Phase I dose-escalation trials with more than one dosing regimen

Burak Kürşad Günhan[1] Sebastian Weber[2]
Abdelkader Seroutou[2] Tim Friede[1]

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[1]Department of Medical Statistics, University Medical Center Göttingen

[2]Novartis Pharma, Basel

Introduction

Background

- In drug development, earliest trials on humans
  $\Longrightarrow$ **phase I dose-escalation trials**
- Relationship between dose and toxicity
- Aim: Maximum tolerable dose (MTD)
- Small cohorts of patients, and treated in cycles
- Observed toxicities: dose limiting toxicities (DLTs) and non-DLTs
- Based on DLTs data in first cycle

Background (cont.)

Cohort	Dose (mg)	Number of pats	Number of DLTs	MTD

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1	1	3	0	No

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1	1	3	0	No
2	2	5	0	No
3	4	4	0	No

Background (cont.)

Cohort	Dose (mg)	Number of pats	Number of DLTs	MTD
1	1	3	0	No
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3	4	4	0	No
4	8	5	1	No

Background (cont.)

Cohort	Dose (mg)	Number of pats	Number of DLTs	MTD
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3	4	4	0	No
4	8	5	1	No
5	8	6	1	Yes!

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3	4	4	0	No
4	8	5	1	No
5	8	6	1	Yes!

Standard Methods

- Main approaches: algorithm-based (3+3) and model-based
- Model-based approaches display better performance.

Bayesian Logistic Regression Model (BLRM) (Neuenschwander et al., 2008)

- For dose d
  - Number of DLTs: $r_d \sim \text{Bin}(\pi_d, n_d)$
  - DLT probabilities: $\text{logit}(\pi_d) = \log(\alpha_1) + \alpha_2 \log(d/d^*)$

  where d^* is the reference dose.
- Interpretation of α_1 is odds of a DLT probability at d^*.

Bayesian Logistic Regression Model (cont...)

- Metric for dose recommendation
  $\Longrightarrow$ Posterior distribution of π_d is used.

- Three categories for π_d
  - $\pi_d < 0.16$ Underdosing (UD)
  - $0.16 \leq \pi_d < 0.33$ Targeted toxicity (TT)
  - $\pi_d \geq 0.33$ Overdosing (OD)

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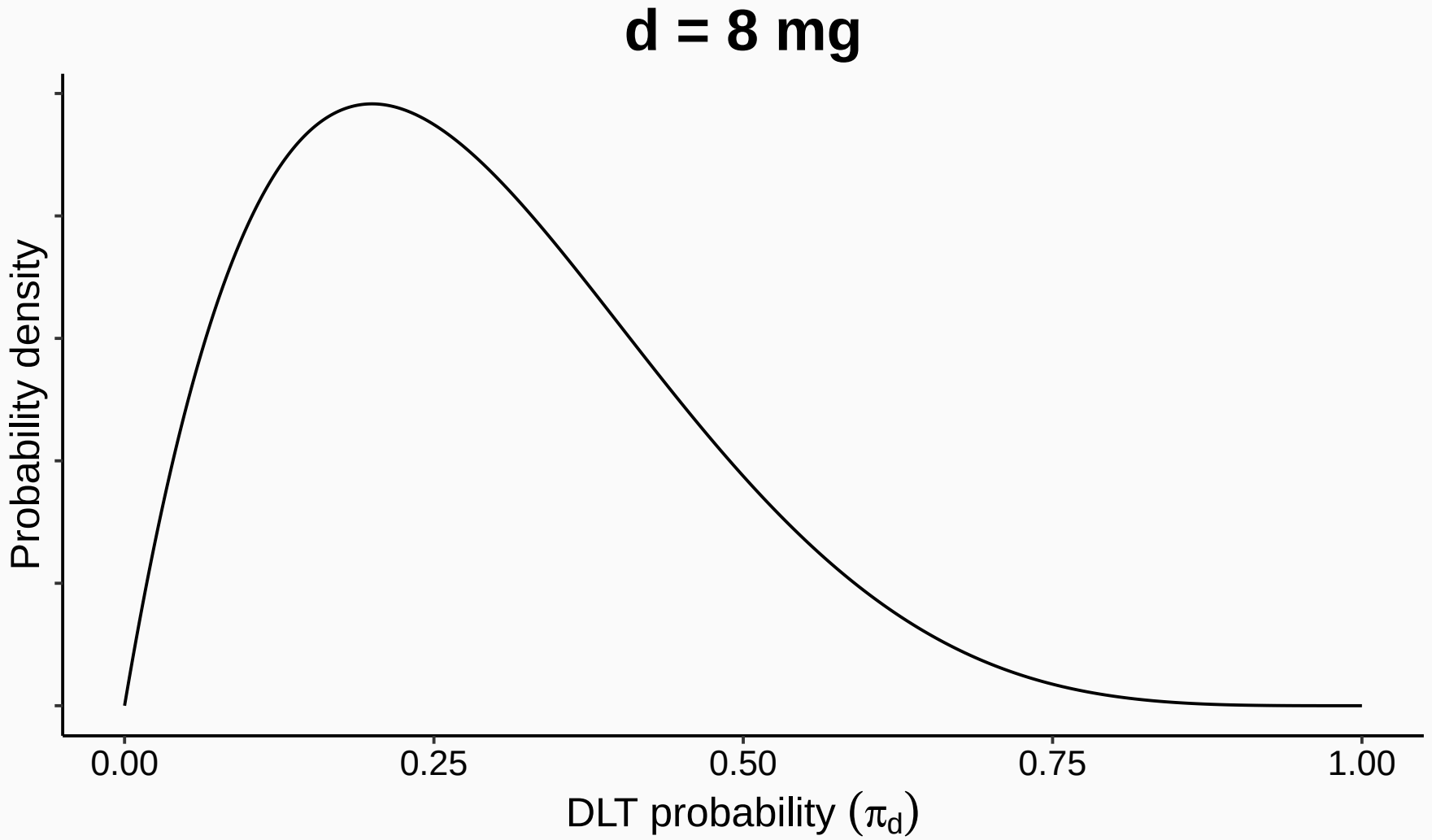
- **Escalation with overdose control** (EWOC) principle
  $\Longrightarrow$ $P(\pi_d \geq 0.33)$ should not exceed 0.25.

Visualization of EWOC principle



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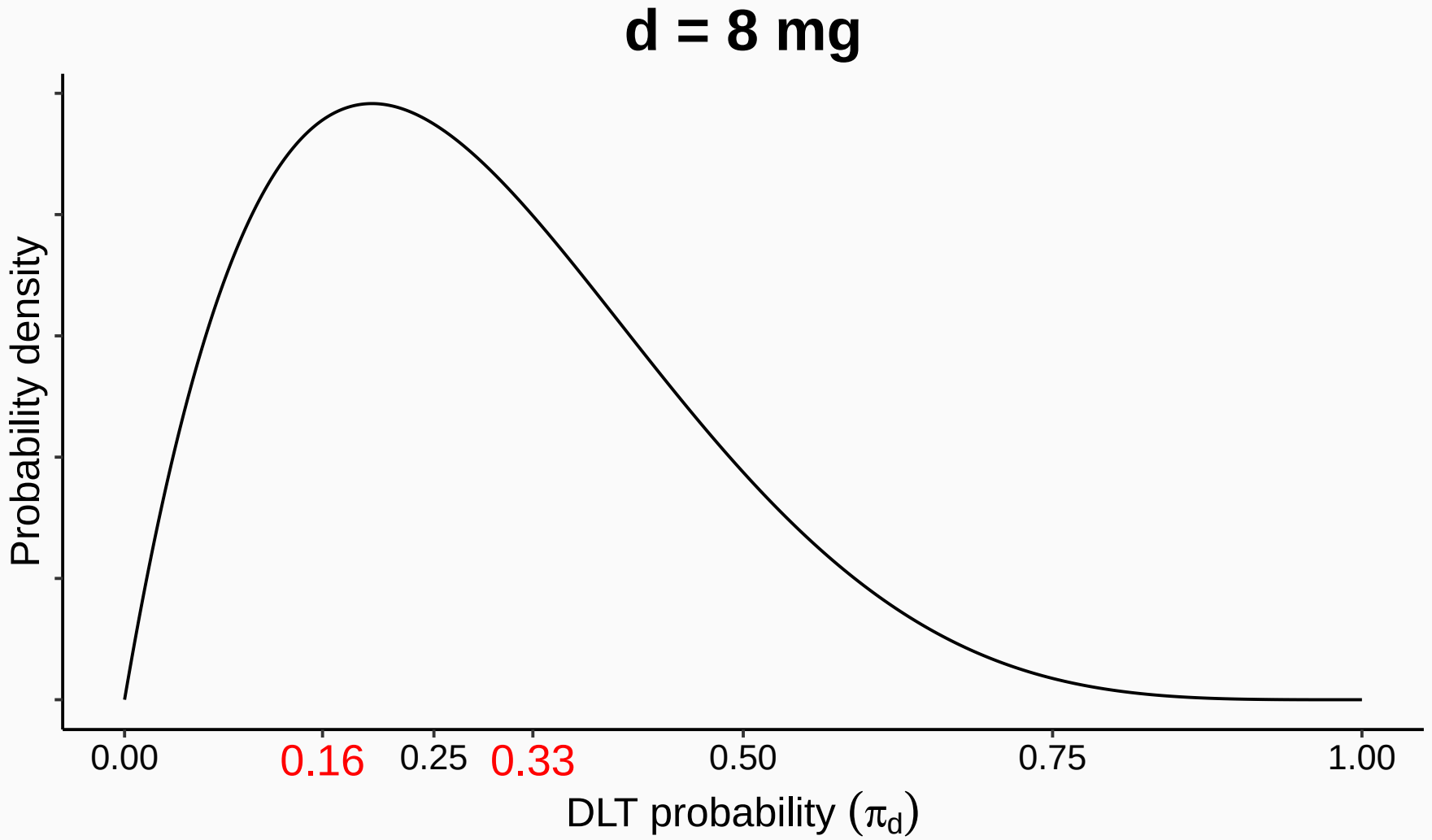

