Bayes Bayesian Biostatistics Leiden, NL 2026

Integrating Preclinical Insights for Adaptive Dose Escalation in Phase I Oncology Trials

Helen Barnett[1], Mélanie Guhl[2], Fulvio Di Stefano[3], Donia Skanji[4], Sandrine Guilleminot[5], Gaëlle Saint-Hilary[2,3], Pavel Mozgunov[2,6], Marie-Karelle Riviere[2]

22nd October 2026

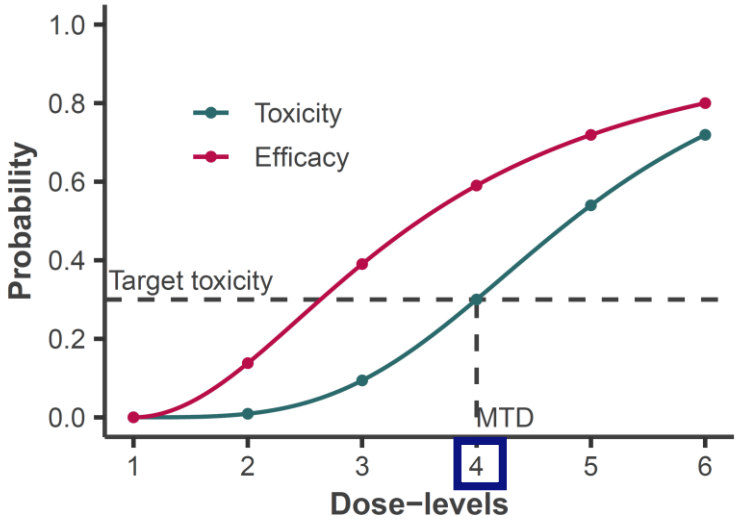
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Lancaster University

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Phase I oncology trials



First in human (FIH) trial

- Dose limiting toxicities (DLT)
- Maximum tolerated dose (MTD)

➢ **Safety profile** in humans

Dose escalation

- Assignments to **undertoxic** (unefficient) / **overtoxic** doses (safety hazard)

➢ Efficiency/safety balance

Limited sample size

- Idea: **leveraging prior information**

➢ Enhance first in human trial efficiency while ensuring safety

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Use of prior information in FIH

FDA guidelines: preclinical studies on rodent and non rodent species

➢ **Animal data should always be available**

Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Current state of the art

- Maximum safe **starting dose**
- Often required by regulators
- Limited, suboptimal use

➢ **Integrating animal data** in the study design

- FDA Optimus project *"develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection"*

- Translation of **dose-toxicity relationship** from animal to human
- What happens in case of discordance?

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Motivating case study

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Phase I study

- 30 patients considered
- Statistical design (BLRM with EWOC)
- Recommendation of MTD

Two preclinical toxicity studies

- Rat (rodent) and monkey (non rodent)
  - ➢ Dose range 25-1400mg
  - ➢ Starting dose 50mg

Study	Species	Dose (mg/kg)	Number of animals	Toxicities
1		7.5	20	12
		15	20	15
		30	32	32
2		3	6	0
		7.5	6	4
		15	10	10

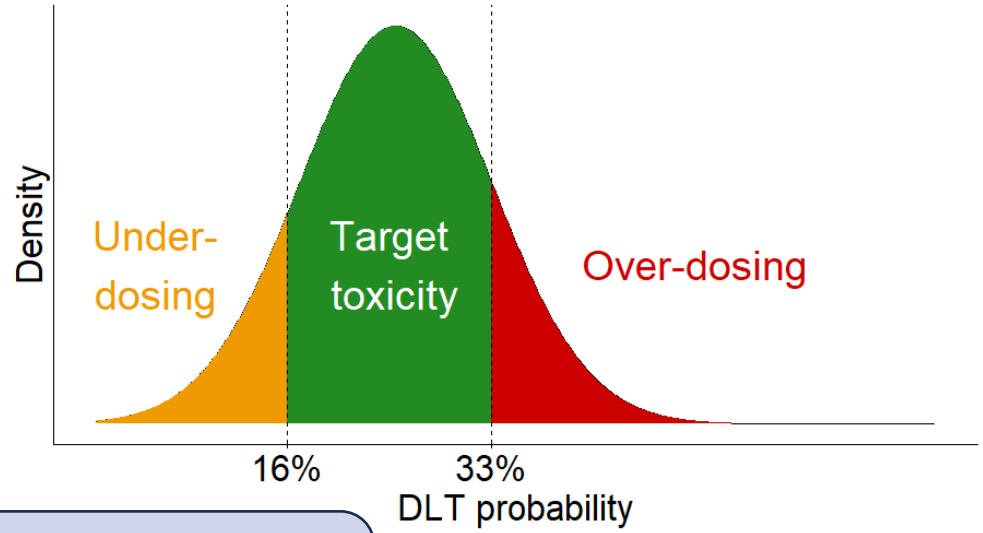
The presented data is simulated for confidentiality reasons

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Bayesian Logistic Regression Model

Model based approaches

- Use of preclinical data



Bayesian Logistic Regression Model (BLRM)[1]

$$logit(p_{i^*j}) = \theta_{1i^*} + \exp(\theta_{2i^*}) \log\left(\frac{d_{i^*j}}{d_{Ref}}\right)$$

- p_{i^*j} probability of DLT at dose d_{i^*j}
- d_{i^*j} doses for $j = 1, \ldots, J$ with d_{Ref} reference dose
- $\theta_{i^*} = (\theta_{1i^*}, \theta_{2i^*})$ parameter vector describing the dose-toxicity relationship

[1]Neuenschwander et al., Stat in Med, 2008

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Preclinical data incorporation methods

Assumptions : **same model**, one animal per study i

$$logit(p_{ij}) = \theta_{1i} + \exp(\theta_{2i}) \log\left(\frac{\boldsymbol{\delta_i d_{ij}}}{d_{Ref}}\right)$$

- δ_i allometric factor
- FDA[2] recommendations on allometric scaling[3]:

	BW (kg)			HED (mg/kg)		HED (mg/m2)	
Species	**Reference**	**Working range**	**BSA** (m^2)	λ	ν	λ	ν
Mouse	0.02	(0.011, 0.034)	0.007	-2.562	0.298	1.050	0.283
Hamster	0.08	(0.047, 0.157)	0.016	-2.002	0.302	1.609	0.287
Rat	0.15	(0.080, 0.270)	0.025	-1.820	0.323	1.792	0.309
Ferret	0.30	(0.160, 0.540)	0.043	-1.669	0.323	1.943	0.309
Guinea pig	0.40	(0.208, 0.700)	0.050	-1.532	0.315	2.079	0.301
Rabbit	1.80	(0.900, 3.000)	0.150	-1.127	0.290	2.485	0.274
Dog	10	(5, 17)	0.500	-0.616	0.301	2.996	0.286
Monkeys	3	(1.400, 4.900)	0.250	-1.127	0.273	2.485	0.256

[2]FDA Guidance for Industry, 2005

[3]Zheng et al., SMMR, 2019

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Prior distributions

Multivariate normal (MVN) prior

$$\theta_{i^*} \sim MVN(m_r, R_r) = \pi_r(\theta_{i^*})$$

Power prior

$$\pi(\theta_{i^*}|D_0, \alpha) \propto \sum_{i=1}^{I} L(\theta_i|D_{0i})^{\alpha_i}\ \pi_r(\theta_{i^*})$$

→ **Choice of $\alpha \in [0, 1]$**

Meta-analytic predictive (MAP) prior

$$\theta_i|\mu_i, \psi \sim MVN(\mu_i, \psi)$$
$$\mu_i \mid m, \Sigma \sim MVN(m, \Sigma)$$
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$$\theta_{i^*} \sim MVN(\mu_i, \psi) \text{ with probability } w_i$$
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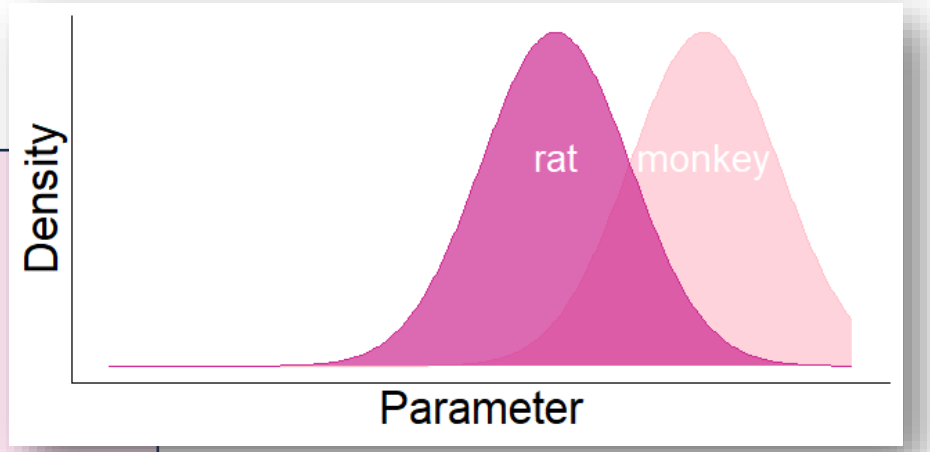
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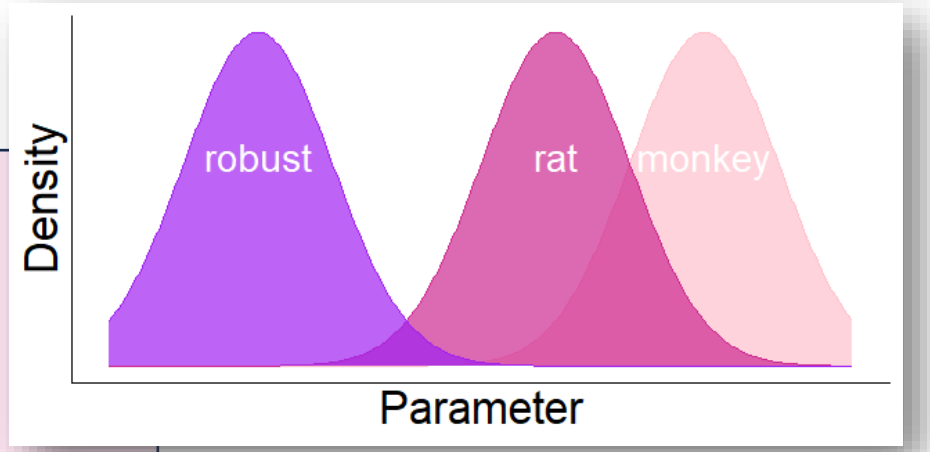
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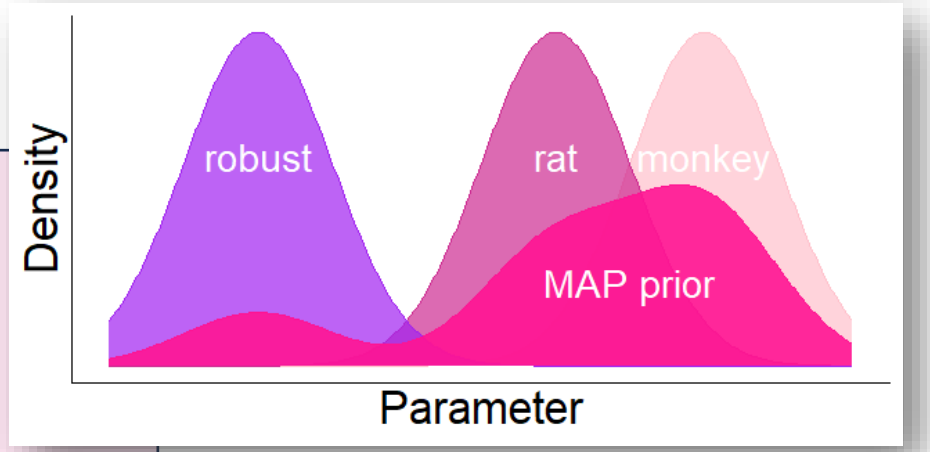
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Calibration of data inclusion in priors

External data: survey[4] on concordance between animal and human studies



Rats

86 concordant studies

75 non concordants

→ $p_{RAT} = 0.53$



Monkeys

41 concordant studies

17 non concordant

→ $p_{MONKEY} = 0.71$



Anti-cancer therapies

$p_{AK} = 0.84$

Power prior

- $\alpha_{RAT} = p_{AK} * p_{RAT}$
- $\alpha_{MONKEY} = p_{AK} * p_{MONKEY}$

MAP prior

- $w_r = 1 - p_{AK}$
- $w_{RAT} = p_{AK} * \frac{p_{RAT}}{p_{MONKEY}+p_{RAT}}$
- $w_{MONKEY} = p_{AK} * \frac{p_{MONKEY}}{p_{MONKEY}+p_{RAT}}$

[4]Olson et al., Regul Toxicol Pharmacol, 2000

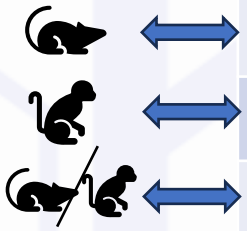
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Simulation study settings

Ten scenarios with different distributions of the DLT probabilities and MTD (in **bold**)

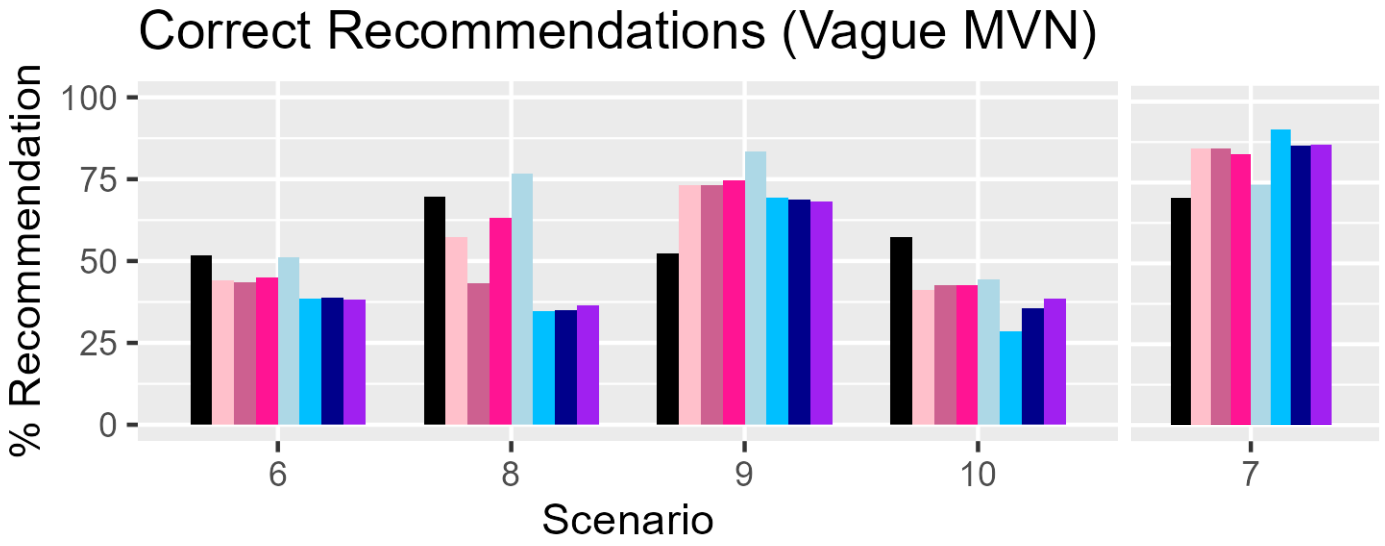
- Plausible range of dose responses

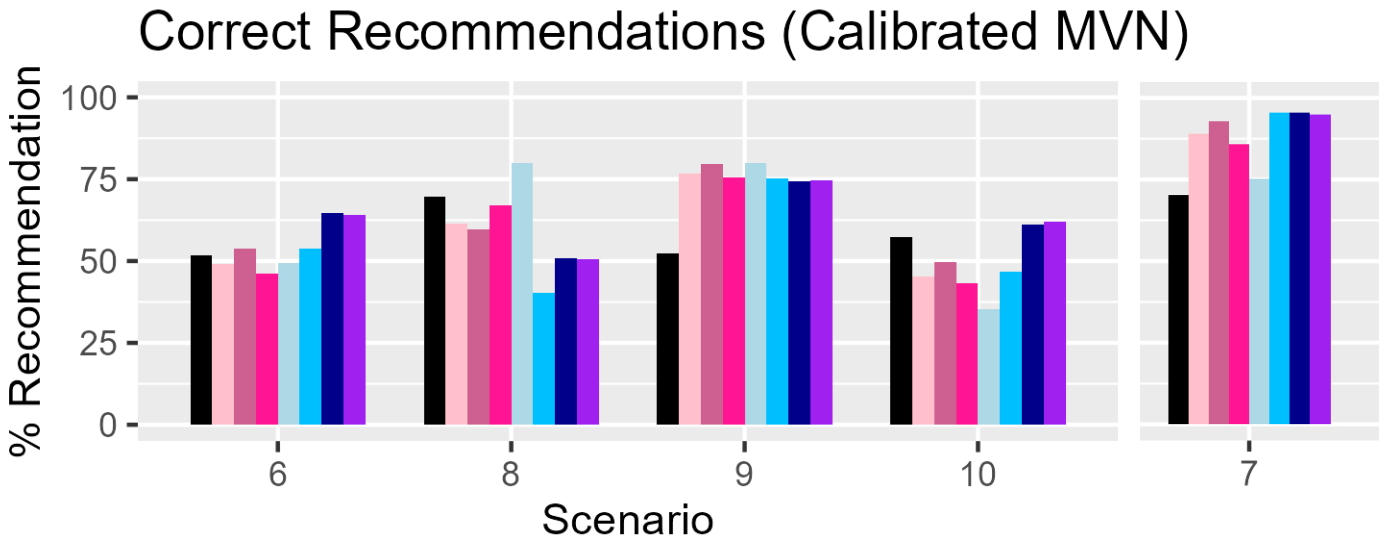
Scenario	25mg	50mg	100mg	200mg	400mg	800mg	1400mg
1	0.0001	0.01	0.02	0.03	0.07	0.12	**0.20**
2	0.01	0.03	0.05	0.10	0.14	**0.28**	0.40
3	0.03	0.05	0.10	**0.18**	**0.30**	0.46	0.60
4	0.02	0.04	0.08	**0.24**	0.35	0.40	0.45
5	0.05	0.10	**0.25**	0.40	0.55	0.70	0.85
6	0.11	**0.28**	0.37	0.44	0.61	0.73	0.80
7	0.36	0.53	0.69	0.82	0.90	0.95	0.97
8	**0.21**	0.38	0.61	0.81	0.93	0.98	0.99
9	0.09	**0.17**	0.38	0.72	0.93	0.99	0.99
10	0.15	**0.27**	0.49	0.76	0.93	0.99	0.99



