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Regulatory aspects of model based dose selection

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Does the regulator care about dose selection?

- **Dose selection frequently poor**
  - few doses tested
  - dose range tested too narrow
  - small studies, lack of power
  - inadequate endpoints
  - dose finding not done at all
- **Phase III study may, nevertheless, be successful**
  - approval is granted if
    - efficacy confirmed in a clinically relevant endpoint(s)
    - no (relevant) safety concerns
    - benefit risk favorable
- **However …**

Dose selection considered to be “shared risk”

- **Shared risk between**
  - companies
  - regulators
  - prescribers
  - patients
- **Proper dose selection**
  - increases confidence in the submitted data package
  - may result in more informative SmPC
  - may have an impact on the need and size of
    - post approval studies
    - studies in specific populations
  - may be required to inform proper dosing in children
  - etc.

Incentive for proper (expensive) dose finding ?

- **Single pivotal study + proper dose finding ?**
  - to be discussed
- **Increasing the chances of approval**
  - optimizing benefit-risk
  - increasing the robustness of the whole package
- **Improving the (early) dialogue with the regulators**
  - increasing the acceptability of the Phase III package
- **Providing evidence to support extrapolation to**
  - different age
  - organ impairment
  - ethnic groups
    - may reduce additional requirements
    - may enhance labelling

Dialogue with the regulators

- **EMA scientific advice procedure**
  - ≈ 150 requests per year that include questions on dose selection
  - = 1/3 of procedures that discuss clinical development
- **SAWP Qualification opinions**
  - e.g. MCPMod

EUROPEAN MEDICINES AGENCY
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23 January 2014
EMA/CHMP/SAWP/757052/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

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Key general aspects to consider

- **Study goal**
  - dose response and target dose estimation to forward to Phase III

    vs.
  - confirmation of efficacy
- **Model based dose response estimation**
  - regression and model selection
  - validity
    - bias and coverage probability
  - robustness
    - model uncertainty
- **Study efficiency**
  - optimal design

Study goal

- **Dose response on its own**
  - positive dose response signal
  - exploring potential dose adjustments
- **Target dose estimation**

  dose selection w.r.t efficacy target
  - relative to placebo
  - relative to active comparator
- **Select a dose (doses) to put forward to Phase III**
  - optimal expected risk benefit
    - dose response models for efficacy and safety
  - development efficiency

Dose selection as an estimation problem

- **Estimation of**
  - dose response relation
    - e.g. $E(Y(d)) = f_\theta(d)$
  - target dose, e.g.
    - compared to placebo:
      - $d^* = \min \{d; E(Y(d)) \geq E(Y(0)) + c\}$
    - compared to active comparator:
      - $d^* = \min \{d; E(Y_{test}(d)) \geq E(Y_{reference})\}$
- **Proof of concept**
  - demonstration of positive dose response signal
- **Regression model**
  - focusing on interpolation
  - abandoning pairwise comparison to placebo

Pairwise comparisons to placebo

- **Pairwise comparison not suited for optimal selection**
  - dose finding is an estimation exercise
  - questionable conclusions from significant or insignificant differences depending on the goal of the study
    - significant doses may be too high
    - insignificant doses in small studies may still be useful
  - inefficient studies
    - lack of power due to multiplicity adjustments
- **Pairwise comparison to placebo as pivotal evidence ?**
  - may be an (inefficient) way to avoid second pivotal study
  - proper (model based) dose finding w/o confirmatory comparison of single dose group to placebo to be discussed as additional pivotal evidence

Model based approaches

- **Borrowing strength between dosages**
  - model to provide link between dose groups
- **Model justification**
  - heuristic models
  - different options to choose from
  - model uncertainty
- **Different alternatives to discuss, e.g.**
  - emax, logistic etc vs spline-based procedures

    vs
  - PK-PD derived models, DER models
- **Differences between different options ?**
  - MCPMod, model averaging, spline-based, etc.
  - compare e.g. distributions of target dose estimates

Model based approaches

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

Model based approaches in Phase III

- **Non-adaptive design**
  - confirmation of a specific dose would require
    - pairwise comparison incl. multiplicity adjustment
      - each dose group stands for its own

      or
    - model based confirmation of a specific dose
      - borrowing strength between dose groups
    - should we allow for the use of the data from different dose groups to generate pivotal confirmatory evidence?
      - e.g. assuming a strictly monotonic dose response

        ⇒ null hypotheses on no overall dose response and on no efficacy in a specific group are equivalent
      - are we ready for accepting this?
- **Adaptive designs**
  - similar

    but
  - potential efficiency gain by selecting dose groups at interim informed by model based dose selection

