PSI 2026 Conference, ICC Belfast

BOIN VS. BLRM

A Systematic Performance Comparison in Phase 1 Dose Escalation

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PSI 2026 CONFERENCE

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AGENDA

01

INTRODUCTION

Phase 1 Oncology Trials

Definition & Challanges

NIH NATIONAL CANCER INSTITUTE

phase I clinical trial

(fayz ... KLIH-nih-kul TRY-ul)

The first step in **testing a new treatment in humans**. A phase I clinical trial tests the safety, side effects, best dose, and timing of a new treatment. [..] Phase I clinical trials usually include **only a small number of patients** [..]

SAFETY

TOLERABILITY

Traditional primary goal

MTD

Maximum Tolerated Dose: the highest dose at which an acceptable proportion of patients experience dose-limiting toxicities (DLTs).

Phase 1 Oncology Trials

The Importance of the right design

The Impact of Early-Phase Trial Design in the Drug Development Process FREE

Mark R. Conaway ✉; Gina R. Petroni

Check for updates

— Author & Article Information

2019

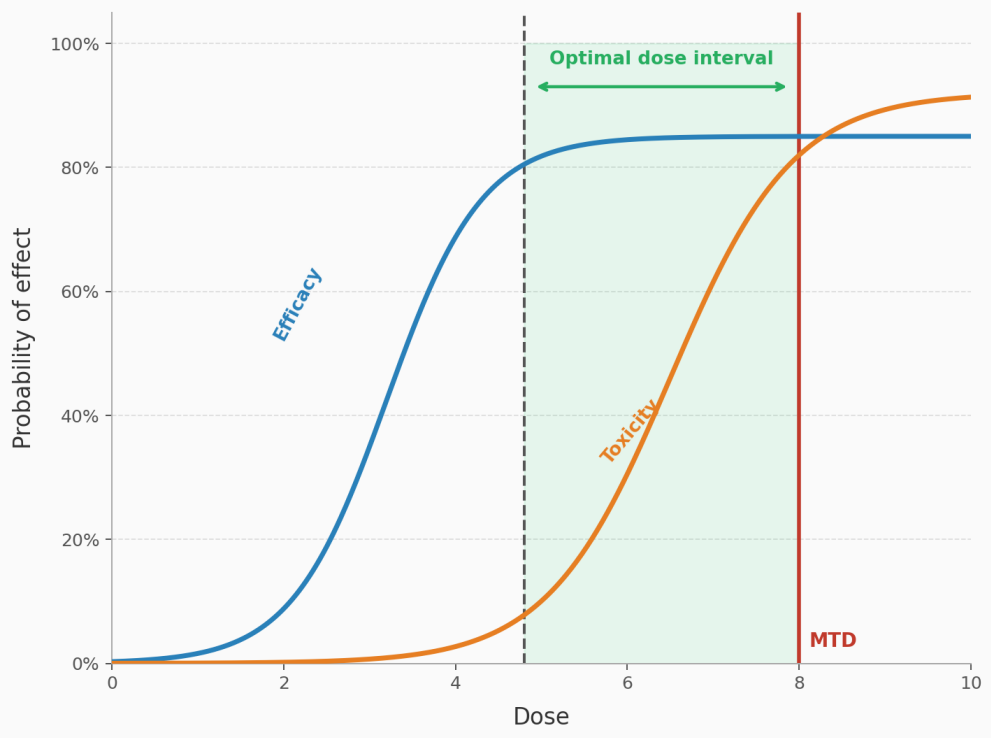
"Using the CRM or BOIN, rather than the 3+3, substantially enhances the proportion of effective agents that have successful phase III trials"

- Inaccurate dose selection can compromise efficacy assessment in later phases
- Early design decisions can ultimately influence the probability of regulatory success and patient benefit
- Better dose-finding approaches improve the chances of identifying the **optimal therapeutic dose**

FDA Project Optimus

What & Why

Identifying an **optimized dosage** can be aligned with the goal of **expediting clinical development** and **reducing the failure rate**



FDA Oncology Center of Excellence initiative (2021) to **reform dose optimization** in oncology drug development

Newer drugs have **non-linear dose-toxicity relationships**

Shift from determining the MTD to finding the **optimal biological dose** (**OBD**) that best **balances safety and efficacy**

02

PHASE 1 DOSE FINDING DESIGNS

Phase 1 Dose Finding Designs

Introduction

Rule Based

Dose assignment decisions are determined by a predefined set of algorithmic rules based on observed dose-limiting toxicities (DLTs).

3+3

Model-Assisted

Support dose-escalation decisions through prespecified decision rules derived from an underlying probability model.

BOIN

Model-based

Uses a statistical model to estimate the dose–toxicity relationship. Dose selection is guided by the estimation of toxicity probabilities relative to a target toxicity level.

BLRM

Phase 1 Dose Finding Designs

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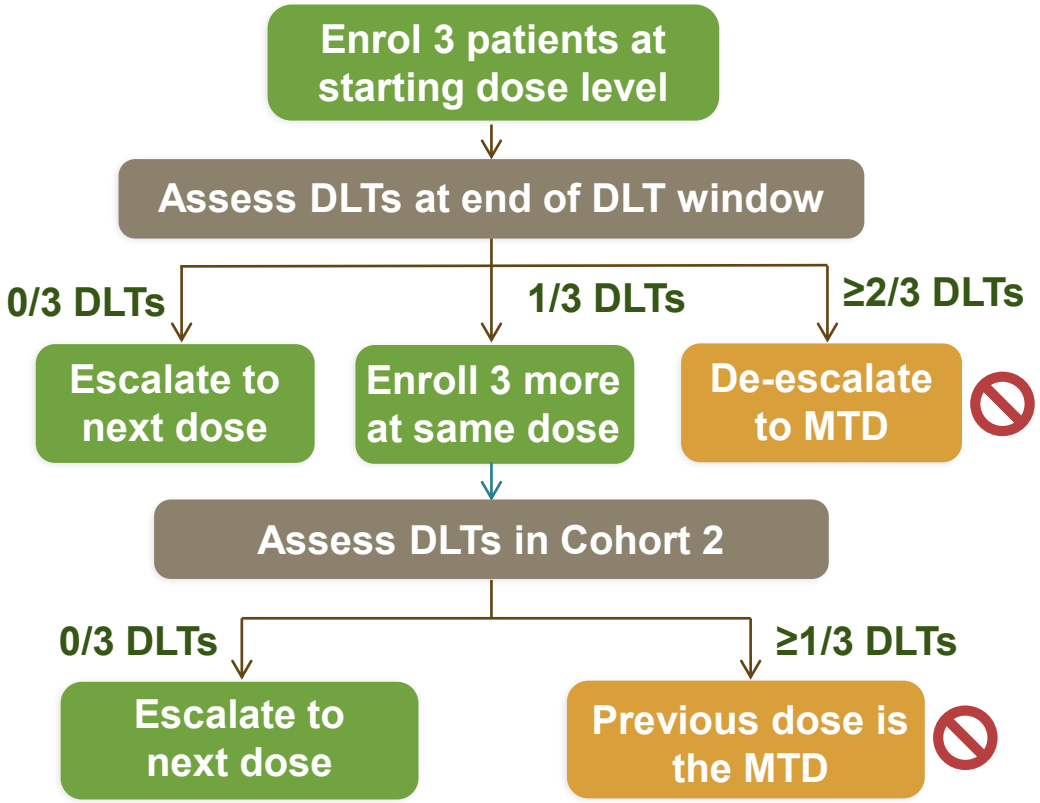
BLRM

