INTRODUCING BAYESIAN DOSE ESCALATION IN AN INDUSTRIAL ENVIRONMENT: CHALLENGES AND OPPORTUNITIES BEYOND STATISTICS

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Outline

- Available algorithmic designs
- Bayesian approaches for dose escalation
- Communicating Bayesian Designs
- Implementing Bayesian Designs in Practice – A company perspective

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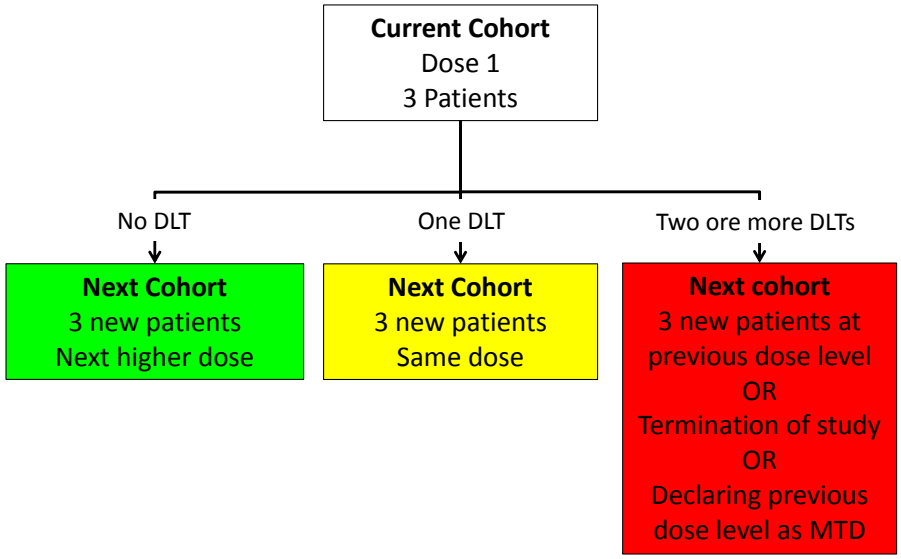
Available Algorithmic Designs (3+3)



Advantages:

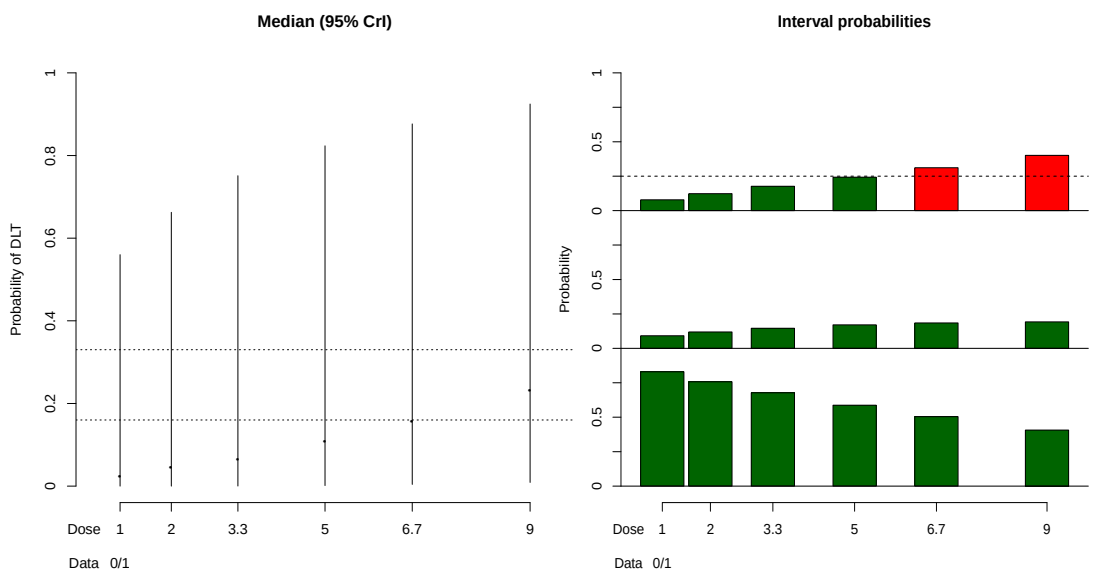
- Easy to implement
- Used for over 50 years
- No need of a statistician

