

Model based dose finding

Discussion of presentations given by Björn Bornkamp and Andrew Hooker

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Key features to discuss

- **Study goal**
 - dose response and target dose estimation
- **Model based dose response estimation**
 - regression and model selection
 - Validity
 - bias and coverage probability
 - Robustness
 - model uncertainty
- **Efficiency**
 - optimal design
- **Exploration vs confirmatory**
 - confirmatory evidence ?



Study goal (1)

- **Dose response on its own**
 - positive dose response signal
 - exploring potential dose adjustments
- **Target dose estimation**
 - e.g. minimum effective dose
- **Select a dose to put forward in Phase III**
 - optimal expected risk benefit
 - dose response models for efficacy and safety
 - development efficiency



Study goal (2)

- **Estimation of**
 - dose response relation
 - target dose
- **Proof of concept**
 - demonstration of positive dose response signal
- **Regression model**
 - focussing on interpolation
 - abandoning pairwise comparison to placebo
 - dose finding as an estimation exercise
 - questionable conclusions from significant or insignificant differences depending on the goal of the study



Model based dose response estimation (1)

- **Borrowing strength between dosages**
 - model to provide link between dose groups
- **Model justification**
 - heuristic models
 - different options to choose from
 - model uncertainty
- **Alternatives to discuss, e.g.**
 - PK-PD derived models
 - spline-based procedures
- **Differences between different options ?**
 - MCPMod, model averaging, spline-based, etc.
 - compare e.g. distributions of target dose estimates



Model based dose response estimation (2)

- **Relevant model features**
 - validity of the conclusions
 - e.g. bias and coverage probability of target dose estimation
 - robustness against model deviation
- **Potential model extension**
 - longitudinal data
 - incorporating covariates
 - exploring dose adjustments for special populations
 - multivariate dose response
 - efficacy and safety



Efficiency

- **Optimal design**
 - criteria for optimality
 - e.g. precision of target dose estimation
 - local optimality only
 - depends on parameter to be estimated
 - efficiency of locally optimal design as a benchmark
 - larger number of dose groups for robustness
- **Adaptive design**
 - protection against mis-specified design and bad starting values
 - relative efficiency vs locally optimal design
 - less efficient than possible in theory
 - more robust



Validity of conclusions

- **Target dose estimation**
 - coverage probability and bias
 - conf. interv. compromised if based on finally selected model
- **Account for model selection**
 - fully prespecified procedure
 - use e.g. bootstrap
- **Confirmatory conclusions**
 - based on model assumptions
 - in contrast to single comparison of a specific dose vs placebo
 - power vs. robustness
 - dose finding study to be used as pivotal evidence
 - prespecification + type-1 error control of relevant comparisons

