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Bridging the gap between preclinical animal studies and phase I first-in-human trials

Nonclinical Biostatistics Conference, New Jersey

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Acknowledgement

My thanks to the committee for the invitation.

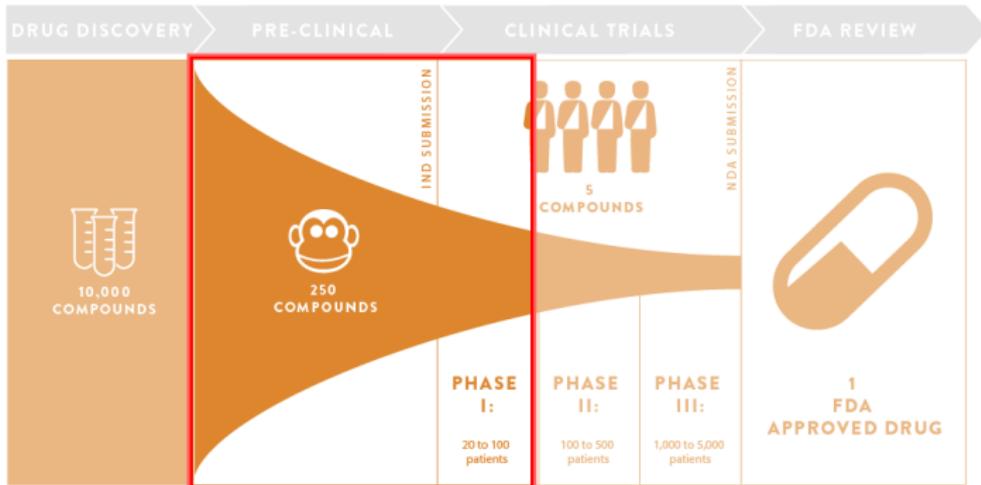
Joint work with Dr Lisa Hampson.

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Medical
Research
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Early drug development



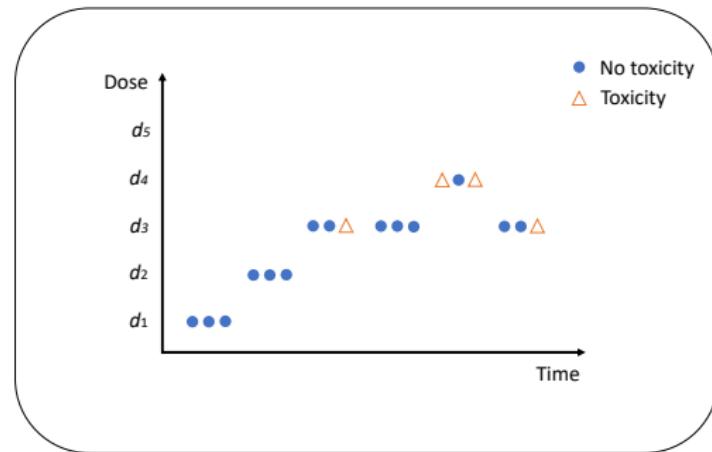
Current use of preclinical data in practice:

- Inform the choice of a *safe starting dose* in phase I trials
- NOT incorporated in the conduct or analysis of human trials

“Can phase I trials be more efficient by using animal data?”

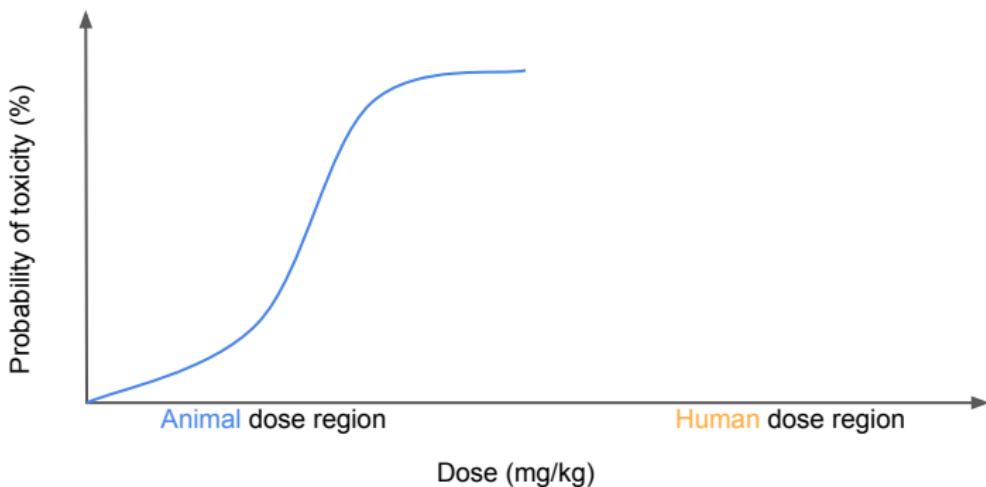
Phase I dose-escalation trials

- \mathcal{I} doses for evaluation: $d_1, \dots, d_{\mathcal{I}}$
- Binary outcome: toxicity or no-toxicity
- Bayesian logistic regression model:
$$\text{logit}(p_i) = \theta_1 + \exp(\theta_2) \log(d_i), \quad \text{for } i = 1, \dots, \mathcal{I}.$$
- **Idea:** represent animal data into a prior for $\theta = (\theta_1, \theta_2)$