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Simulation study results – low MTD scenarios



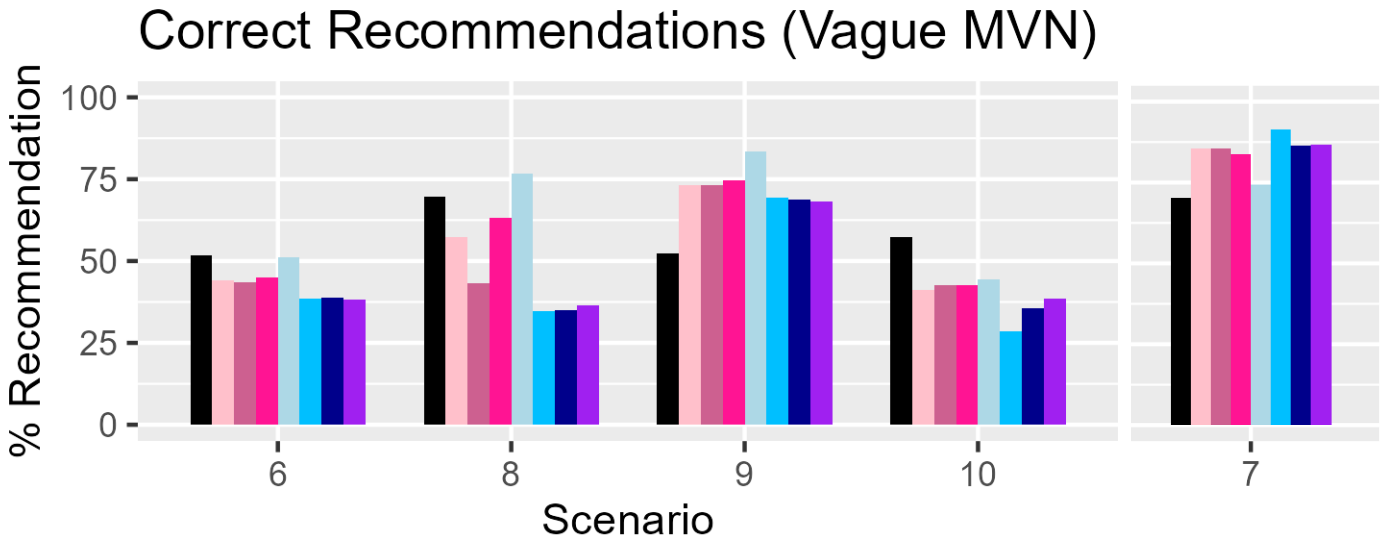


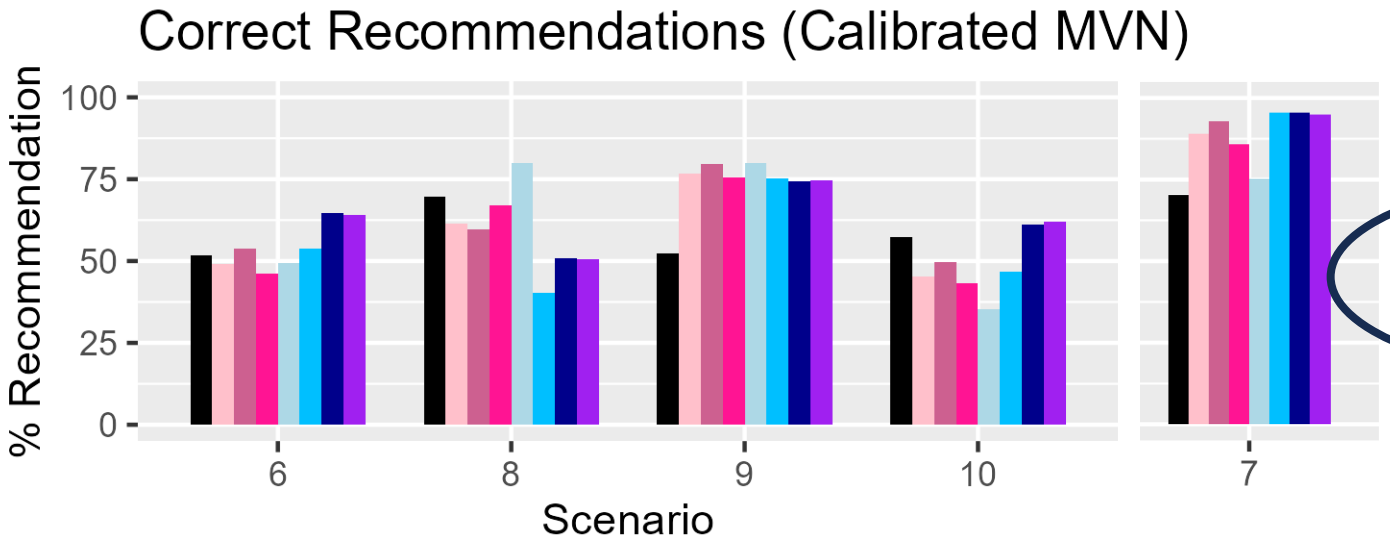
- Scenarios concordant with animal data
- **More correct recommendations** with calibrated MVN in some cases…

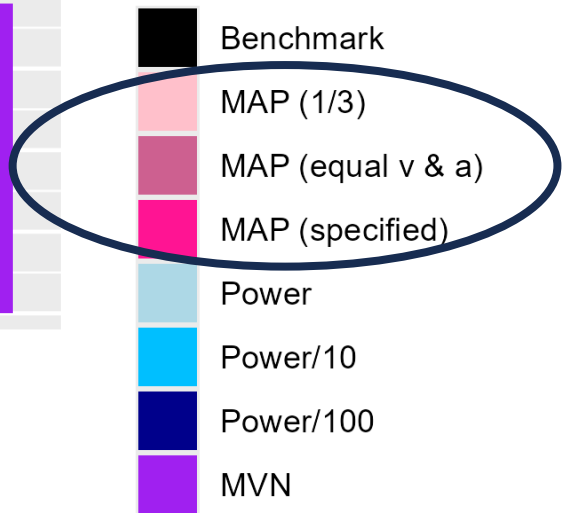


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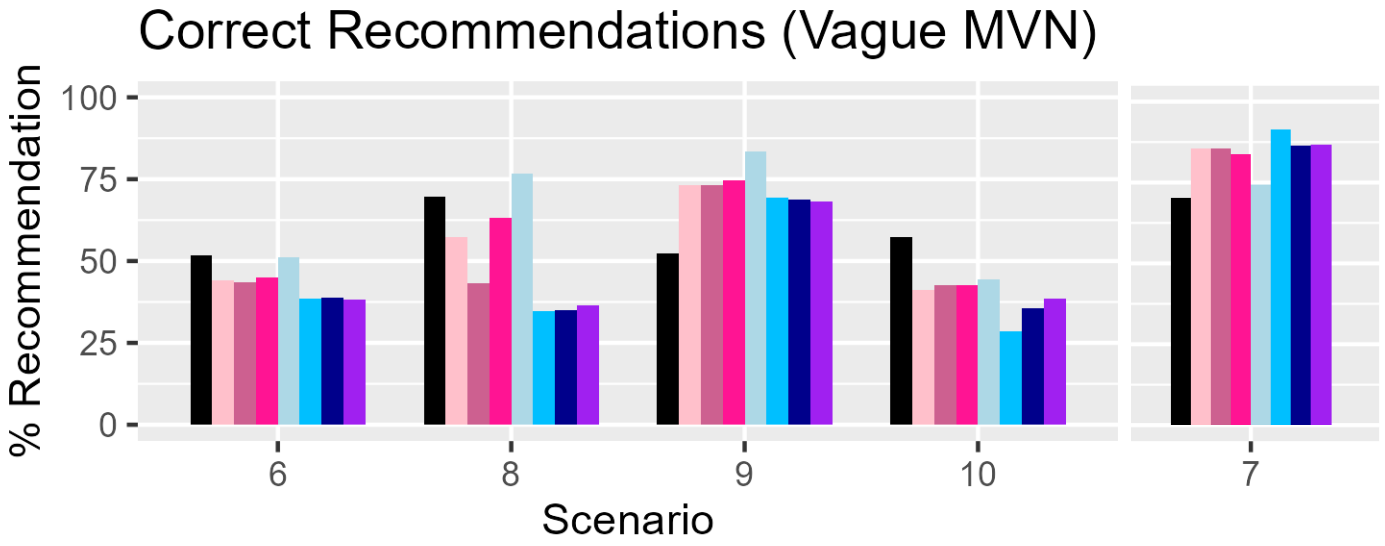


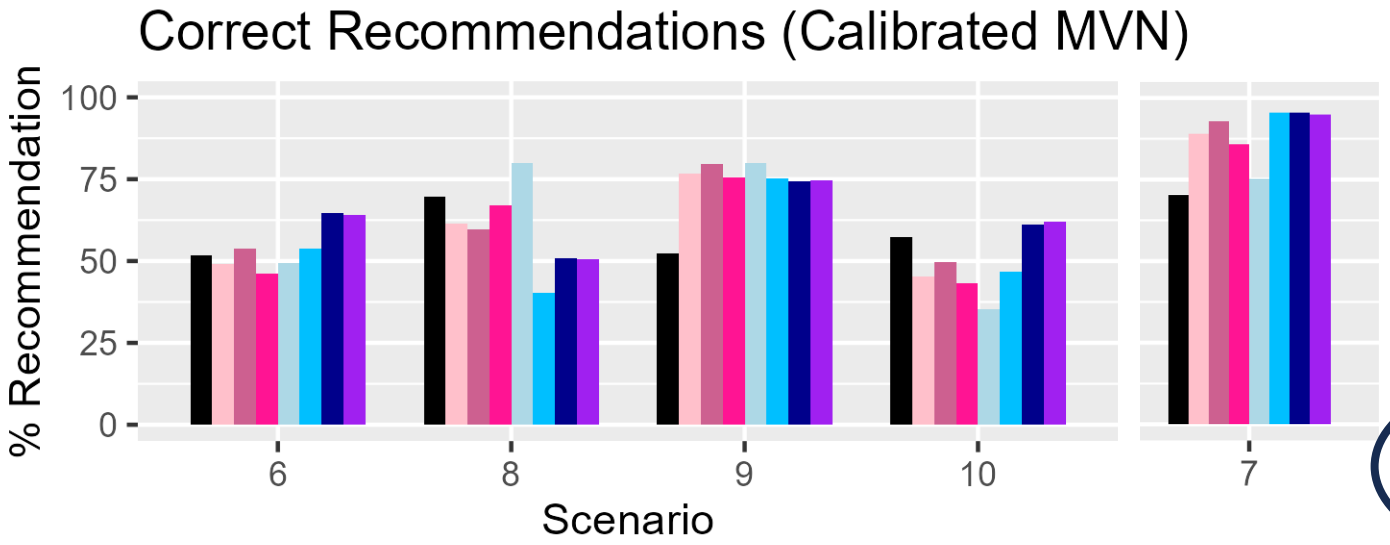


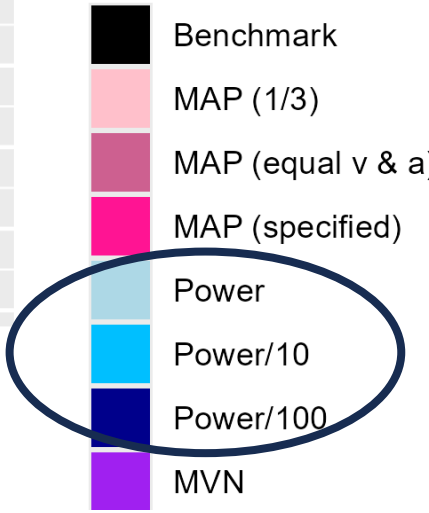
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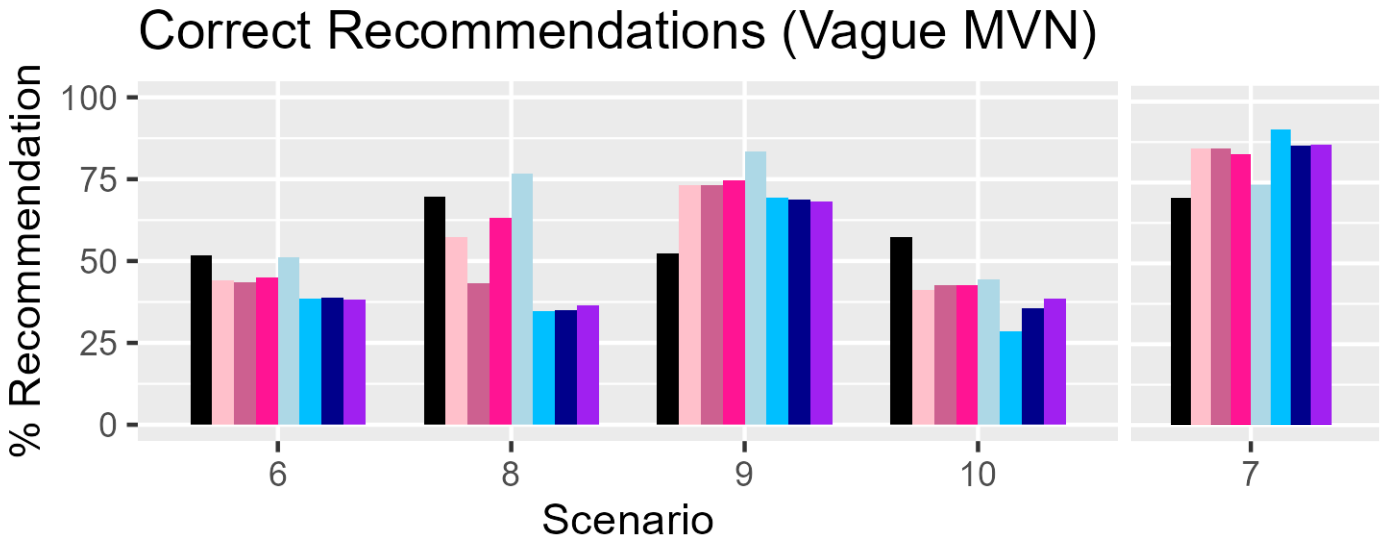


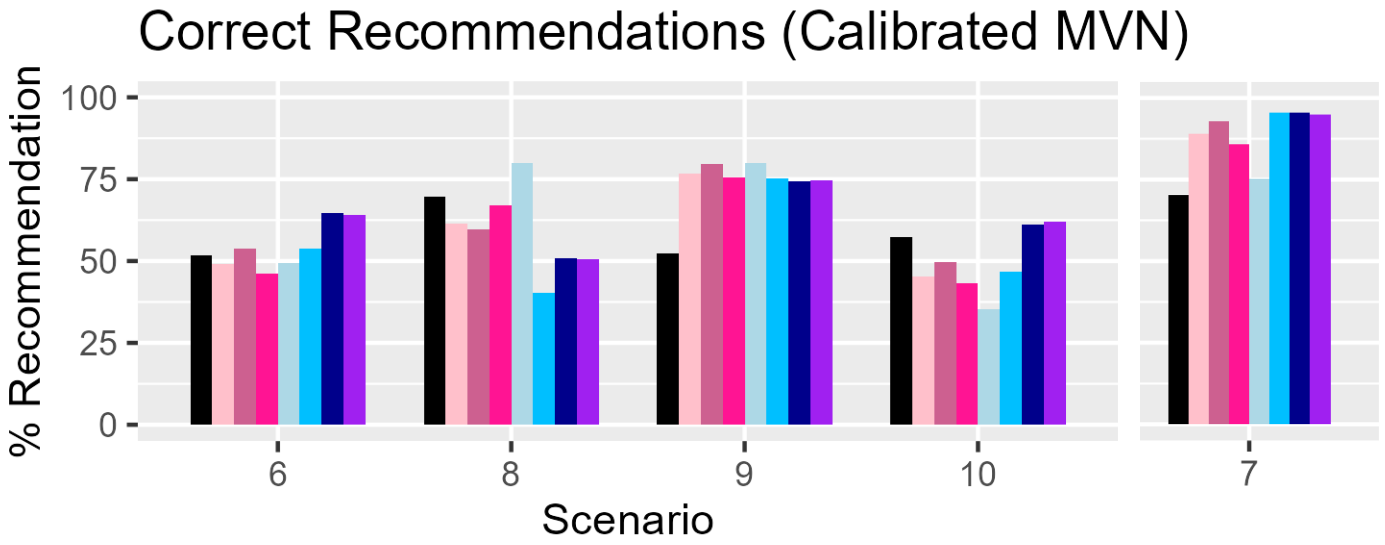


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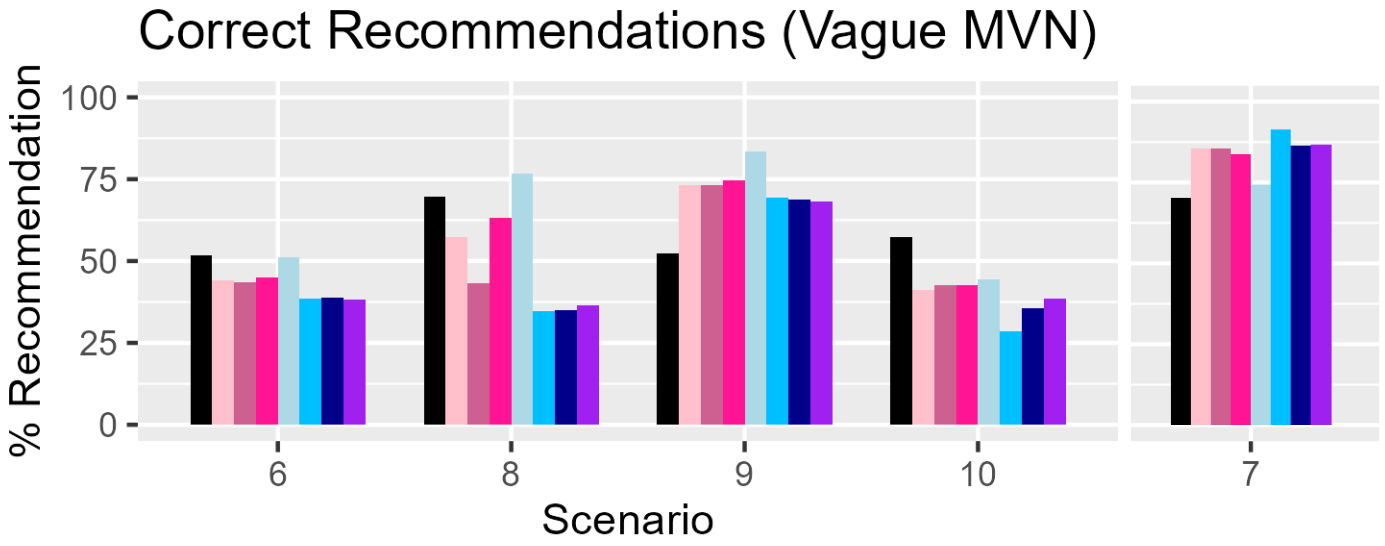