3+3 Design

Rule Based



Patients enrolled in sequential cohorts of 3 starting from lowest dose

ADVANTAGES

- Simple, no software needed
- Familiar to investigators and regulators
- Intuitive escalation logic

LIMITATIONS

- Ignores previous doses
- Fixed cohort sizes
- High variability in MTD selection
- Many patients at subtherapeutic doses
- No intermediate dose levels

Bayesian Optimal INterval (Local)

Model Assisted

$\hat{\pi}_d$: observed DLT rate at the current dose d

π_T : target DLT rate / toxicity probability

- $\hat{\pi}_d < \lambda_e \rightarrow$ Escalate to next dose
- $\lambda_e \leq \hat{\pi}_d \leq \lambda_d \rightarrow$ Expand at current dose
- $\hat{\pi}_d > \lambda_d \rightarrow$ De-escalate to lower dose

$P(\pi_d > 33\%) > 0.95$ $\rightarrow$ Eliminate dose + above

Boundaries λ_e and λ_d are computed using $\varphi_1 = 0.6 \cdot \pi_T$ and $\varphi_2 = 1.4 \cdot \pi_T$.

ADVANTAGES

- Optimal decision boundaries
- Flexible cohort sizes
- Relatively simple, easy to pre-specify
- Multiple well-validated extensions available

LIMITATIONS

- Does not borrow strength across dose levels
- Lack of flexibility on intermediate doses

MP1

Bayesian Logistic Regression Model

Model Based

The **number of DLTs at dose d** follows a **Binomial distribution with probability π_d**. The 2-parameter model links dose to DLT probability:

$$\text{logit}(\pi_d) = \log(\alpha) + \beta \cdot \log(d / d^*)$$

$\alpha, \beta > 0$, d^* reference dose

EWOC criterion constrains escalation:

- $P(\pi_d > 33\%) < 25\%$ → Escalate
- $P(\pi_d > 33\%) \geq 25\%$ → De-escalate

Target interval dose: $P(\pi_d \in [16\%, 33\%])$

ADVANTAGES

- Borrows form all data
- Predicts DLT at unobserved doses
- EWOC for strong overdose control
- Incorporates prior clinical knowledge
- Well-suited to complex settings

LIMITATIONS

- Prior specification can be challenging
- Less transparent to clinical teams
- Can be computationally intensive

Head-to-Head

Design Feature Comparison

Feature	3+3	Local-BOIN	BLRM
Design type	Rule-based	Model-assisted	Model-based
Statistical model	None	Pre-computed boundaries	2-parameter logistic
Cohort size flexibility	3 or 6	Any size	Any size
Uses all dose data	No	No	Yes
Dose–response prediction	No	No	Yes
Overdose control	Implicit	Elimination rule	EWOC criterion
Prior information	No	No/Limited	Yes
Complexity	Very low	Low	High
Regulatory acceptance	High (legacy)	High (established)	High (growing)

