A robust Bayesian meta-analytic approach for incorporating animal data into Phase I oncology trials

Lisa Hampson
Statistical Methodology, Novartis, Basel

Haiyan Zheng, Simon Wandel

EFSPI Meeting on 'Recent Advances in Clinical Trial Design'
Leiden, 23rd March 2018

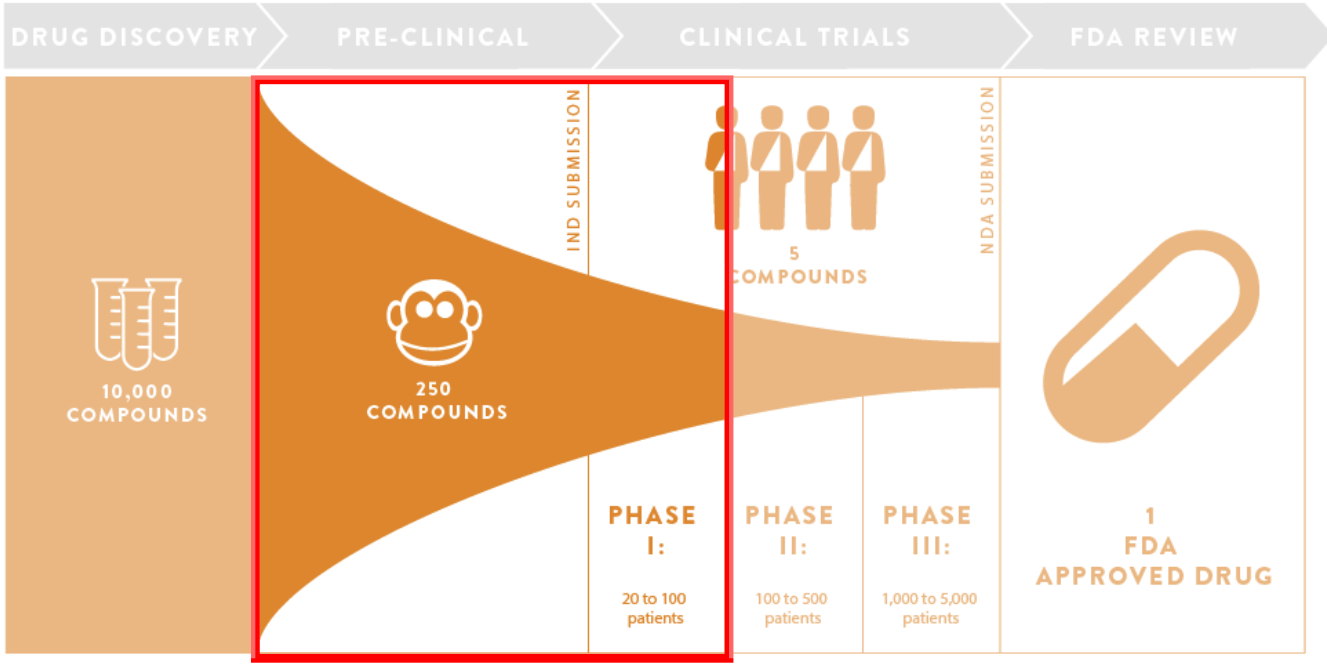
Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 633567.

Dr Hampson's contribution to this project was supported by the UK Medical Research Council (grant MR/M013510/1).

We are grateful to Dr. Beat Neuenschwander for helpful methodological discussions.

Motivation



- Phase I trials attempt to characterise the safety profile of a new medicine and establish a maximum tolerated dose (MTD).
- Animal data are commonly used to inform the choice of starting dose but are rarely used in the analysis.

Can we improve trial operating characteristics and the precision of the MTD estimate by borrowing strength from animal data?

Phase I dose-escalation trials in oncology

- Endpoint: Dose Limiting Toxicity (DLT) vs no DLT
- Participants are typically patients for whom standard therapies have failed
- Dose-escalation traditionally followed algorithmic rules, e.g. 3+3 design.
- However, Bayesian model-based procedures, assuming a 1- or 2-parameter model for dose-toxicity relationship, are increasing in use.

Assume that the risk of experiencing a DLT on dose d can be modelled as:

$$r|n, p \sim \text{Binomial}(p, n)$$
$$\text{logit}(p) = \theta_1 + \exp(\theta_2)\log(d/d_{\text{Ref}}).$$

- Different intervals may characterise safe doses in different animal species.
- Expect the slope of the dose-toxicity curve to be similar across species.

Notation

In this presentation, we will use the following notation:

- M studies have been performed in K animal species labelled $S_1, \ldots, S_K$.
- $\mathcal{A}_i \in \{S_1, \ldots, S_K\}$ denotes the species studied in trial i.
- In study i, doses $d_{i1}, \ldots, d_{iJ_i}$ were available for administration.
- In study i, r_{ij} out of n_{ij} animals who received dose d_{ij} experienced a DLT.
- p_{ij} denotes the risk of a DLT on dose d_{ij} in species $\mathcal{A}_i$ studied in study i.

Meta-analytic model for animal data

For study i:

$$r_{ij}|n_{ij}, p_{ij} \sim \text{Binomial}(p_{ij}, n_{ij}), \qquad \text{for } j = 1, \ldots, J_i$$
$$\text{logit}(p_{ij}) = \theta_{1i} + \exp(\theta_{2i}) \log(\delta_{\mathcal{A}_i} d_{ij}/d_{\text{Ref}}),$$

- δ_{S_k} translates doses given to species S_k onto an equivalent human dosing scale.
- $\delta_{S_k} > 1$ implies dose d has a higher DLT risk in species S_k than in humans.

Within a species, study-specific parameters are exchangeable:

$$\boldsymbol{\theta}_i|\boldsymbol{\mu}_{\mathcal{A}_i}, \Psi \sim \text{BVN}(\boldsymbol{\mu}_{\mathcal{A}_i}, \Psi) \qquad \text{for } i = 1, \ldots, M$$

where for animal species S_k

$$\boldsymbol{\mu}_{S_k} = \begin{pmatrix} \mu_{1S_k} \\ \mu_{2S_k} \end{pmatrix} \quad \text{and} \quad \Psi = \begin{pmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ \rho\tau_1\tau_2 & \tau_2^2 \end{pmatrix}.$$

Meta-analytic model for animal data

After translating the animal dose-toxicity relationships onto a common human dosing scale, we expect there to be similarities between species.