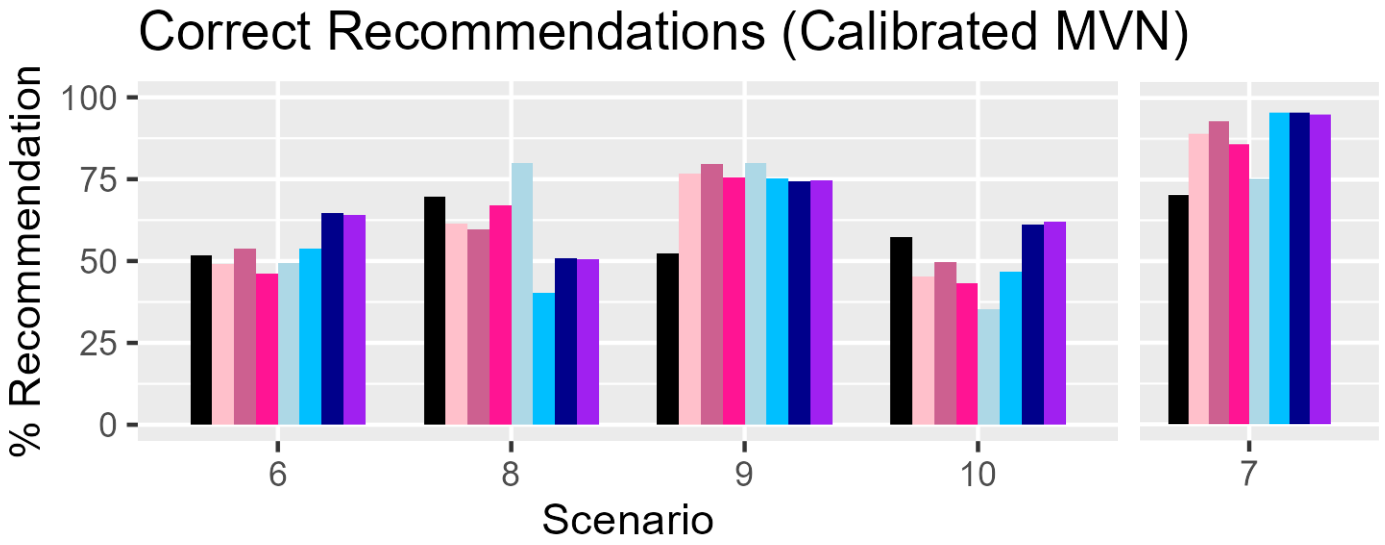
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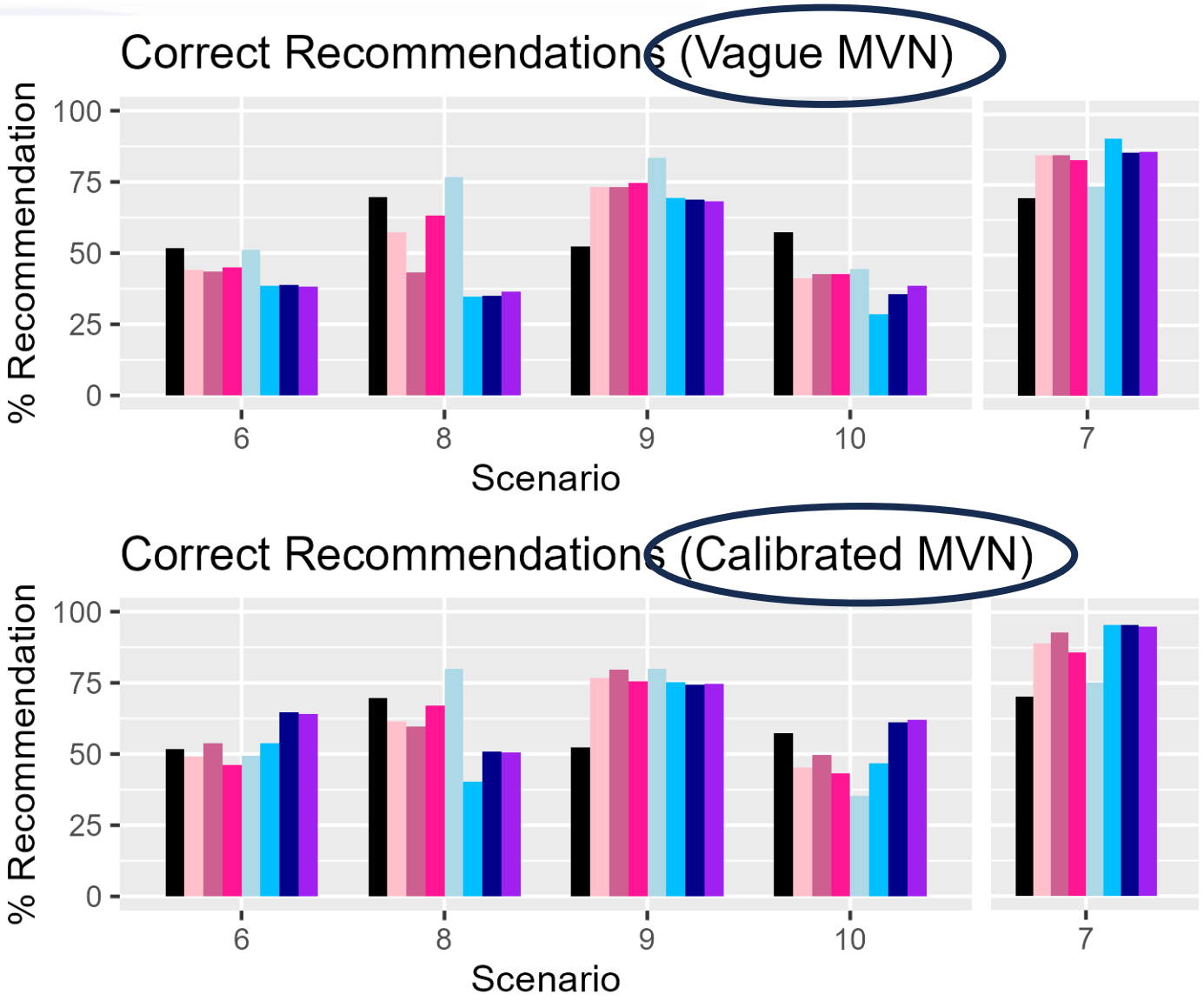


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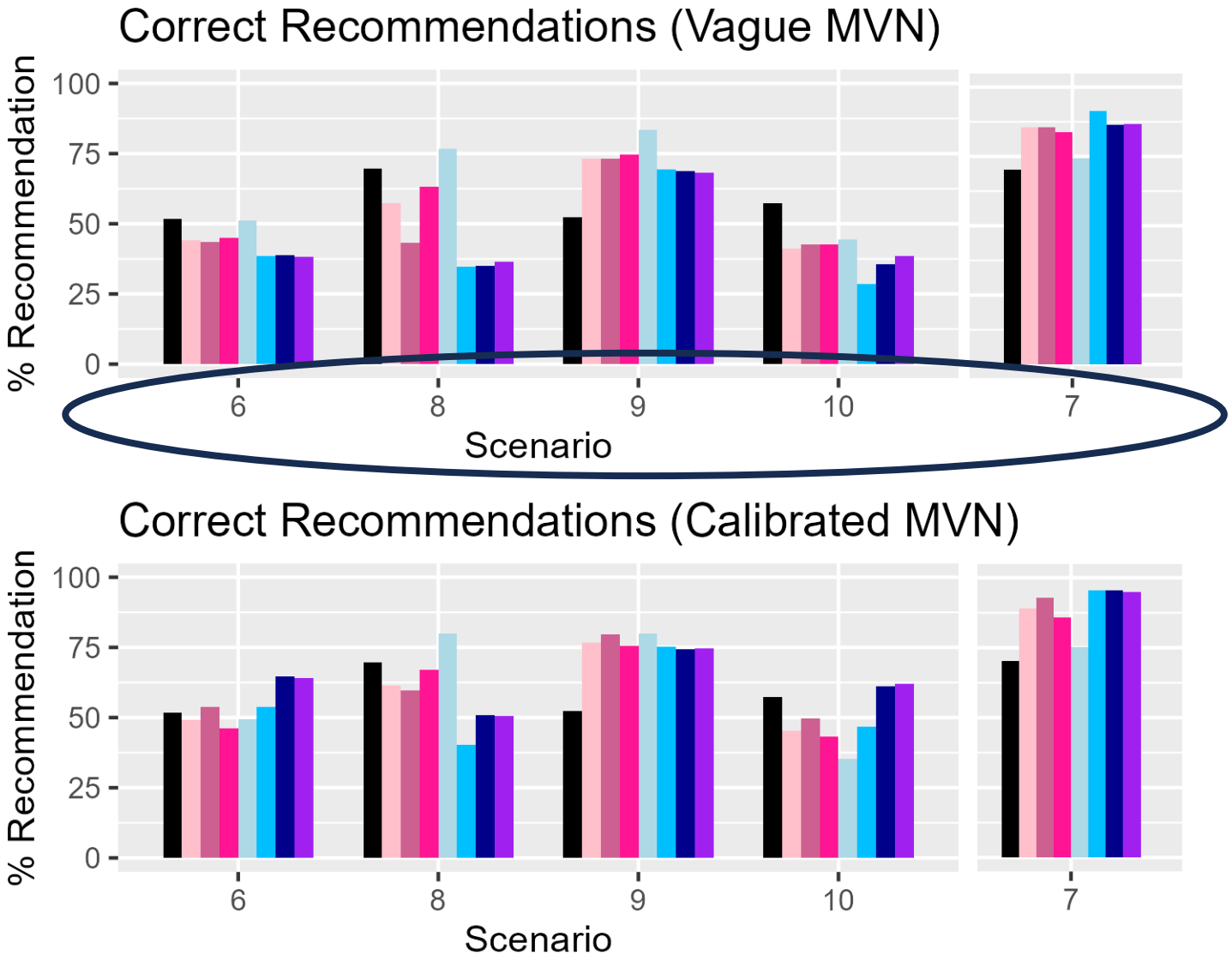
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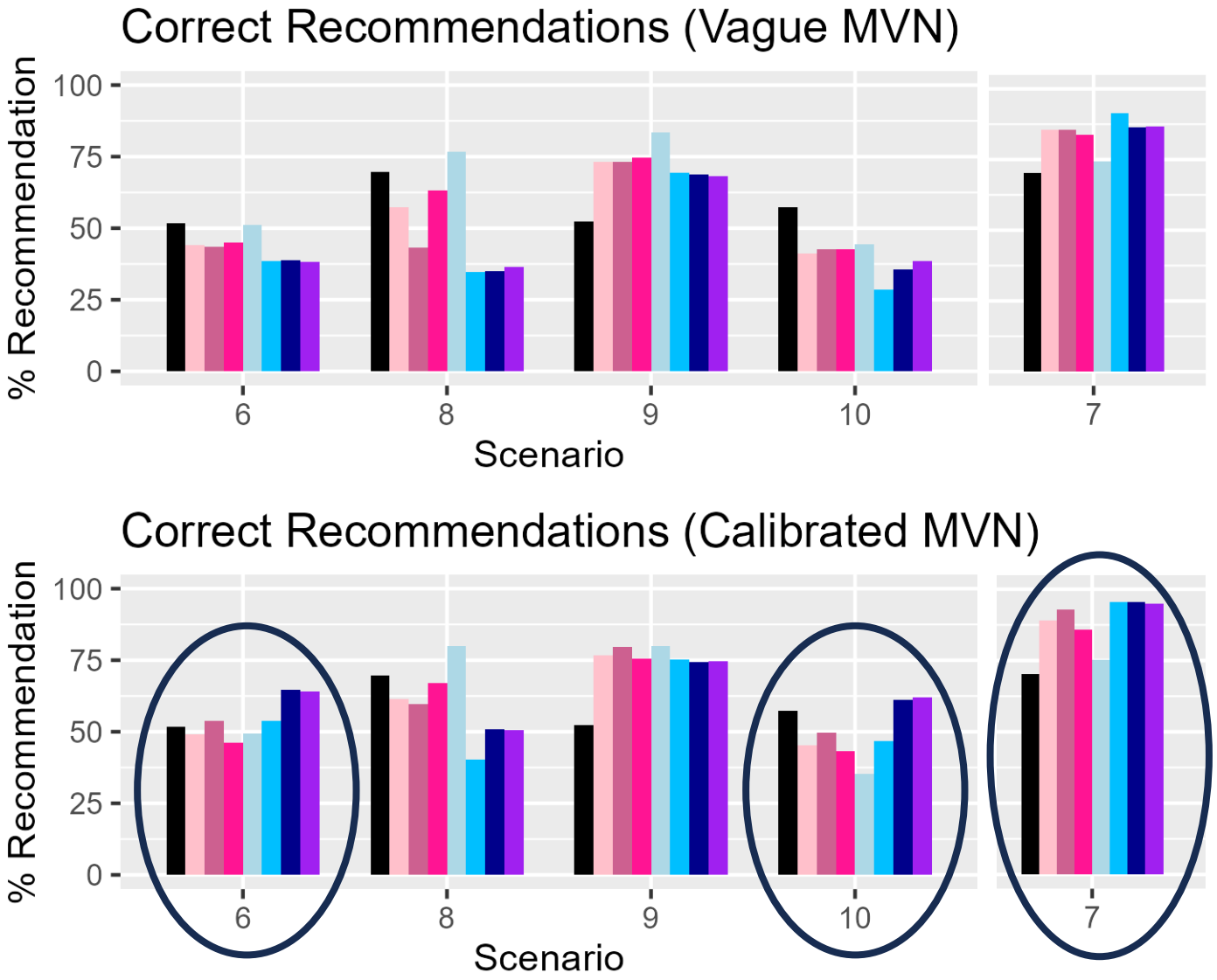
Simulation study results – low MTD scenarios



- Scenarios concordant with animal data
- **More correct recommendations** with calibrated MVN in some cases…

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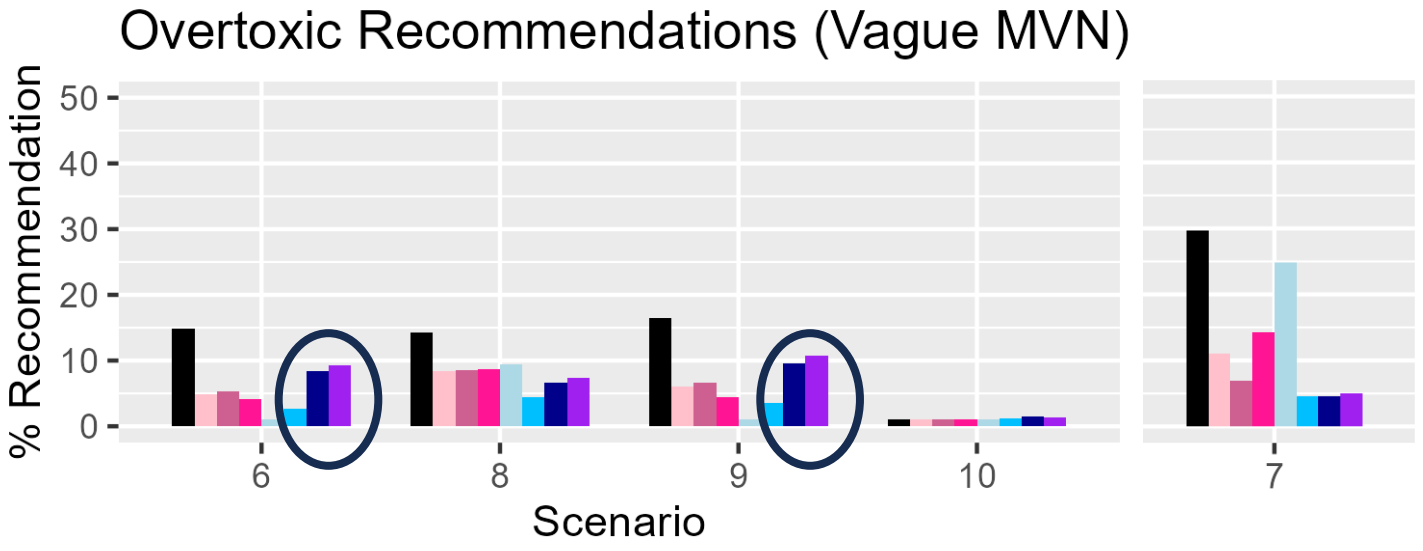
Simulation study results – low MTD scenarios