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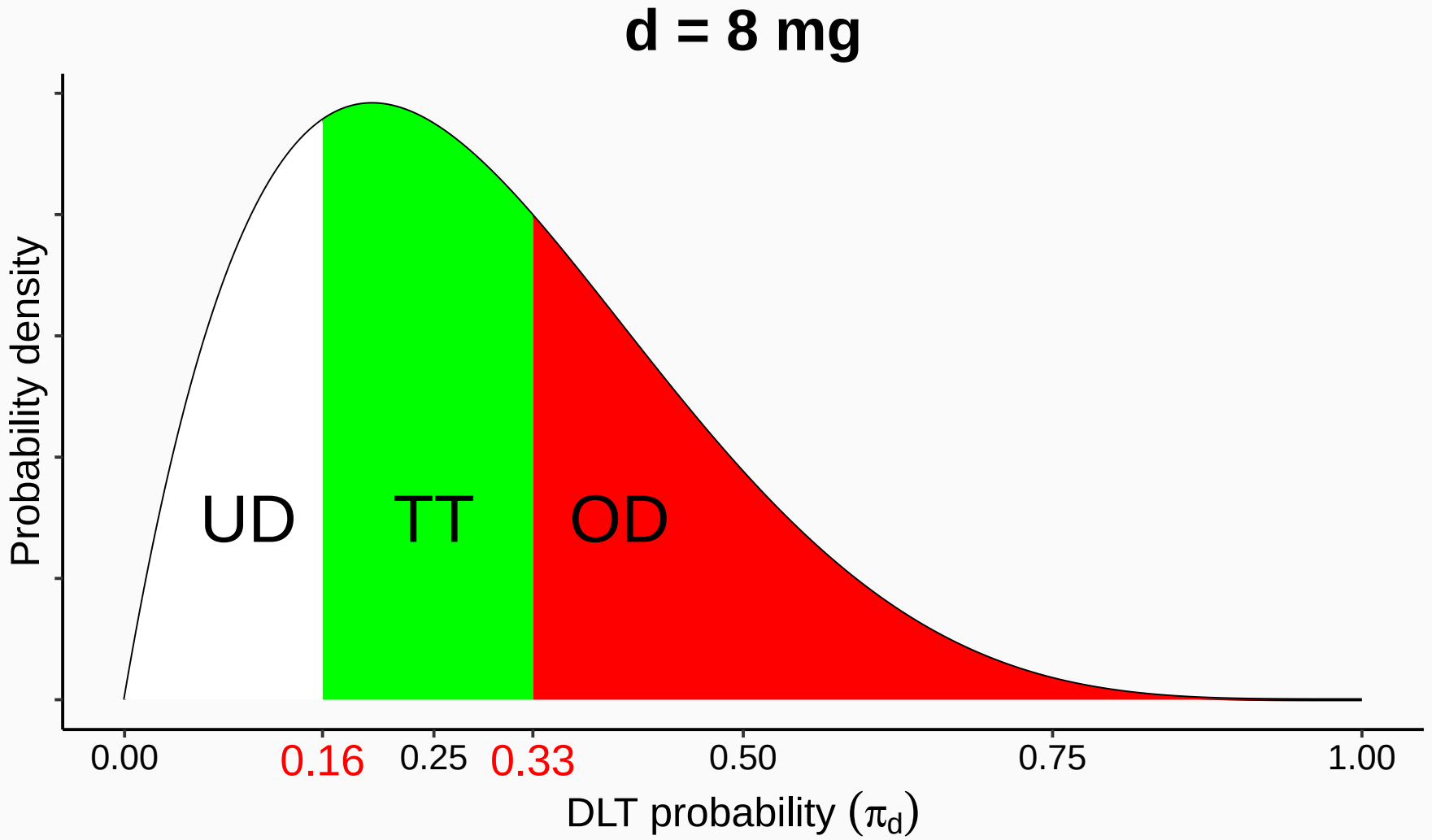

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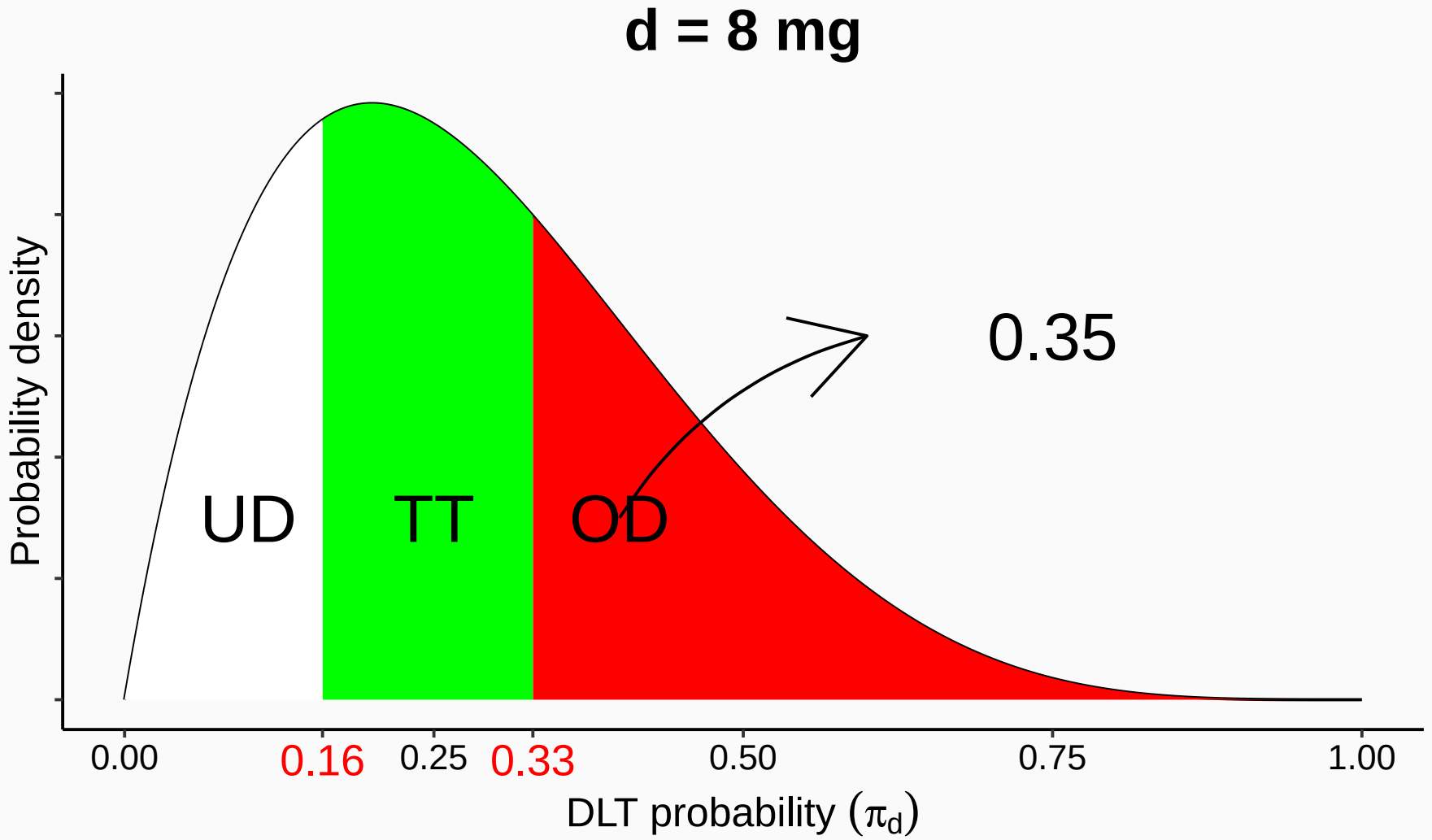