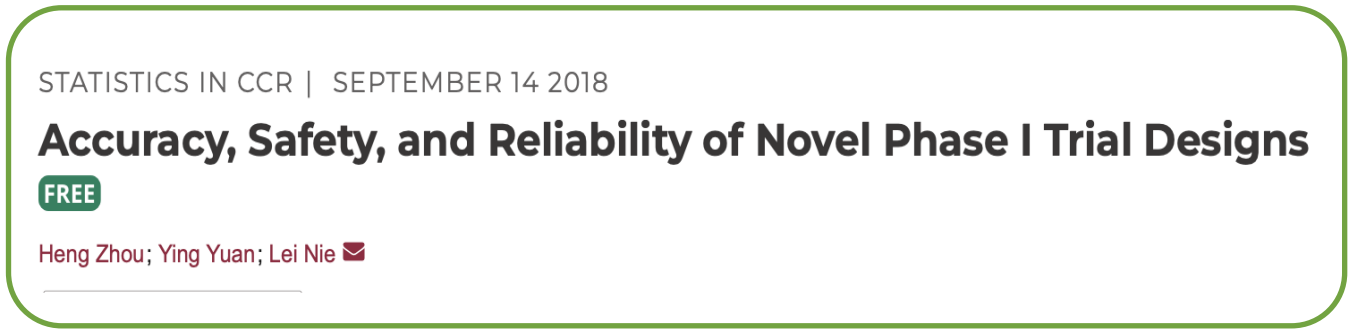
MP1

Aim Of this Work

Design Comparison

compared the operating characteristics of

- 3+3
- Local BOIN
- EWOC-BLRM



ACCURACY

SAFETY

RELIABILITY

03

METHODS

Simulation Setting

Details

5 **Dose levels**
20, 40, 80, 120, 180

500 **Simulated trials**
per scenario per design

2 **Target DLT rates**
$\pi_T = 0.245$ and $\pi_T = 0.276$

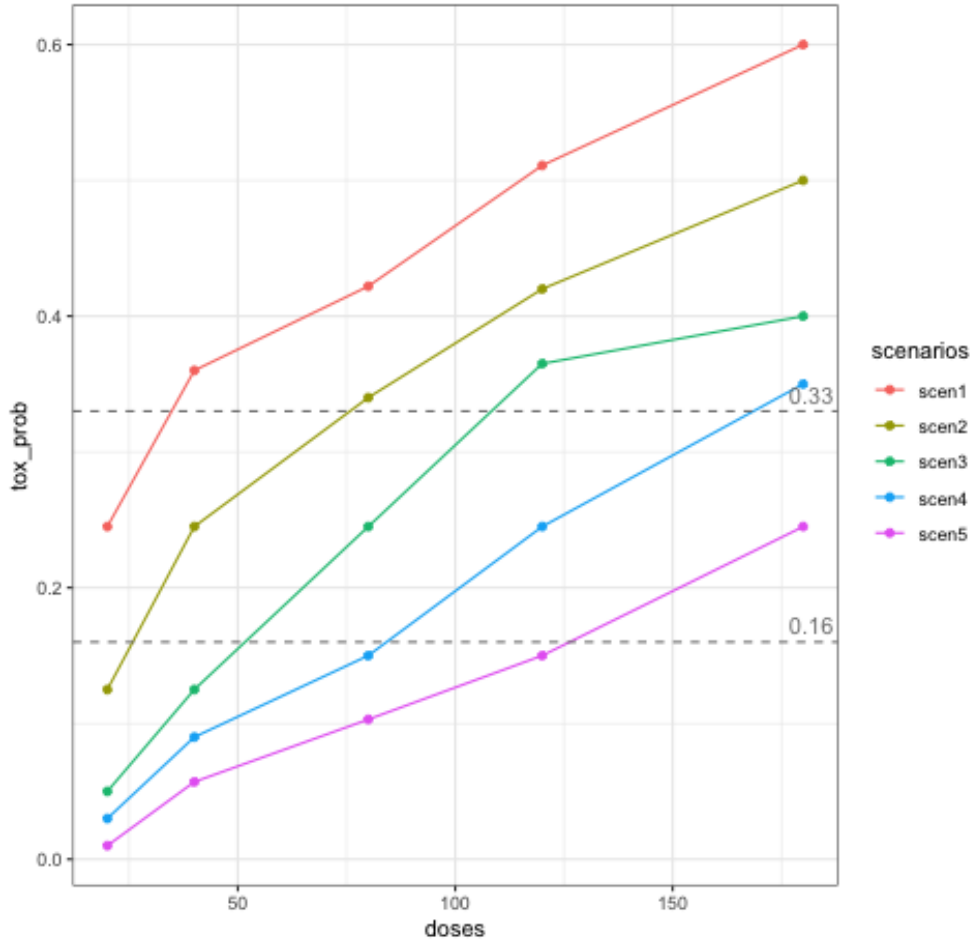
60 **Max sample size**
patient per trial

10 **Toxicity Scenarios**
one for each dose level and π_T

3 **Patients enrolled per cohort**
for each evaluated dose

Toxicity Scenarios

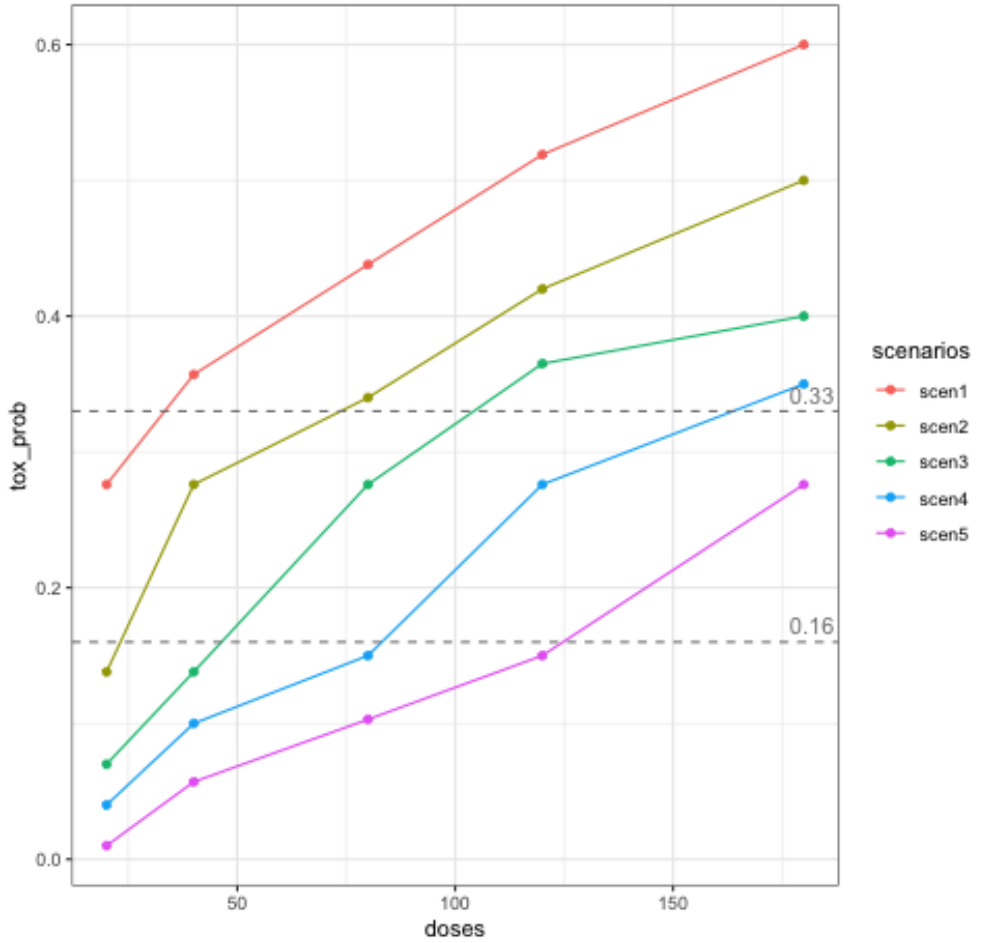
Target dose probability 0.245



	20	40	80	120	180
Scenario 1	**0.245**	0.360	0.422	0.511	0.600
Scenario 2	0.125	**0.245**	0.340	0.420	0.500
Scenario 3	0.050	0.125	**0.245**	0.365	0.400
Scenario 4	0.030	0.090	0.150	**0.245**	0.350
Scenario 5	0.010	0.057	0.103	0.150	**0.245**

Toxicity Scenarios

Target dose probability 0.276



	20	40	80	120	180
Scenario 1	**0.276**	0.357	0.438	0.519	0.600
Scenario 2	0.138	**0.276**	0.340	0.420	0.500
Scenario 3	0.070	0.138	**0.276**	0.365	0.400
Scenario 4	0.040	0.100	0.150	**0.276**	0.350
Scenario 5	0.010	0.057	0.103	0.150	**0.276**