Disadvantages:

- Fixed cohort size
- Algorithm makes the decision
- Only in-cohort information
- Target rate 35%-40% [1]

Bayesian Approaches for Dose Escalation

Logit $\{\pi_\theta(d)\}=\log \alpha + \beta \log (d/d^*)$, $\alpha, \beta > 0$ where $\theta = (\log \alpha, \log \beta)$ and d* is the reference dose [2]



Advantages:

- Flexibility
- Cost-effectiveness
- Risk prevention
- Joint decision making
- Target rate 60%-70%[2]

Disadvantages:

- you need a statistician
- Longer protocol development
- Analysis tools

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Communication of Bayesian Designs

Communication essentials

- F2F with full team / take the time
- Limit use of statistical terminology
- Understand the perspective of the stakeholders (especially non-statisticians)
- Receive feedback

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Communication of Bayesian Designs

Flexibility

- Cohort size
- Dose selection
- Regimen / population
- Avoids amendments

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Communication of Bayesian Designs

Cost-effectiveness

- Accelerated escalation
- Optimal patient number at different doses
- Prior information: replace on-study cohorts

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Communication of Bayesian Designs

Risk prevention

- Avoid closing doses by pure chance findings
- Evaluate intermediate doses
- Incorporate additional information in decision making

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Common misunderstandings of Bayesian Designs

„If the results are the same than a 3+3 why make it complicated? As we do not expect any tox anyway“

„Bayesian escalation requires more patients and time“

„The Bayesian approach is less safe than a 3+3“

„The model selects the dose“

Implementing a Bayesian Dose Finding Design at Boehringer Ingelheim

Why transition from 3+3 design to a Bayesian dose finding design?

- Some past studies where characteristics of the 3+3 design were of disadvantage
  - Observation of early DLTs
  - Study where the 3rd patient of a cohort needs to be replaced close to end of observation period, therefore long study duration

⇨ Need for a more flexible design

Implementing a Bayesian Dose Finding Design at Boehringer Ingelheim

Statistics involvement in the trial process at the moment:

- Centrally:
  - Trial statisticians contact „expert team“
  - Expert team supports:
    - understanding general design and protocol development
    - (Optional) escalation board meeting preparation, TSAP writing, trial implementation, etc.

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Statistics involvement in the trial process in future:

- Locally:
  - Each trial statistician is familiar with the design
  - „Expert team“ only involved in
    - Exceptional cases
    - Specific questions
    - Adaptations of the standard model / development of new models

⇨ To achieve this, a training for all statisticians is planned to be given in autumn

Implementing a Bayesian Dose Finding Design at Boehringer Ingelheim

Future planning with Bayesian statistics:

- More trials using Bayesian dose finding design
- Enhancement of the current design
- Using Bayes in Phase II regarding
  - Confirmation of dose
  - Bayesian decision criteria for Phase II (PoC), cmp Gsponer et al.

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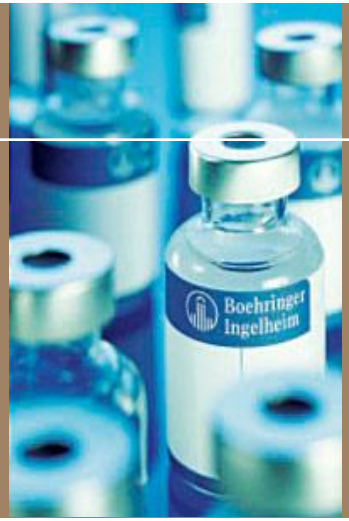

Thank you.

References

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