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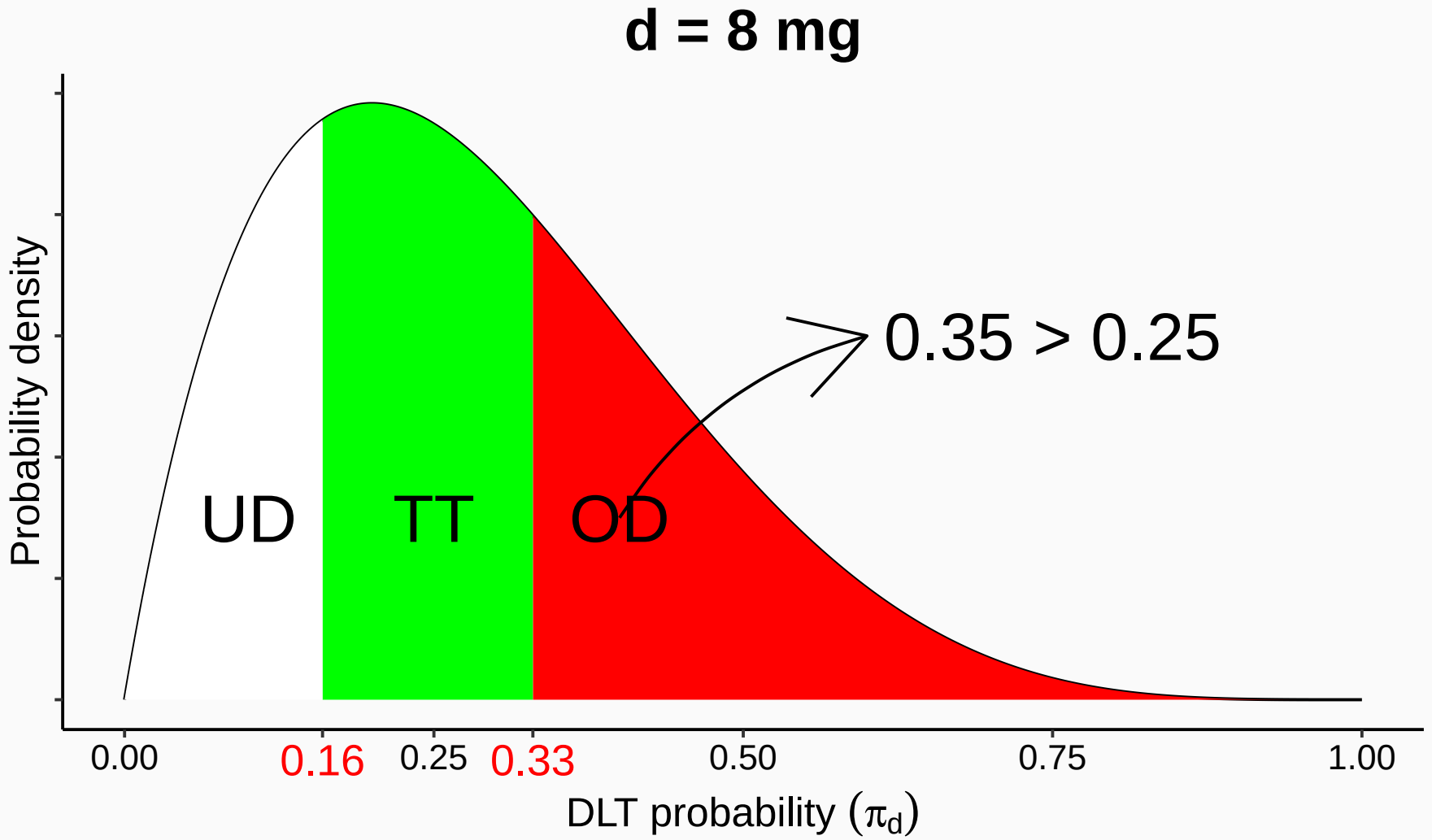

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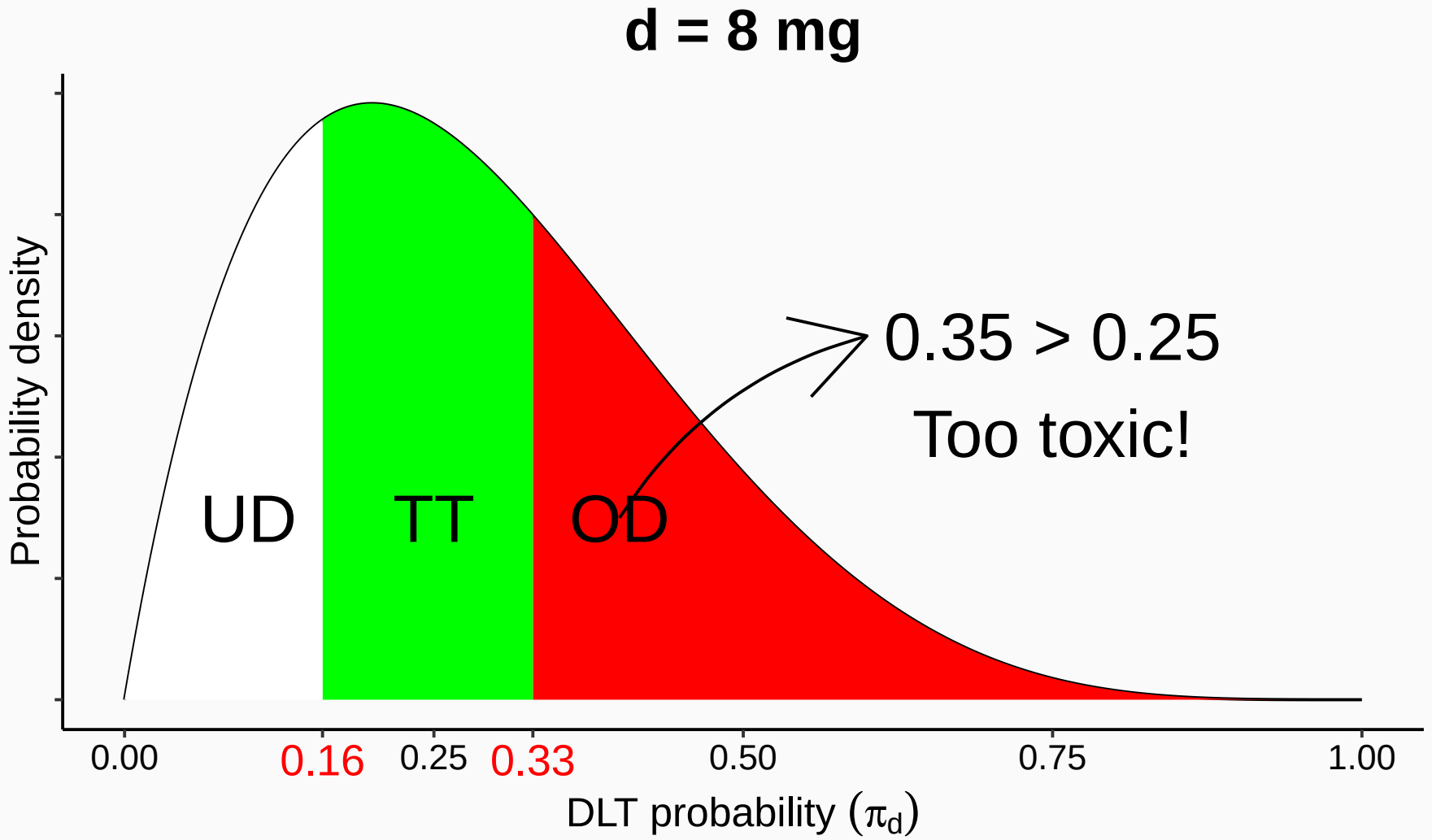

More than one dosing regimen

- Weekly and daily regimens
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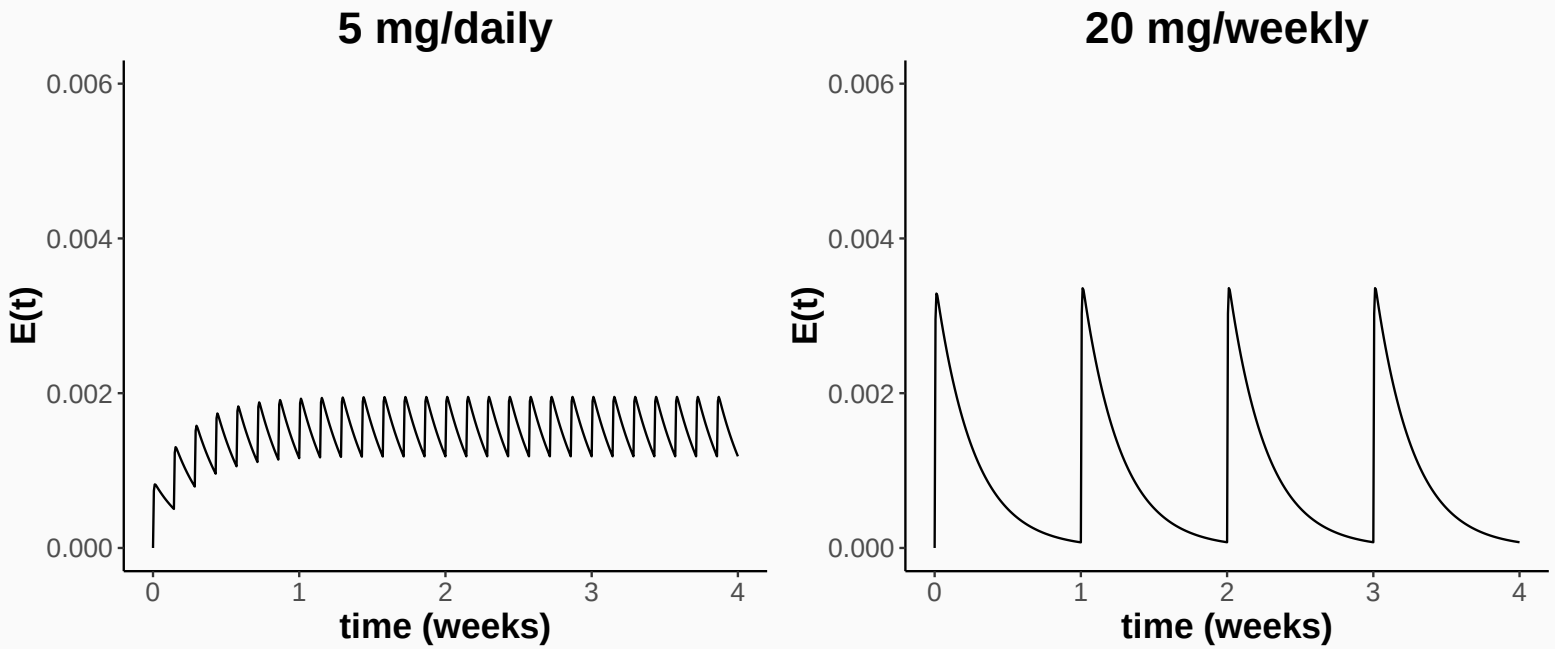
- Ad-hoc approach: BLRM MAP
  - BLRM is used for the first regimen.
  - Meta-analytic-predictive (MAP) prior is derived from analysis based on first regimen.
  - Then, MAP prior is used to analyse the second regimen.

