MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Designing Phase I Single Agent Dose-Escalation Studies

Lecture 2: Model-based dose-escalation designs

Pavel Mozgunov & Thomas Jaki

MRC Biostatistics Unit

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Single-Agent Dose-Finding Study

k increasing doses : $d_1 < d_2 < \cdots < d_k$

Response: $x = \begin{cases} 1 \text{ if a patient experienced a DLT} \\ 0 \text{ otherwise} \end{cases}$

Structure: treat successive cohorts of c subjects

Objective: find the “highest safe dose”

Based on the monotonicity assumption: “**the more the better**”:

Both toxicity and efficacy increase with the dose.

Phase I in-patient trials

- Typically implemented as adaptive designs:

Dose (mg)	1	2.5	5	10	15	20	25
# patients	3	3	3				
# DLT	0	0	1				

- What dose should be selected for the next cohort?
  1. More patients on the same dose (5mg)
  2. More patients on a lower dose (2.5mg)?
  3. Patients on a higher dose (10mg)?

- A good design will achieve
  - a high probability of the true MTD selection
  - most patients being treated on the MTD
  - few patients being overdosed

Phase I designs for in-patient trials

- **Rule-based** designs
  - No statistical inference
  - Popular among clinicians
  - Poor statistical properties (“operating characteristics”)
- **Model-based** designs
  - Use a simple model for the dose-toxicity relationship
  - Good operating characteristics
  - Might lead to non-intuitive escalations/de-escalations
- **Model-assisted** designs
  - Do not impose a particular “shape” on the dose-response
  - Use a statistical model
  - Still based on the monotonicity and a set of up-and-down rules

Seeking a quantile

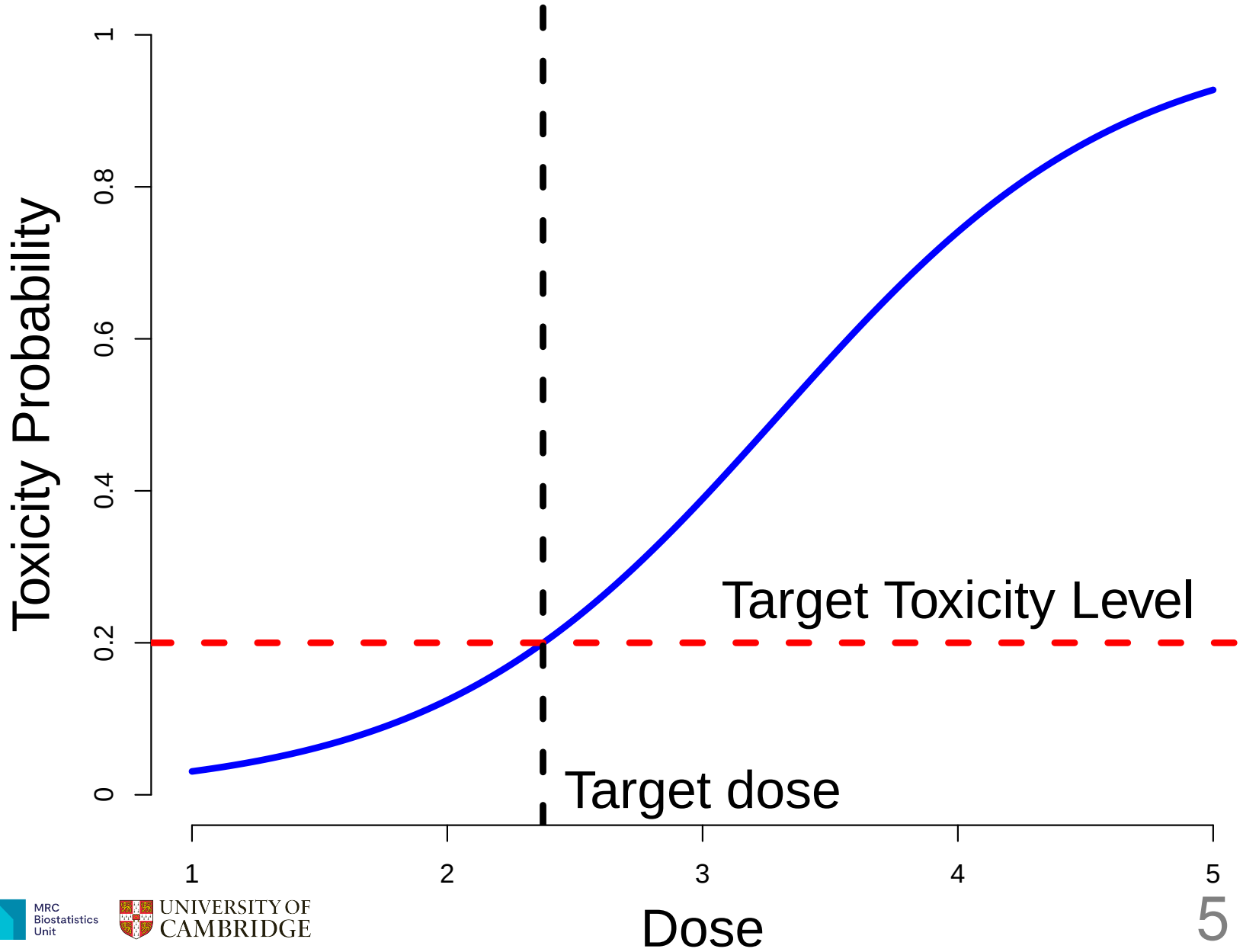
MTD – maximal dose acceptably tolerated by a particular patient population