We define a 'supra-species' model to allow borrowing across animal species:

$$\boldsymbol{\mu}_{S_1}, \ldots, \boldsymbol{\mu}_{S_K} | \boldsymbol{m}, \Sigma \sim \text{BVN}(\boldsymbol{m}, \Sigma)$$

where

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

Elements of Σ describe the between-species variability present if $\delta_{S_1}, \ldots, \delta_{S_K}$ do not account for all differences between species and humans.

Data from a Phase I trial

We label the Phase I trial in humans as study $i^\star$, and label humans as species $\mathcal{H}$.

Stipulating $\delta_{\mathcal{H}} = 1$, we model the human data as:

$$\begin{aligned} r_{i^\star j} | n_{i^\star j}, p_{i^\star j} &\sim \text{Binomial}(p_{i^\star j}, n_{i^\star j}), \\ \text{logit}(p_{i^\star j}) &= \theta_{1i^\star} + \exp(\theta_{2i^\star}) \log(d_{i^\star j}/d_{\text{Ref}}). \end{aligned}$$

where d_{Ref} is a reference dose in humans.

The parameters of the Phase I study are $\boldsymbol{\theta}_{i^\star} = (\theta_{1i^\star}, \theta_{2i^\star})$.

Data from a Phase I trial

We label the Phase I trial in humans as study $i^\star$, and label humans as species $\mathcal{H}$.

Stipulating $\delta_{\mathcal{H}} = 1$, we model the human data as:

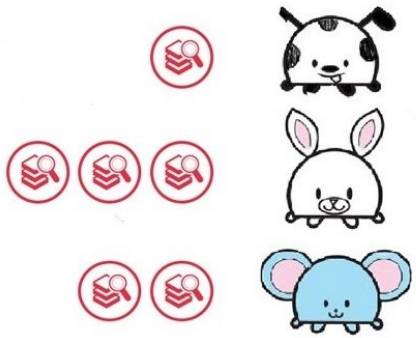
$$r_{i^\star j} | n_{i^\star j}, p_{i^\star j} \sim \text{Binomial}(p_{i^\star j}, n_{i^\star j}),$$
$$\text{logit}(p_{i^\star j}) = \theta_{1i^\star} + \exp(\theta_{2i^\star}) \log(d_{i^\star j}/d_{\text{Ref}}).$$

where d_{Ref} is a reference dose in humans.

The parameters of the Phase I study are $\boldsymbol{\theta}_{i^\star} = (\theta_{1i^\star}, \theta_{2i^\star})$.

How do we relate $\boldsymbol{\theta}_{i^\star}$ to study-specific parameters in animals?

Relating animal and human model parameters



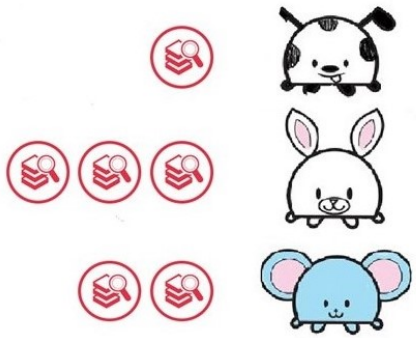
Species S_1 : $\theta_1 \mid \mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_1}, \psi)$

Species S_2 : $\theta_2, \theta_3, \theta_4 \mid \mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_2}, \psi)$

$\vdots$ $\vdots$

Species S_K : $\theta_{M-1}, \theta_M \mid \mu_{S_K}, \psi \sim \text{BVN}(\mu_{S_K}, \psi)$

Relating animal and human model parameters



Species S_1 : $\theta_1 \mid \mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_1}, \psi)$

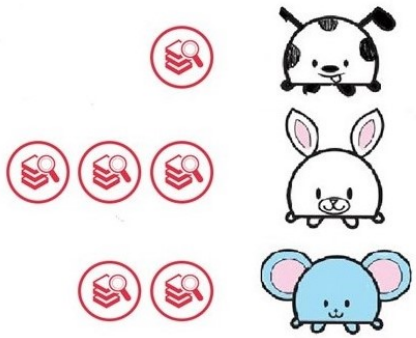
Species S_2 : $\theta_2, \theta_3, \theta_4 \mid \mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_2}, \psi)$

$\vdots$ $\vdots$

Species S_K : $\theta_{M-1}, \theta_M \mid \mu_{S_K}, \psi \sim \text{BVN}(\mu_{S_K}, \psi)$

Place prior probabilities on Exchangeability and Non-Exchangeability scenarios.

Relating animal and human model parameters



Species S_1 : $\theta_1 \,|\mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_1}, \psi)$

Species S_2 : $\theta_2, \theta_3, \theta_4 \,|\mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_2}, \psi)$

$\vdots$ $\qquad\qquad$ $\vdots$

Species S_K : $\theta_{M-1}, \theta_M \,|\mu_{S_K}, \psi \sim \text{BVN}(\mu_{S_K}, \psi)$

Place prior probabilities on Exchangeability and Non-Exchangeability scenarios.

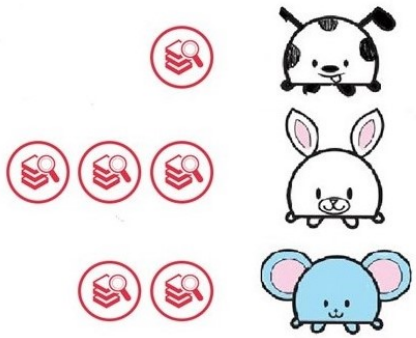
EX: $\boldsymbol{\theta}_{i\star}$ is exchangeable with study-specific parameters of one animal species:

$$\boldsymbol{\theta}_{i\star} \,|\boldsymbol{\mu}_{S_1}, \Psi \sim \text{BVN}(\boldsymbol{\mu}_{S_1}, \Psi) \quad \text{with probability } \omega_1,$$

$$\vdots$$

$$\boldsymbol{\theta}_{i\star} \,|\boldsymbol{\mu}_{S_K}, \Psi \sim \text{BVN}(\boldsymbol{\mu}_{S_K}, \Psi) \quad \text{with probability } \omega_K.$$

Relating animal and human model parameters



Species S_1 : $\theta_1 \mid \mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_1}, \psi)$

Species S_2 : $\theta_2, \theta_3, \theta_4 \mid \mu_{S_1}, \psi \sim \text{BVN}(\mu_{S_2}, \psi)$

$\vdots$ $\qquad$ $\vdots$

Species S_K : $\theta_{M-1}, \theta_M \mid \mu_{S_K}, \psi \sim \text{BVN}(\mu_{S_K}, \psi)$

Place prior probabilities on Exchangeability and Non-Exchangeability scenarios.