TITE-PK

Time-to-event pharmacokinetic model (TITE-PK)

- Time-to-first-DLTs model using an **exposure** measure
- Exposure measure based on drug **pharmacokinetics**
- Use of planned dosing regimen and known PK parameters



Time-to-event pharmacokinetic model (TITE-PK) (cont.)

- A time-varying Poisson process
- Hazard is given by

$$\begin{aligned} h(t) &= \beta\, E(t) \\ \implies H(t) &= \beta\, \mathrm{AUC}_E(t). \end{aligned}$$

- Follow-up time until the end of cycle 1 (t^*)
- Dosing regimen (amount d and frequency f)
- End-of-cycle 1 DLT probability

$$\begin{aligned} P(T \leq t^* | d, f) &= 1 - S(t^* | d, f) \\ S(t^* | d, f) &= \exp(-H(t^* | d, f)) \end{aligned}$$

Time-to-event pharmacokinetic model (TITE-PK) (cont.)

- $E(t)$ is scaled using **reference regimen** (d^* and f^*) at t^*:

$$\text{AUC}_E(t^*|d^*, f^*) = 1.$$

- Analogous to reference dose in the BLRM

- Crucial for prior specification

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- TITE-PK is implemented in **Stan**.

Simulations

Settings

- Comparison of the performance: TITE-PK vs BLRM
- Data generation under each model separately
- Using exactly same **decision criteria**

  $r_d \geq 6$ where d is declared as the MTD, etc.

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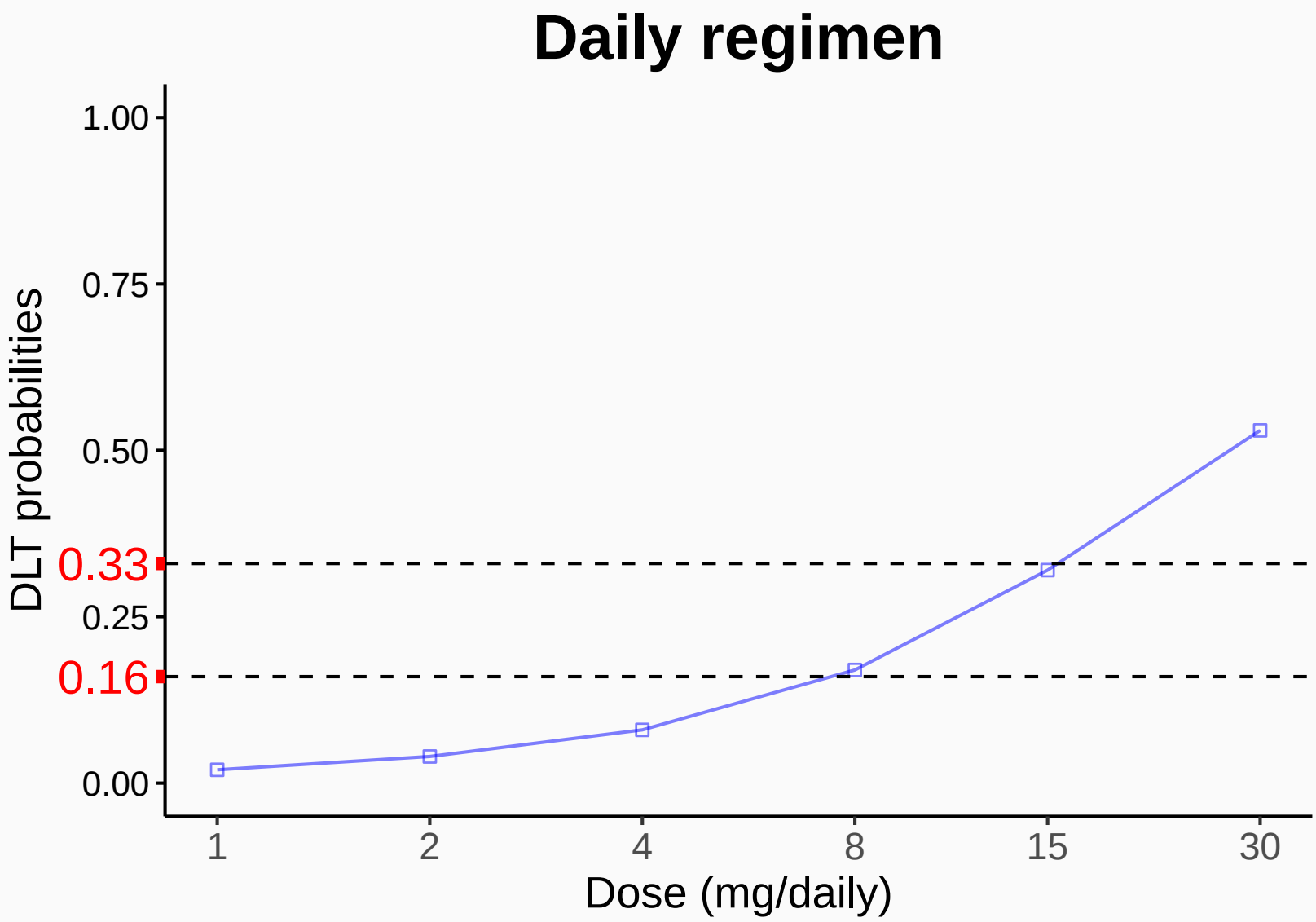
- Using exactly same **decision criteria**

  $r_d \geq 6$ where d is declared as the MTD, etc.
- Consider two different set of scenarios
  - **Only** daily regimen

    1, 2, 4, 8, 15, 30 mg/daily
  - Firstly weekly regimen, then daily regimen

    8, 16, 32, 64, 115, 230 mg/weekly
- Choice of prior: Matching a priori DLT probabilities

Dose-toxicity scenarios



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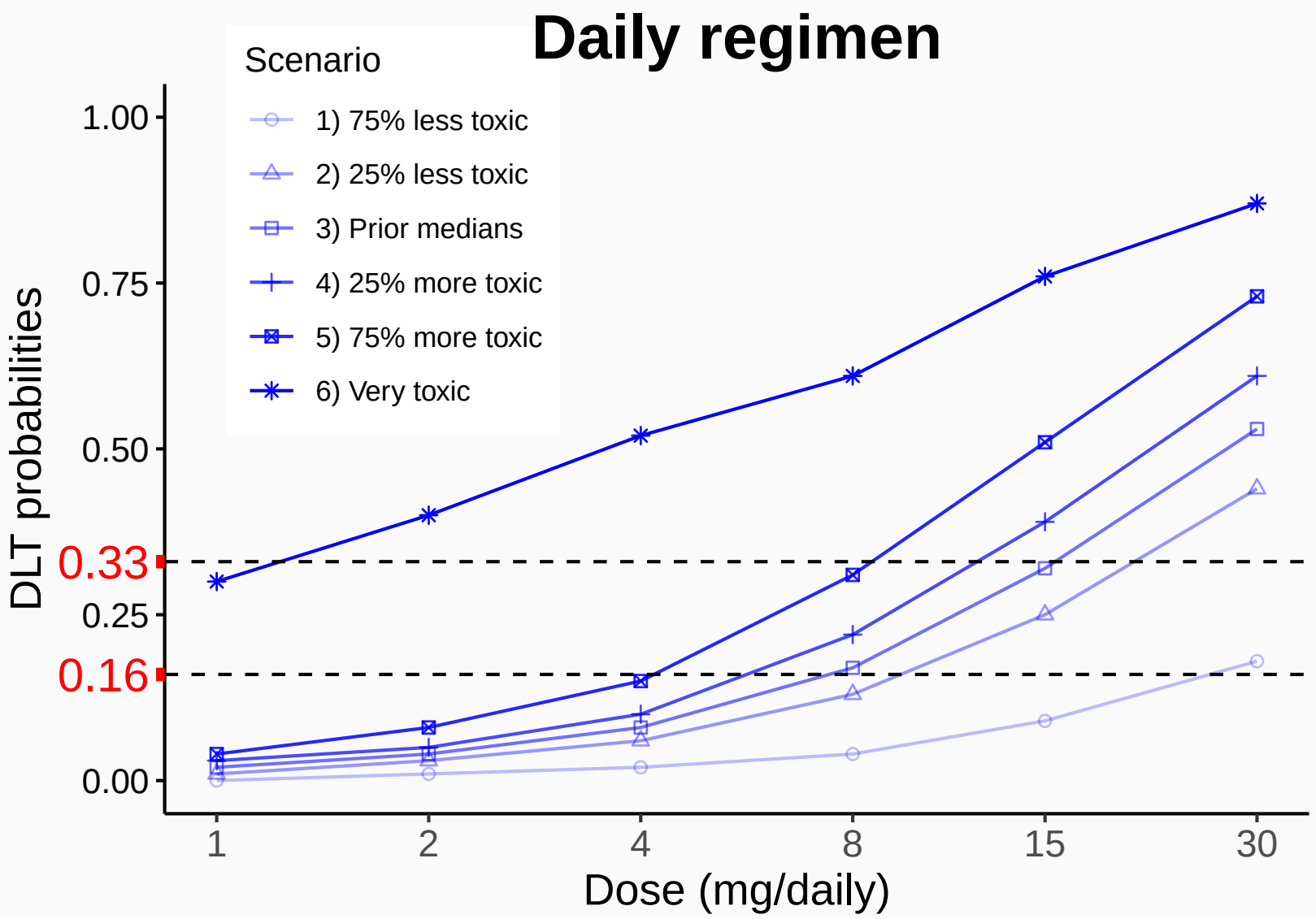