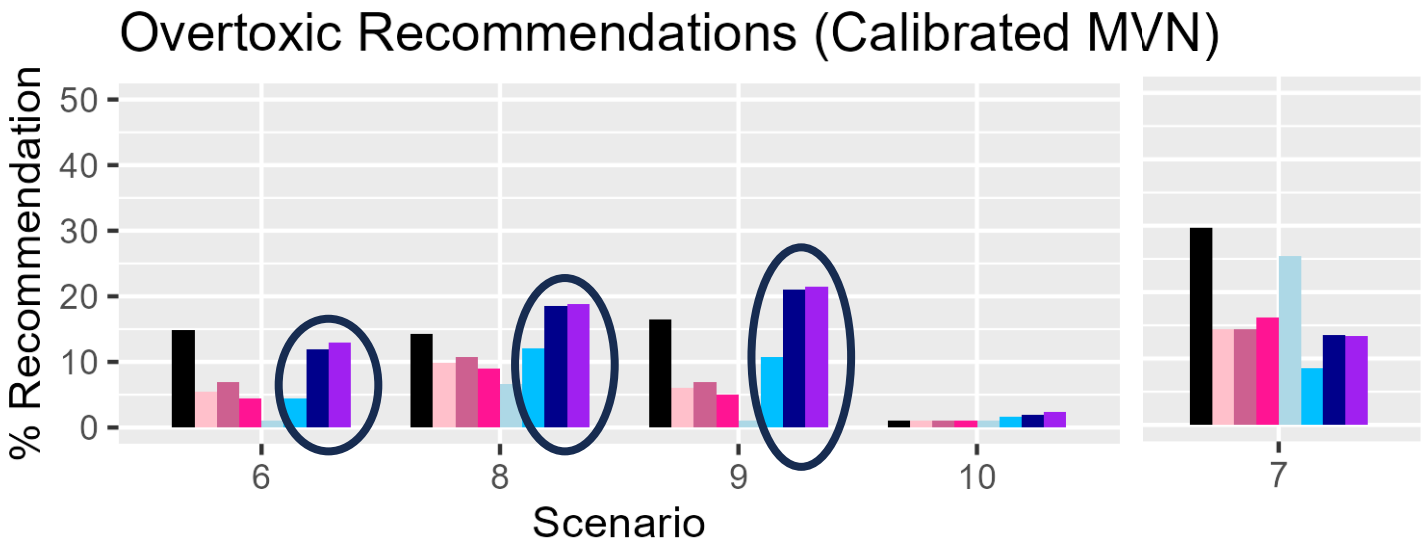


- Scenarios concordant with animal data
- **More correct recommendations** with calibrated MVN in some cases…

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Simulation study results – low MTD scenarios



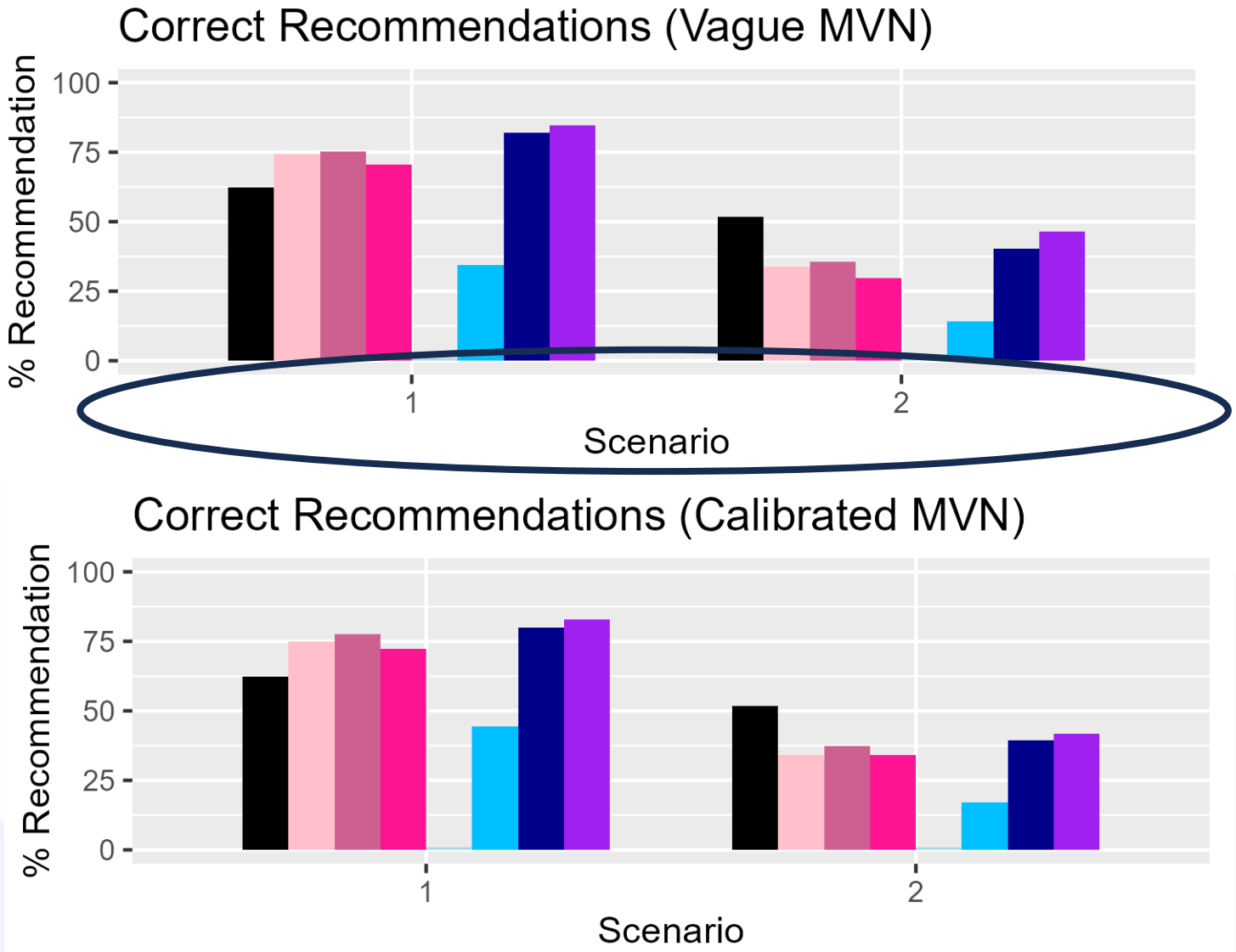


- Scenarios concordant with animal data
- **More correct recommendations** with calibrated MVN in some cases…
- … at the cost of **more overtoxic recommendations**



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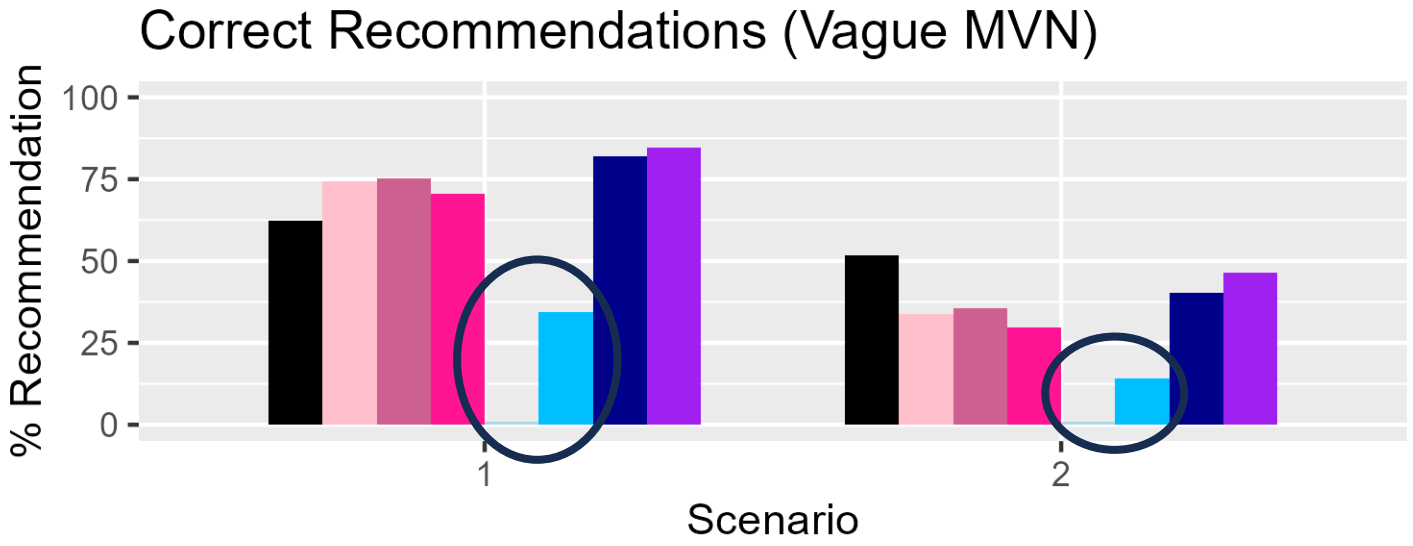
Simulation study results – high MTD scenarios

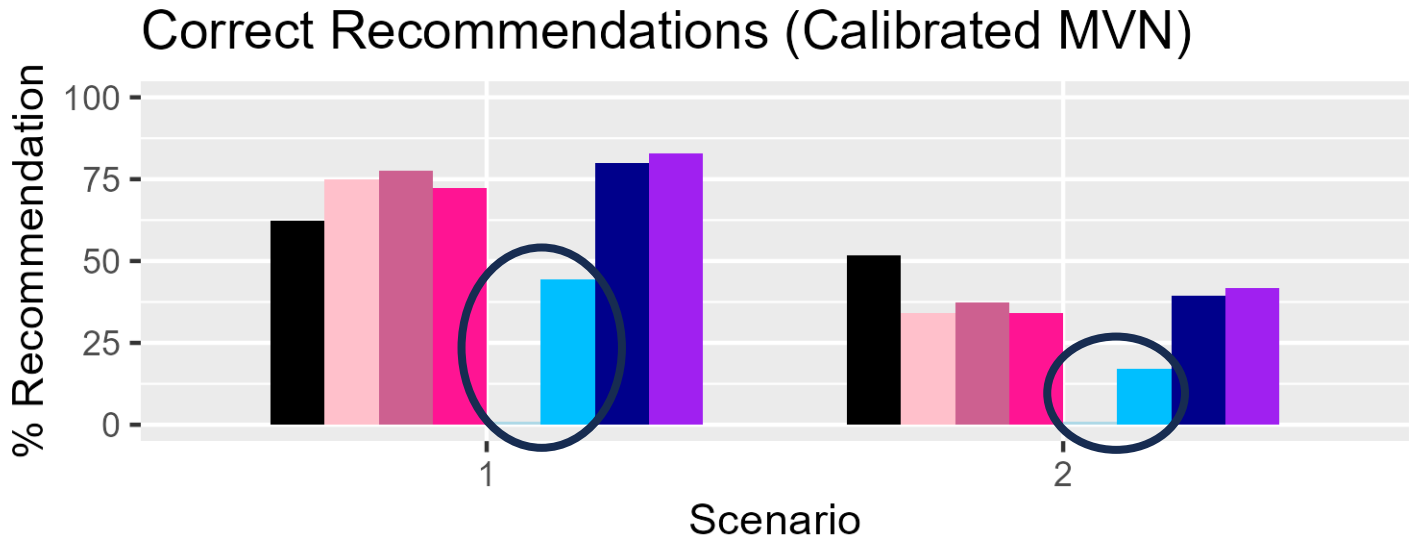


- Scenarios discordant with animal data
- Power prior **unefficient**

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Simulation study results – high MTD scenarios



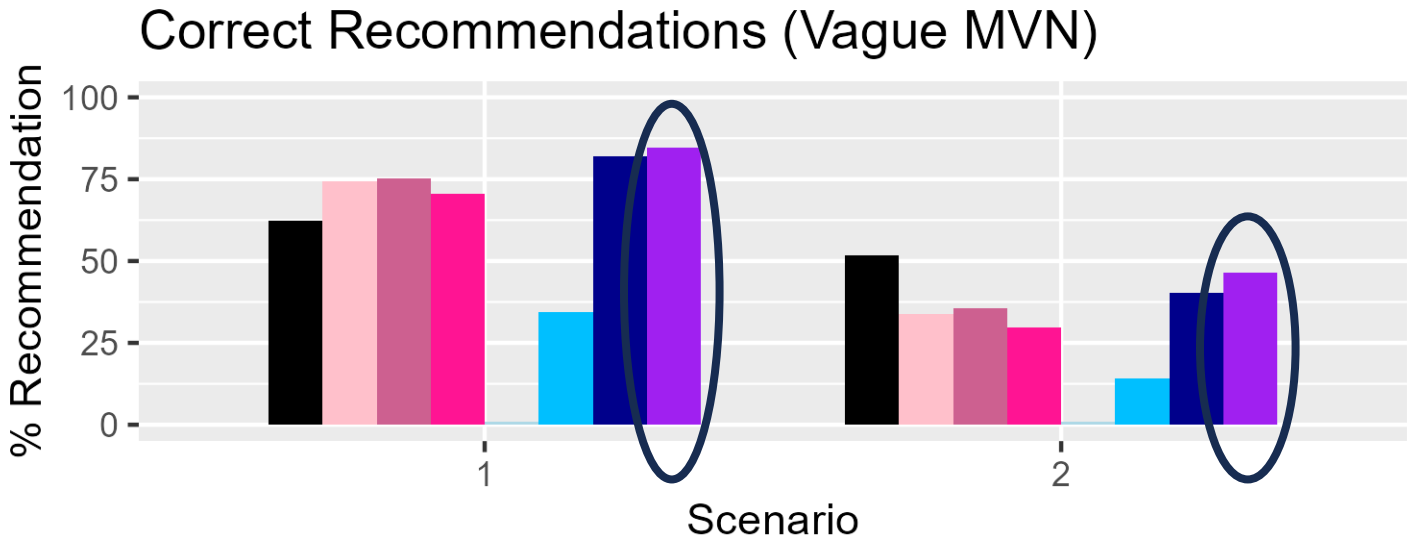


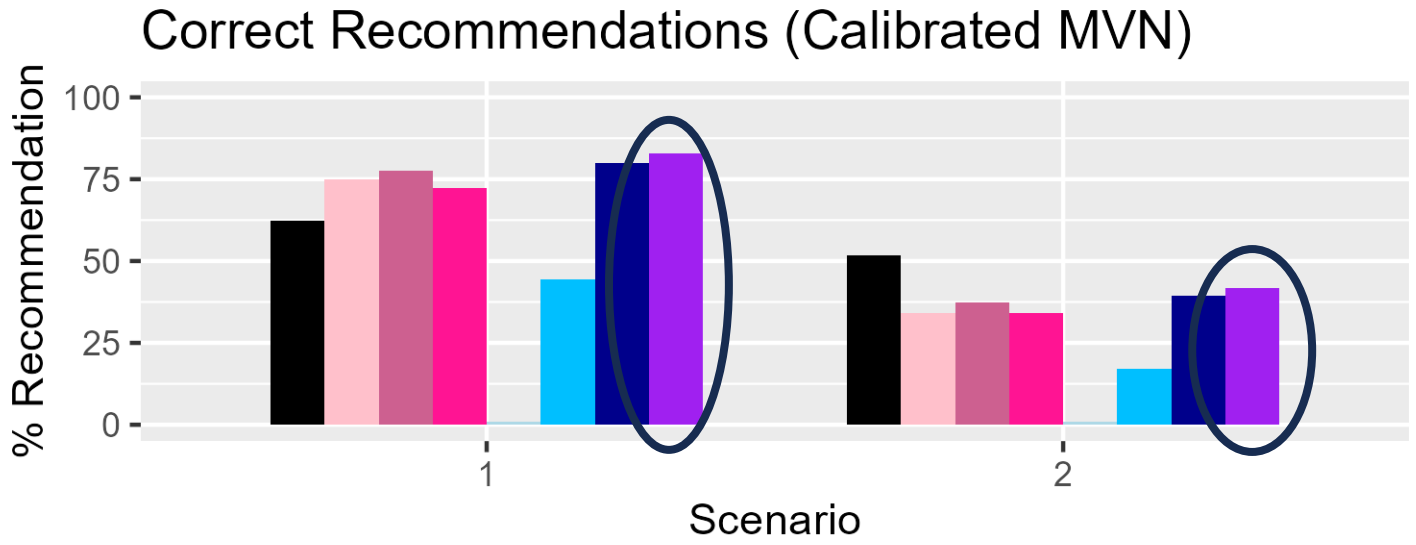
- Scenarios discordant with animal data
- Power prior **unefficient**

Benchmark
MAP (1/3)
MAP (equal v & a)
MAP (specified)
Power
Power/10
Power/100
MVN

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Simulation study results – high MTD scenarios



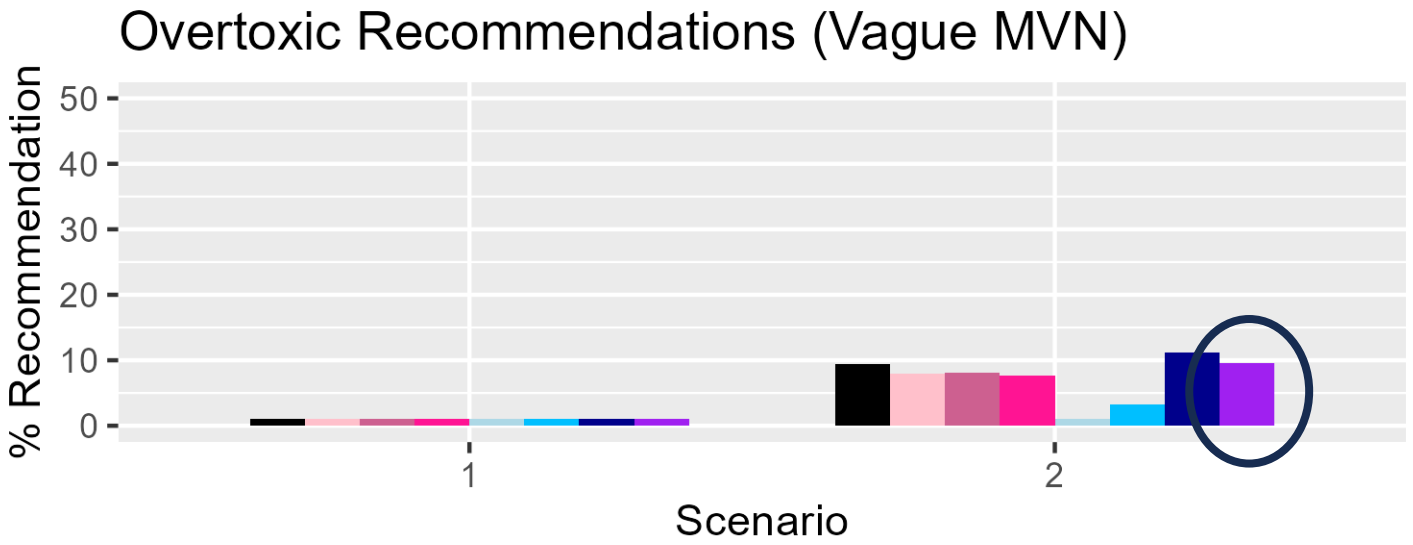


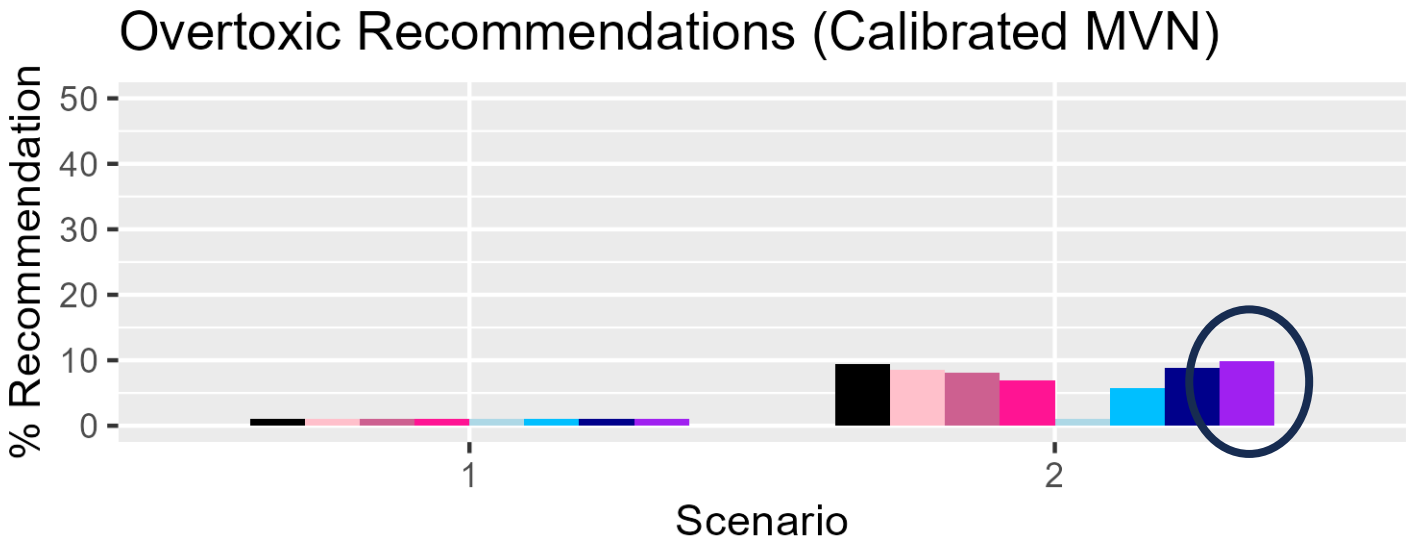
- Scenarios discordant with animal data
- Power prior **unefficient**