EX: $\boldsymbol{\theta}_{i\star}$ is exchangeable with study-specific parameters of one animal species:

$$\boldsymbol{\theta}_{i\star} \mid \boldsymbol{\mu}_{S_1}, \Psi \sim \text{BVN}(\boldsymbol{\mu}_{S_1}, \Psi) \quad \text{with probability } \omega_1,$$

$$\vdots$$

$$\boldsymbol{\theta}_{i\star} \mid \boldsymbol{\mu}_{S_K}, \Psi \sim \text{BVN}(\boldsymbol{\mu}_{S_K}, \Psi) \quad \text{with probability } \omega_K.$$

NEX: $\boldsymbol{\theta}_{i\star}$ has an independent weakly informative prior distribution:

$$\boldsymbol{\theta}_{i\star} \sim \text{BVN}(\boldsymbol{m}_0, R_0) \quad \text{with probability } \omega_R = 1 - (\omega_1 + \ldots + \omega_K).$$

Priors for translation factors

FDA Guidance for Industry (2005)

Convert an animal dose to a human equivalent dose (HED) using a correction factor which adjusts for differences in size.

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times \underbrace{\frac{(\text{BW}/\text{BSA})_{\mathcal{A}}}{(\text{BW}/\text{BSA})_{\mathcal{H}}}}_{\text{translation factor } \delta},$$

BW = Body Weight (kg); BSA = Body Surface Area (m^2).

Priors for translation factors

FDA Guidance for Industry (2005)

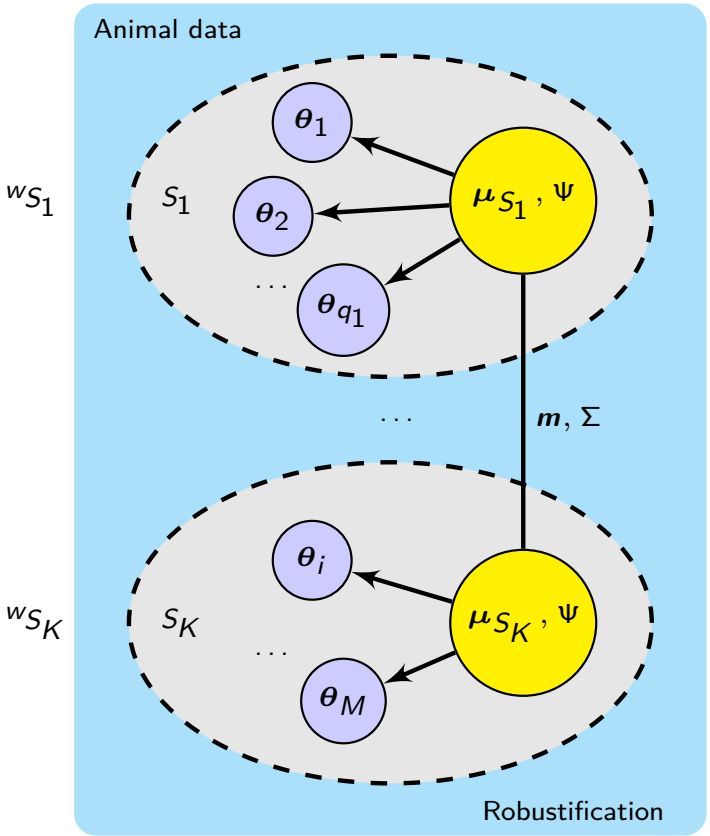
Convert an animal dose to a human equivalent dose (HED) using a correction factor which adjusts for differences in size.

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times \underbrace{\frac{(\text{BW}/\text{BSA})_{\mathcal{A}}}{(\text{BW}/\text{BSA})_{\mathcal{H}}}}_{\text{translation factor } \delta},$$

BW = Body Weight (kg); BSA = Body Surface Area (m^2).

- Translation factor is usually treated as a fixed constant, ignoring our uncertainty.
- We account for uncertainty by stipulating a log-normal prior: $\delta_{S_k} \sim LN(\lambda, \gamma^2)$
- Prior informed by information in FDA Guidance on 'Estimating the Maximum Safe Starting Dose'.

Priors for other model parameters



Between-trial heterogeneity:
$\boldsymbol{\theta}_i|\boldsymbol{\mu}_{\mathcal{A}_i}, \Psi \sim \text{BVN}(\boldsymbol{\mu}_{\mathcal{A}_i}, \Psi)$ for $i = 1, \ldots, M$.

Between-trial SDs:
$\tau_1 \sim HN(scale = 0.5)$, $\tau_2 \sim HN(scale = 0.25)$.

Between-species heterogeneity:
$\boldsymbol{\mu}_{S_1}, \ldots, \boldsymbol{\mu}_{S_K}|\boldsymbol{m}, \Sigma \sim \text{BVN}(\boldsymbol{m}, \Sigma)$

Weakly informative priors for elements of $\boldsymbol{m}$.

Between-species SDs:
$\sigma_1 \sim HN(scale = 2)$, $\sigma_2 \sim HN(scale = 1)$.