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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 the conclusions

- **Target dose estimation**
  - coverage probability and bias
  - conf. interv. compromised if based on finally selected model
- **Account for model selection**
  - proper confidence intervals
    - require fully pre-specified 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 ?
    - pre-specification + type-1 error control of relevant comparisons

Robustness of the model: Dose finding using an active comparator

- determining the dose that yields the same efficacy as the active comparator
- motivating example in type 2 diabetes

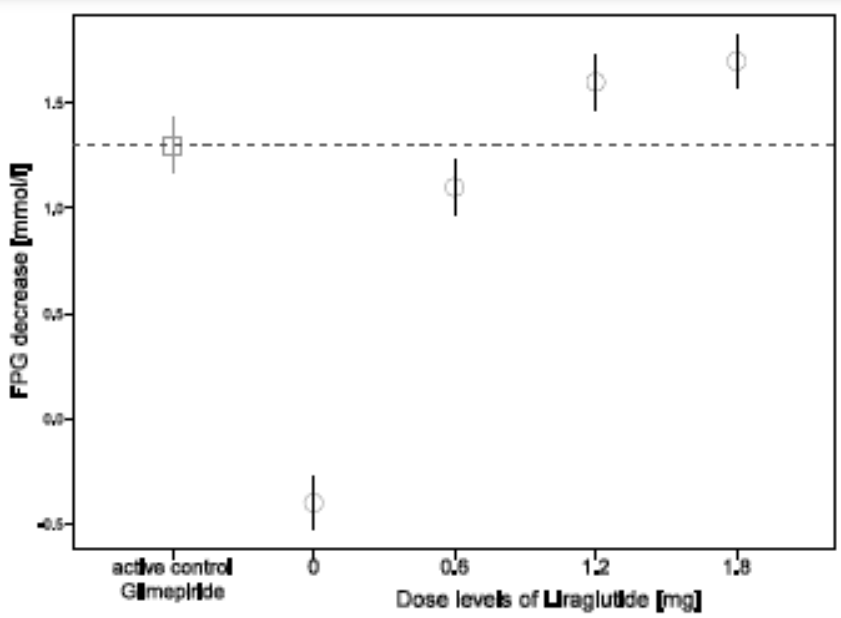

Figure 1 FPG decrease of the experimental drug dose levels and active control at the end of the study displayed as mean± assumed standard error (SE) reported in Nauck et al. (2009).

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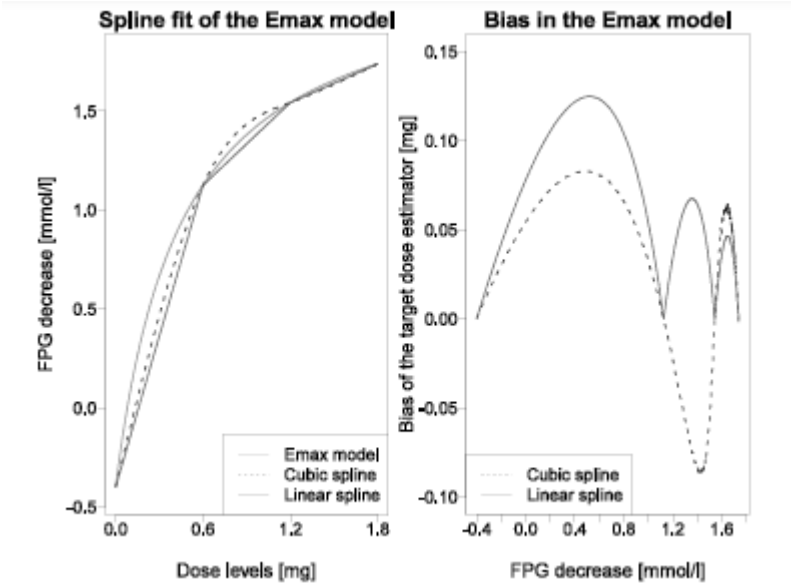
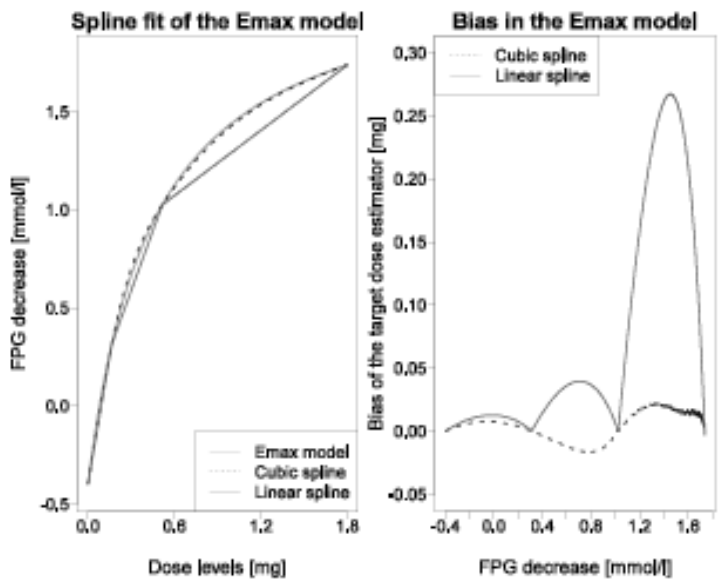
Helms, Benda, Zinserling, Kneib, Friede (2015). Spline-based procedures for dose-finding studies with active control. SiM 34.