Benchmark
MAP (1/3)
MAP (equal v & a)
MAP (specified)
Power
Power/10
Power/100
MVN

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Simulation study results – high MTD scenarios



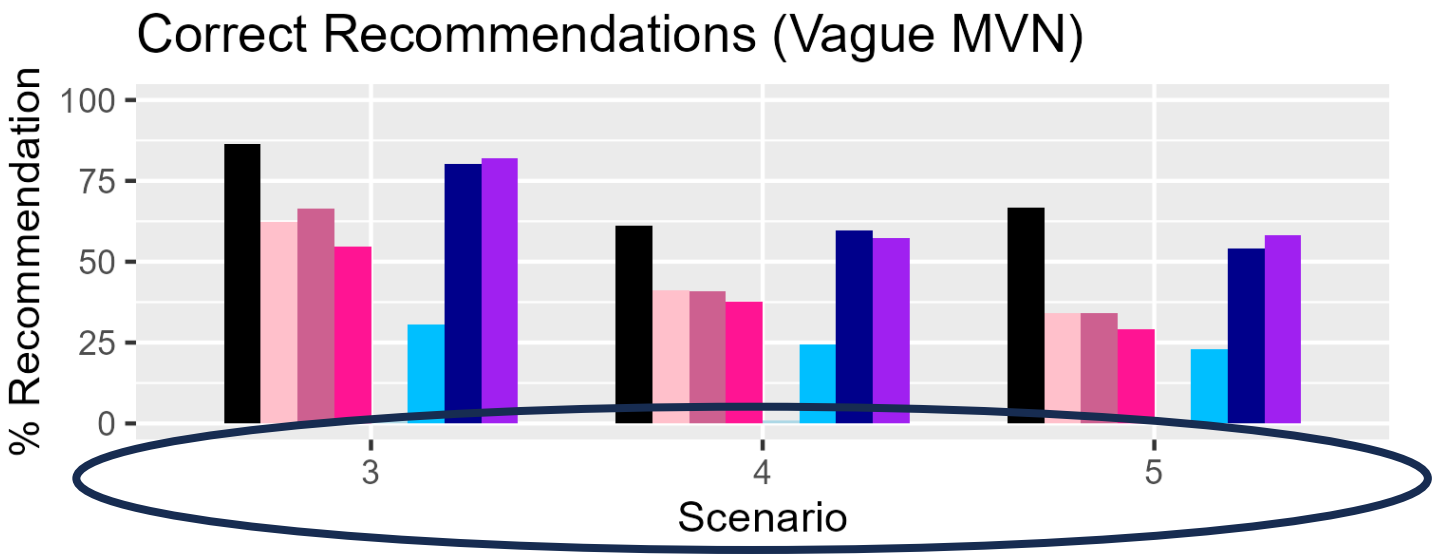


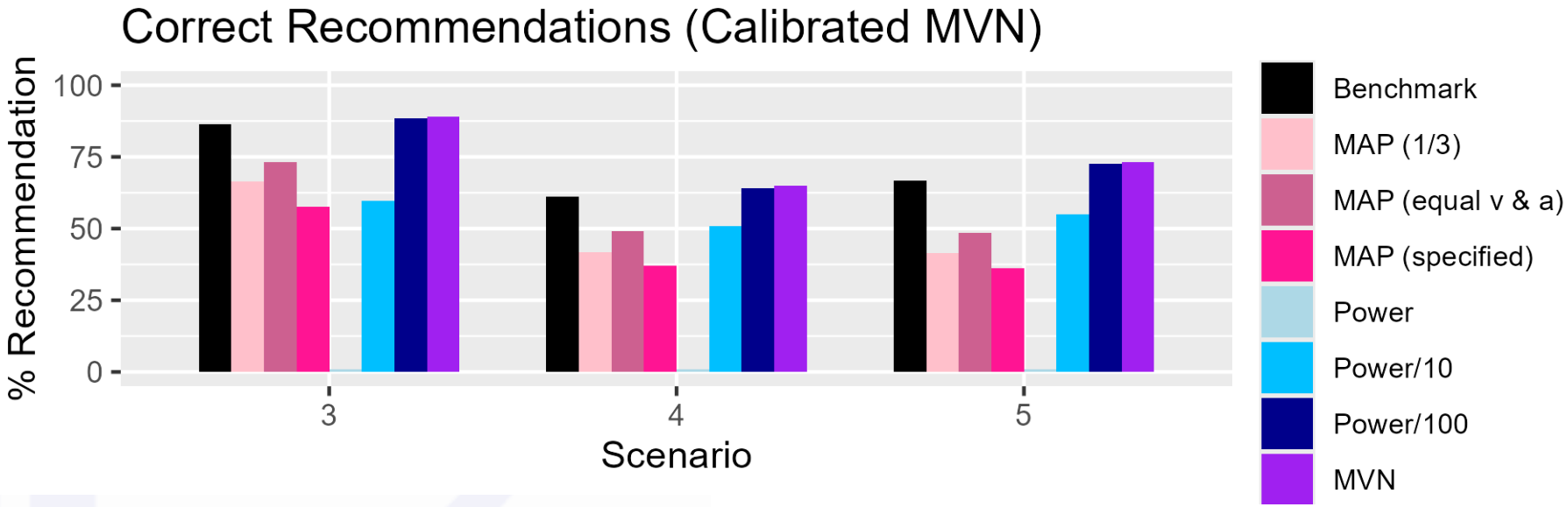
- Scenarios discordant with animal data
- Power prior **unefficient**
- Overtoxic recommendations low because true MTD is high

Benchmark
MAP (1/3)
MAP (equal v & a)
MAP (specified)
Power
Power/10
Power/100
MVN

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Simulation study results – middle ground

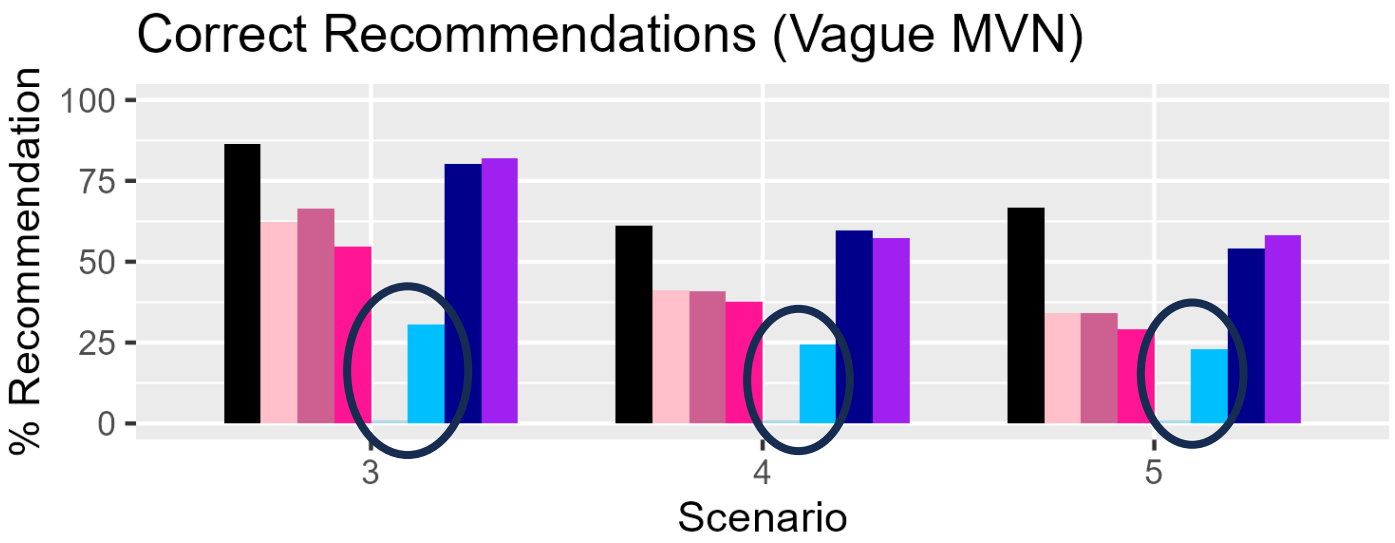


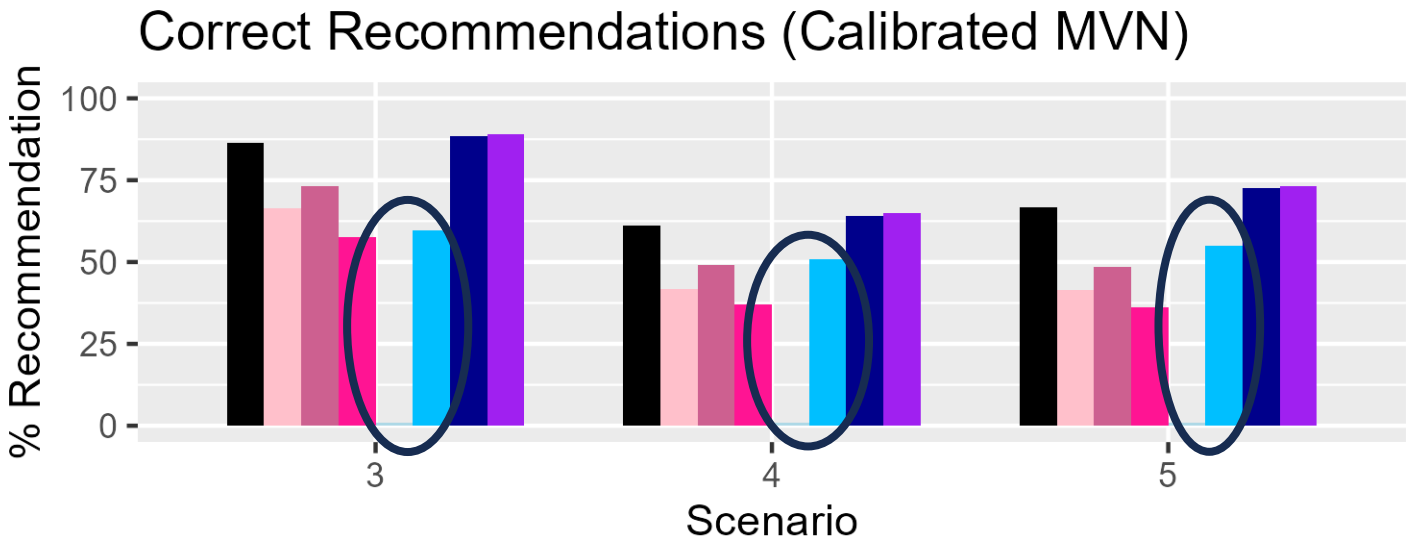


- Power prior still **unefficient**
- Some scenarios with **< 40% correct recommendations with MAP**

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Simulation study results – middle ground



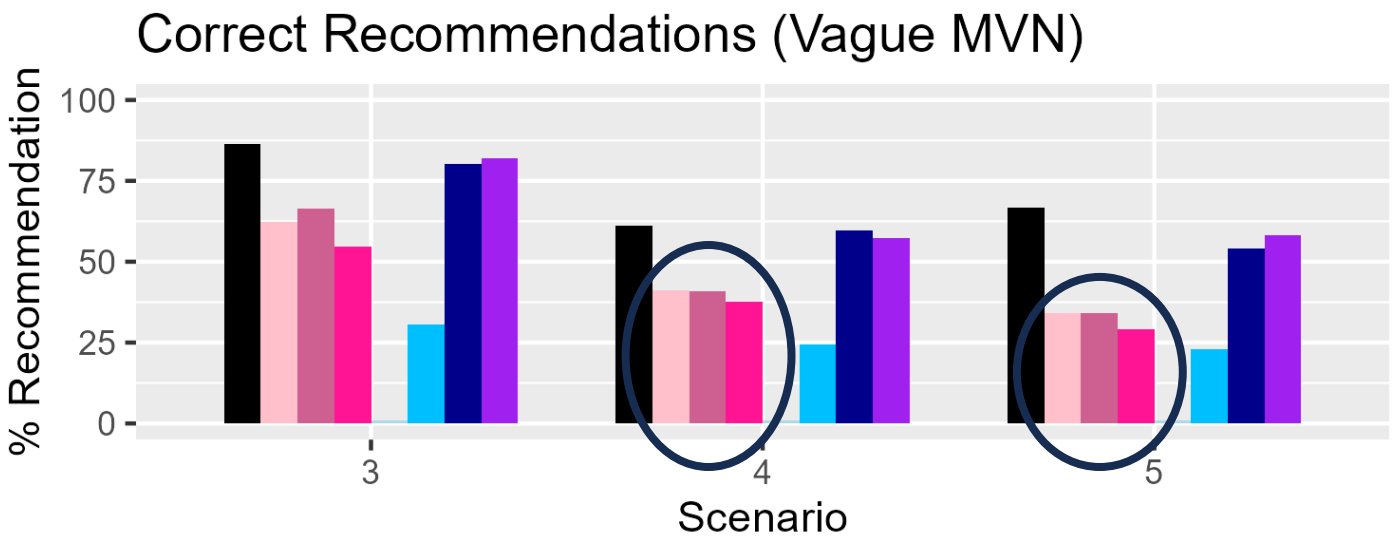


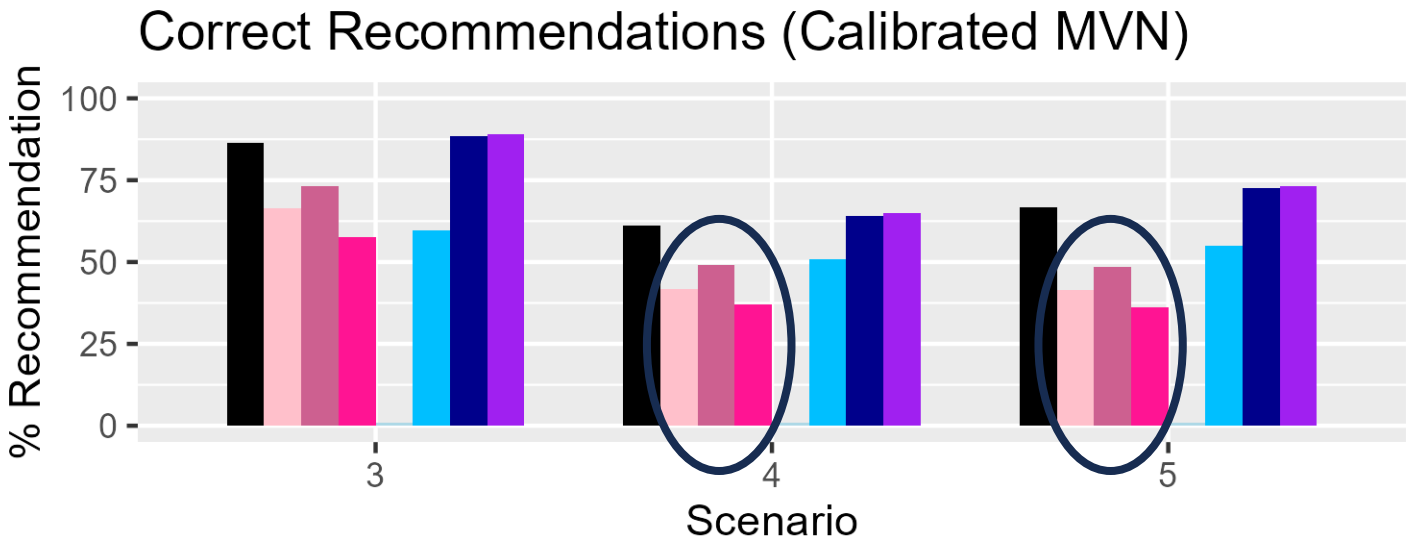


- Power prior still **unefficient**
- Some scenarios with **< 40% correct recommendations with MAP**

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Simulation study results – middle ground



