MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Thoughts on Late-Onset Toxicities in dose-finding studies

Thomas Jaki

✉ thomas.jaki@mrc-bsu.cam.ac.uk

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Dose-escalation trials

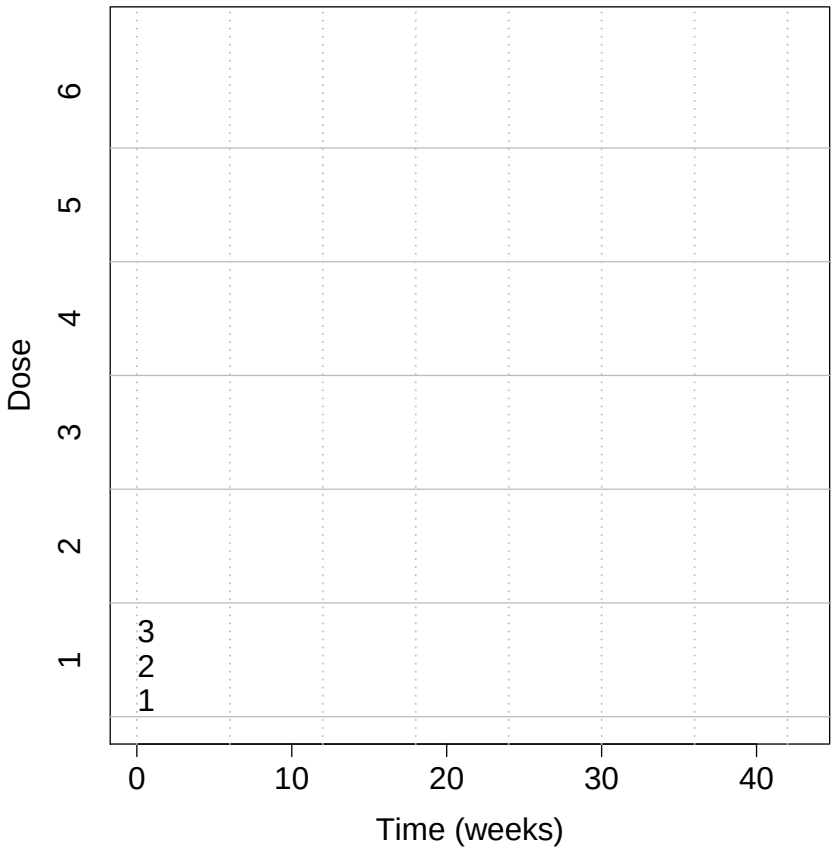
- Often first experimentation of a new drug in humans
- Emphasis is on finding safe doses
- Trials are small, typically 20-50 patients
- Patients are added sequentially after side-effects from previous patients have been assessed

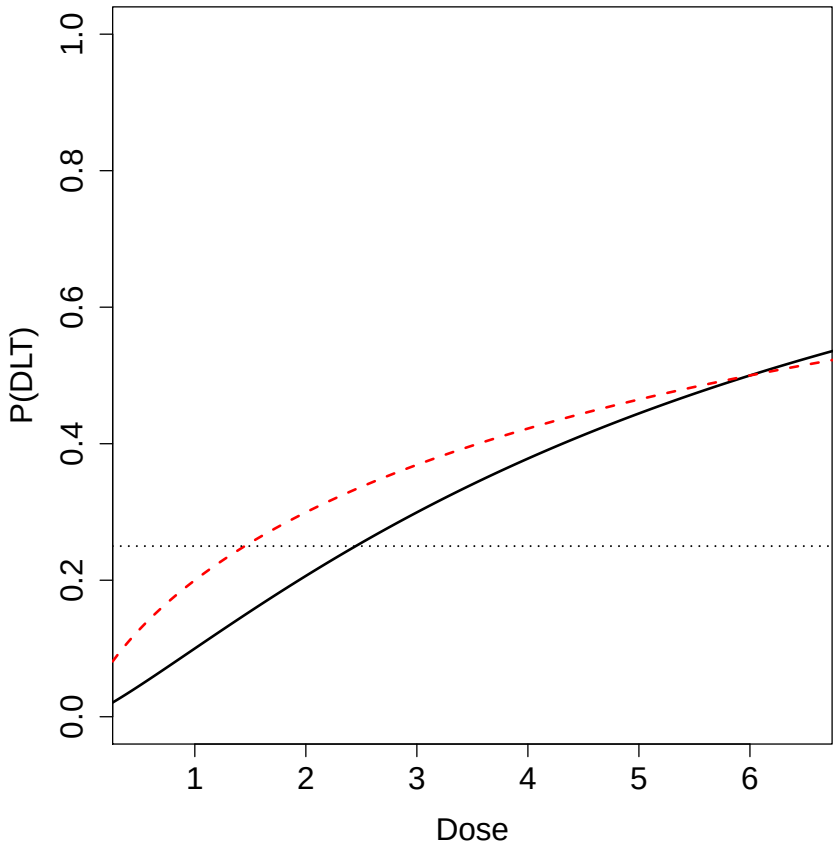
Assessing side-effects of a dose

- Occurrence of a dose-limiting toxicity (DLT)
- Determine the acceptable toxicity risk
- DLT usually assessed during first cycle of treatment