GB1

Models Specifications

BLRM prior elicitation

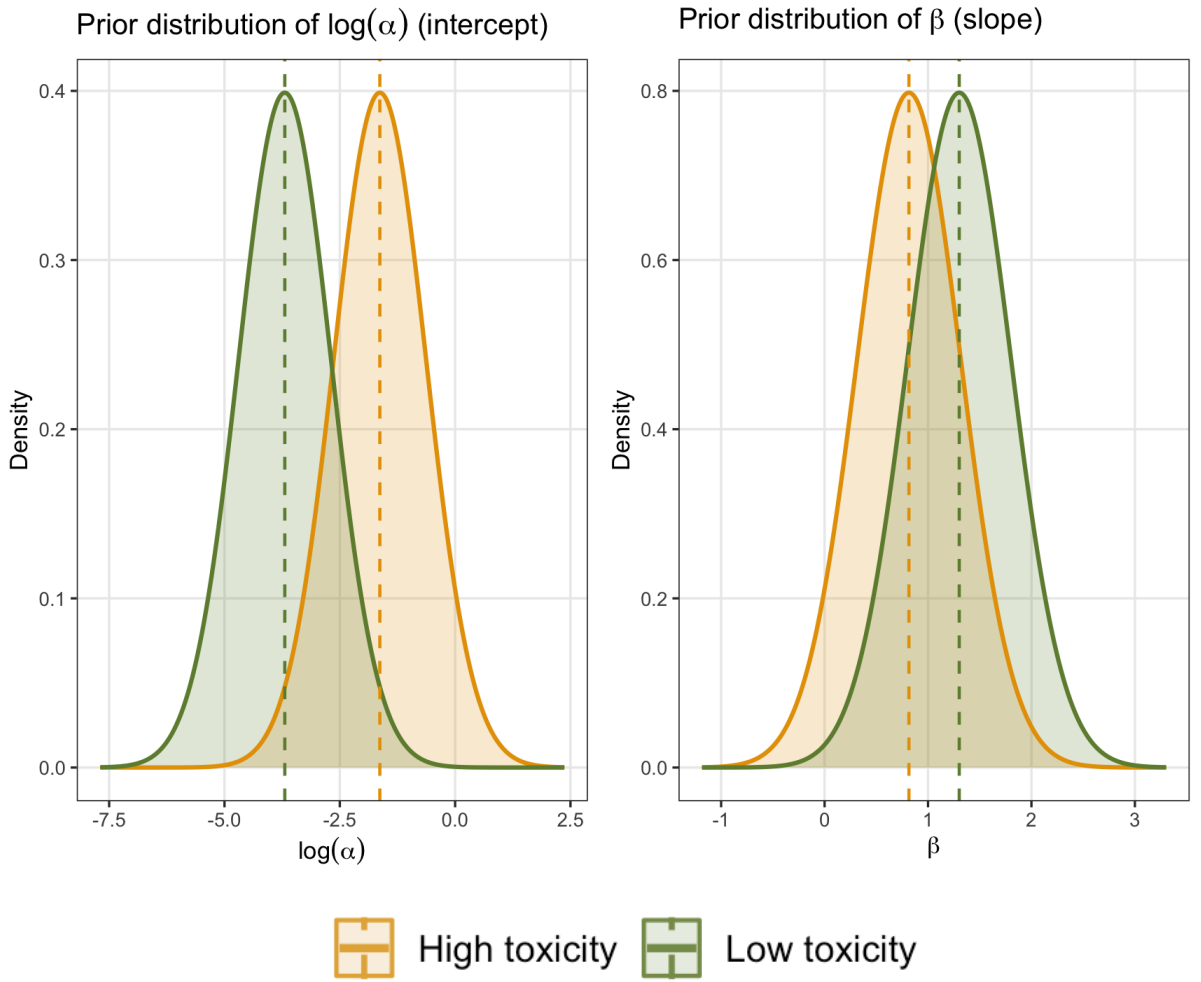
Low toxicity component:

- Doses fixpoints: 20, 180
- Prior means: 0.01, 0.15

High toxicity component:

- Doses fixpoints: 20, 180
- Prior means: 0.1, 0.4

Prior Component	Mixture Weight	Mean Vector	STD Vector	Correlation
Low	0.5	-3.693	1	0
		0.264	0.5	
Hig	0.5	-1.632	1	0
		0.204	0.5	

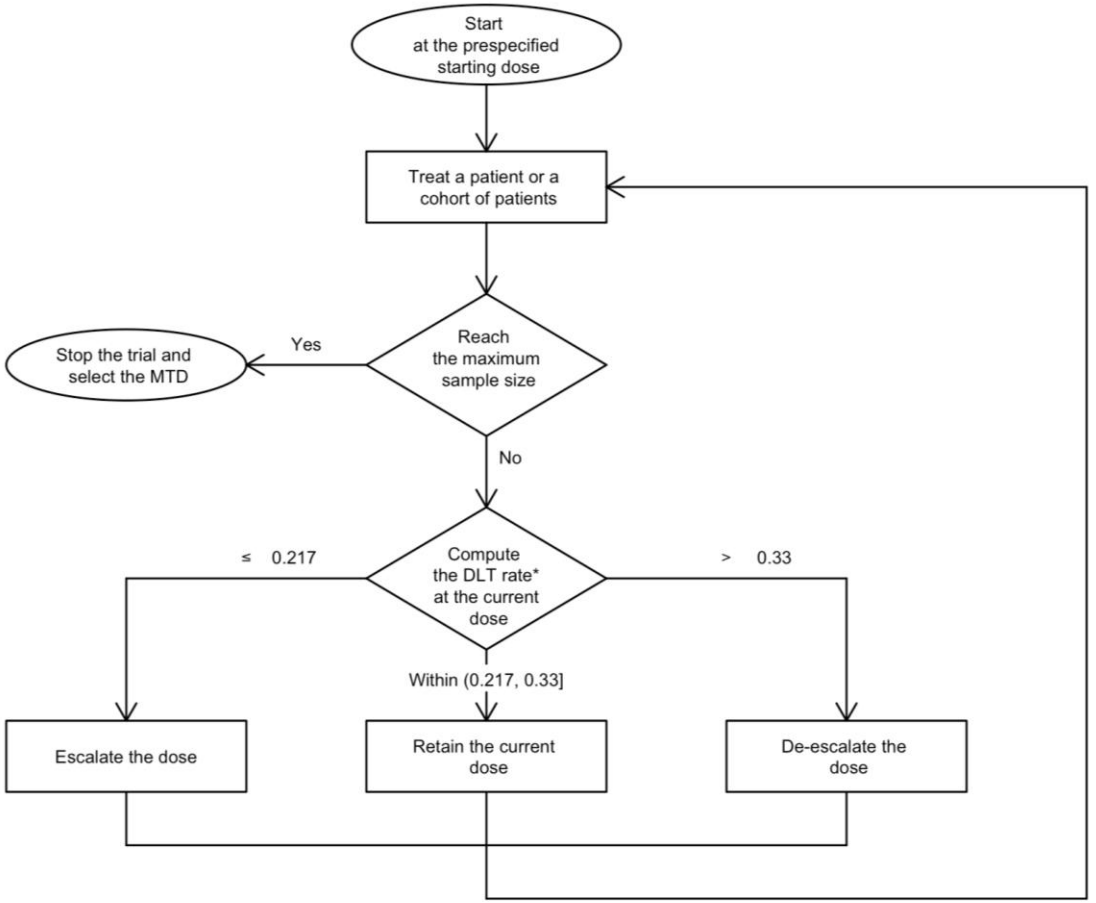


Models Specifications

Local BOIN

Default BOIN parameters

Parameter	Value
Target Probability	0.276
φ_1	0.166
φ_2	0.386
λ_e	0.217
λ_d	0.33
Underdose bound	0.217
Overdose bound	0.33



Liu and Yuan (2015)

Performance Metrics

3 evaluation scales

ACCURACY

- **% of Correct Selection (PCS)**
- % correct MTD selection — primary measure of design accuracy