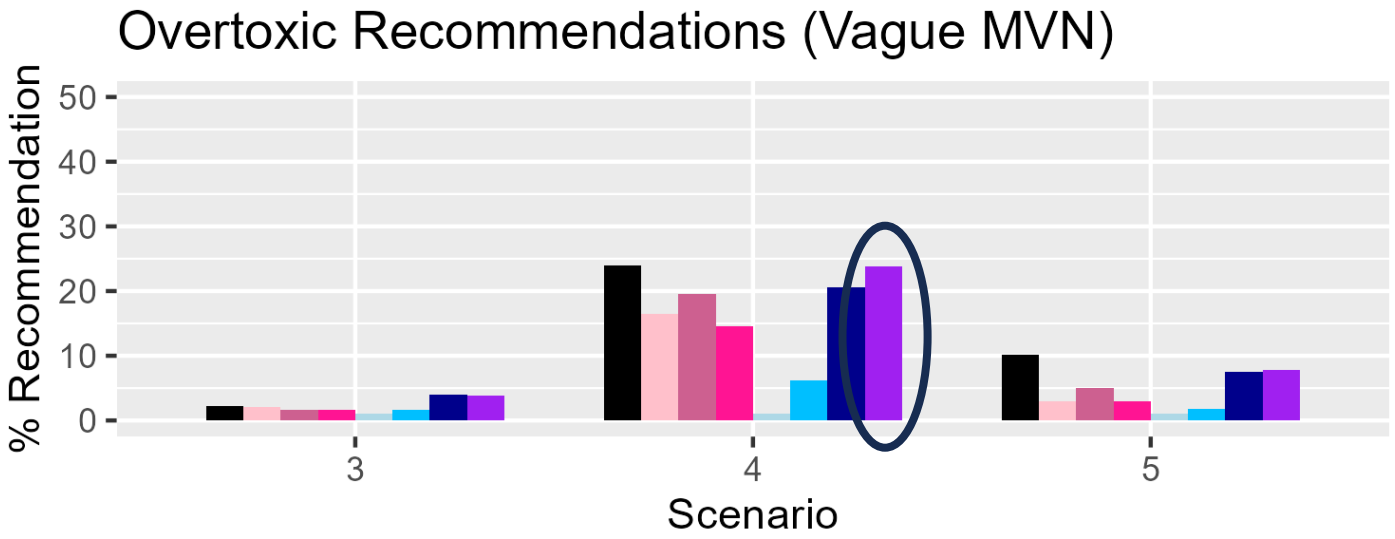


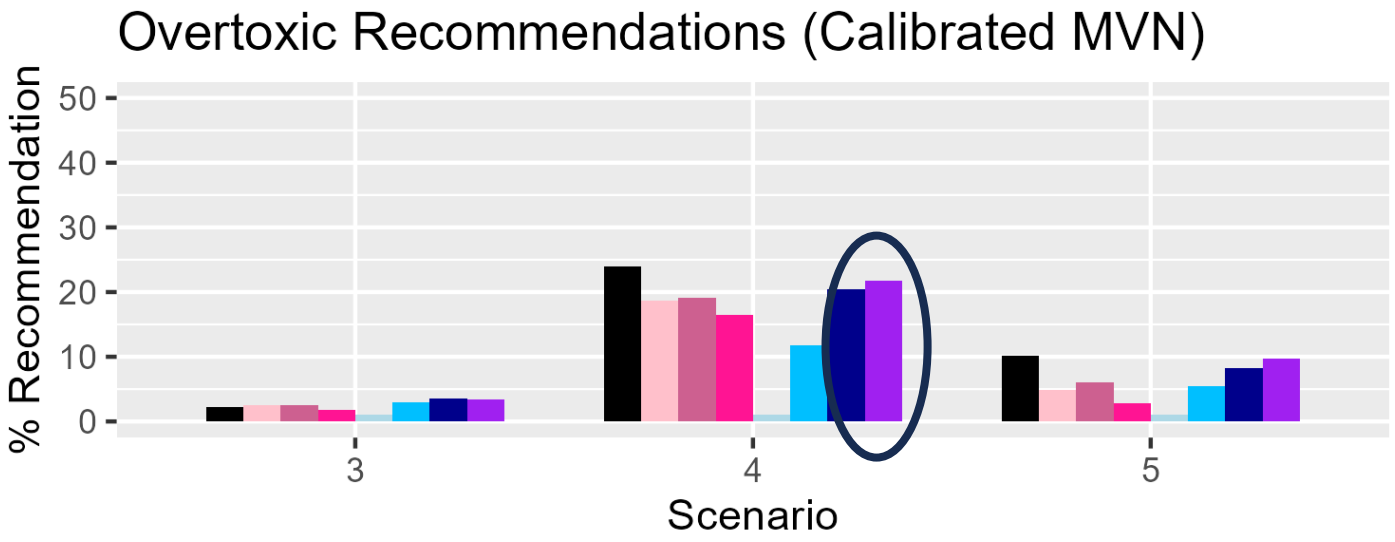


- Power prior still **unefficient**
- Some scenarios with **< 40% correct recommendations with MAP**

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Simulation study results – middle ground





- Power prior still **unefficient**
- Some scenarios with **< 40% correct recommendations with MAP**



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Summary

	+	−
MVN prior	• Quicker escalation	• Less safety • Does not use historical data
Power prior	• Incorporates historical data	• Unflexible and hard to calibrate • Poor performance when discordance
MAP prior	• Flexible • Safest way to incorporate animal data • Performant in extreme cases • Safer than calibrated MVN	• Less efficient than calibrated MVN • Not performant in the middle ground

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Published article



MAIN PAPER

Integrating Preclinical Insights for Adaptive Dose Escalation in Phase I Oncology Trials

Helen Barnett, Melanie Guhl, Fulvio Di Stefano, Donia Skanji, Sandrine Guilleminot, Gaelle Saint-Hilary, Pavel Mozgunov, Marie-Karelle Riviere

First published: 19 April 2026 | https://doi.org/10.1002/pst.70093 | VIEW METRICS

Pavel Mozgunov and Marie-Karelle Riviere contributed equally to this study.

Codes: https://github.com/Saryga-SAS/preclinical_insights_dose_escalation

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Bayes Bayesian Biostatistics Leiden, NL 2026

Thank you for your attention



SERVIER

UNIVERSITY OF CAMBRIDGE

Lancaster University

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BACK UP

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Extended EWOC criterion

- BLRM: next dose = highest probability of target DLT

➢ Escalation with overdose control (EWOC)

Overdose control criterion[1]:

$$P(p_{i^*j} > 0.33|Data) \leq \varepsilon$$

➢ Conservative for unexplored doses

Proposed extension for less conservative escalation:

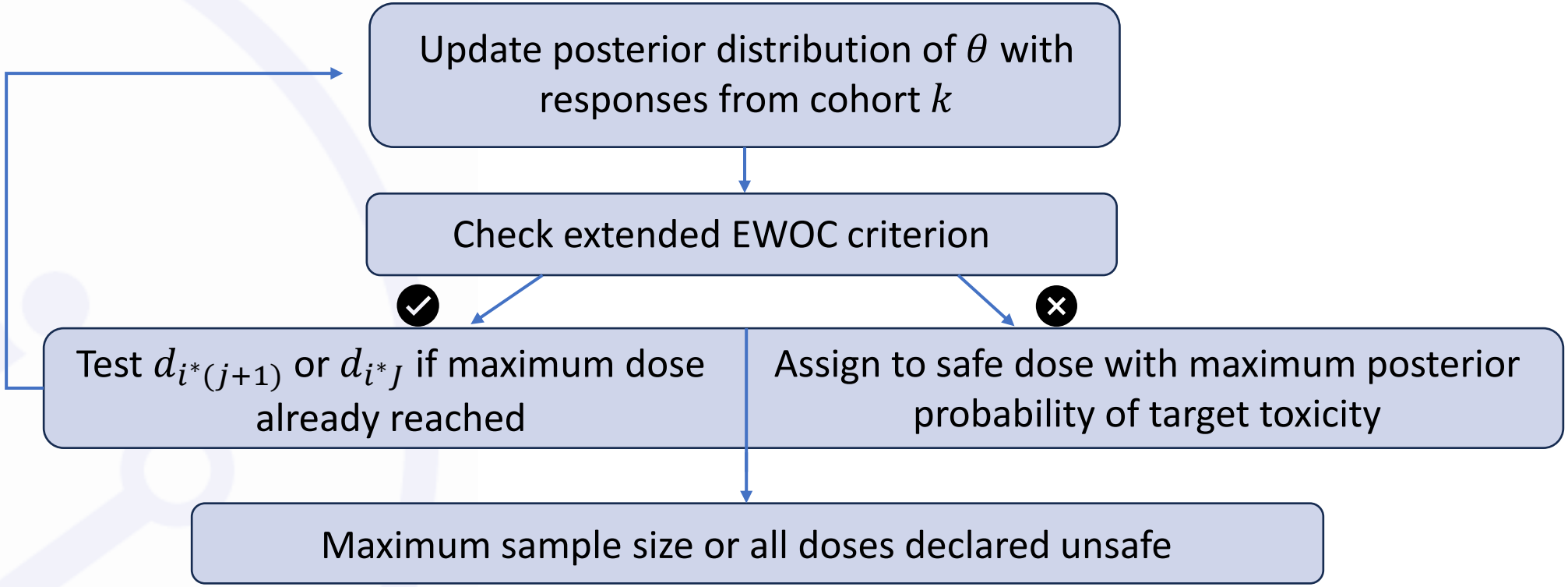
if dose $d_{i^*(j+1)}$ unexplored and d_{i^*j} safe, then escalation

[1]Neuenschwander et al., Stat in Med, 2008

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BLRM model procedure

Dose escalation procedure after cohort k (dose j)



- MTD = dose with highest posterior probability of target toxicity
- Dose recommended at any stage is based on all previous doses and preclinical DLT information

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Full MAP prior hierarchical model[3]

$$\theta_i \mid \mu_i, \psi \sim MVN(\mu_i, \psi)$$

$$\psi = \begin{pmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ \rho\tau_1\tau_2 & \tau_1^2 \end{pmatrix}$$

$$\mu_i \mid m, \Sigma \sim MVN(m, \Sigma)$$

$$m = \begin{pmatrix} m_1 \\ m_2 \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} \sigma_1^2 & \kappa\sigma_1\sigma_2 \\ \kappa\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

$$m_1 \sim N(\nu_1, s_1^2), m_2 \sim N(\nu_2, s_2^2)$$
$$\tau_1 \sim halfN(\zeta_1), \tau_2 \sim halfN(\zeta_2), \rho \sim U(-1,1)$$
$$\sigma_1 \sim halfN(c_1), \sigma_2 \sim halfN(c_2), \kappa \sim U(-1,1)$$

$$\theta_{i^*} \sim MVN(\mu_i, \psi) \text{ with prior probability } w_i$$
$$\theta_{i^*} \sim MVN(m_r, R_r) \text{ with prior probability } w_r$$

$$\sum_{i=1}^{I} w_i + w_r = 1$$

$$m_r = \begin{pmatrix} m_{r1} \\ m_{r2} \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} \sigma_{r1}^2 & 0 \\ 0 & \sigma_{r2}^2 \end{pmatrix}$$

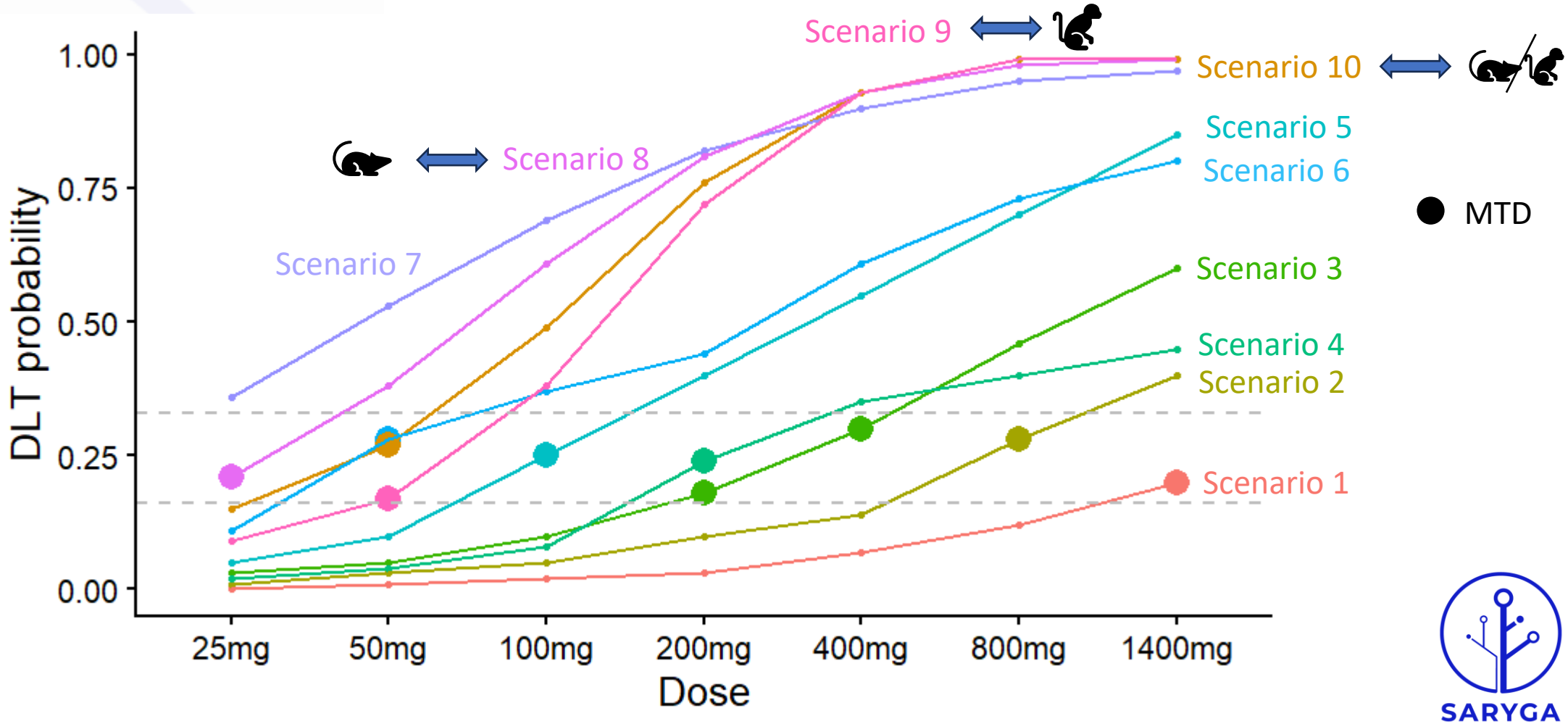
[3]Zheng et al., SMMR, 2019

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Simulation study settings

Ten scenarios with different distributions of the DLT probabilities and MTD

- Plausible range of dose responses



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Simulation study

Calibration of priors:

- MVN: vague and calibrated
- Power prior: scaled by a factor 1, 1/10, 1/100
- MAP prior:
  - Equal weights for rat, monkey and robust component (1/3)
  - Equal weights between animal prior and robust component (equal v&a)
  - Specified weights based on concordance data (specified)

Outcomes:

- Percentage of correct recommendations of MTD
- Percentage of overtoxic recommendations
- Number of patients allocated to MTD (not shown)
- Number of patients allocated to toxic doses (not shown)

Reference : non parametric benchmark

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Full prior parameterisation

MVN

Vague

$$m_r = \begin{pmatrix} \log(\frac{0.2}{1-0.2}) \\ 0 \end{pmatrix}$$

$$R_r = \begin{pmatrix} 4 & 0 \\ 0 & 1 \end{pmatrix}$$

Calibrated

$$m_r = \begin{pmatrix} \log(\frac{0.1}{1-0.1}) \\ 0 \end{pmatrix}$$

$$R_r = \begin{pmatrix} 1 & 0 \\ 0 & 0.25 \end{pmatrix}$$

Power

$$\begin{cases} \alpha_{RAT} = p_{AK} * p_{RAT} \\ \alpha_{MONKEY} = p_{AK} * p_{MONKEY} \end{cases}$$

Power/10

$$\begin{cases} \alpha_{RAT} = p_{AK} * p_{RAT} /10 \\ \alpha_{MONKEY} = p_{AK} * p_{MONKEY}/10 \end{cases}$$

Power/100

$$\begin{cases} \alpha_{RAT} = p_{AK} * p_{RAT}/100 \\ \alpha_{MONKEY} = p_{AK} * p_{MONKEY}/100 \end{cases}$$

MAP(1/3)

$$w_r = w_{RAT} = w_{MONKEY} = \frac{1}{3}$$

MAP(equal v&a)

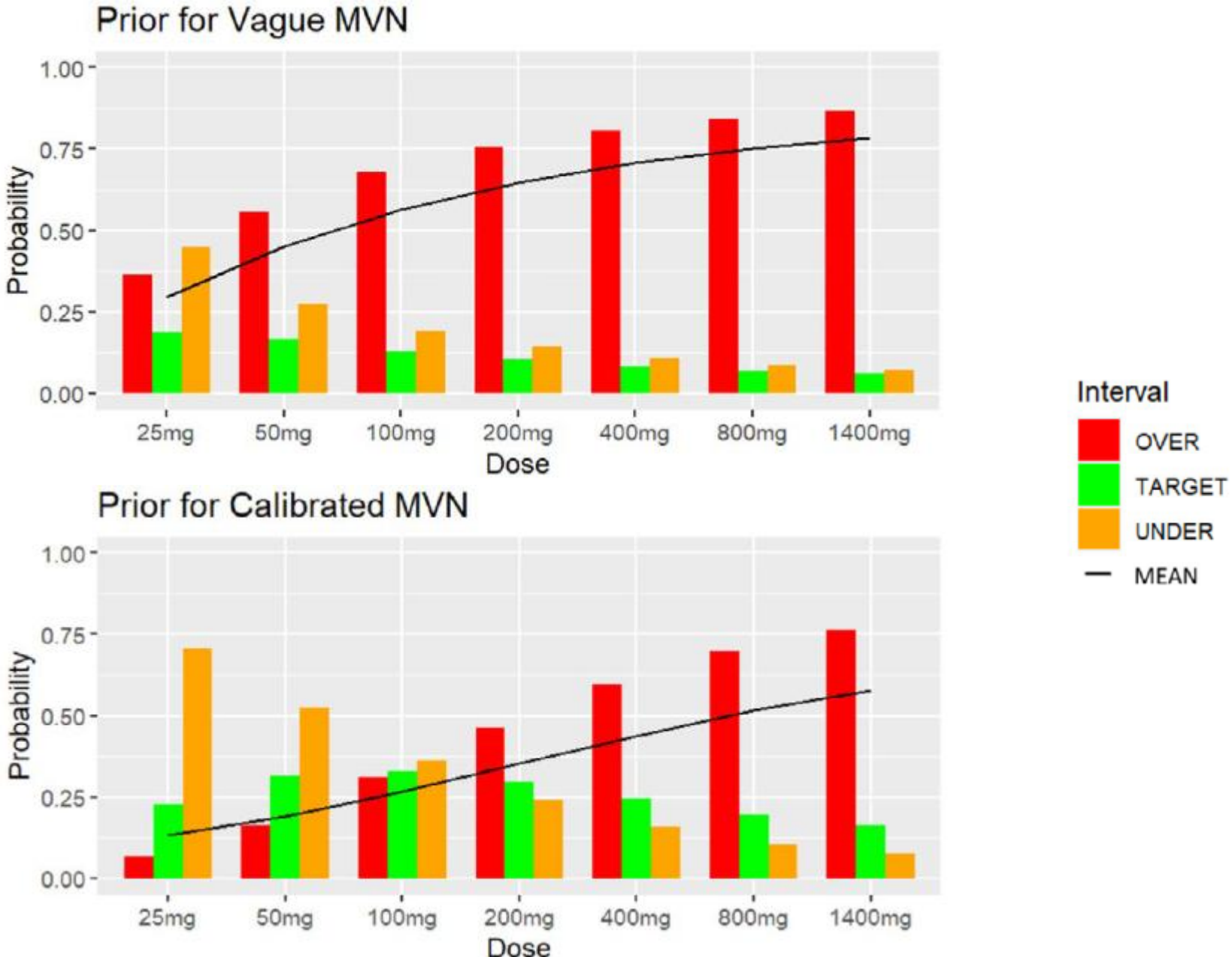
$$\begin{cases} w_r = 0.5 \\ w_{RAT} = 0.5 * p_{RAT}/(p_{MONKEY} + p_{RAT}) \\ w_{MONKEY} = 0.5 * p_{MONKEY}/(p_{MONKEY} + p_{RAT}) \end{cases}$$