Example escalation

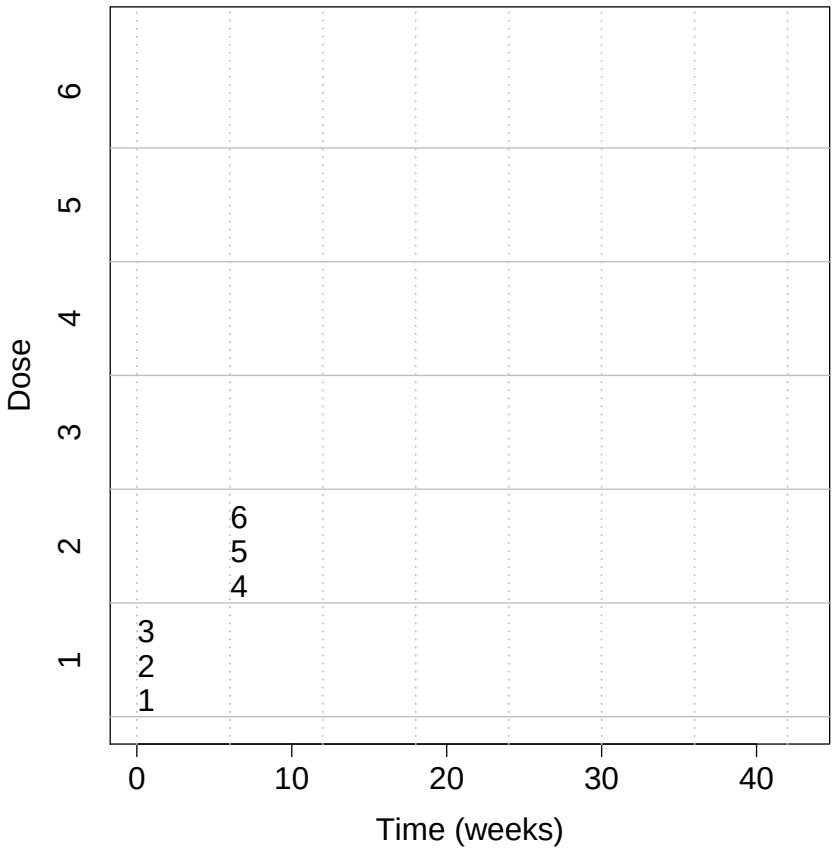
Cohort 1

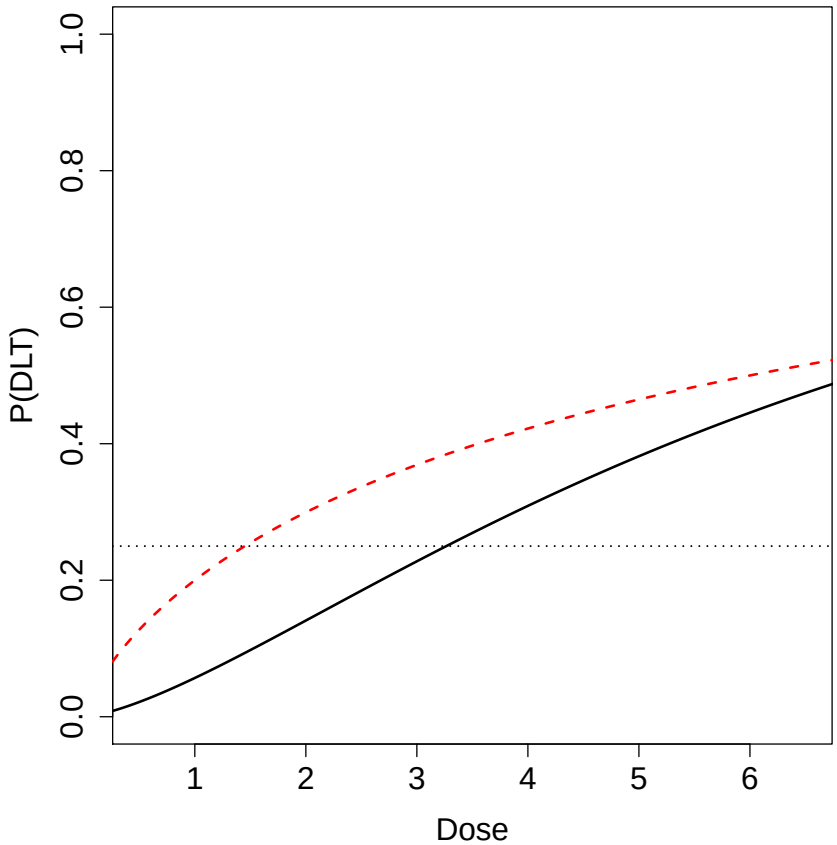




Example escalation