Performance measures

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IV. Proportion of trials with MTD in UD ($< 16\%$)

V. Proportion of trials with MTD in TT ($16\% - 33\%$)

VI. Proportion of trials with MTD in OD ($\geq 33\%$)

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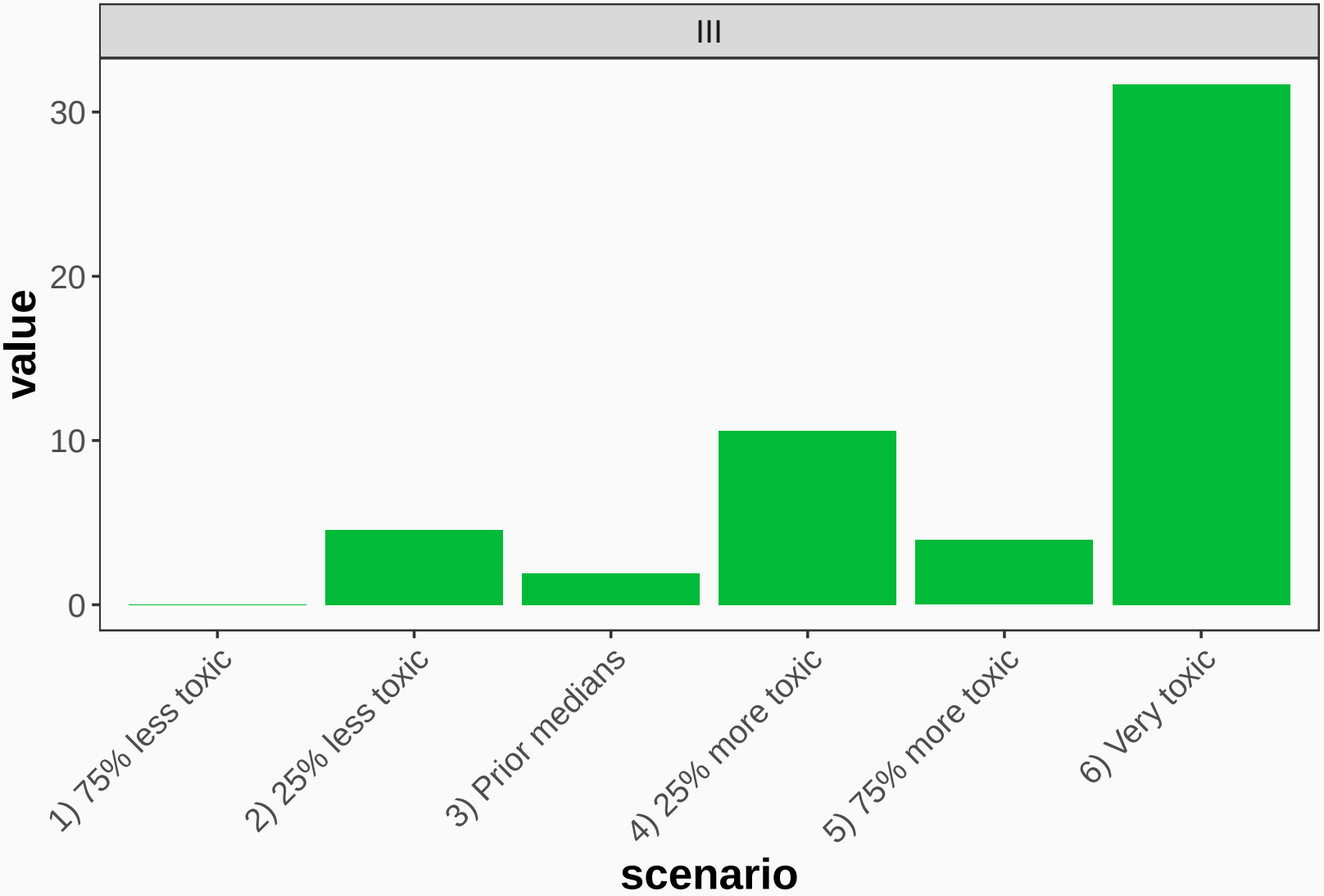
Stopped (eg. too toxic)