MAP(specified)

$$\begin{cases} w_r = 1 - p_{AK} \\ w_{RAT} = p_{AK} * p_{RAT}/(p_{MONKEY} + p_{RAT}) \\ w_{MONKEY} = p_{AK} * p_{MONKEY}/(p_{MONKEY} + p_{RAT}) \end{cases}$$

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Prior characteristics



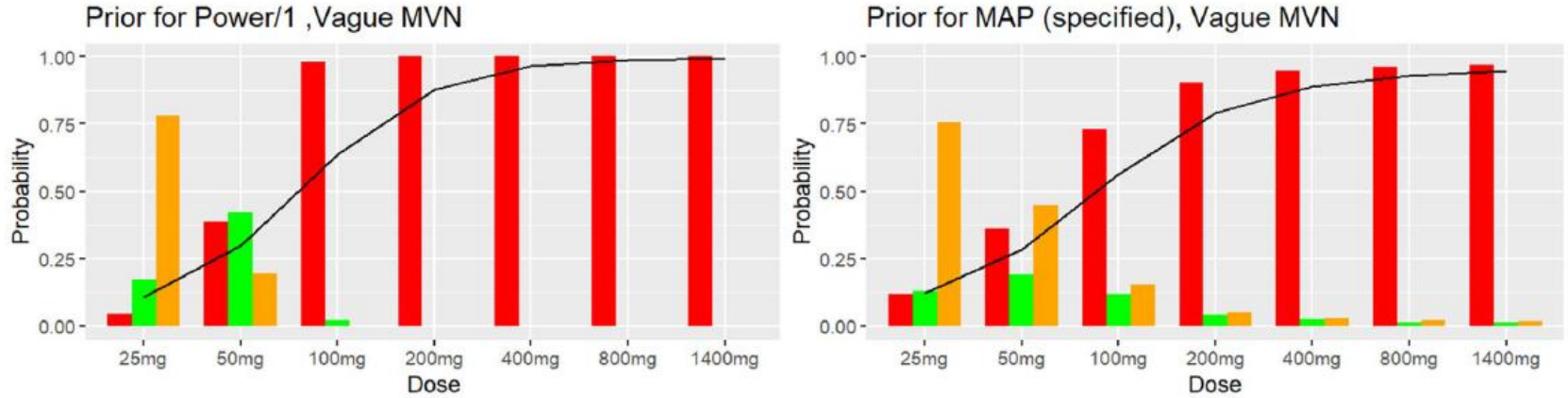
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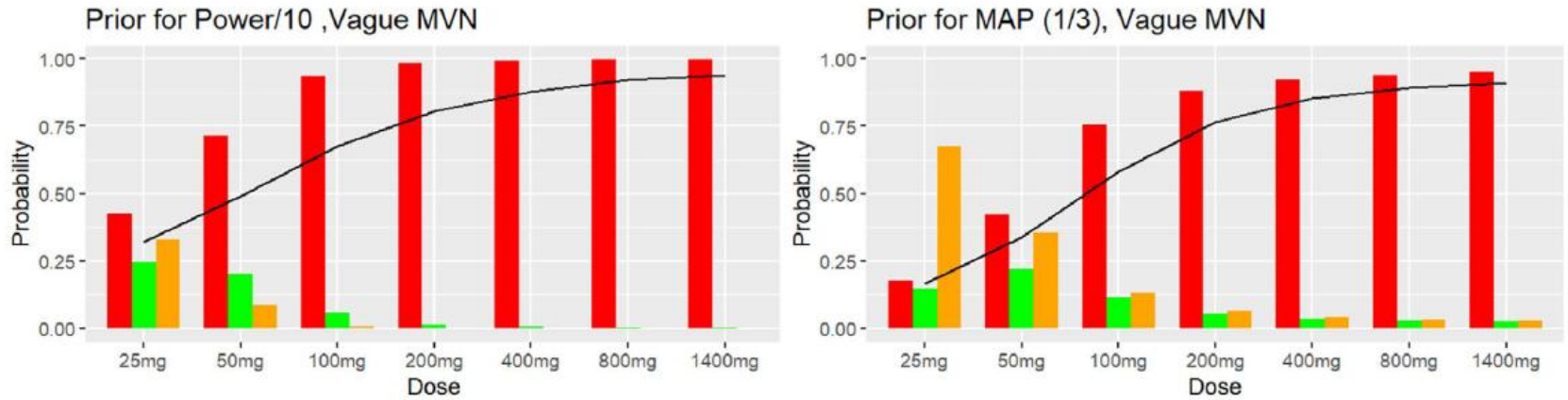
Prior characteristics

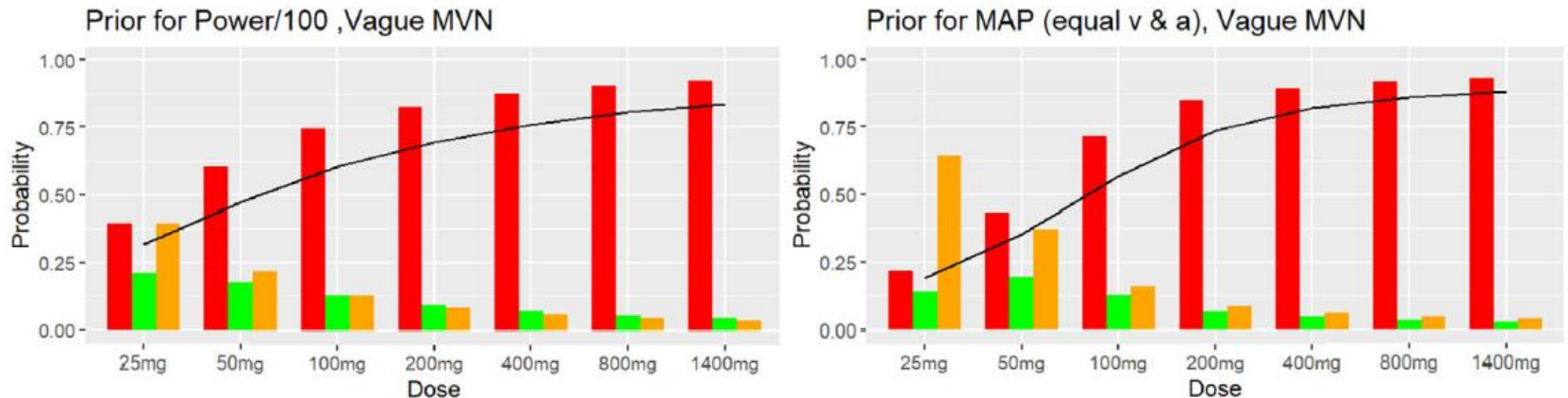
Prior weight	Rat	Monkey
MAP (1/3)	0.33	0.33
MAP (equal v & a)	0.21	0.29
MAP (specified)	0.36	0.48
Power	0.45	0.60
Power/10	0.04	0.06
Power/100	0.004	0.006

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Prior characteristics



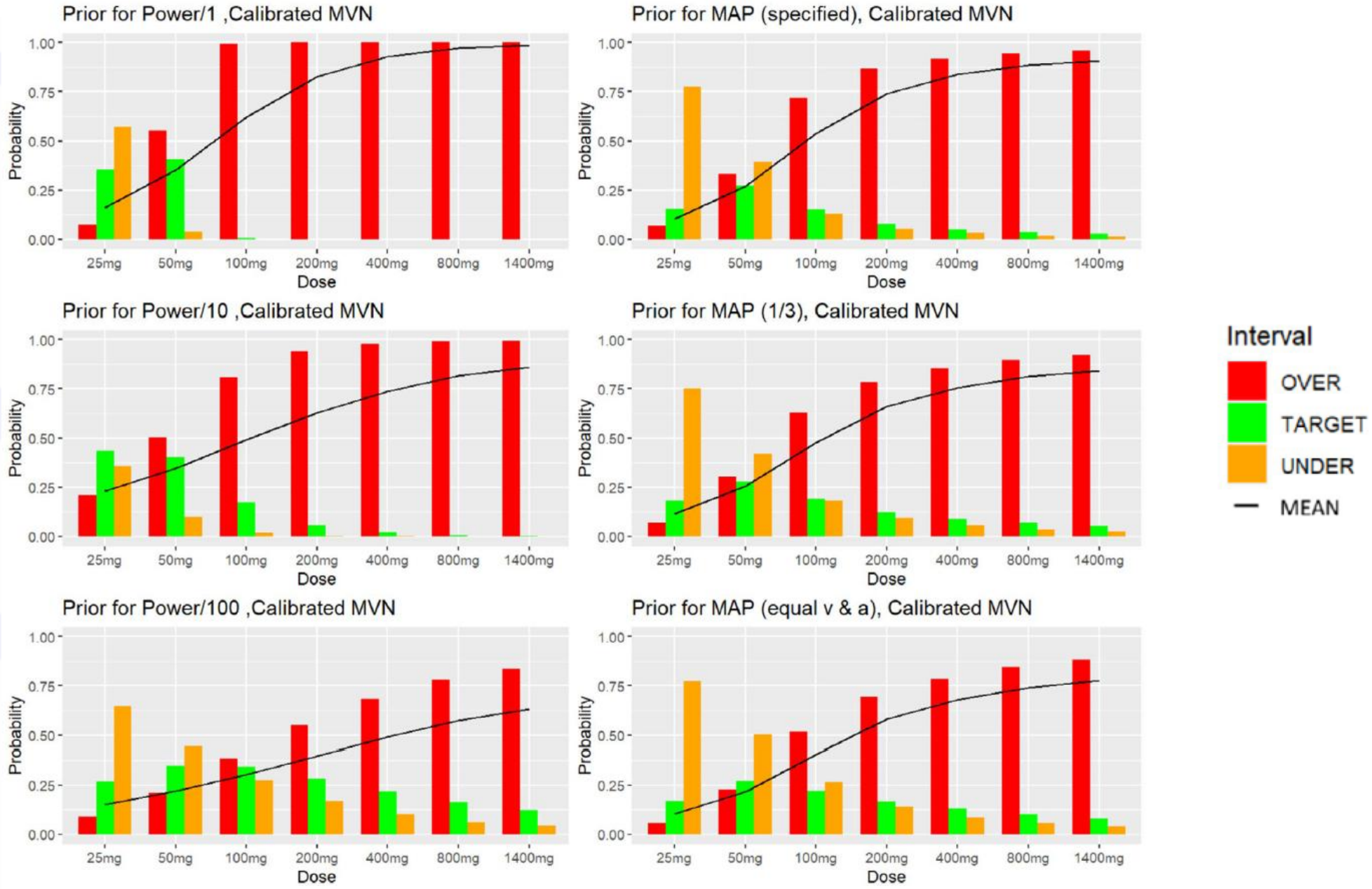






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Prior characteristics



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Prior characteristics

From the article supplementary material

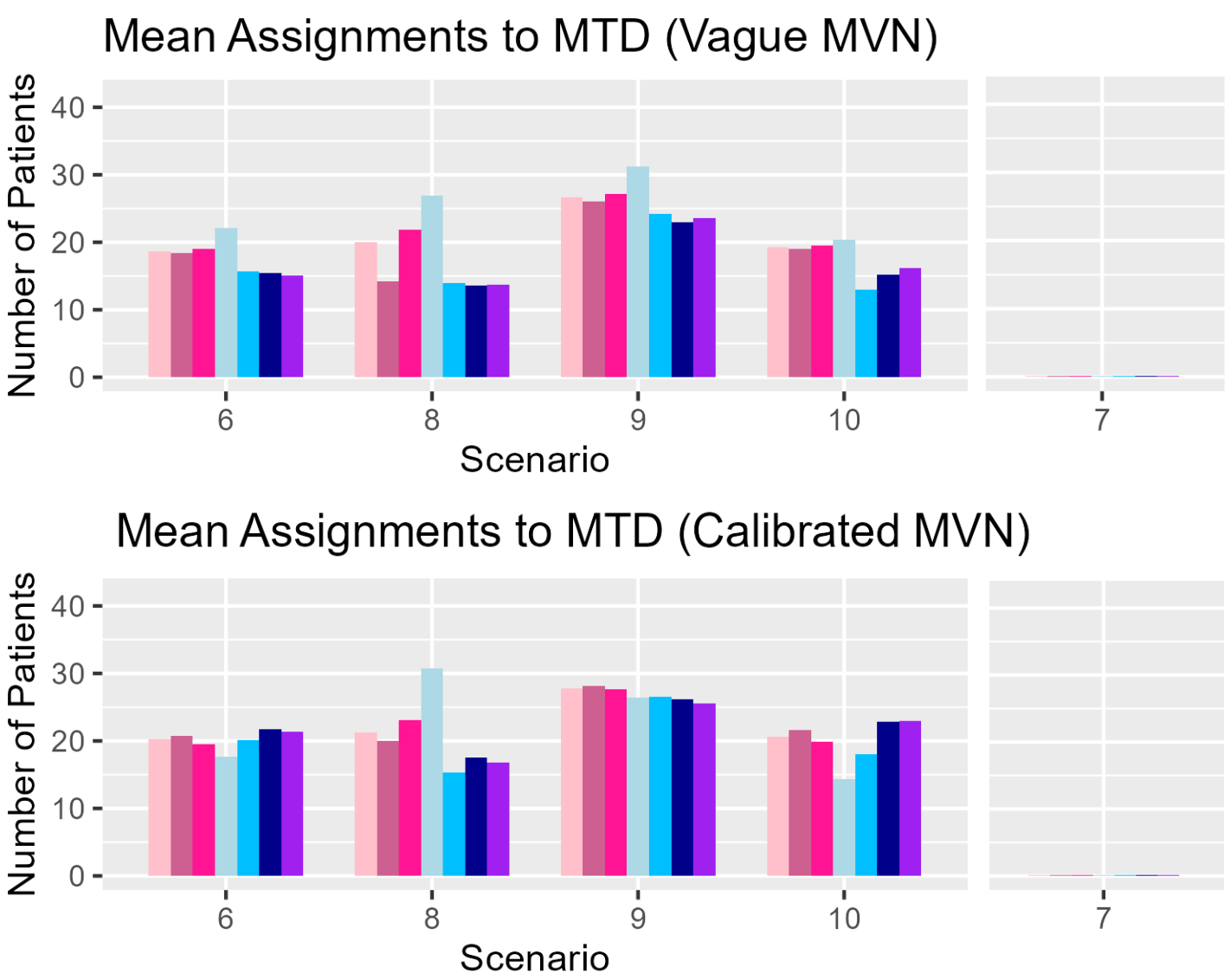
2 Prior Effective Sample Size (ESS)

Method		25mg	50mg	100mg	200mg	400mg	800mg	1400mg
Calibrated MVN	MVN	8.2	6.2	4.5	3.4	2.8	2.4	2.3
	MAP (specified)	4.9	2.8	1.9	1.4	1.1	1.0	1.0
	MAP (1/3)	5.5	3.2	1.9	1.3	1.0	1.0	1.0
	MAP (equal v & a)	5.2	3.3	2.0	1.3	1.1	1.1	1.2
	Power	11.8	14.7	18.8	21.8	25.5	31.4	37.8
	Power/10	8.8	8.7	7.4	6.0	5.3	5.0	5.0
	Power/100	8.2	6.3	4.6	3.5	2.9	2.6	2.4
Vague MVN	MVN	1.7	1.3	1.1	1.0	0.9	0.9	0.9
	MAP (specified)	2.0	1.5	1.3	1.2	1.0	0.8	0.8
	MAP (1/3)	1.9	1.7	1.6	1.3	1	0.9	0.8
	MAP (equal v & a)	1.7	1.5	1.4	1.2	0.9	0.8	0.8
	Power	8.4	8.8	11.3	17.7	26.5	36.4	45
	Power/10	2.9	3.7	4.3	4.5	4.4	4.4	4.4
	Power/100	1.9	1.7	1.4	1.3	1.3	1.2	1.2

Table 1: Prior Effective Sample Size per dose level of all of the considered priors.