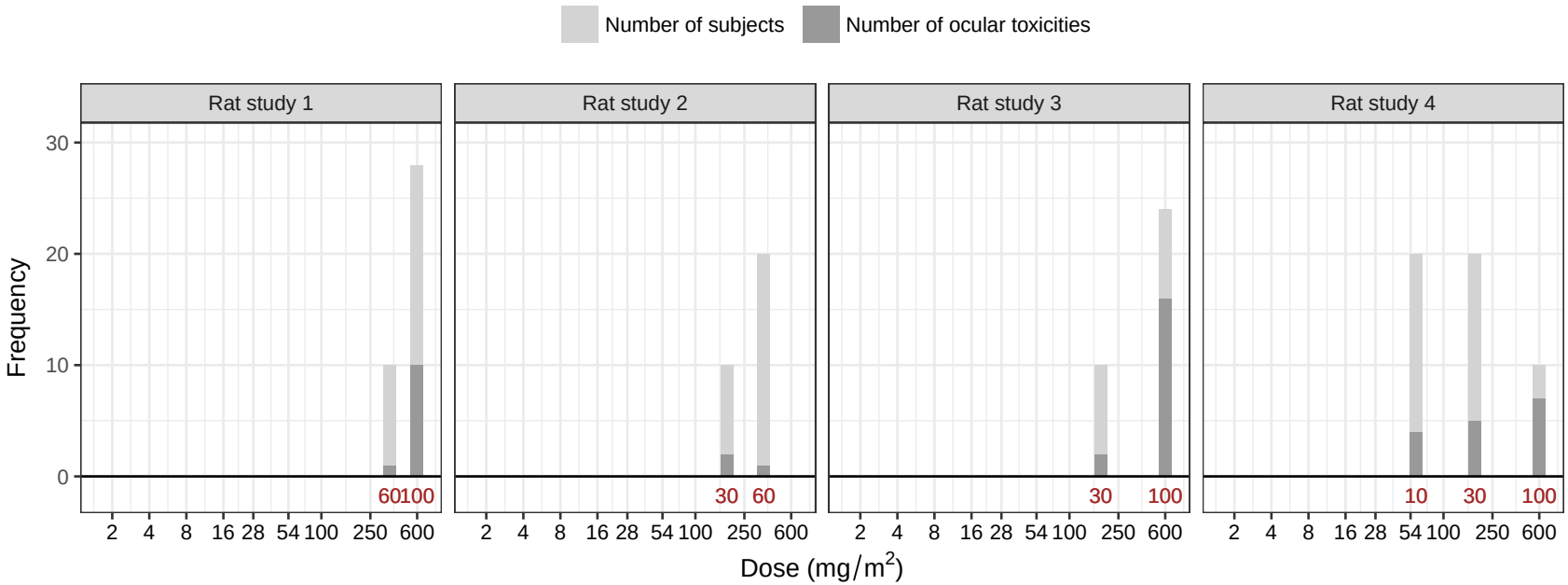
For both random effects distributions, place $U(-1, 1)$ priors on correlation.

Example 1: ocular toxicities

Roman et al. (2016)

AUY922 is an anti-cancer drug. Ocular events thought to potentially occur in humans.

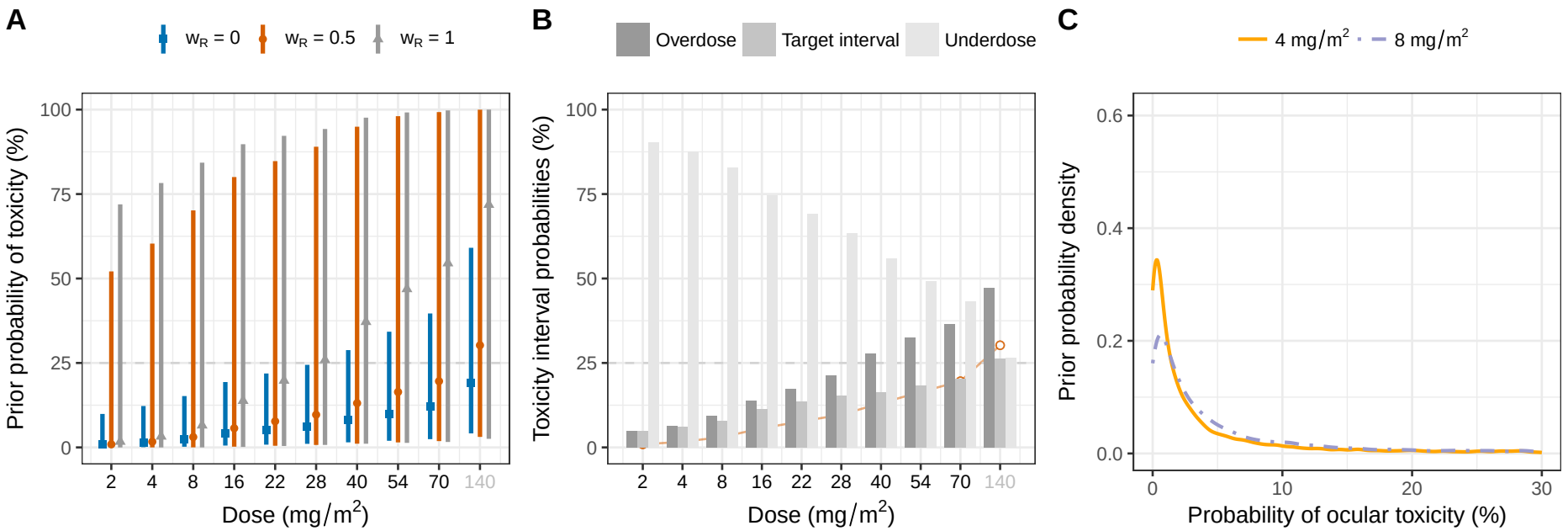
- 4 studies were performed in 152 rats to better understand the risk of ocular toxicity.
- Data shown for Studies 1 and 2 summarise the outcomes for male rats.
- Simulated data are shown for Studies 3 and 4.
- Doses in brown are the doses administered to rats.



Example 1: priors for Phase I

Implement model with $M = 4$, $K = 1$, $\delta_{\text{Rat}} \sim LN(2.8, 0.3^2)$ to derive prior for the risk of ocular toxicity in a Phase I trial.

Figure shows the impact of prior robustification weight ω_R.



Underdose: risk ≤ 0.16; Target: risk $\in [0.16, 0.33)$; Overdose: risk ≥ 0.33.

Example 1: Effective Sample Size (ESS)

Compute the ESS by first approximating the DLT risk prior by a Beta(a, b) distribution with matching mean and variance.

ESS is then $(a + b)$.