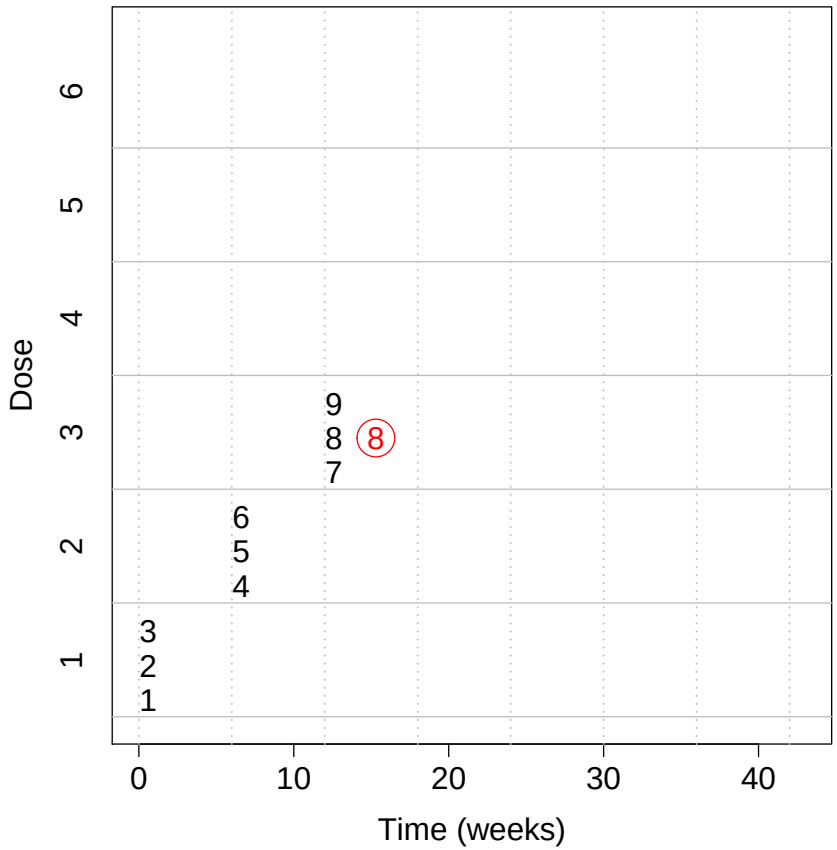
Cohort 2

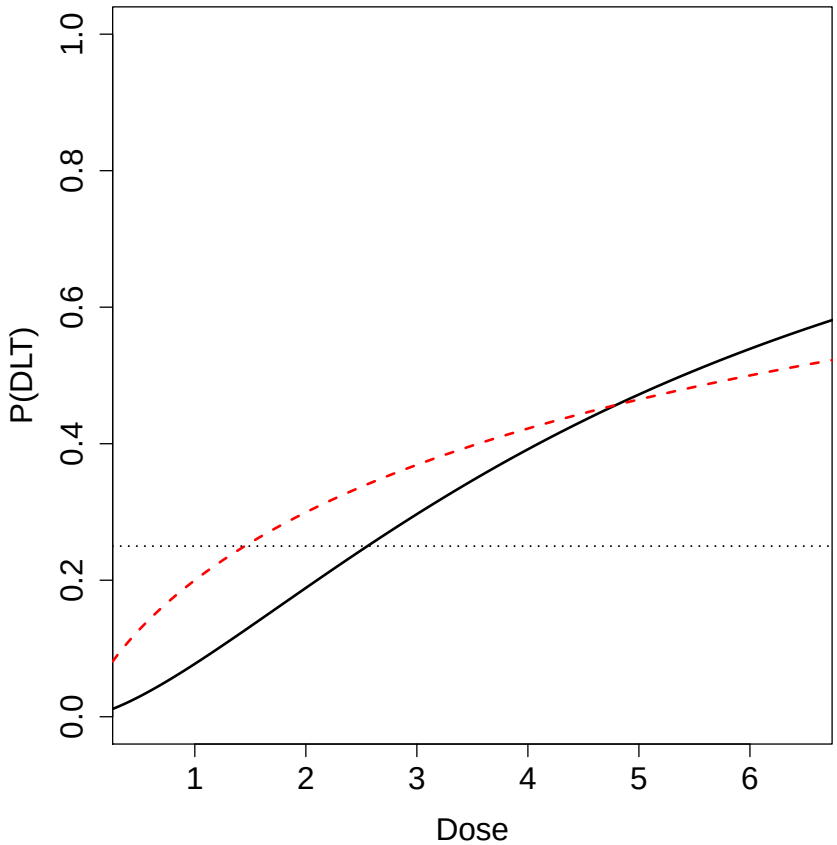




Example escalation

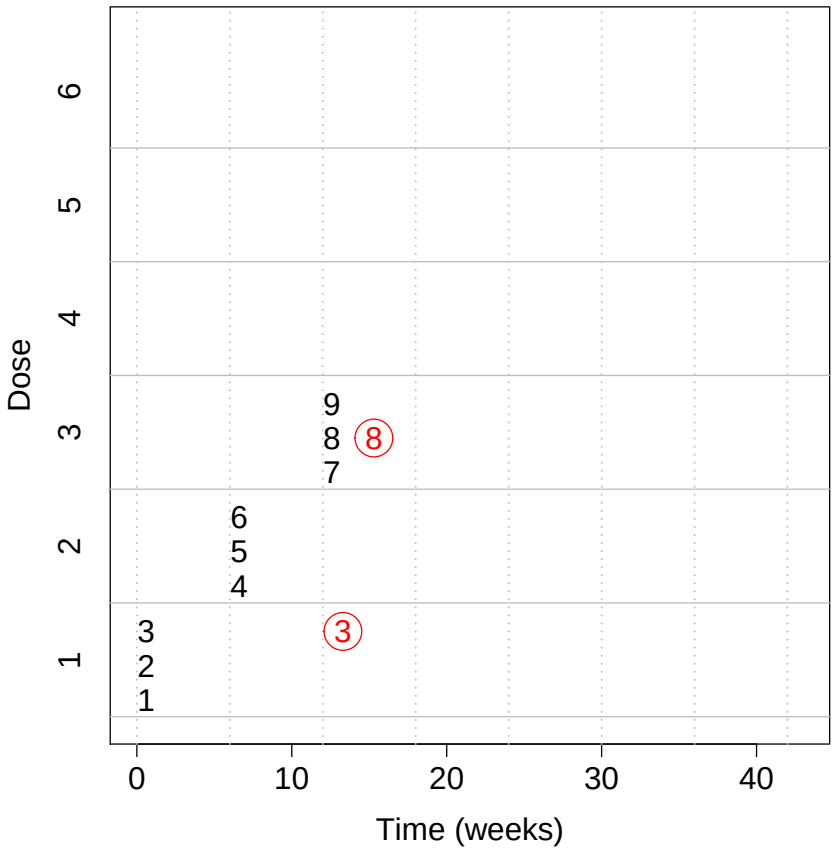