- **Volatility**
- SD of selected MTD index across trials — design consistency

- **Avg % at MTD**
- Mean % patients treated at the true MTD — allocation efficiency

SAFETY

- **$Safety_1$**
- % trials selecting a toxic dose (DLT > 33%) as the MTD

- **$Safety_2$**
- Avg % patients treated at toxic doses (DLT > 33%)

RELIABILITY

- **Overdosing risk**
- % trials with > 25% patients above the true MTD

- **Risk of poor allocation**
- % trials with < 6 patients at MTD

- **De-escalation failure rate**
- % trials failing to de-escalate after ≥ 2/3 DLTs

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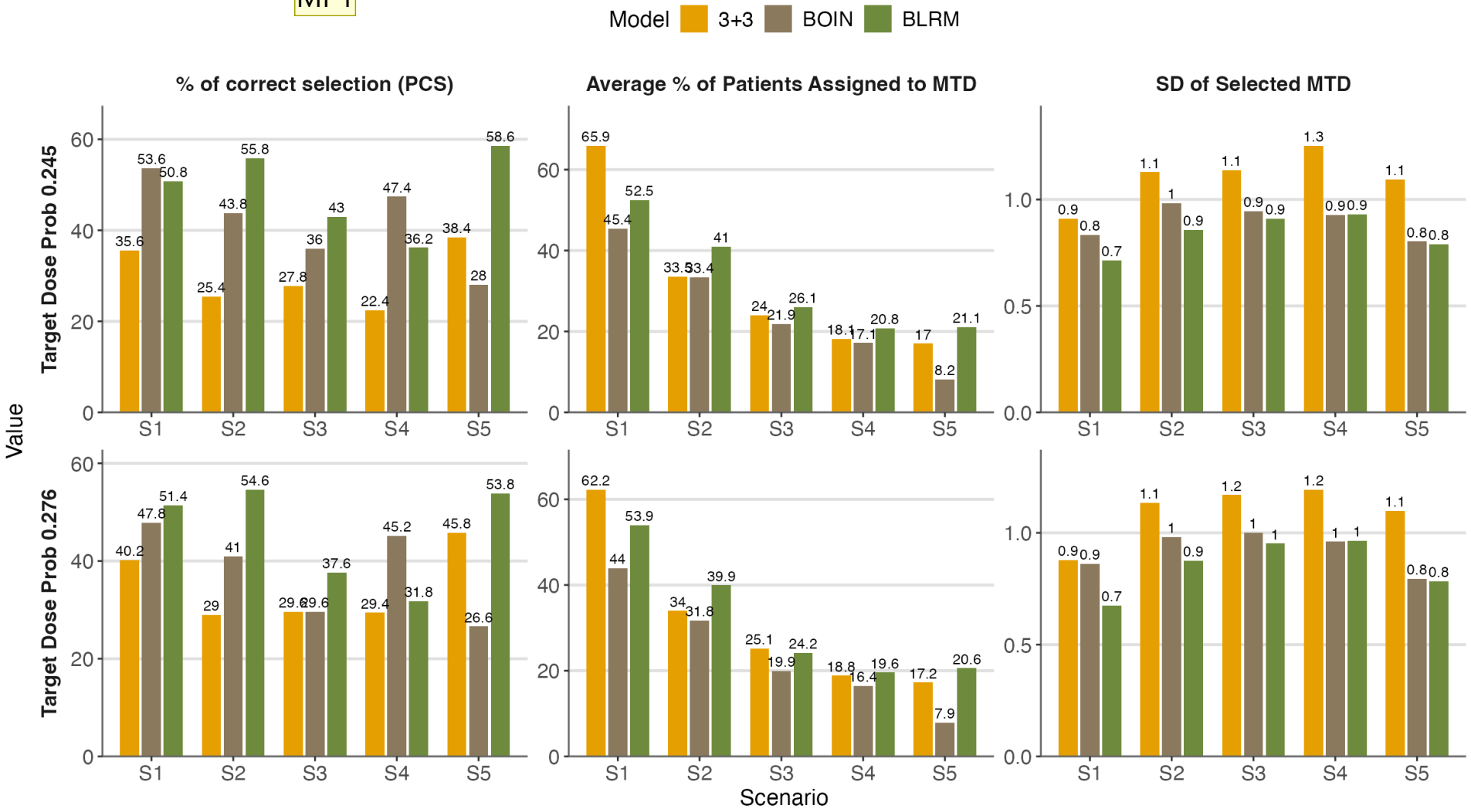
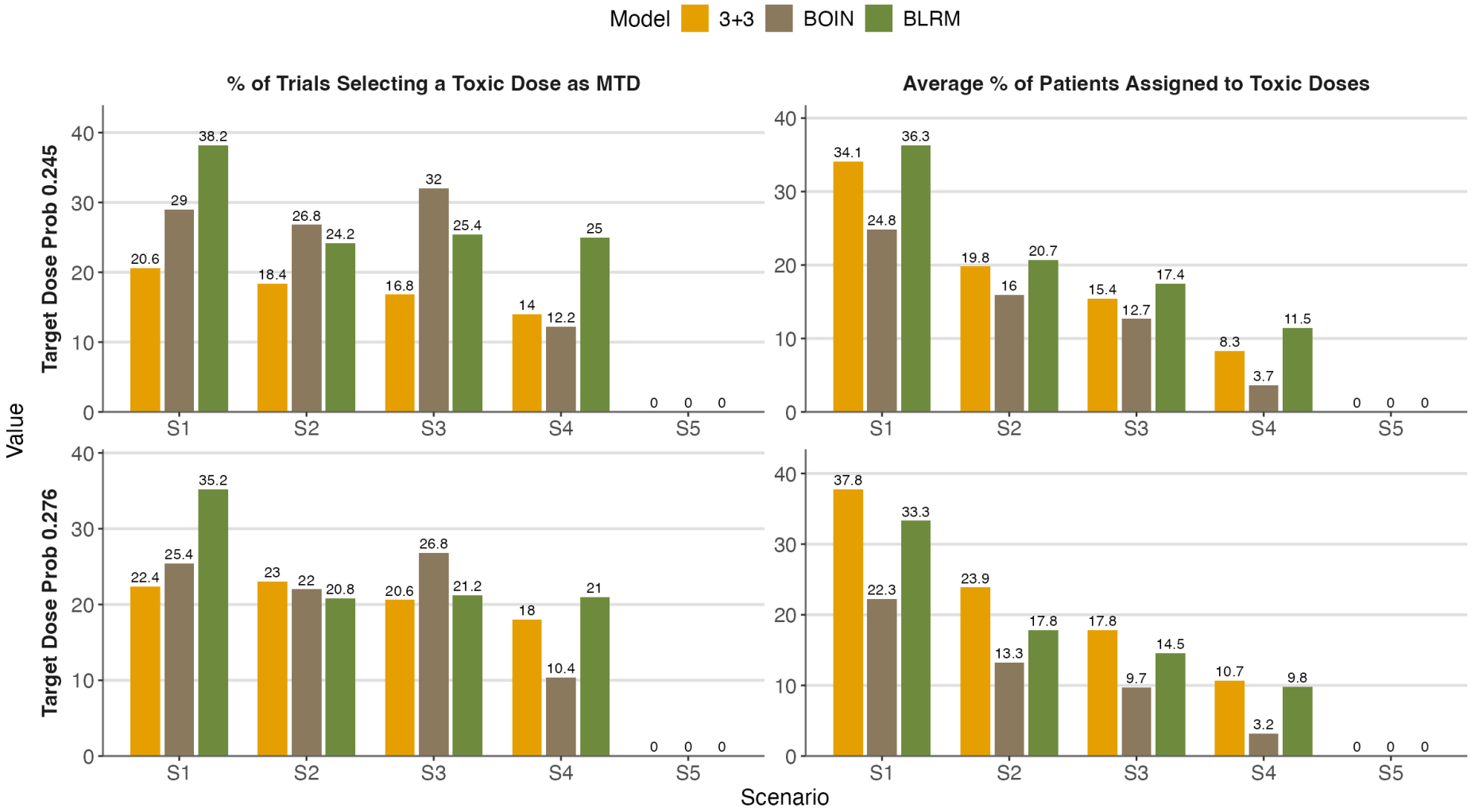
RESULTS