Average N

Average DLT

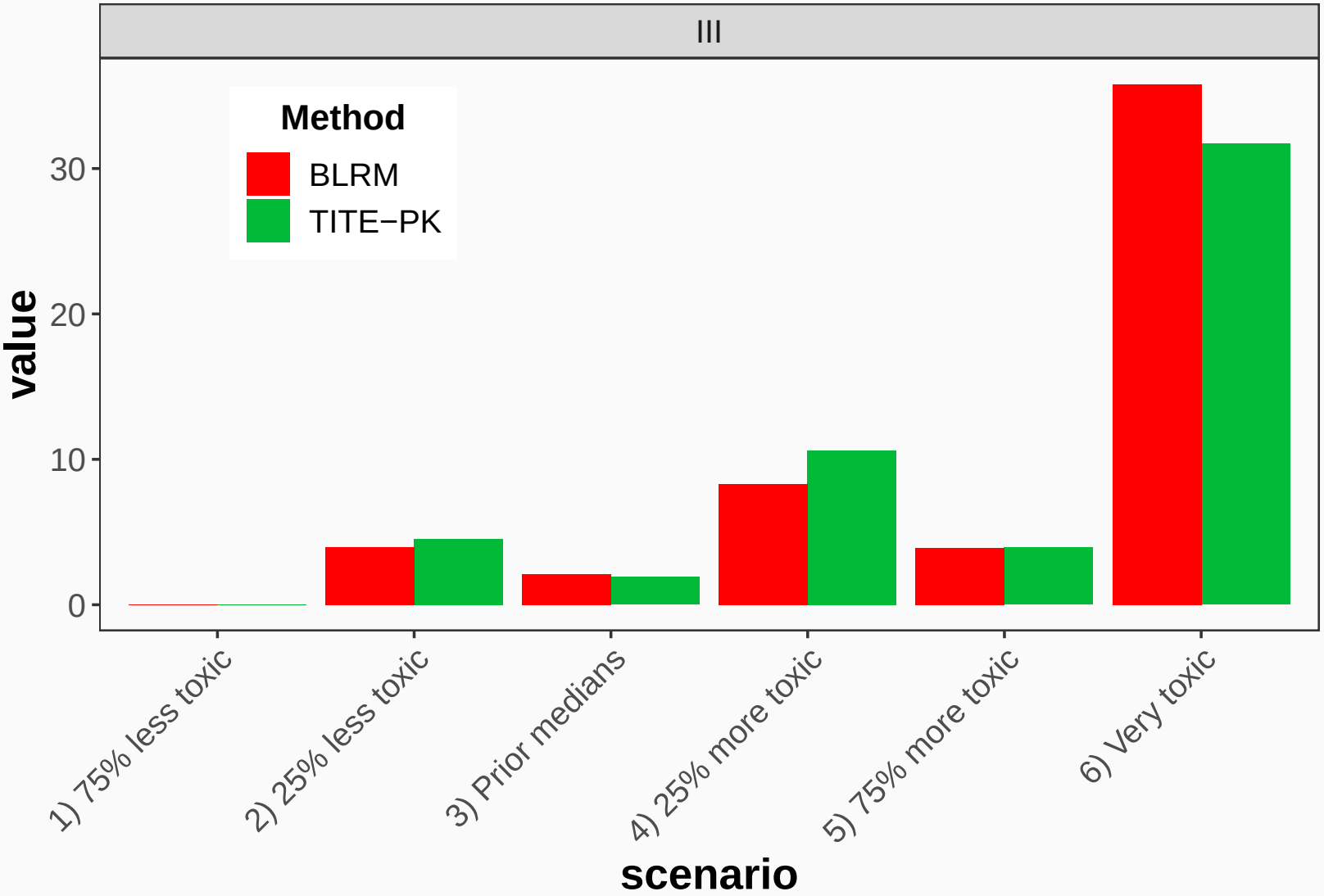
Results

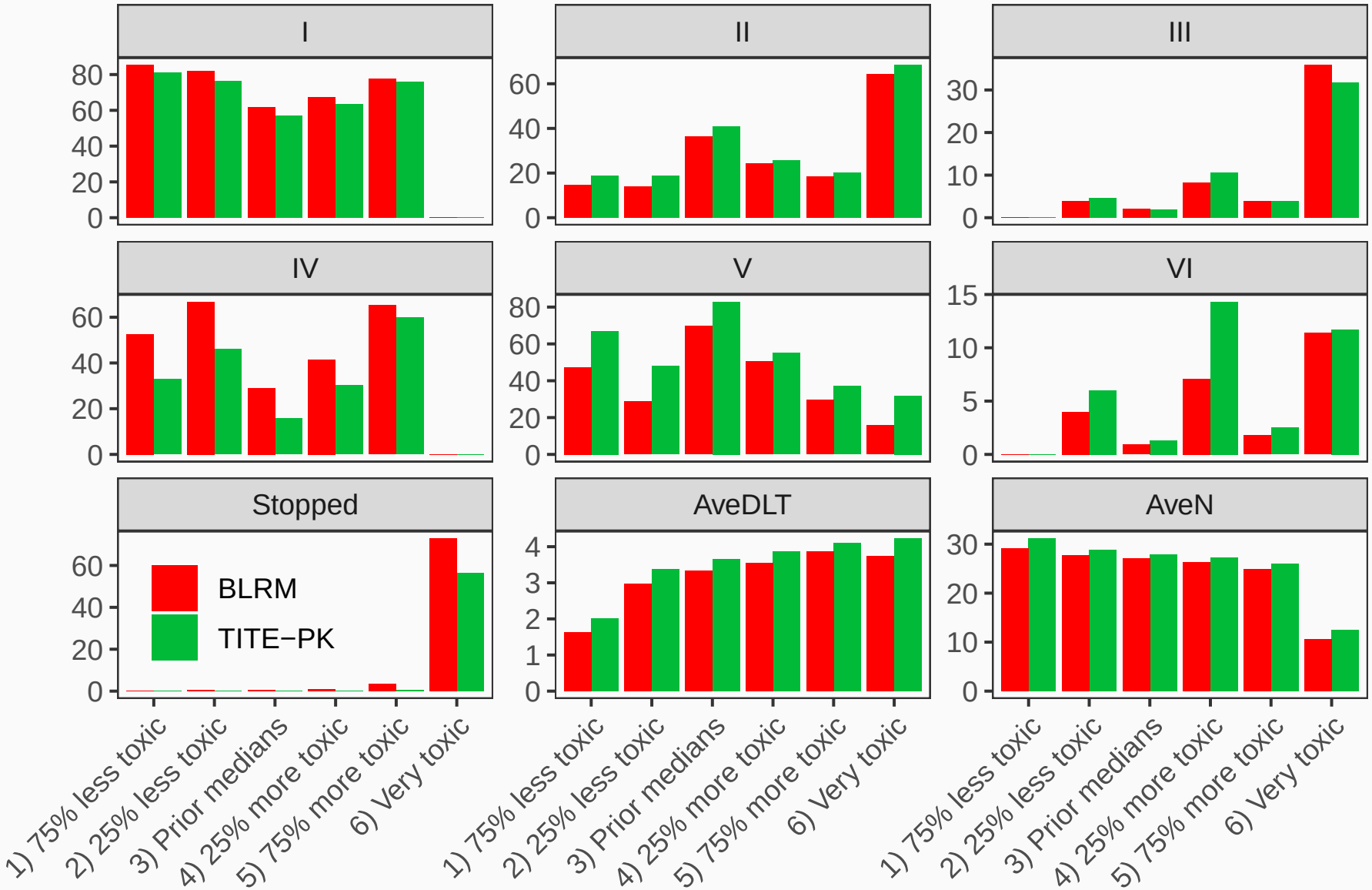
Measure III: Average proportion of patients in OD ($\geq 33\%$)



Results: TITE-PK vs BLRM

Measure III: Average proportion of patients in OD ($\geq 33\%$)





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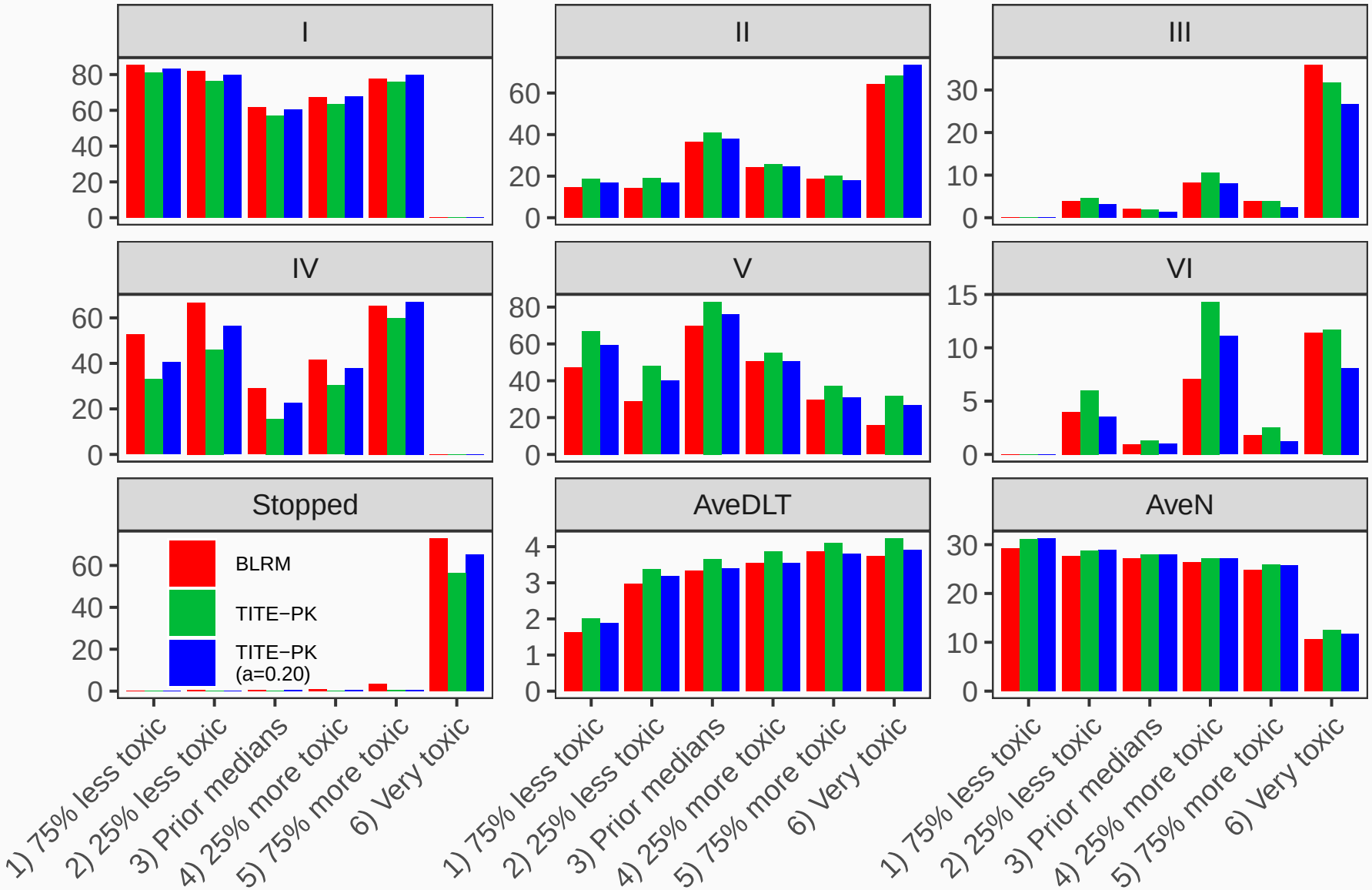
IV. Trials with MTD in UD V. Trials with MTD in TT VI. Trials with MTD in OD