Cohort 3

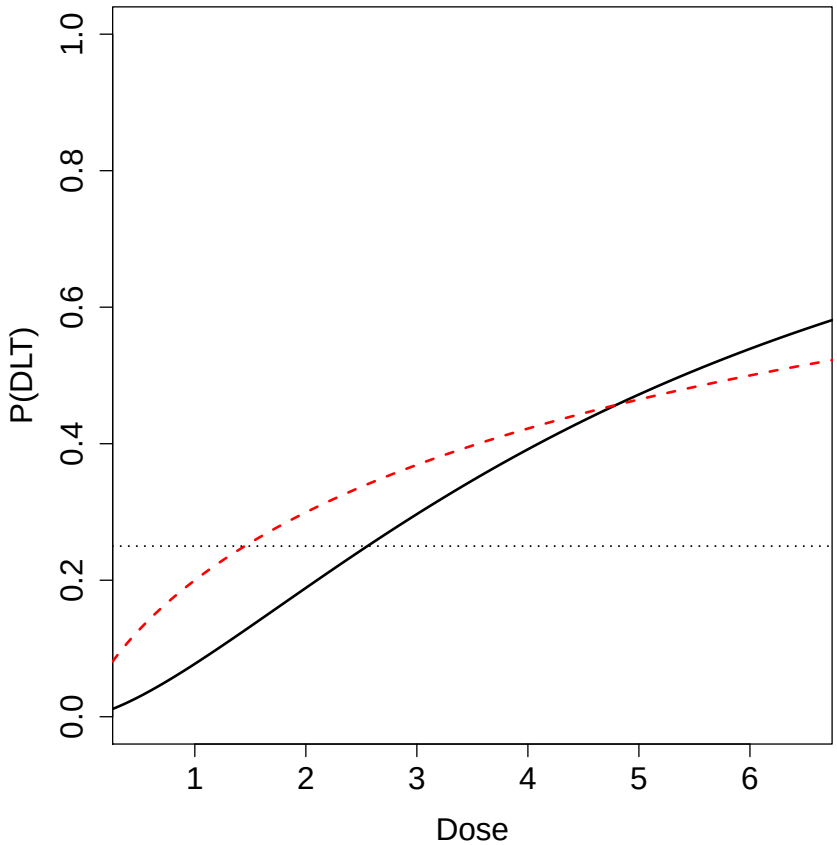




Example escalation

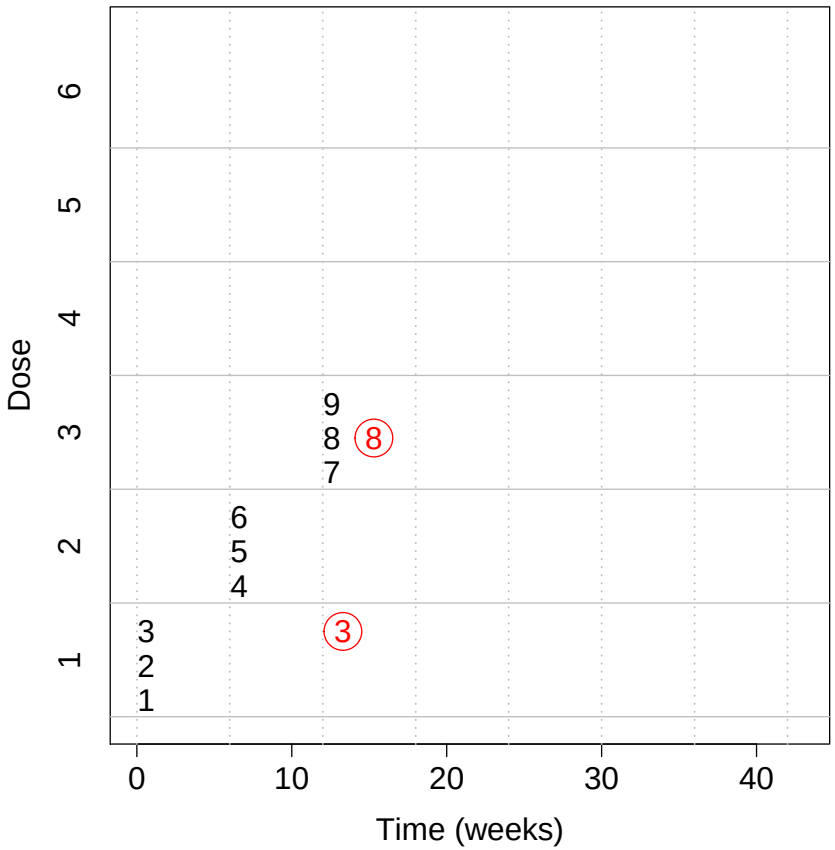
Delayed DLT

