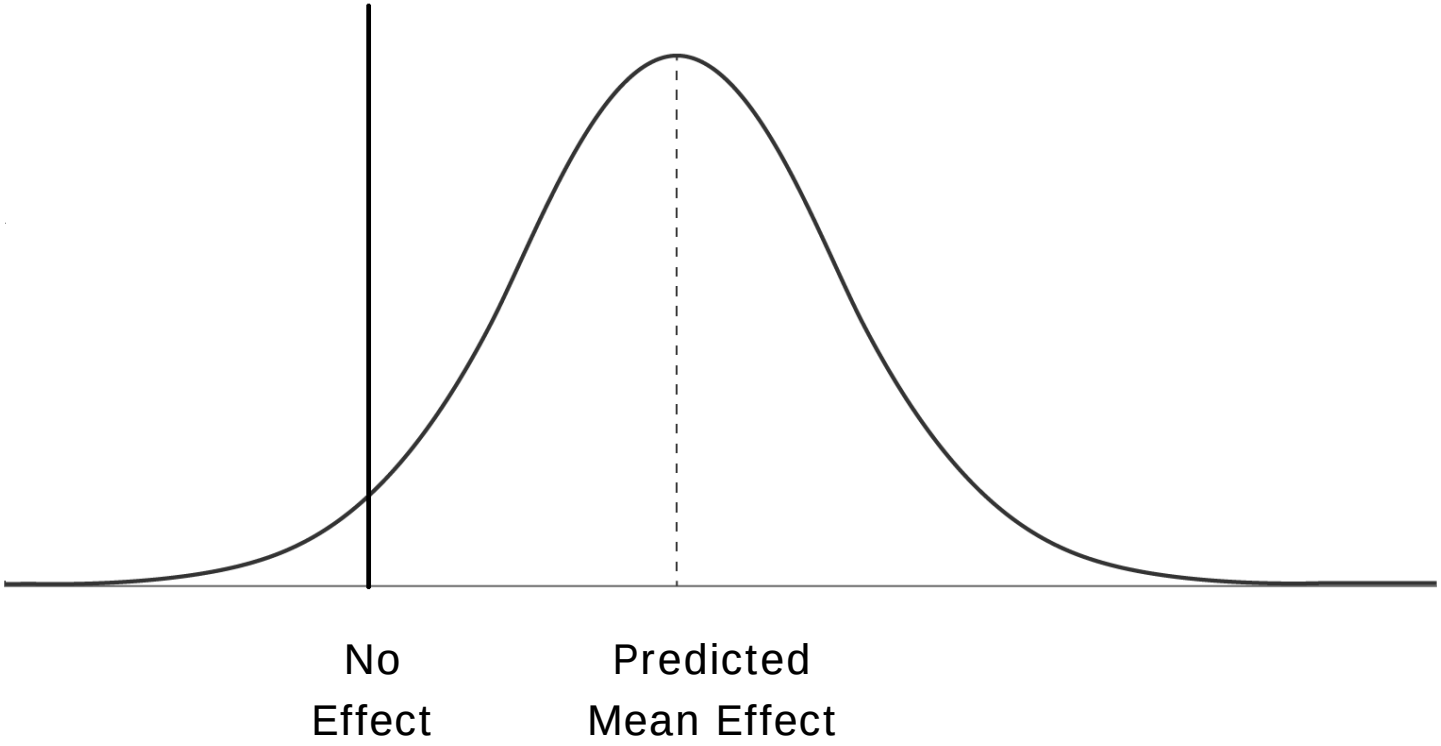
Confirming predicted efficacy



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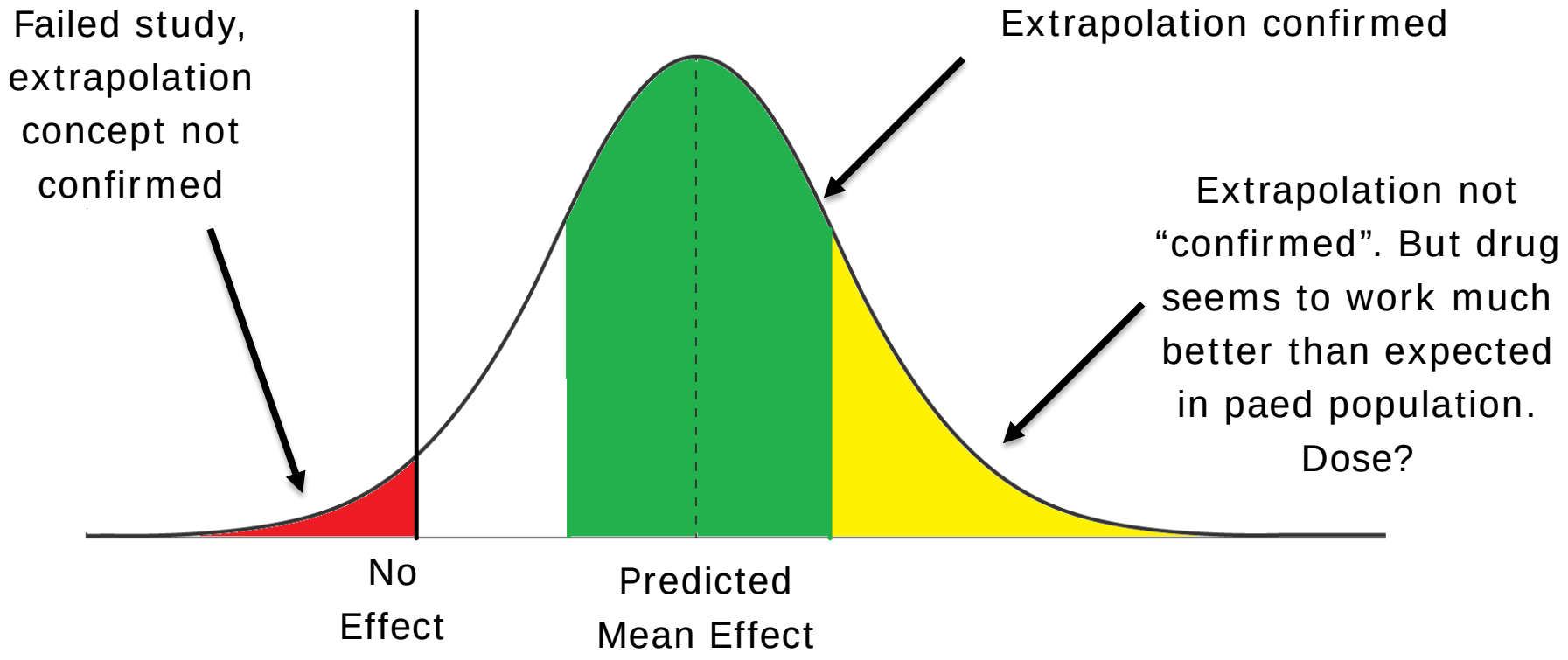
What do the (point estimate) results *actually* look like?



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What about the unshaded area?

- This is where biggest interpretation issues lies
- This is *independent* of the statistical framework chosen
- *However*, this does look an awful lot to Bayesian prior-data conflict
- Methods exist that aim to handle this, e.g.:
  - Test-then-pool
  - Dynamic Borrowing
- Open question – should regulators just “trust the model” or should they look at the data itself (and not the posterior distribution)?