$\rightarrow$ vague

*TD*100θ – dose at which the probability of toxicity is θ (for $0 < \theta < 1$), e.g. TD20

$\rightarrow$ more specific

TD20


Toxicity Probability
0
0.2
0.4
0.6
0.8
1
Target Toxicity Level
Target dose
1
2
3
4
5
Dose

A Bayesian inference for Phase I trials

- Due to a small sample size, it is common to use Bayesian inference in early phase dose-escalation trials;
- Bayesian paradigm: Posterior $\propto$ Data $\times$ Prior
- Let α be the parameter of interest with prior distribution $f_0(\alpha)$.
- The observations are $\mathbf{x} = \{x_1, x_2, \ldots, x_n\}$;
- The likelihood function $L(\mathbf{x}|\alpha)$ is the distribution of $\mathbf{x}$ conditional on specific values of α.

Then:

$$f(\alpha|\mathbf{x}) = \frac{f(\mathbf{x}|\alpha)f_0(\alpha)}{f(\mathbf{x})}$$

A Bayesian model-based design

Planning a trial:

1. Choose doses $d_1, \ldots, d_k$;
2. Choose a form of dose-response relationship $p(d_i, \alpha)$ where α are model parameters;
3. Impose a prior distribution for α;
4. Choose a criterion to allocate patients;
5. Choose stopping rules

A Bayesian model-based design

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Conducting a trial:

1. Sequentially update estimates of α ;
2. Select the dose for the next cohort using the criterion;
3. Stop if at least one of the stopping rules is met.

Continual Reassessment Method (CRM)

Response: $x = \begin{cases} 1 \text{ if a patient experienced a DLT} \\ 0 \text{ otherwise} \end{cases}$

Model: $p(\pi_i, \alpha) = \pi_i^{exp(\alpha)}$

Skeleton: π_i is a prior guess of the DLT risk

Prior on α: Normal $\alpha \sim \mathcal{N}(\mu, \sigma^2)$

Allocation Rule: min $|p(\pi_i, \hat{\alpha}) - \theta|$ where $\hat{\alpha} = \mathbb{E}(\alpha)$

Bayesian updating

1. Specify the prior distribution of α
2. Assign the first cohort to the starting dose (e.g. prior MTD)
3. Given the data, update the distribution of α