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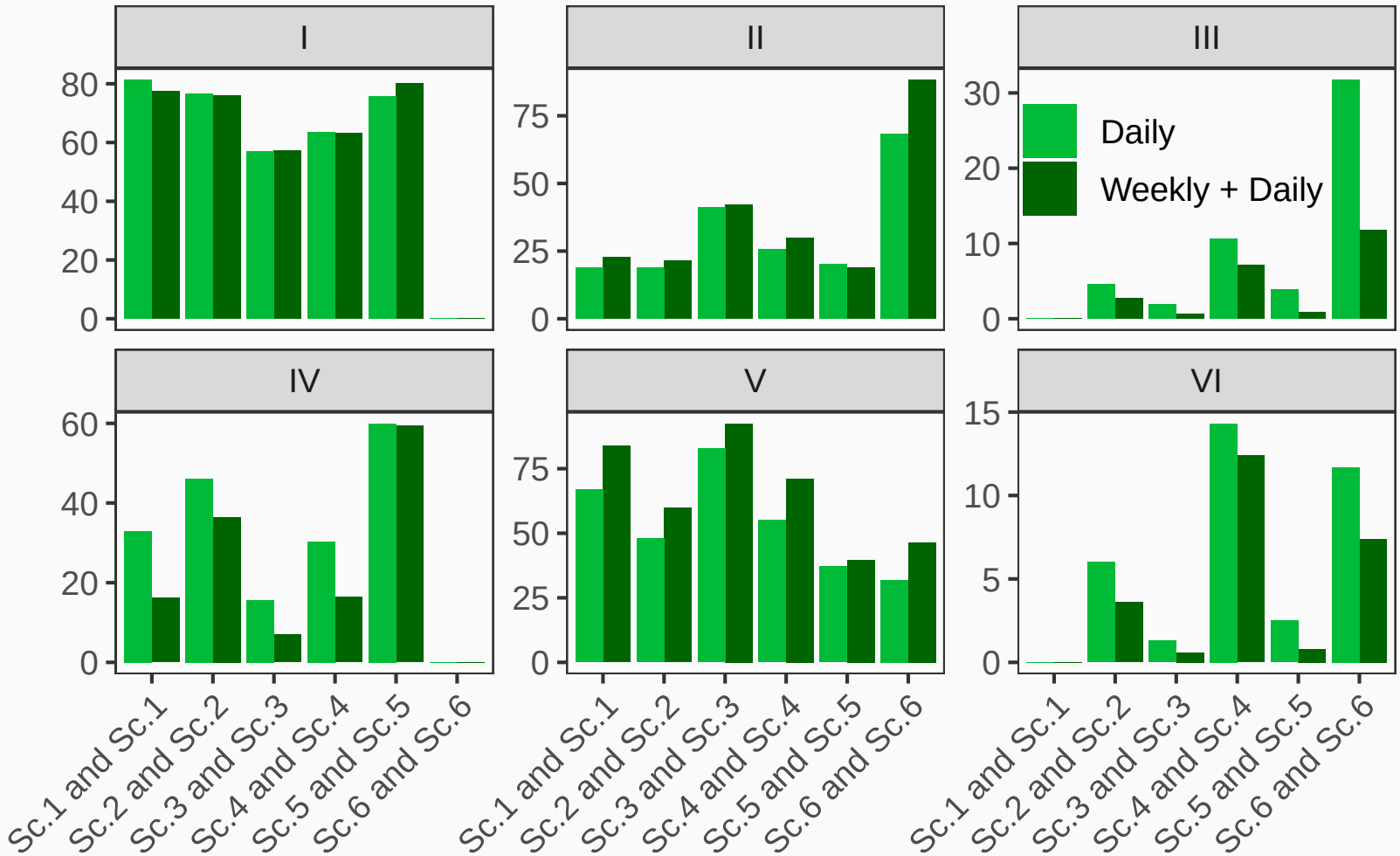
Weekly + Daily regimen: TITE-PK



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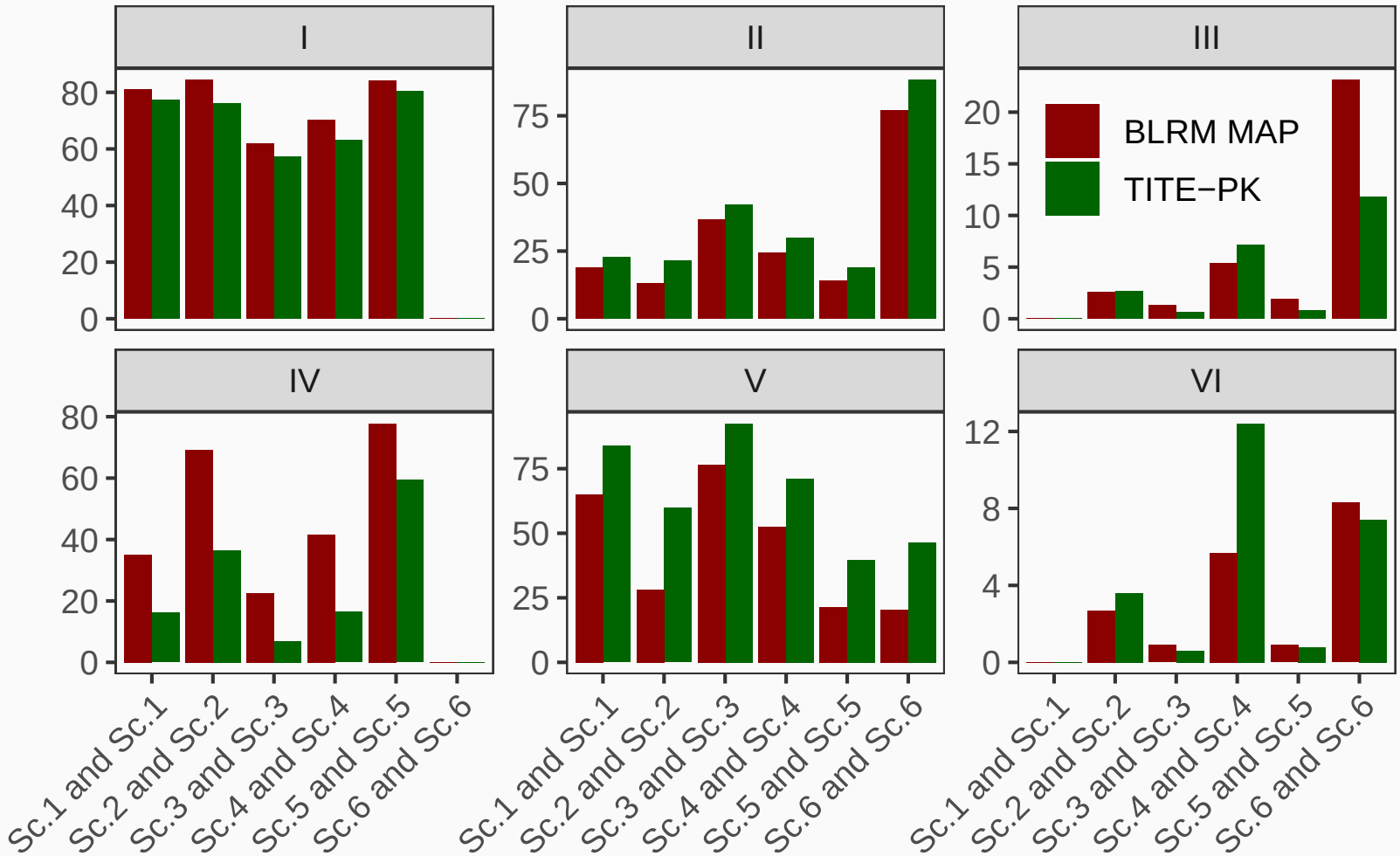
Weekly + Daily regimen: TITE-PK vs BLRM MAP



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Discussions

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- TITE-PK displays desirable performance in simulations
- Preserves advantages of BLRM (e.g. interpretable parameters, EWOC principle)
- Allows trials with dose regimen changes using PK principles
- Takes into account timing of DLTs

Discussions

- TITE-PK displays desirable performance in simulations
- Preserves advantages of BLRM (e.g. interpretable parameters, EWOC principle)
- Allows trials with dose regimen changes using PK principles
- Takes into account timing of DLTs
- A Bayesian adaptive model to support the design and analysis of phase I dose-escalation trials

Possible extensions

- Multiple compounds
- Usage of MAP prior
- Long-term safety events

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- Multiple compounds
- Usage of MAP prior
- Long-term safety events
- A motivating example is discussed in our preprint (arXiv:1811.09433)
- Code: https://github.com/gunhanb/TITEPK_code

References

Carpenter, B., Gelman, A., Hoffman, M., Lee, D., Goodrich, B., Betancourt, M., Brubaker, M., Guo, J., Li, P., and Riddell, A. (2017). Stan: A probabilistic programming language. *Journal of Statistical Software, Articles*, 76(1):1–32.

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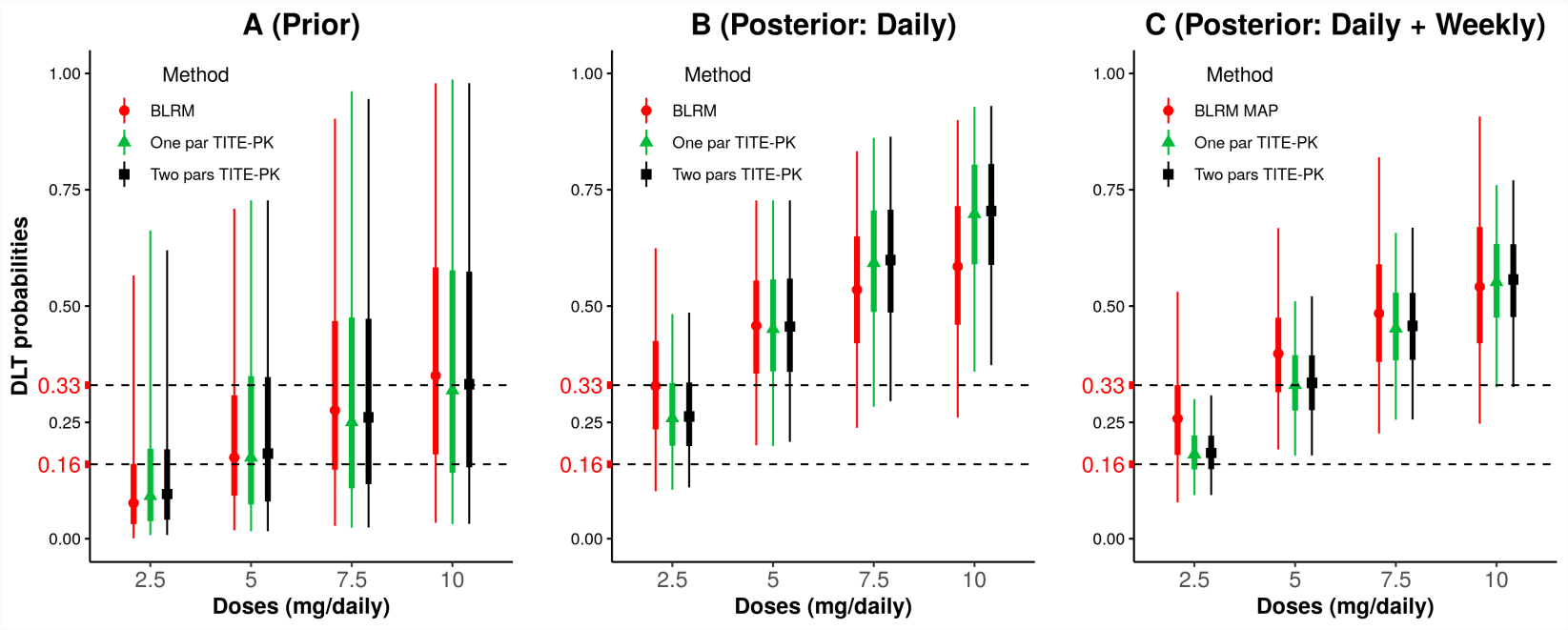
Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D., and Neuenschwander, B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, 70(4):1023–1032.