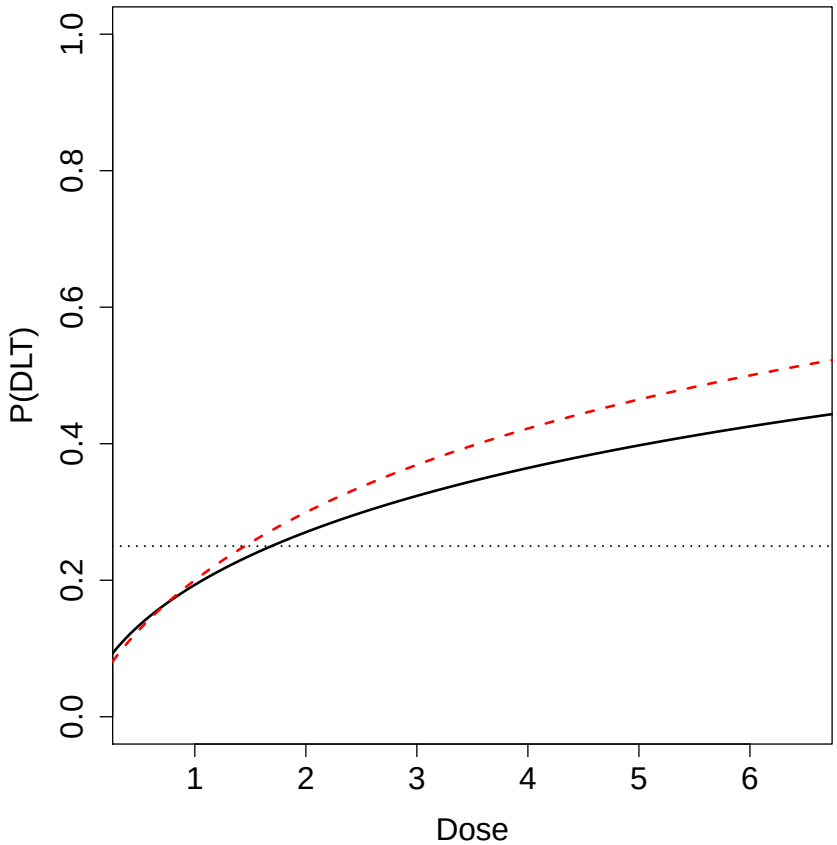




Example escalation

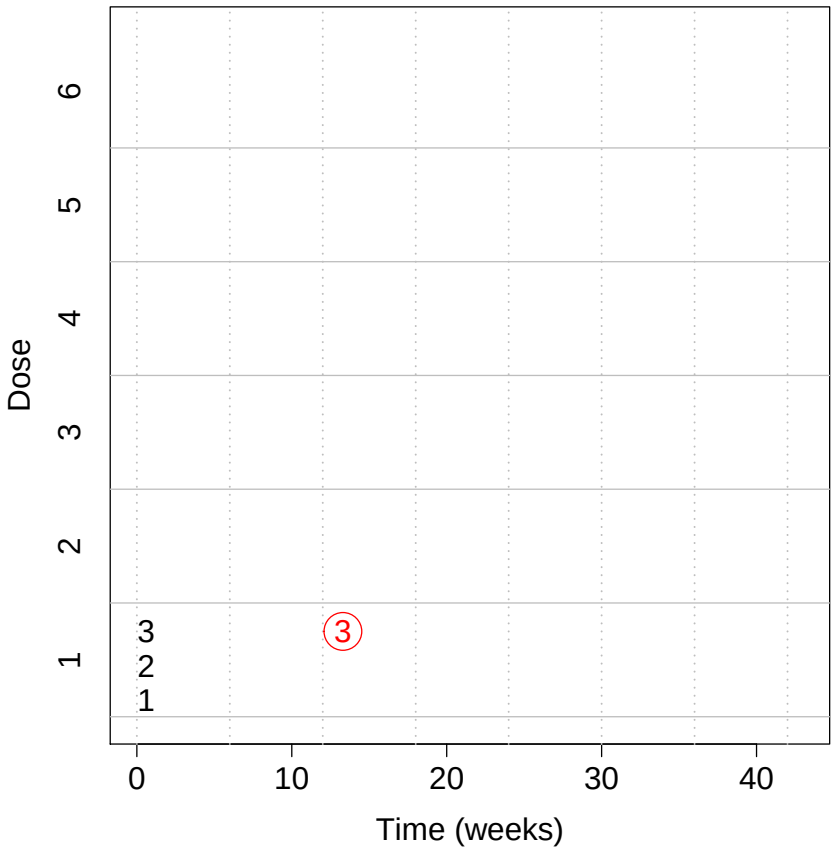
Delayed DLT modelled

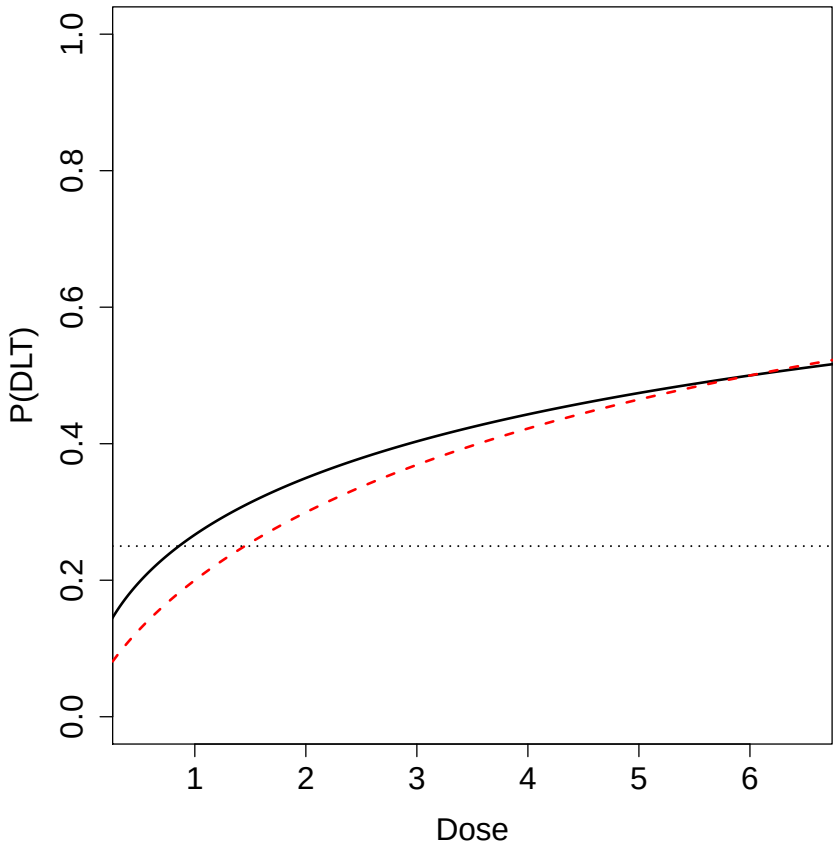