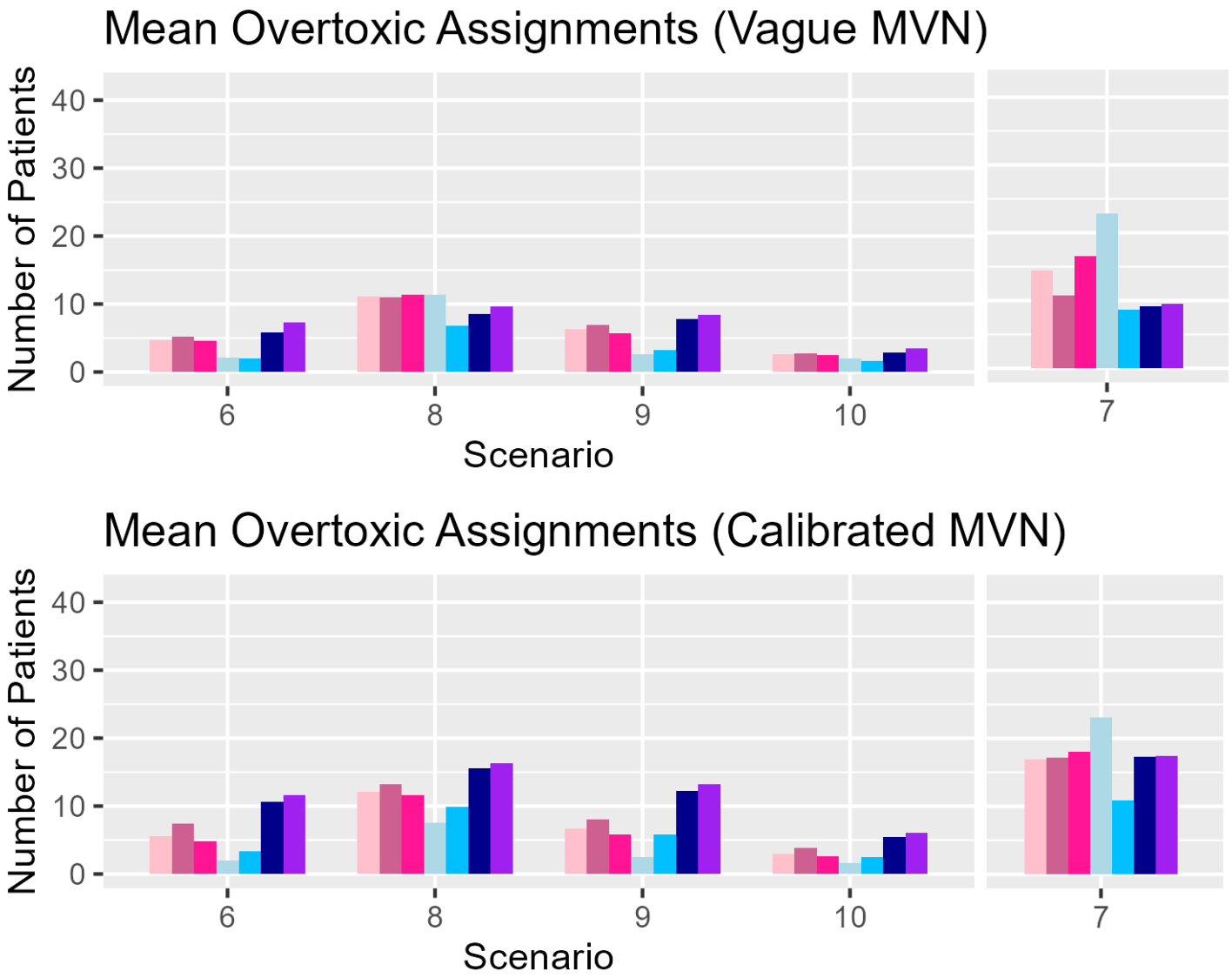
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Simulation study results – low MTD scenarios



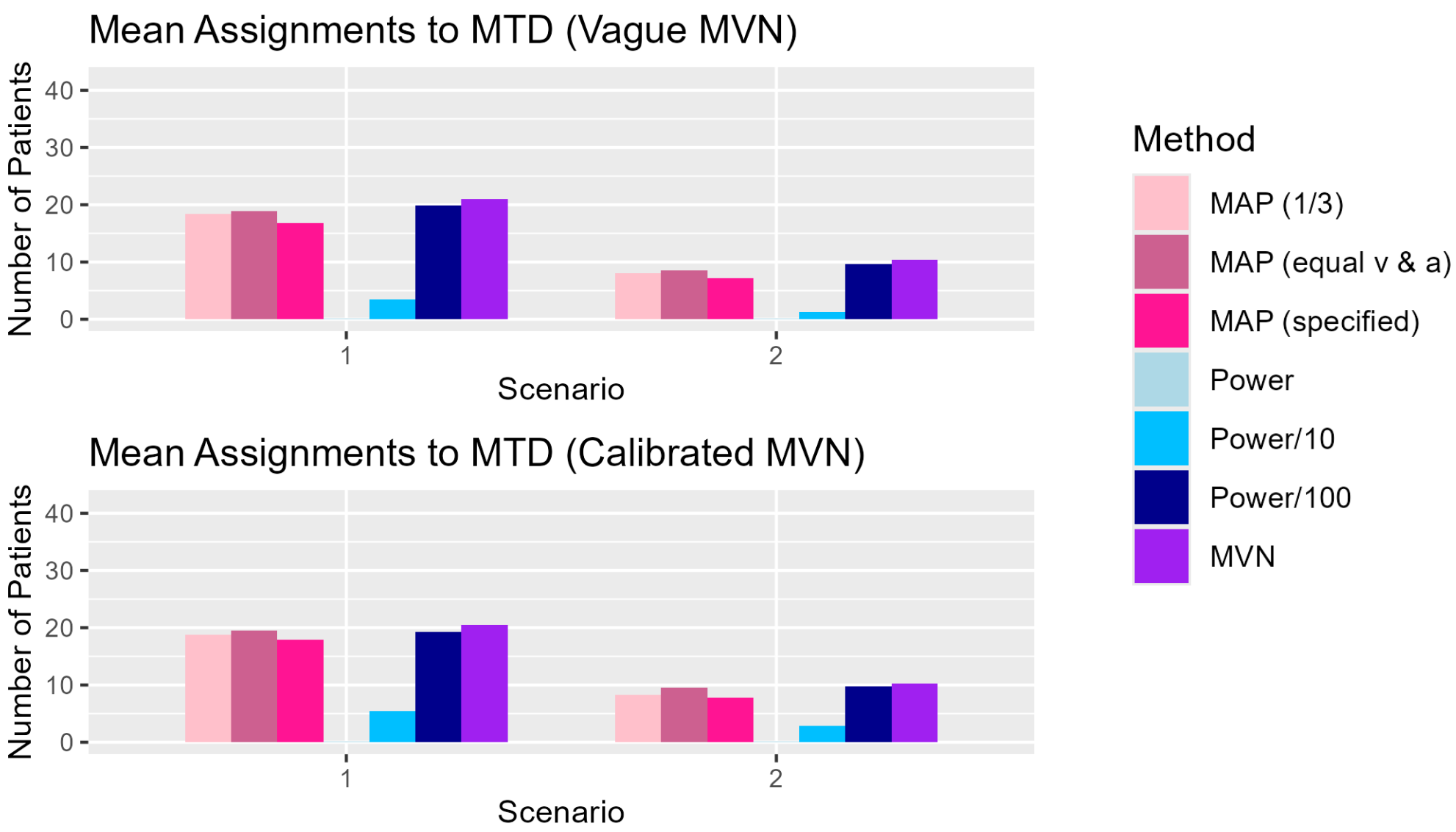
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Simulation study results – low MTD scenarios



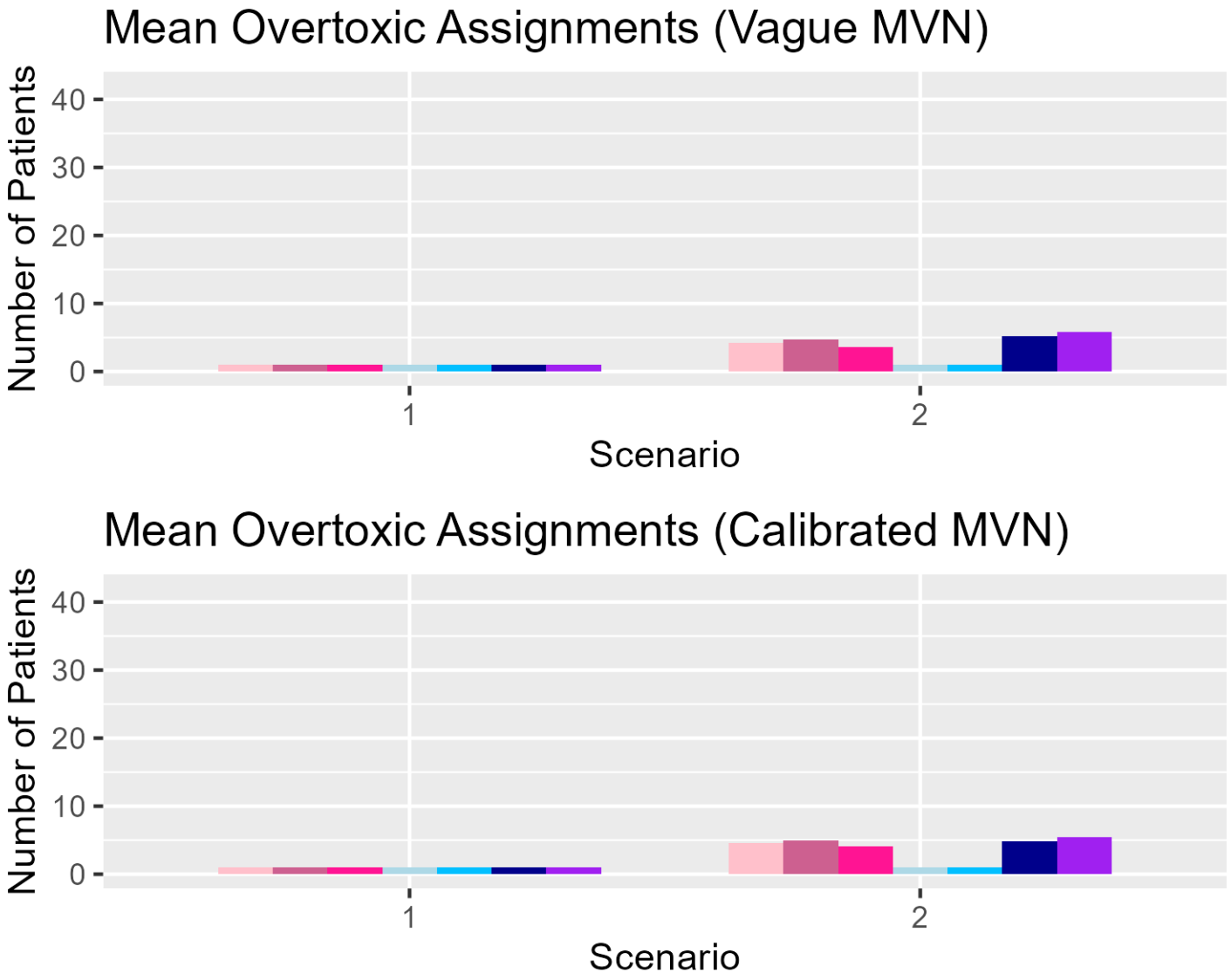
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Simulation study results – high MTD scenarios



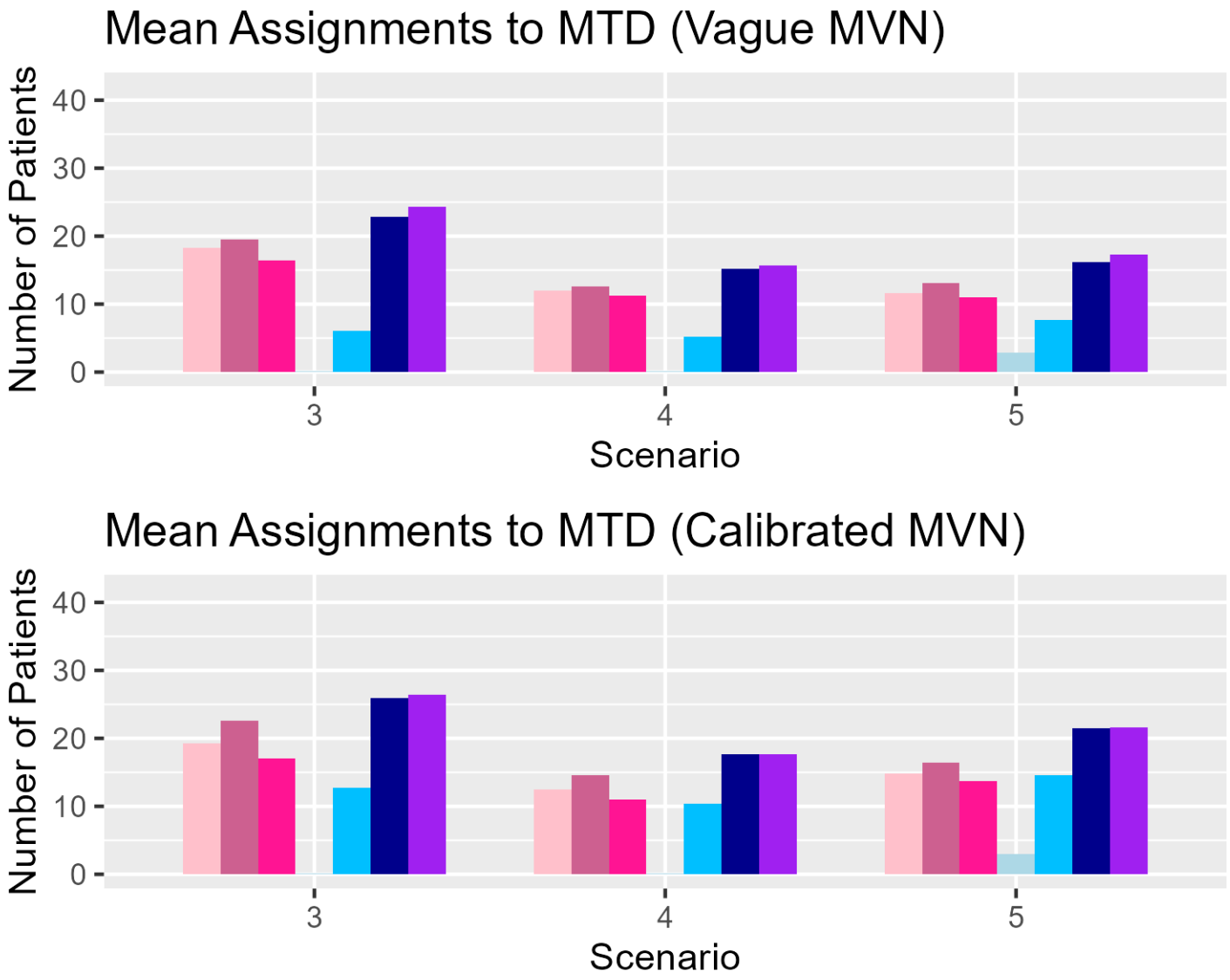
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Simulation study results – high MTD scenarios



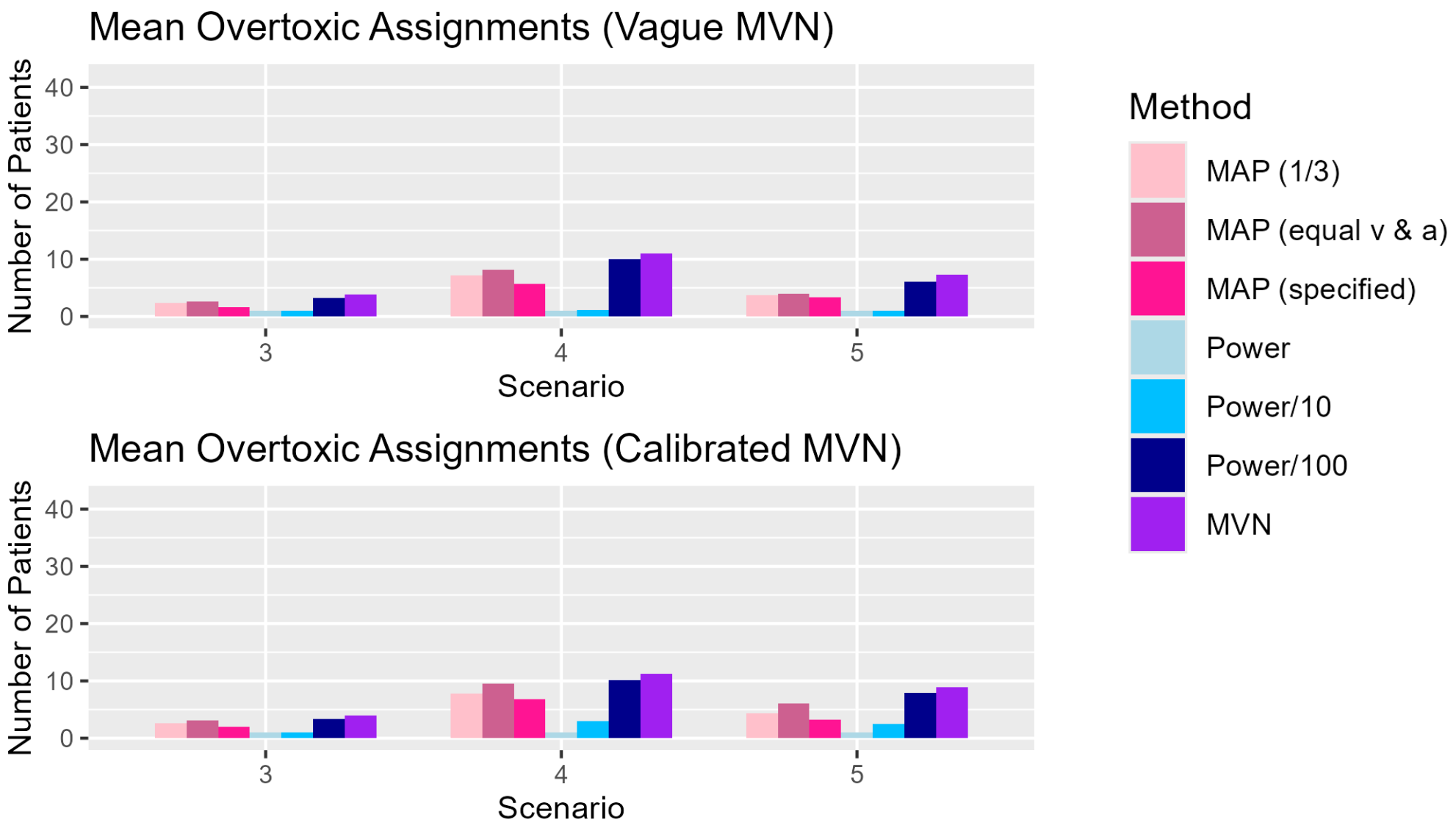
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Simulation study results – middle ground



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