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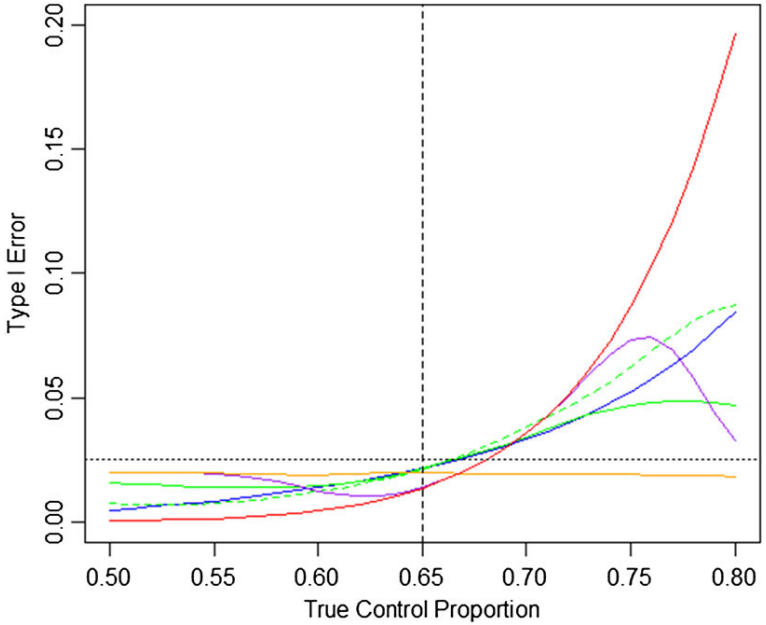
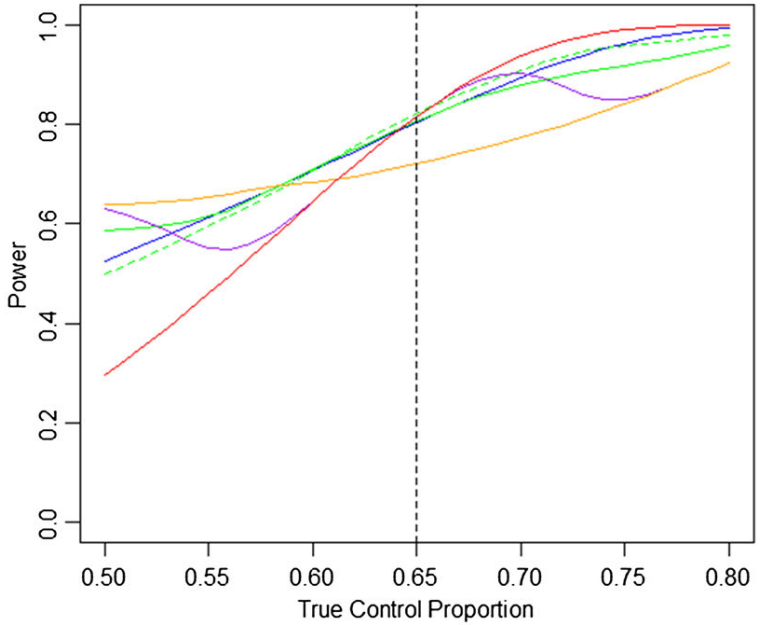
Different Bayesian Models





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Discussion of models

- Model is borrowing control arm data only
  - Need to understand what happens when you borrow treatment effect
- Comparison is to a frequentists test at 5% two-sided
  - Obviously Bayes looks more powerful!
- Unbound Type 1 Error is not ideal
  - Naïve Bayes may not be the best way forward
- In all of these approaches, the Type 1 Error is raised in the area where there is prior data conflict and likely a smaller treatment difference in the trial (i.e. the unshaded zone)

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Other regulatory considerations with Bayesian models

- Tend to make more assumptions
- In particular values and distributions of parameters defining priors
- Not necessarily much, if any, data to back these up
- Small changes in these parameters might lead to large changes in output and hence interpretation – potential lack of robustness
- Unclear interpretation of these parameters – we don't know what 'small' or 'large' looks like
- Sensitivity analyses even more crucial than usual to assess this
  - The door is open – but this does bring new challenges we are ready for

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Solution?

- Power trials based on an acceptable degree of precision, agreed with regulators, and calculate frequentist confidence intervals
- Question is *not* whether this includes a null value, but how well it overlaps with adult data?
  - Paediatric confidence interval contains adult point estimate?
- Sometimes we don't need different statistical frameworks for design and analysis, but better metrics for planning studies defining success
  - If we ask for an experiment on children, we should be doing so because we need the information to make a decision

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What place for Bayesian methods?

- Better predictive modelling
  - Sometimes we might know the response will be different, but we can accept this and model it
  - Better use of alternative data sources – other RCTs, RWE to support this
- More robust pharmacological modelling
- Sensitivity Analyses
  - Maybe as regualtros become more sued to them as sensitivity analyses we might start thinking about using them as the main analyses

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Conclusions

- Paediatric studies should be designed to answer a relevant scientific question
- Regulators encourage the use of the most powerful statistical techniques, limiting unnecessary exposure to control or sub-optimal doses
- Not everything is about p-values
- But that doesn't mean that Bayesian methods are *automatically* the solution
- The EU extrapolation reflection paper allows many different, creative ways of generating crucial data for decision making

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