Example escalation

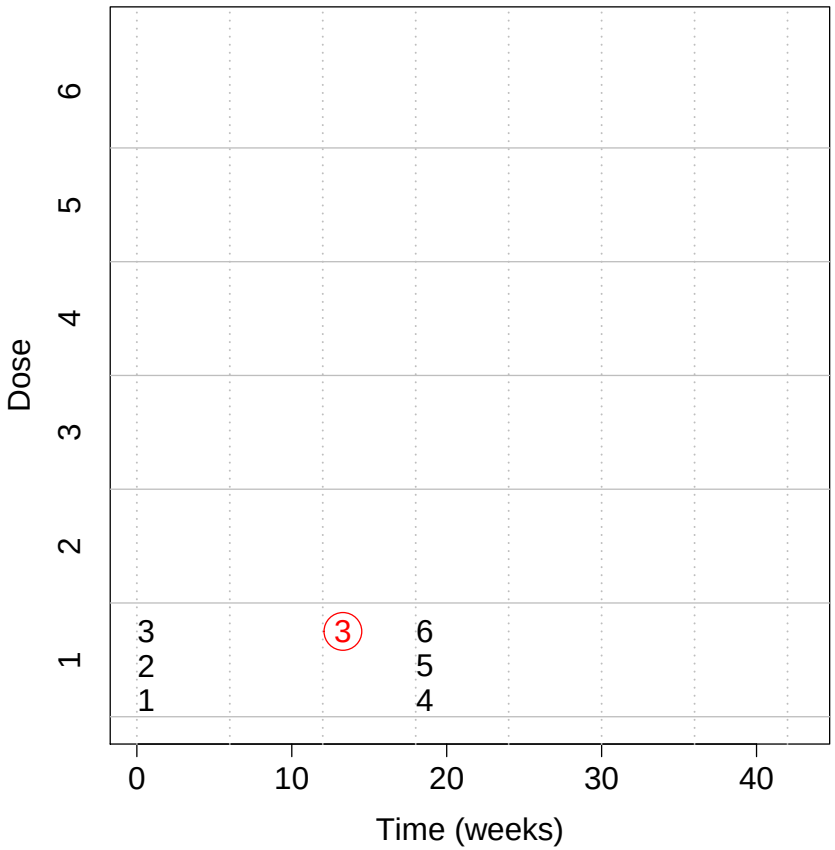
Longer DLT interval

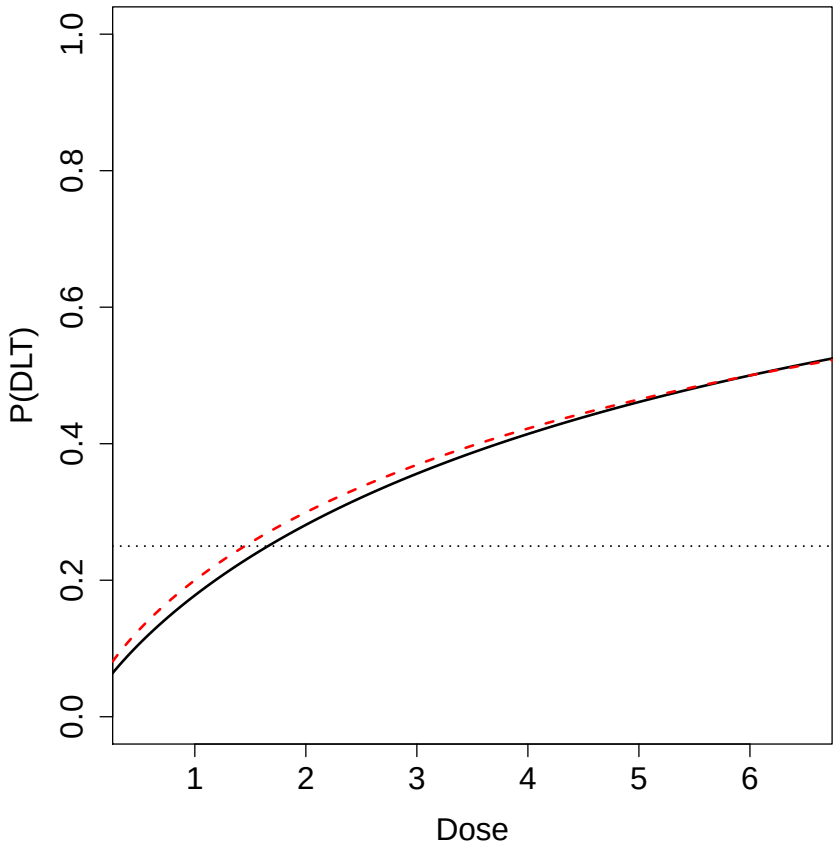




Example escalation