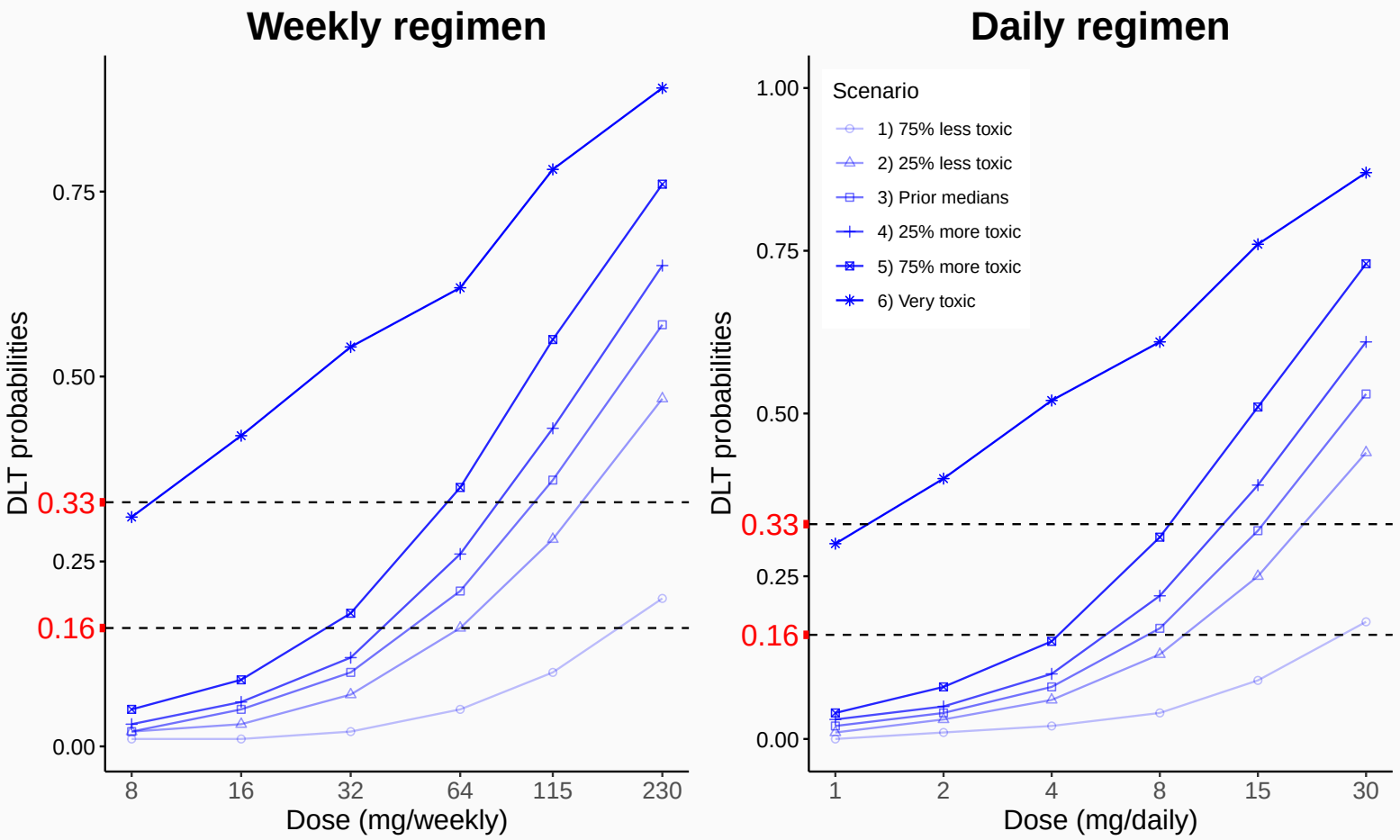
Application: Everolimus



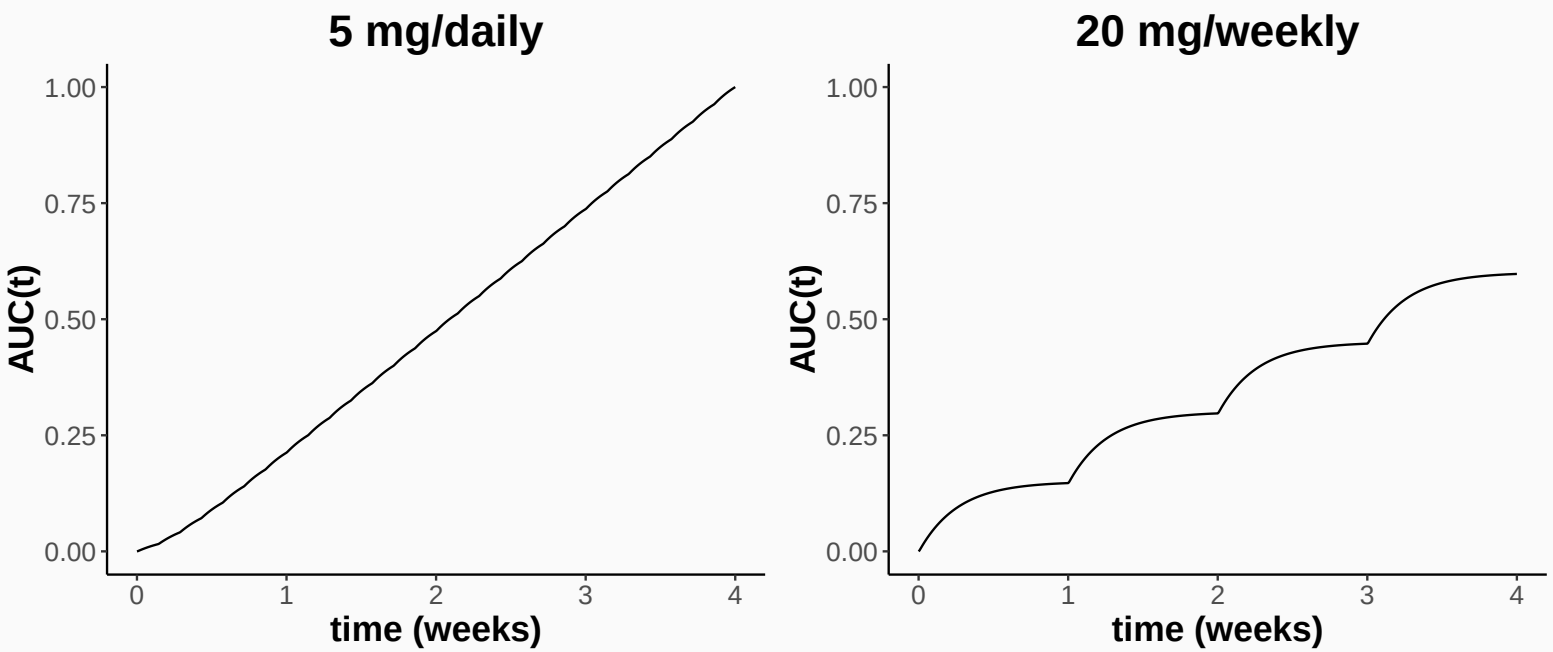
Dose-escalation decision criteria

- Cohort sizes randomly from (3, 4, 5, 6)
- Next dose / Current dose ≤ 2
- Minimum number of patients at MTD: 6
- Maximum number of patients: 60
- Minimum number of patients: 21
- MTD declaration: $P(OD) \leq 0.25$ and $P(TT) \geq 0.50$

Weekly + Daily regimen: Scenario



AUC


5 mg/daily
20 mg/weekly
AUC(t)
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
time (weeks)

Priors

- BLRM: BVN prior with following parameters:
  $(m_1 = \text{logit}(\pi_{d^*} = 0.175), m_2 = 0, s_1 = 2, s_2 = 1, \rho = 0)$
- TITE-PK: $\log(\beta) \sim \mathcal{N}(\text{cloglog}(P(T \leq t^* | d^*, f^*) = 0.175), 1.75^2)$.