Accuracy

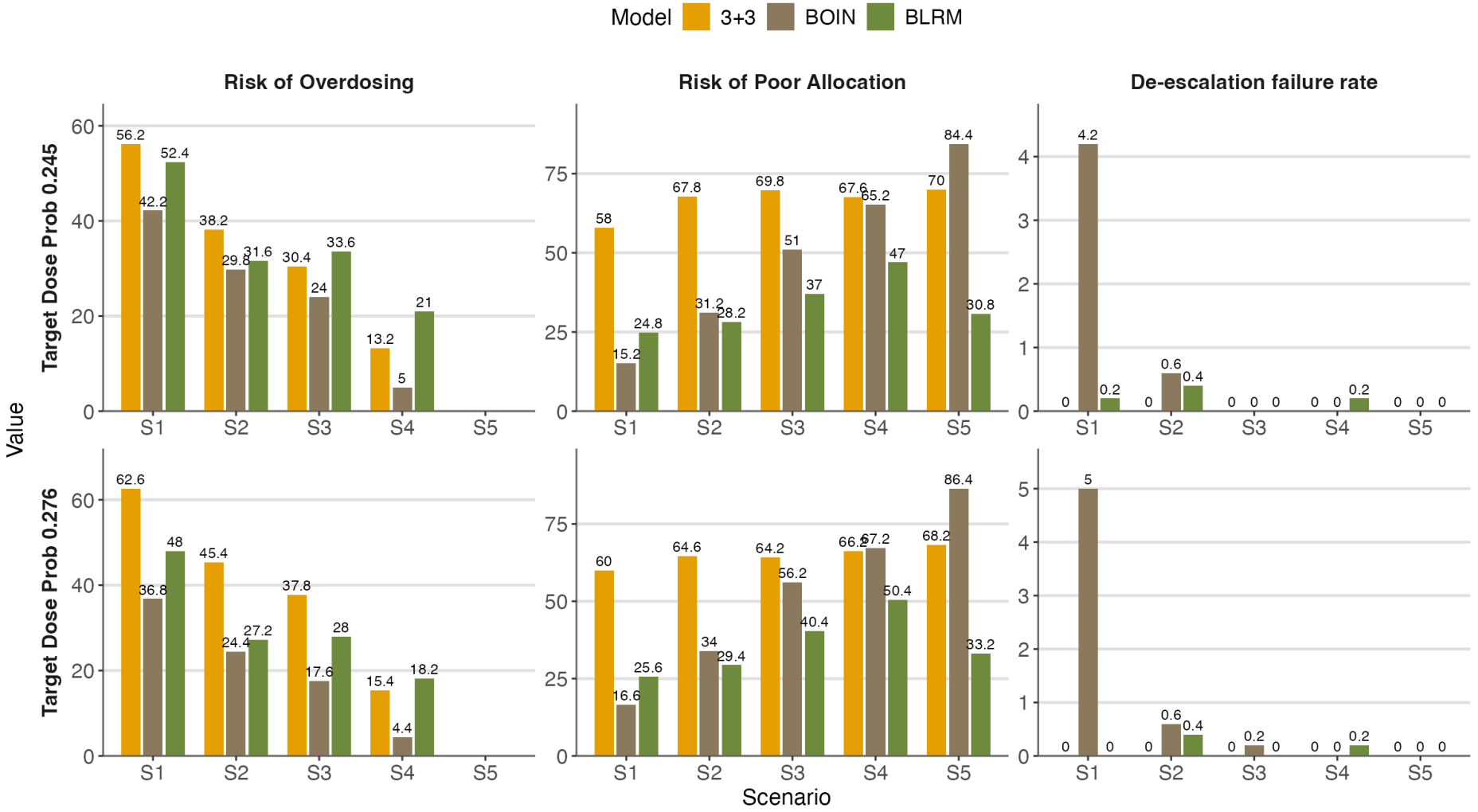
MP1



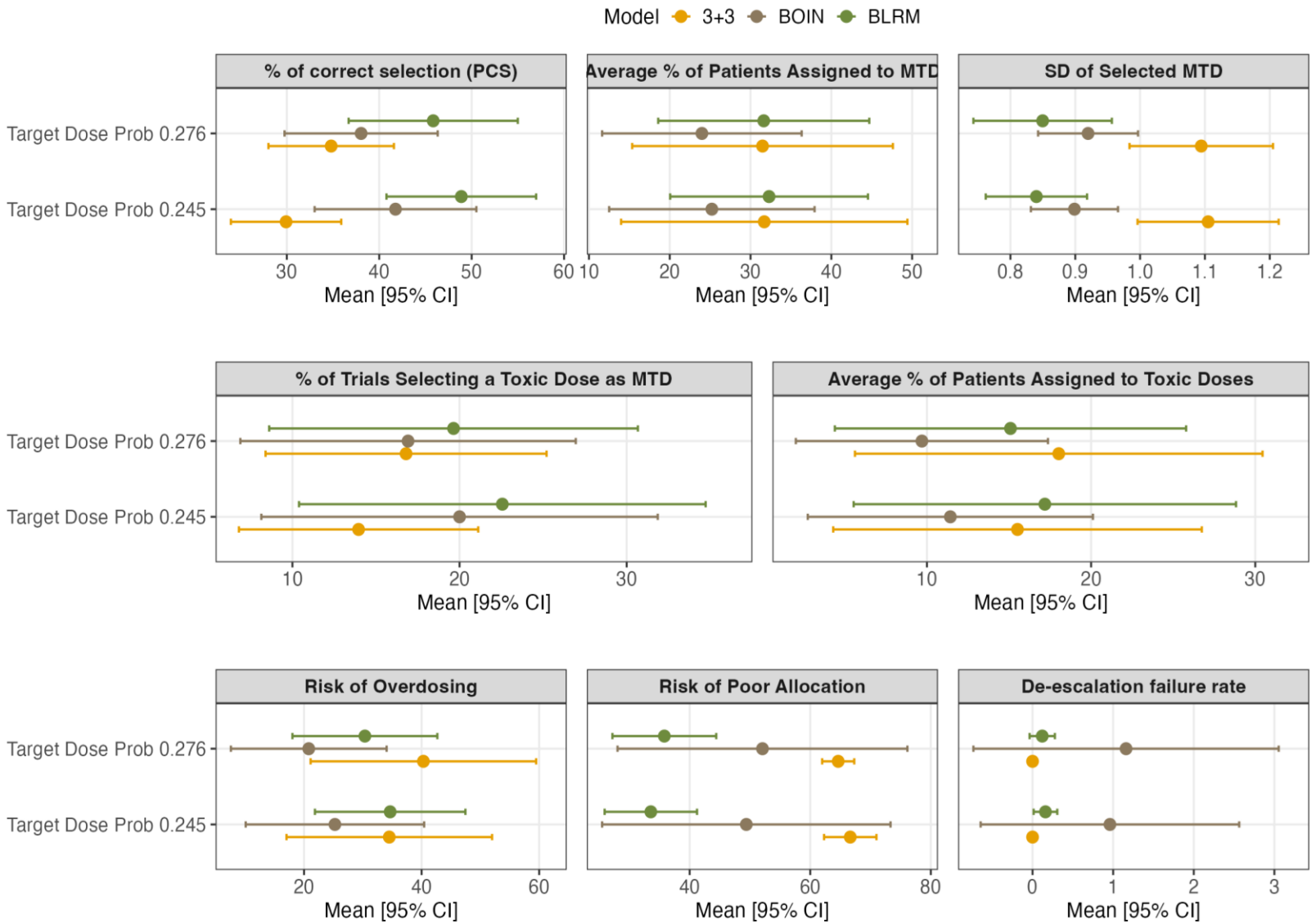
Safety


Model 3+3 BOIN BLRM
% of Trials Selecting a Toxic Dose as MTD
Average % of Patients Assigned to Toxic Doses
Target Dose Prob 0.245
Target Dose Prob 0.276
Value
Scenario
S1 S2 S3 S4 S5
20.6 29 38.2
18.4 26.8 24.2
16.8 32 25.4
14 12.2 25
0 0 0
34.1 24.8 36.3
19.8 16 20.7
15.4 12.7 17.4
8.3 3.7 11.5
0 0 0
22.4 25.4 35.2
23 22 20.8
20.6 26.8 21.2
18 10.4 21
0 0 0
37.8 22.3 33.3
23.9 13.3 17.8
17.8 9.7 14.5
10.7 3.2 9.8
0 0 0

Reliability



Average Performances



Results Summary

Overall Performance Ranking

Accuracy

★★★ **BLRM** – Highest overall accuracy across most scenarios

★★☆ **BOIN** – Competitive performance, particularly when the target dose is located in the lower dose range

★☆☆ **3+3** – Consistently lowest probability of correct MTD selection

Safety

★★★ **BOIN** – Lowest proportion of patients treated above the MTD and lowest overdosing risk in most scenarios

★★☆ **3+3** – Conservative escalation limits selection of toxic doses, although often at the cost of underdosing

BLRM – Lowest proportion of trials selecting a toxic dose as MTD in half of the scenarios with respect to BOIN

Reliability

★★★ **BLRM** – Lowest variability in dose selection and best patient allocation to the target dose

★★☆ **BOIN** – Intermediate reliability with good consistency across scenarios

★☆☆ **3+3** – Highest risk of poor dose allocation and greatest variability in identifying the true MTD

05

DISCUSSION

Discussion

Take home message

- BLRM → more efficient learning across dose levels → **best identification of the true MTD**