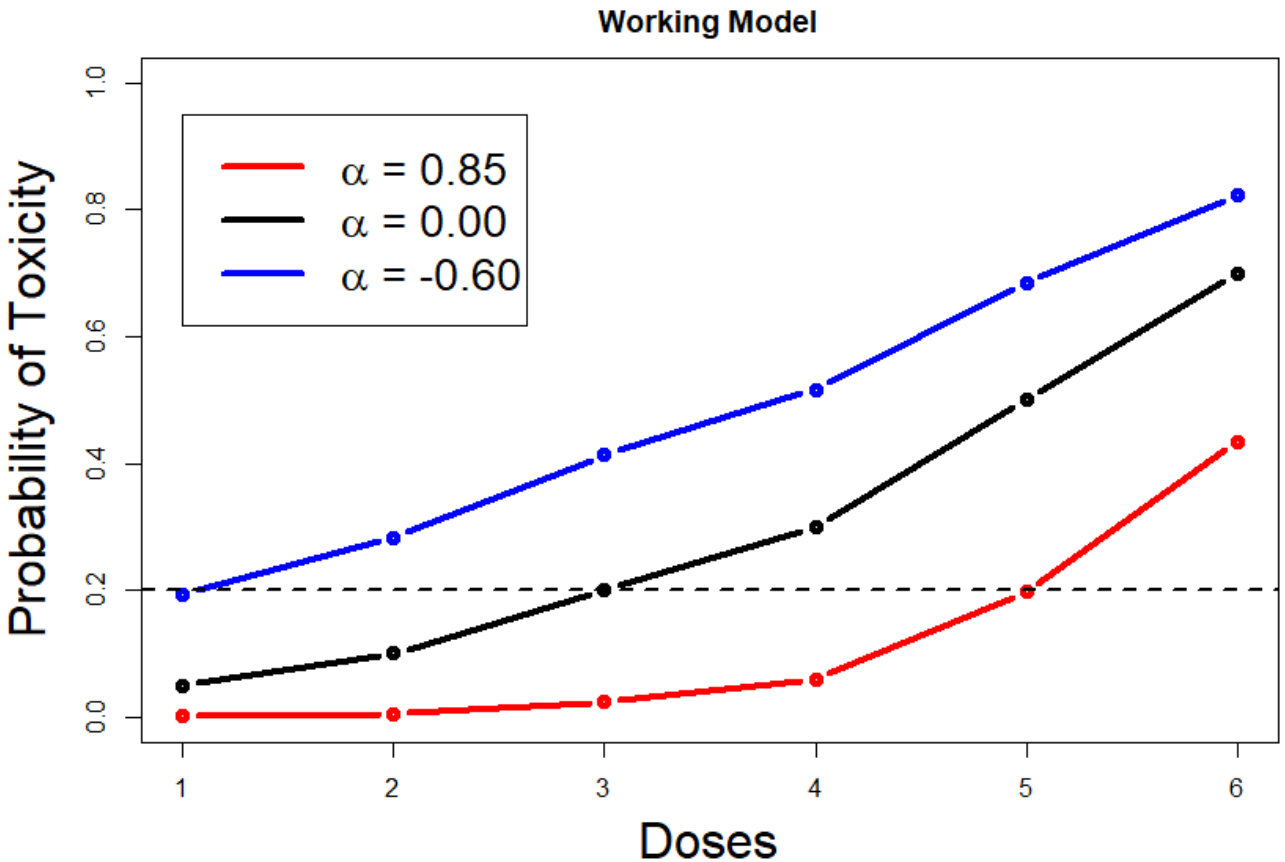
$$\text{Posterior} \propto \text{Prior} \times \text{Data}$$

4. Find the estimate of α: $\hat{\alpha}$
5. Find estimates of toxicity probabilities as $\hat{p}_i = \pi_i^{\exp(\hat{\alpha})}$
6. Allocate the next cohort to the dose having the estimated toxicity closest to the target level θ.
7. Repeat steps 3-6