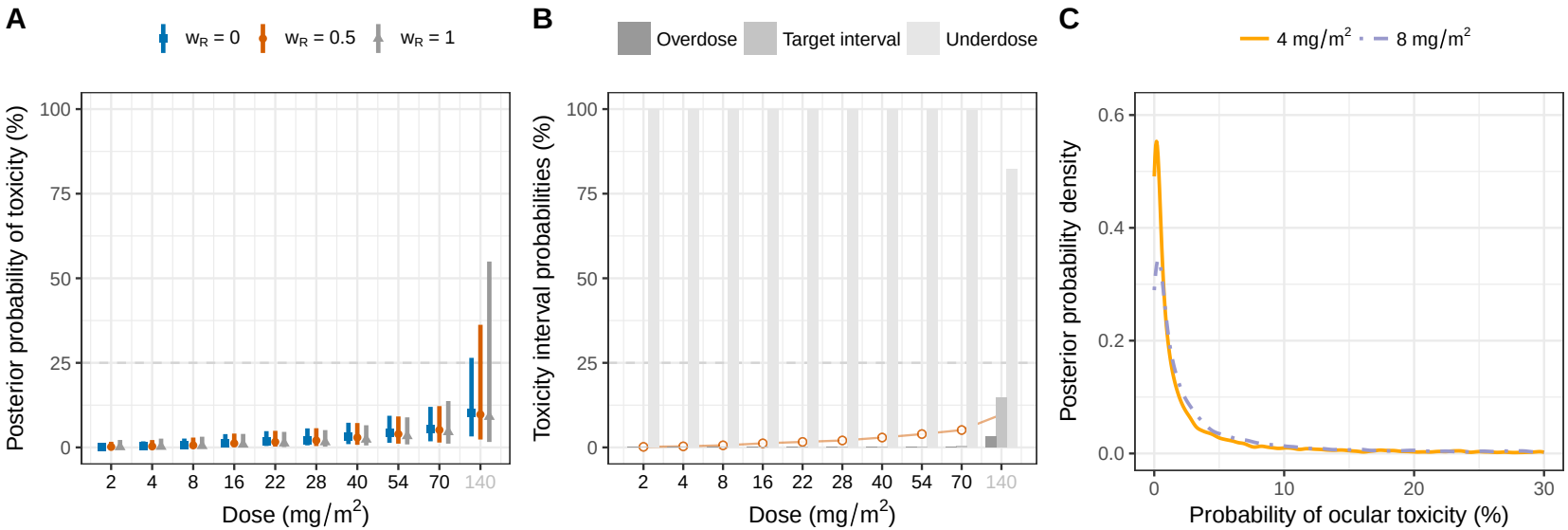
	Dose (mg/m^2)									
	2	4	8	16	22	28	40	54	70	140
Prior means	0.057	0.074	0.101	0.145	0.175	0.206	0.259	0.303	0.339	0.428
Prior SD	0.133	0.151	0.175	0.206	0.225	0.243	0.277	0.299	0.313	0.328
ESS	2.0	2.0	2.0	1.9	1.8	1.8	1.5	1.3	1.3	1.2

Example 1: posteriors after a Phase I trial

Sessa et al. (2013)

Phase I trial of AUY922 recruited 93 patients. Dose escalation followed a BLRM design monitoring DLTs due to any cause. Ocular toxicities were also recorded.

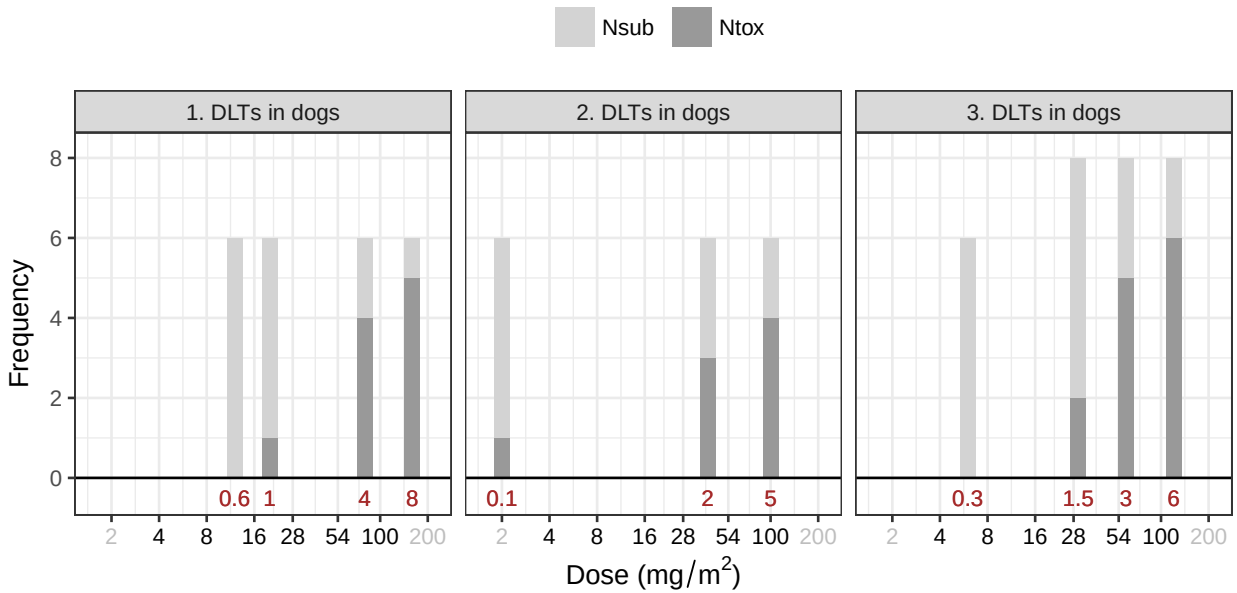
	Dose (mg/m^2)								
	2	4	8	16	22	28	40	54	70
Number of patients	3	3	4	6	11	8	16	18	24
Number of ocular AEs	0	0	0	0	0	0	0	0	2



Example 2: pre-clinical dog data

Suppose 3 studies in 72 dogs were performed to evaluate the safety of a new drug.