Longer DLT interval





Example escalation

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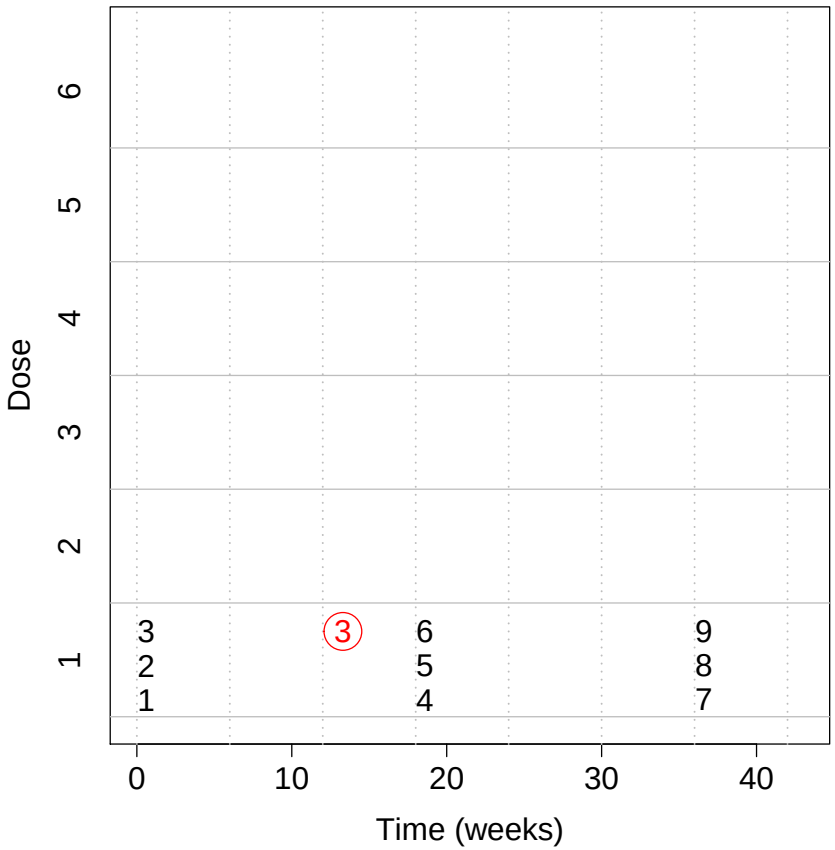