Representation of the model

Values for π_i

π_1	π_2	π_3	π_4	π_5	π_6
0.05	0.10	0.20	0.30	0.50	0.70



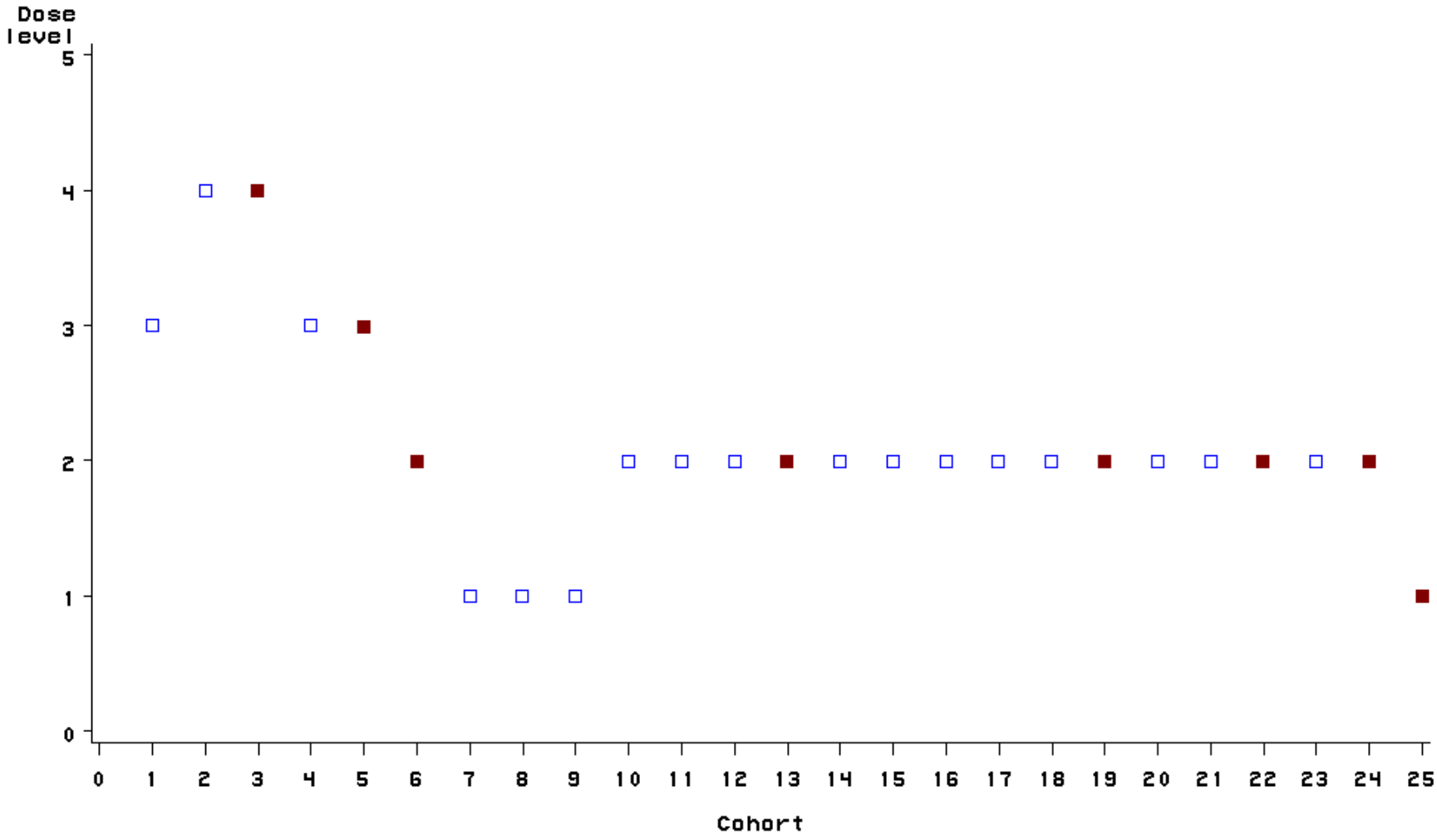
Example

Assign values for π_i

π_1	π_2	π_3	π_4	π_5	π_6
0.05	0.10	0.20	0.30	0.50	0.70

Thus first subject receives d_3

Simulated data



Criticisms of the original CRM

Criticisms:

- Starting dose is usually high;
- Treats too many subjects on high doses (too aggressive);
- Doses can be skipped;
- No appropriate stopping rule.

Modifications:

- Start at the lowest dose;
- Safety constraints;
- Alternative allocation rules;
- No dose skipping;
- Formal stopping rules.