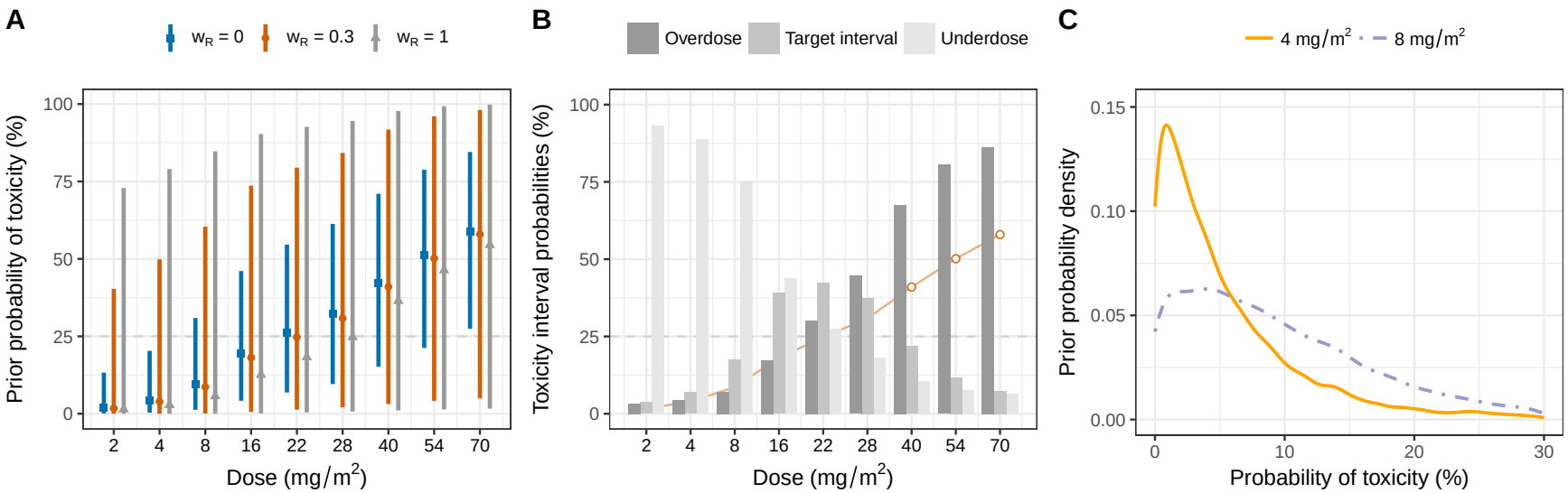
Figure shows simulated DLT data in dogs.



Example 2: pre-clinical dog data

Suppose 3 studies in 72 dogs were performed to evaluate the safety of a new drug.

Figure shows predictive priors for DLT risks in a Phase I trial.



Example 2: dose-escalation procedure

- A Phase I trial will enrol patients in cohorts of 3.
- Doses 2, 4, 8, 16, 22, 28, 40, 54, 70 mg/m^2 will be available for dosing.
- Base decisions on robust Bayesian hierarchical model incorporating dog data.

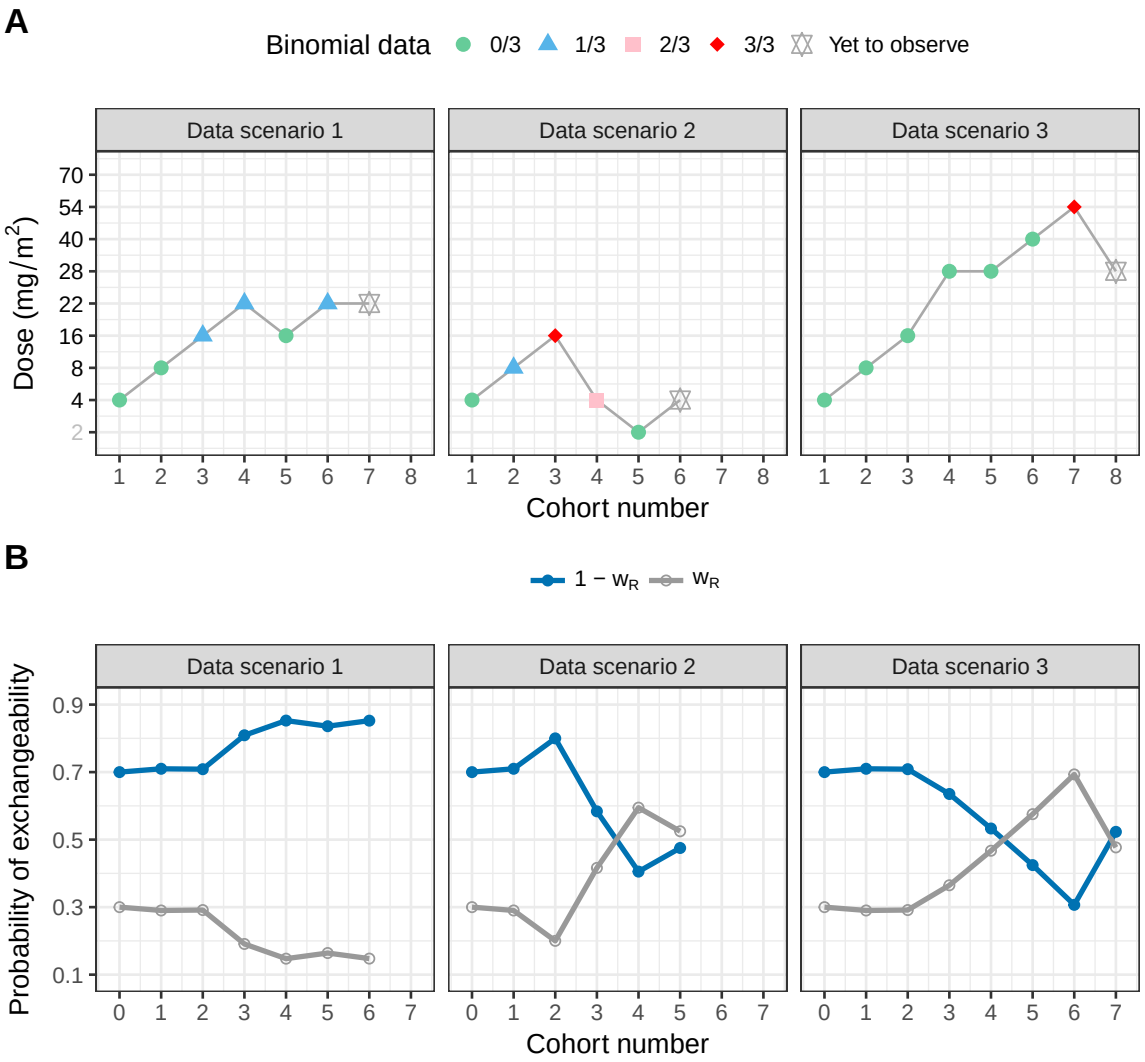
Escalation rule:After cohort $h-1$, escalate according to an EWOC criterion:

$$\hat{d}_{\text{sel}}^{(h)} = \max\{d_{i^\star j} \in \mathcal{D}_{i^\star} : \mathbb{P}(p_{i^\star j} \geq 0.33 | \text{dog and human data}) \leq 0.25\}$$

Constraint: Maximum 2-fold increase in dose.