Robustness of the model

- **depending on the assumed (parametric) model and the design**
- **example: spline vs emax**
  - target dose defined by efficacy of an active comparator
  - using spline based methods if emax is true



conventional design



optimal design (for cubic spline)

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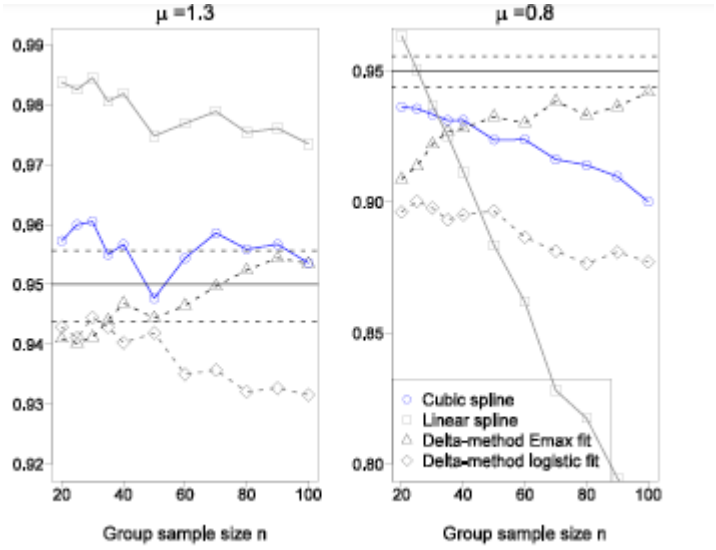
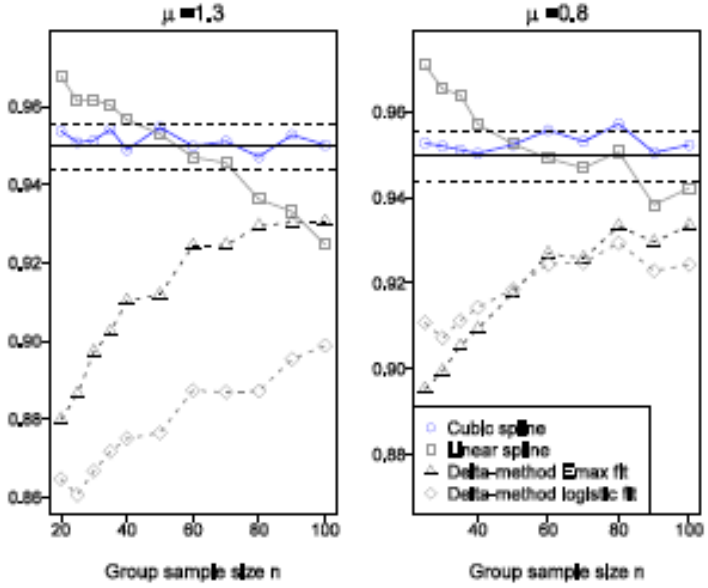
Helms, Benda, Zinserling, Kneib, Friede (2015). Spline-based procedures for dose-finding studies with active control. SiM 34.

Validity of the conclusion

- **coverage probability of the confidence interval of the target dose**
- **example: comparing spline based, emax and logistic fits**
  - target dose defined by efficacy of an active comparator
  - using different methods if emax is true



conventional design



optimal design (for cubic spline)

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Summary

- **Informative dose finding useful for different stakeholders**
  - "shared risk"
- **Model based dose selection based on regression models more powerful than pairwise comparisons**
- **Validity and robustness to be addressed**
- **Different model based approaches possible**
- **Design optimization may increase**
  - efficiency
  - robustness
- **Early discussion with regulators useful for both sides**