Choice of the model

- Pre-defined skeleton $\pi_i, i = 1, \ldots, k$
  - could be elicited from the clinicians on the trial;
  - could be chosen by statisticians (operational skeleton);
- For CRM, prior for $\alpha \sim \mathcal{N}(0, 1.34^2)$ often leads to good OC;
- CRM is very quick to evaluate and run
- Although, the one-parameter model might not reflect the true dose-toxicity relationship...
- we are interested in the **single point**, the MTD, and the one-parameter model is rich enough for this goal
- If questions beyond the MTD identification to be considered - alternative models can provide a better answer.

Bayesian Logistic Regression Model (BLRM)

Model (Version 1):

- $d_{(1)} < \cdots < d_{(k)}$ are doses;
- D_{ref} is a reference dose;

$$p(d_{(j)}, \alpha_1, \alpha_2) = \frac{\exp\{\alpha_1 + \alpha_2 \log \frac{d_{(j)}}{D_{ref}}\}}{1 + \exp\{\alpha_1 + \alpha_2 \log \frac{d_{(j)}}{D_{ref}}\}}$$

- (α_1, α_2) are parameters to be estimated
- requires **prior** distribution on (α_1, α_2)

Bayesian Logistic Regression Model (BLRM)

Model (Version 2):

- $\tilde{d}_j$ are standardised doses (skeleton) obtained from the prior guesses of the DLT risk at each dose;

$$p(\tilde{d}_j, \alpha_1, \alpha_2) = \frac{\exp\{\alpha_1 + \alpha_2 \tilde{d}_j\}}{1 + \exp\{\alpha_1 + \alpha_2 \tilde{d}_j\}}$$

- $\hat{p}_j^{(0)}$ are prior estimates of the DLT probabilities associated with doses d_j $j = 0, \ldots, m$

$$\tilde{d}_j = \frac{\text{logit}(\hat{p}_j^{(0)}) - \hat{\alpha}_1^{(0)}}{\hat{\alpha}_2^{(0)}}$$

- $\hat{\alpha}_1^{(0)}$, $\hat{\alpha}_2^{(0)}$ are prior point estimates of the model parameters;

Ways to include prior information (I)

Approach 1 by Neuenschwander *et al.* (2008)

- Specify two quantiles for toxicity probabilities at all doses
- Define prior distribution for $(\alpha_1;\ \alpha_2)$ such that they are in close agreement with the above

Ways to include prior information (II)

Approach 3 by Whitehead & Williamson (1998)

- Specify two dose levels (the lowest and the highest)
- Illicit probability of toxicity at these levels from experts and determine how many patients this information is worth
- Include “pseudo-patients” in analysis based on above - no need in specifying the prior for $(\alpha_1;\ \alpha_2)$

For example, the clinicians’ believe that

- Toxicity risk at the lowest dose is 20%;
- Confidence in this response rate is equivalent to having 5 patients at the lowest dose;
- Toxicity risk at the highest dose is 40%;
- Confidence in this response rate is equivalent to having 1 patient at the highest dose;

Allocation Criteria

- Escalation with Overdose Control (EWOC) and modifications:

$$\mathbb{E}\left(\nu(\theta - p_i)^+ + (1-\nu)(p_i - \theta)^+\right) \quad \text{e.g.} \quad \nu = 0.25$$

- Convex Bounds Penalization (CIBP) Criterion:

$$\mathbb{E}\left(\frac{(p-\theta)^2}{p^\lambda(1-p)^{2-\lambda}}\right), \quad \lambda \quad - \quad \text{asymmetry parameter} \qquad (1)$$