- BLRM's use of **informative prior can lead to more aggressive escalation when limited data are available** → overdosing risk observed in scenarios where the MTD is located at lower doses → depends on the prior
- **BOIN lowest proportion of patients treated above the MTD**, but **lower accuracy**.
- **BLRM** allows for **intermediate doses**
- **BLRM** allows to **skip doses**
- The **3+3 design** showed the **poorest overall performance**.

THANK YOU FOR YOUR ATTENTION!

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Phase 1 Oncology Trials

The Importance of the right design

- Achieving an accurate MTD estimate is critical:
  - **under-dosing** compromises therapeutic potential,
  - **over-dosing** exposes patients to unacceptable harm

- While ~ 50% to 60% of drugs successfully transition to Phase 2, **~ 70 - 80%** of drugs fail during phase 2 due to lack of efficacy.

- Approximately **90% of drug candidates that enter clinical trials ultimately fail** to reach the market and

FDA Project Optimus

Key Principles & Implications

1 Dose Optimisation

Sponsors must evaluate a range of doses and identify the Recommended Phase 2 Dose (RP2D) based on efficacy and safety, not just the MTD.

2 Dose-Comparison Studies

FDA encourages dose-comparison cohorts or sub-studies within Phase 1/2, enabling direct evidence of dose–response relationships.

3 Adaptive Designs

FDA favours model-based or model-assisted designs (e.g., BOIN, BLRM) over rule-based methods for their statistical rigour and adaptability.

4 Broader Toxicity Endpoints

Beyond DLTs, sponsors should consider patient-reported outcomes, cumulative toxicity, and tolerability at proposed RP2D.

5 Transparency & Reproducibility

Dose-escalation decisions and stopping rules should be pre-specified and transparent; simulation-based evidence is strongly encouraged.