Hierarchical model is implemented setting the prior robustification weight $\omega_R = 0.3$.

Example 2: dose escalation trajectories



Monitor trials until any dose is recommended for a 3rd time.

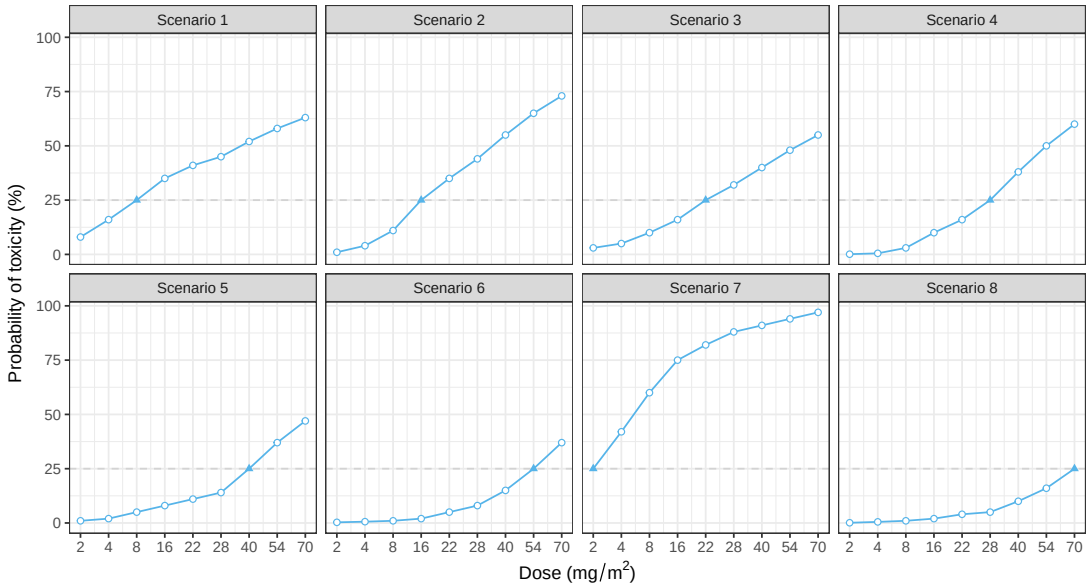
Simulation study

- Simulated 2000 phase I dose-escalation trials enrolling up to 45 patients
- Stop early for safety if lowest dose is not safe enough.

Final dose recommendation:

$$\hat{d}_{\mathrm{M}} = \arg \min_{d_{i\star j} \in \mathcal{D}'_{i\star}} |\tilde{p}_{i\star j} - 0.25|,$$

where $\mathcal{D}'_{i\star}$ comprises all doses tested in humans which satisfy EWOC criterion.



Analysis models

We are interested in 4 analysis models:

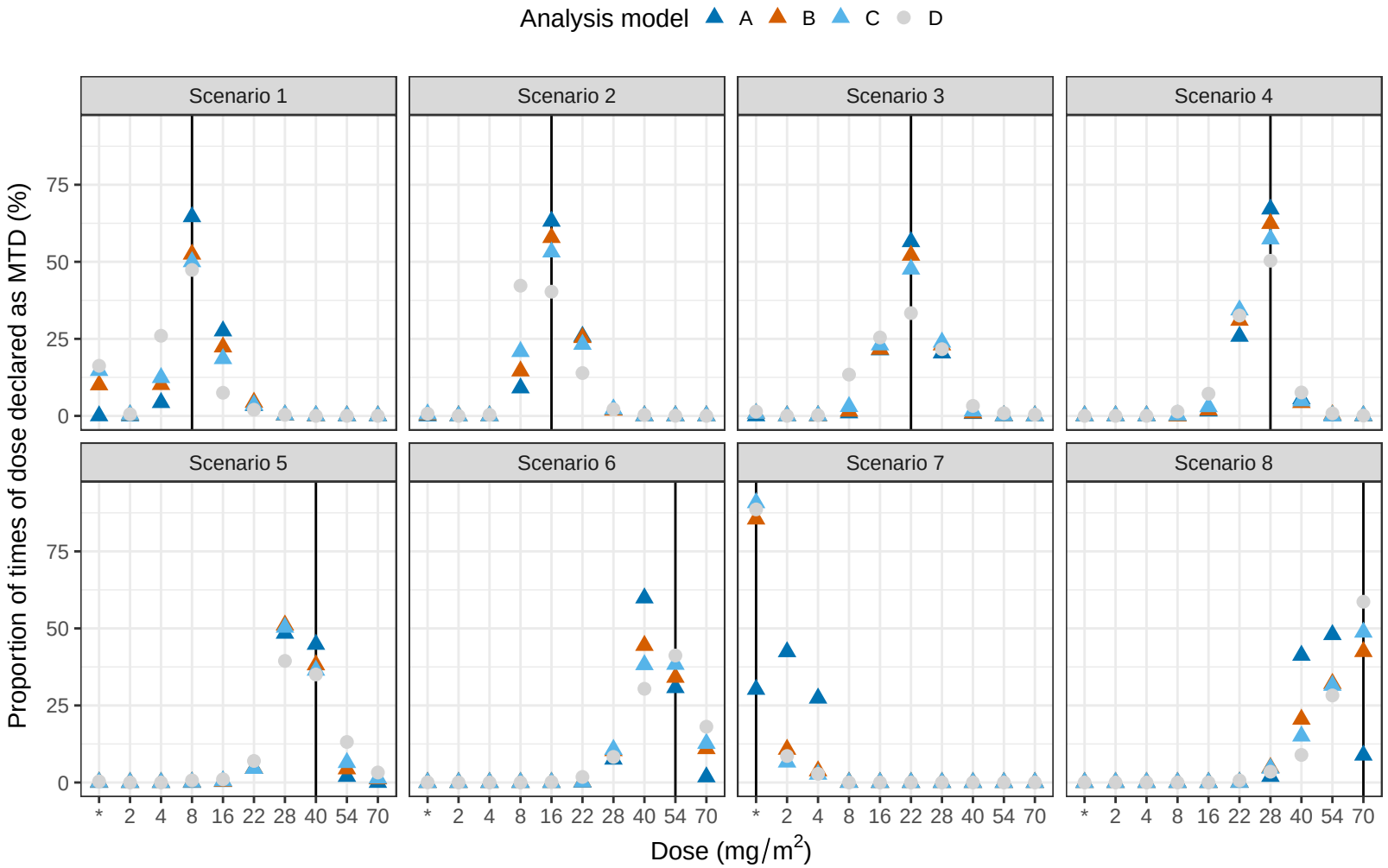
(i) Model A: Model assumes full exchangeability, $w_R = 0$