- Loss function

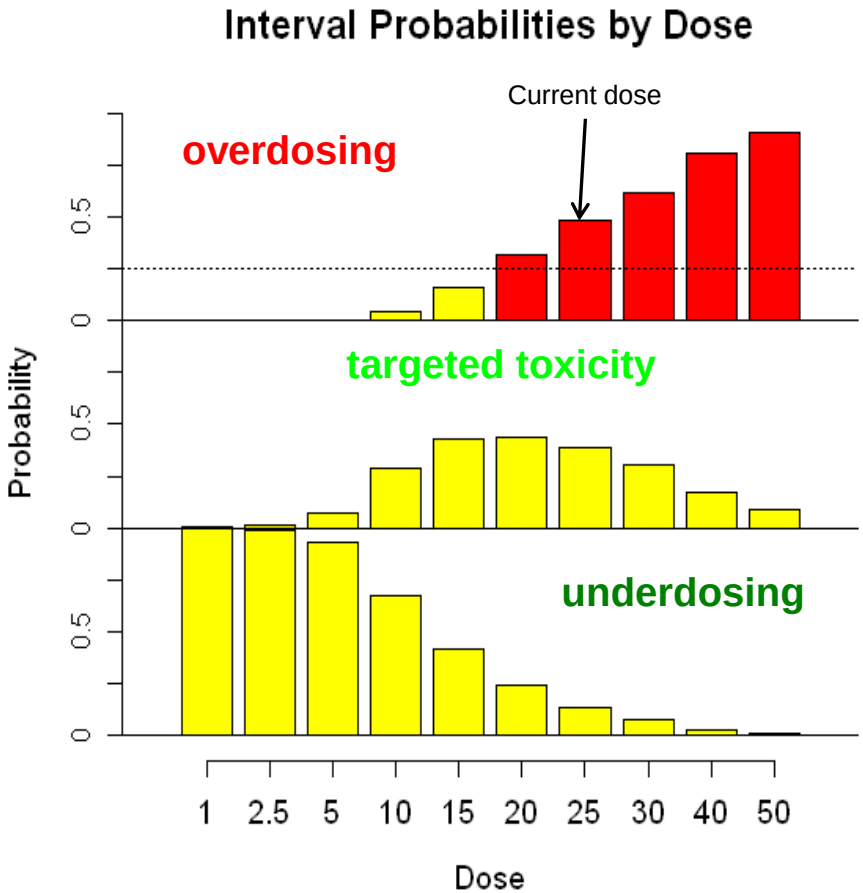
$$L = \begin{cases} 1 \text{ if } p \in (0.00, 0.20); & 0 \text{ if } p \in (0.20, 0.33) \\ 1 \text{ if } p \in (0.33, 0.50); & 2 \text{ if } p \in (0.50, 1.00) \end{cases}$$

- Maximising the probability of being in the target interval while safeguarding the patients

Interval Probability Criterion

Recommend dose such that

- probability of overdosing
  $P(p > 0.33 \mid d) < 0.25$
- probability of target toxicity
  $P(p \in (0.20; 0.33) \mid d) \rightarrow max$



Example

- open-label, multicenter, dose-escalation cancer trial
- Find dose that has 30% risk of toxicity, the TD30.
- Use CRM but do not allow for skipping dose levels
- After 4 cohorts (4 dose levels) no DLTs
- Team decides to skip 2 dose levels
- Two DLTs in two patients

Example

	Dose in mg									
	1	2.5	5	10	15	20	25	30	40	50
No. of patients	3	4	5	4	—	—	2	—	—	—
No. of DLTs	0	0	0	0	—	—	2	—	—	—
Posterior summaries:										
Mean	0.069	0.085	0.099	0.111	0.123	0.144	0.163	0.242	**0.330**	0.465
Std. dev.	0.055	0.062	0.068	0.072	0.076	0.082	0.087	0.101	0.109	0.108

Dose recommendation for next cohort:

- 3+3: Unclear
- CRM: 40mg
- BLRM: 15mg (from previous figure)

Comments

- BLRM is widely used in industry now;
- Specifying priors can be time consuming
- Running/Evaluating requires MCMC

One-parameter or Two-parameter model

- It depends...
- One needs to decide what question they are trying to answer.
  - MTD estimation only?
  - Does one want to know more about the dose-toxicity shape?
  - Are there any further research questions to be answered?
- These all will affect the choice of the model.