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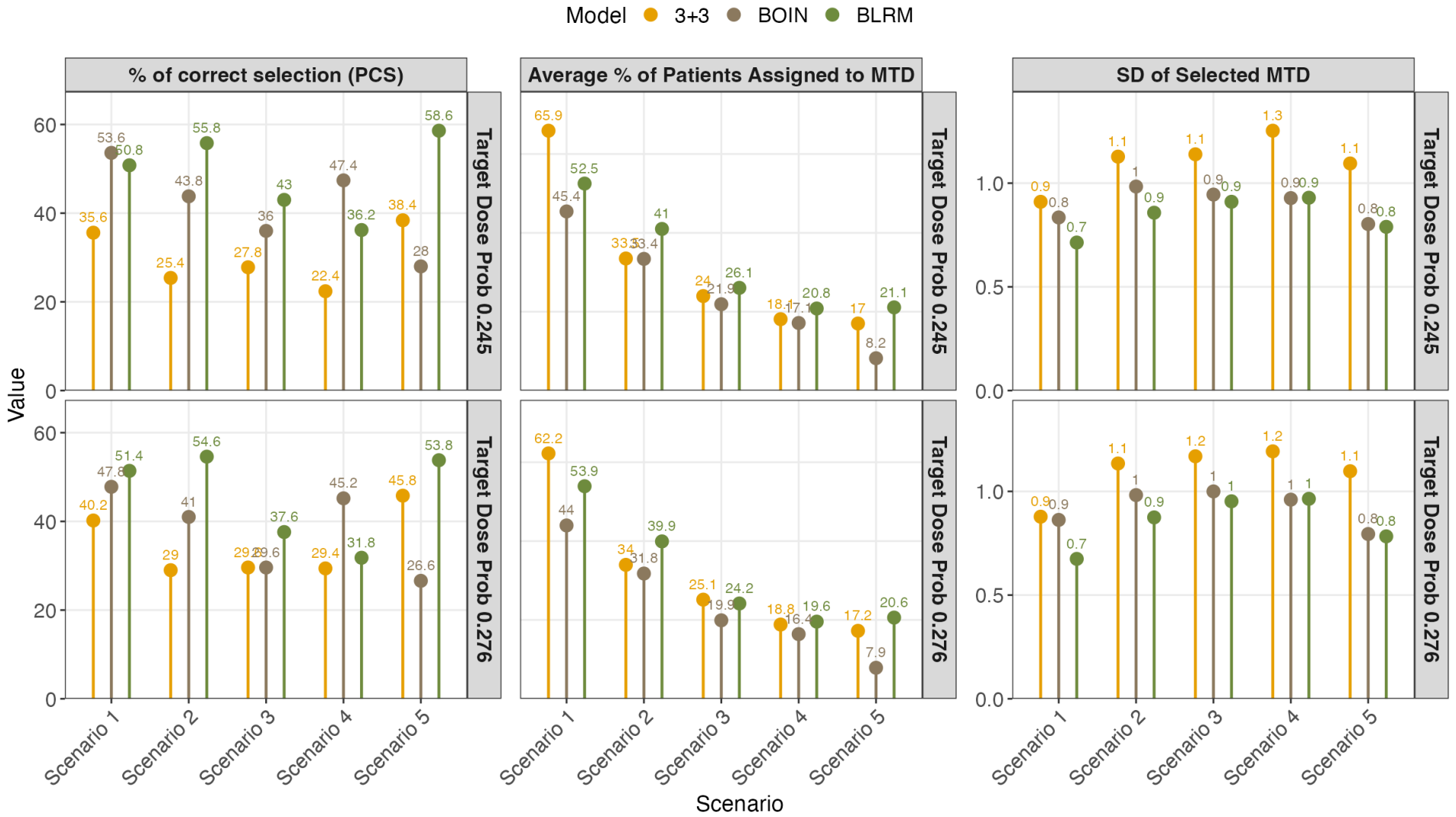
Accuracy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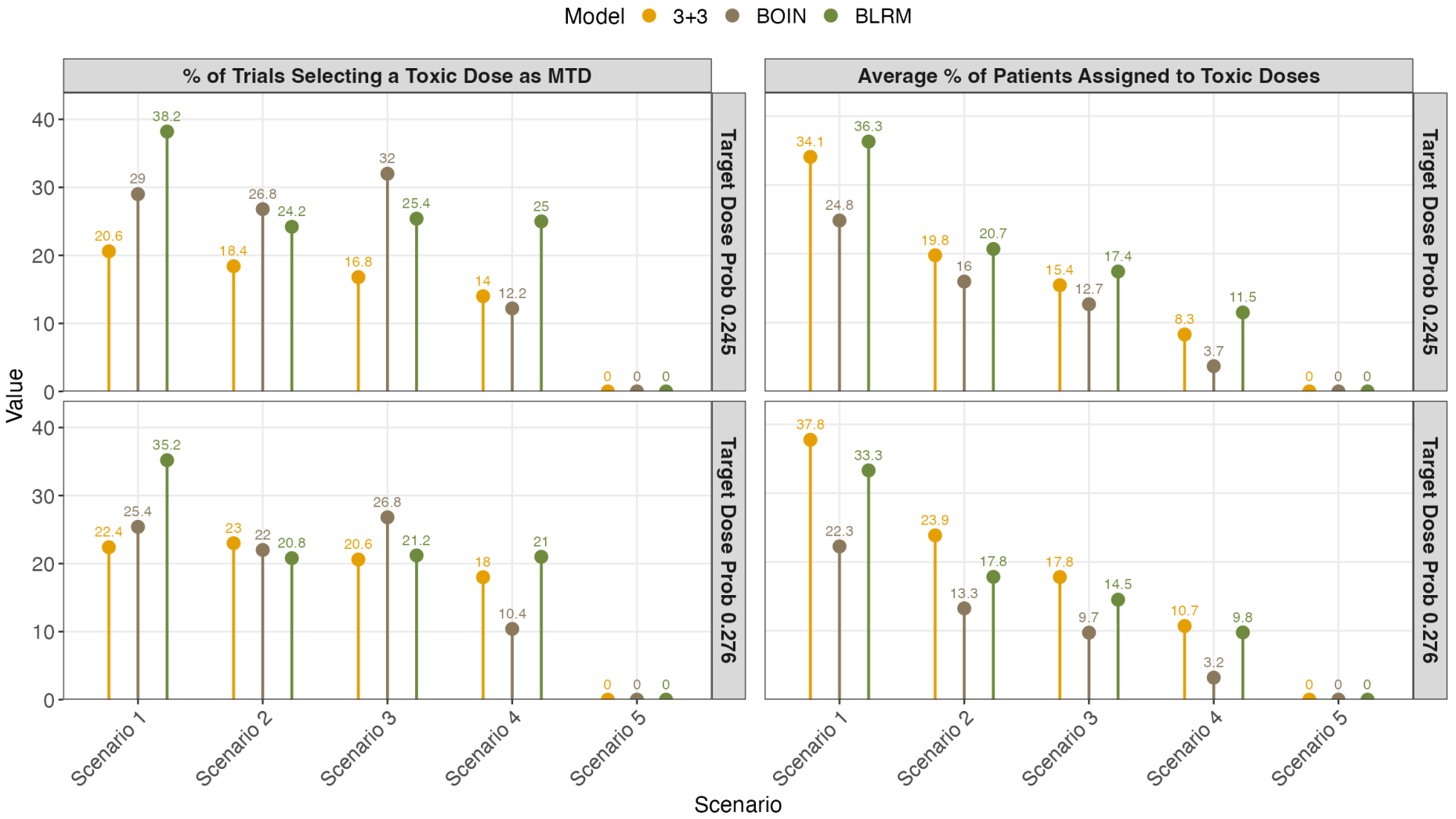
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Reliability