(ii) Model B: Robust model with $w_R = 0.3$

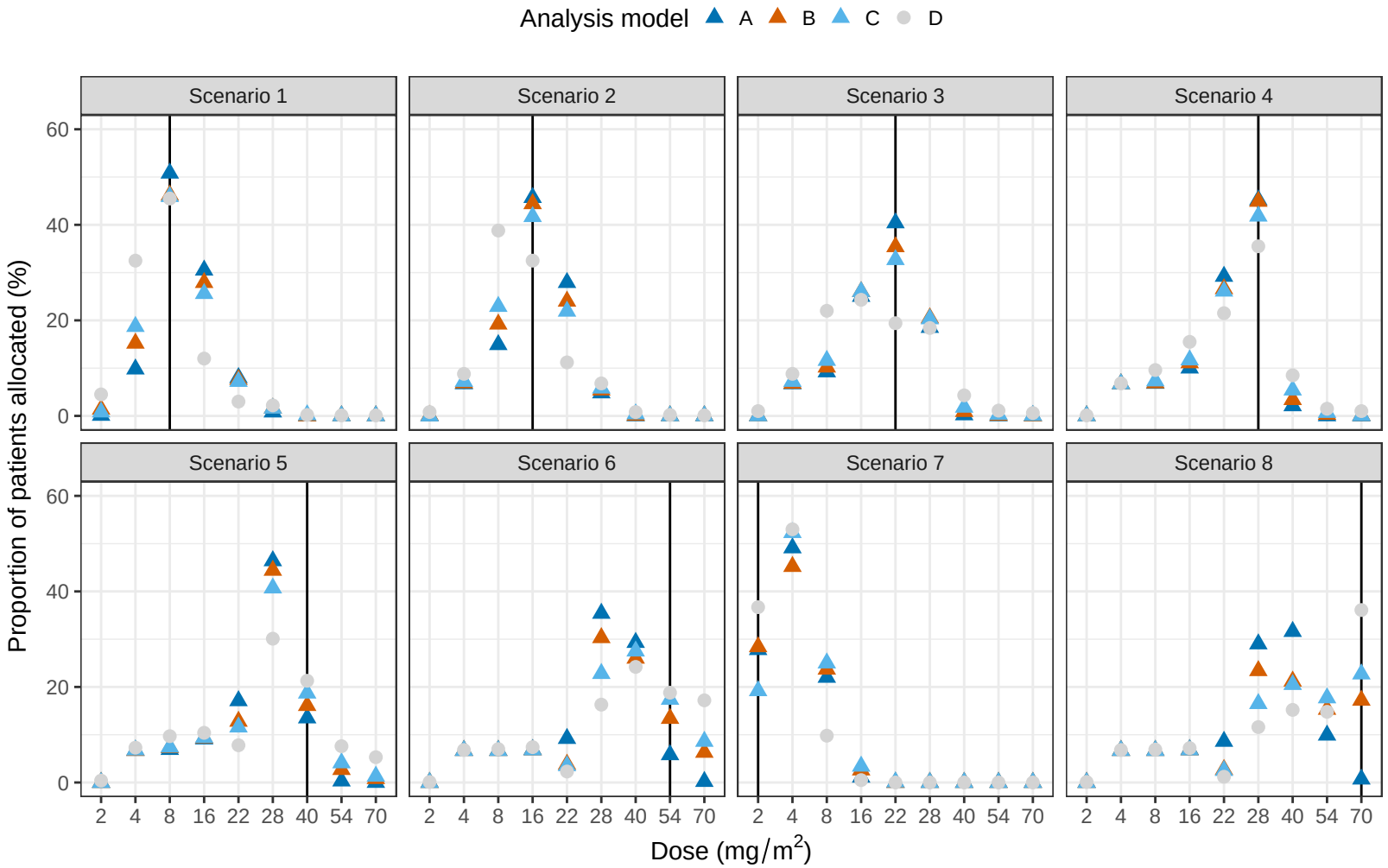
(iii) Model C: Robust model with $w_R = 0.5$

(iv) Model D: Model not permitting historical borrowing, $w_R = 1$

Results: probability of correct selection



Results: proportion of patients allocated



Conclusions

- Proposed a Bayesian hierarchical model for incorporating pre-clinical data
- By allowing for the possibility of non-exchangeability, the model can react more quickly to a prior-data conflict.
- Simulation results have investigated scenarios where we have data on several animal species, and where the Phase I trial permits early stopping.
- Extending approach to accommodate case where there are several human subgroups.

References


Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials *Statistics in Medicine*. 2008;27(13):2420-39.


Roman D, VerHoeve J, Schadt H, et al. Ocular toxicity of AUY922 in pigmented and albino rats *Toxicology and Applied Pharmacology*. 2013;273(2):401-9.


Sessa C, Shapiro GI, Bhalla KN, et al. First-in-human phase I dose-escalation study of the HSP90 inhibitor AUY922 in patients with advanced solid tumours *Clinical Cancer Research*. 2013;19(13):3671-80.


FDA. *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. US Food and Drug Administration: Rockville, MD; 2005.