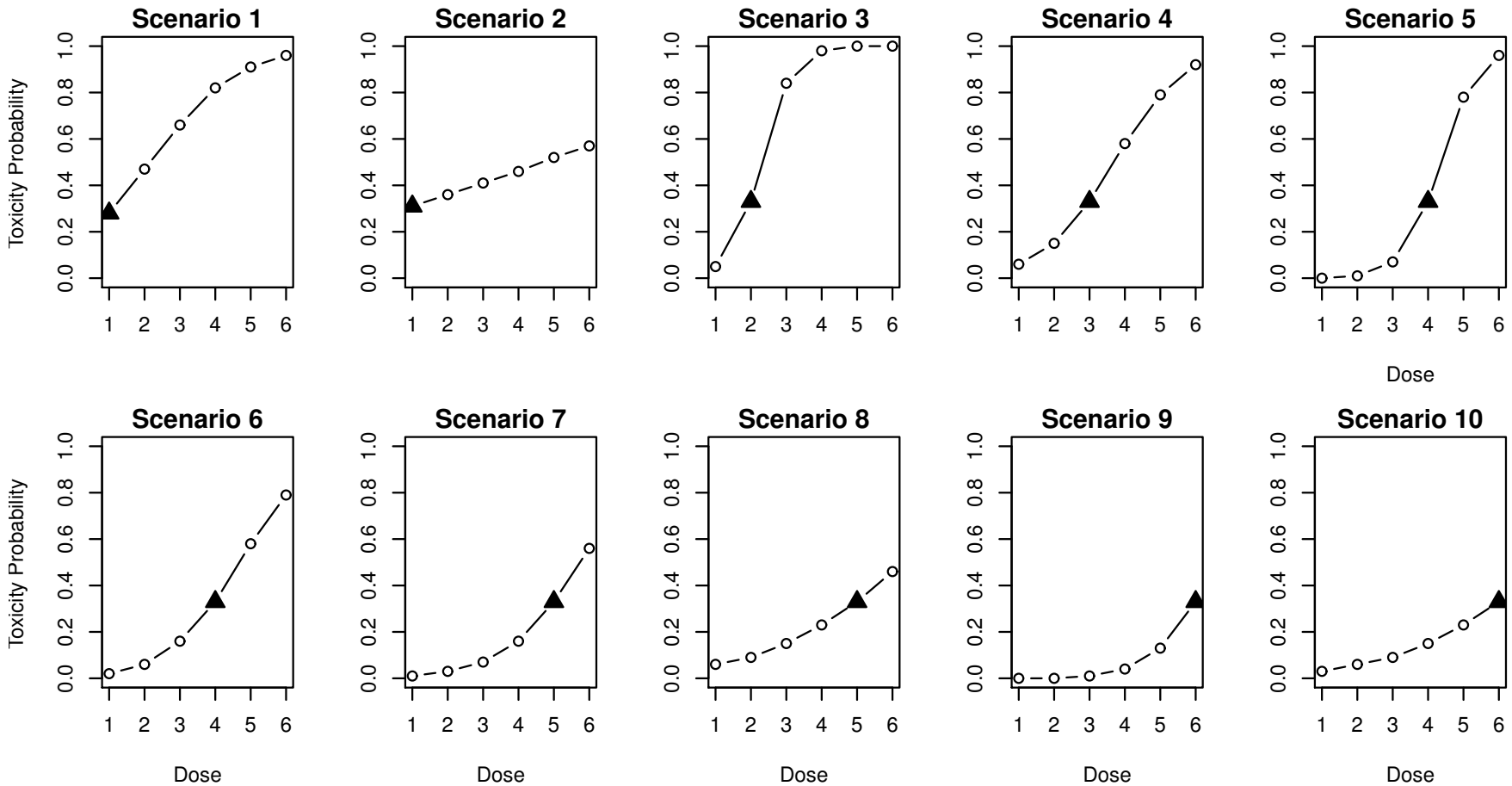
Simulation study: setting

- 6 dose levels; target toxicity level of 33%;
- Compare various model-based designs:
  - Original CRM;
  - CRM with modified criteria (asymmetry = 0.5,0.25,0.10);
  - BLRM with loss function;
  - EWOC;
  - Modified EWOC (TDFB & TR);
- Assessed in terms of
  - Accuracy Index;