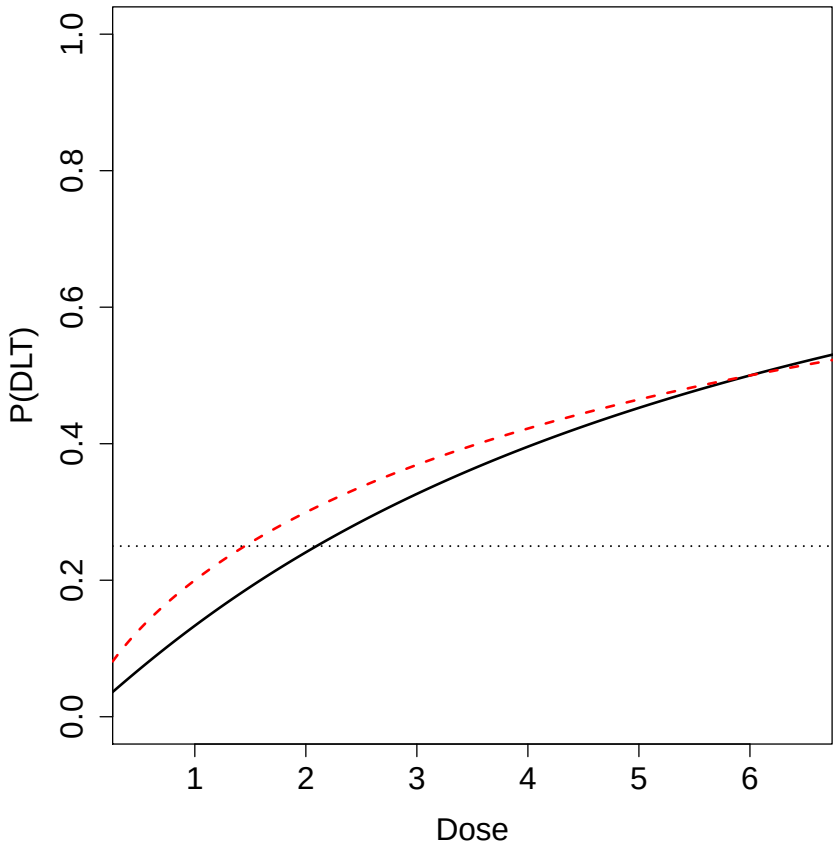

Alternatives

- Avoid cohorts of patients

[1] Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics. 2000 Dec;56(4):1177-82.

[2] Yin J, Qin R, Ezzalfani M, Sargent DJ, Mandrekar SJ. A Bayesian dose-finding design incorporating toxicity data from multiple treatment cycles. Statistics in Medicine. 2017 Jan 15;36(1):67-80.

[3] Doussau A, Thiébaut R, Paoletti X. Dose-finding design using mixed-effect proportional odds model for longitudinal graded toxicity data in phase I oncology clinical trials. Statistics in Medicine. 2013 Dec 30;32(30):5430-47.

Alternatives

- Avoid cohorts of patients
- Time-to-event models (Cheung and Chappell, 2000[1])

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Alternatives

- Avoid cohorts of patients
- Time-to-event models (Cheung and Chappell, 2000[1])
- Use of predictors of DLT
  - lower grade toxicity (e.g. Yin et al, 1997[2]; Doussau et al, 2013[3])
  - Biomarkers

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[1] Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics. 2000 Dec;56(4):1177-82.

[2] Yin J, Qin R, Ezzalfani M, Sargent DJ, Mandrekar SJ. A Bayesian dose-finding design incorporating toxicity data from multiple treatment cycles. Statistics in Medicine. 2017 Jan 15;36(1):67-80.

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Conclusion

"An integrated approach, which synthesizes nonclinical data, with clinical data (including PK/PD data, dose-response and dose-toxicity relationship), and safety data from multiple cycles that potentially incorporate long-term and delayed toxicities is needed." [4]

[4] Nie L, Rubin EH, Mehrotra N, Pinheiro J, Fernandes LL, Roy A, Bailey S, de Alwis DP. Rendering the 3+ 3 design to rest: more efficient approaches to oncology dose-finding trials in the era of targeted therapy. Clinical Cancer Research. 2016 Jun 1;22(11):2623-9.

Thanks for listening!

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UNIVERSITY OF CAMBRIDGE

thomas.jaki@mrc-bsu.cam.ac.uk

www.mrc-bsu.cam.ac.uk