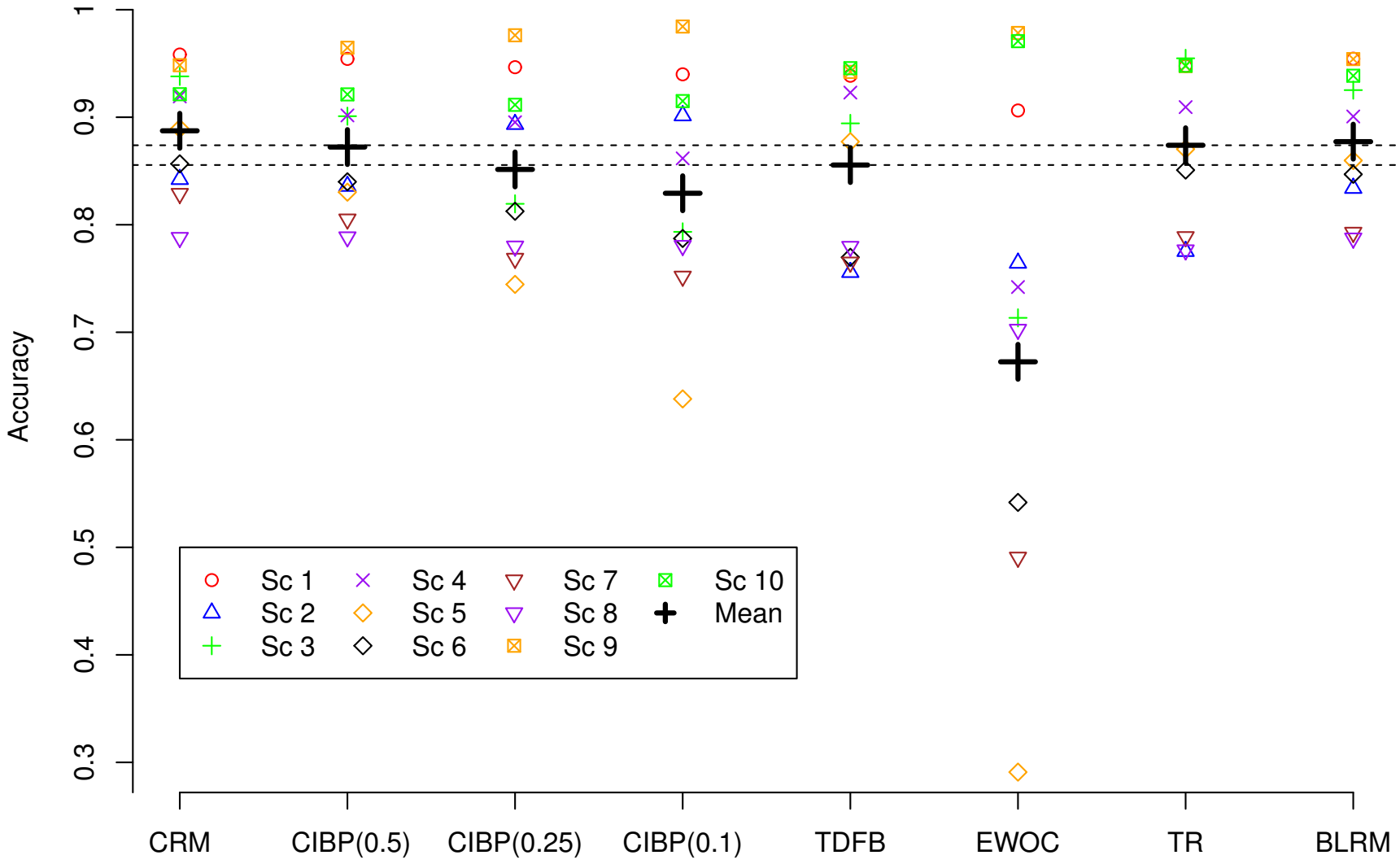
$$\mathcal{A} = 1 - m\frac{\sum_{i=1}^{m}(p_i - TTL)^2 \times Selection\ Proportion_i}{\sum_{i=1}^{m}(p_i - TTL)^2}$$

  - Safety (average number of DLTs)

Simulation study: scenarios



Simulation study: Results. Accuracy



Simulation study: Results. Safety