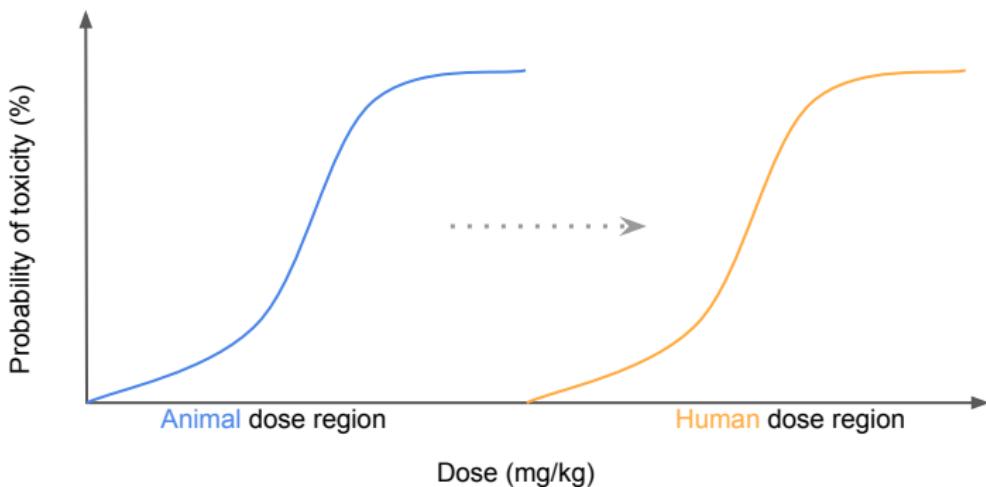
Minimum requirement of animal data

- Animal data suggest a higher dose is more toxic
- At a minimum, two doses have been tested in the experiment



Minimum requirement of animal data

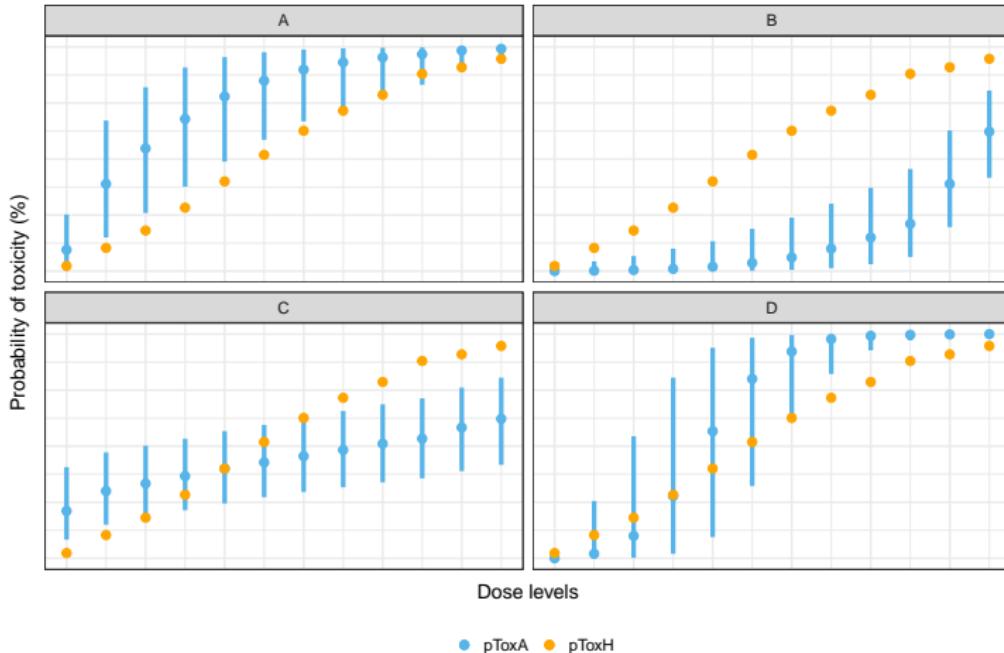
- Animal data suggest a higher dose is more toxic
- At a minimum, two doses have been tested in the experiment
- Animal data translated onto a human equivalent dosing scale



Specify the animal prior

1. Summarise animal data as **pseudo observations** on the lowest and highest doses, d_j , $j = -1, 0$,
 - ▶ $t_{\mathcal{A}j}$ out of $(t_{\mathcal{A}j} + \nu_{\mathcal{A}j})$ animals experienced a toxicity on d_j
2. This specifies independent Beta priors, $p_j \sim \text{Beta}(t_{\mathcal{A}j}, t_{\mathcal{A}j} + \nu_{\mathcal{A}j})$
3. Given $\text{logit}(p_i) = \theta_1 + \exp(\theta_2) \log(d_i)$, derive the priors for p_i , $i = 1, \dots, \mathcal{I}$, and their 2.5th, 50th and 97.5th percentiles
4. Find a bivariate normal prior for $\boldsymbol{\theta} = (\theta_1, \theta_2)$, which agrees with the exact summaries, as the animal prior

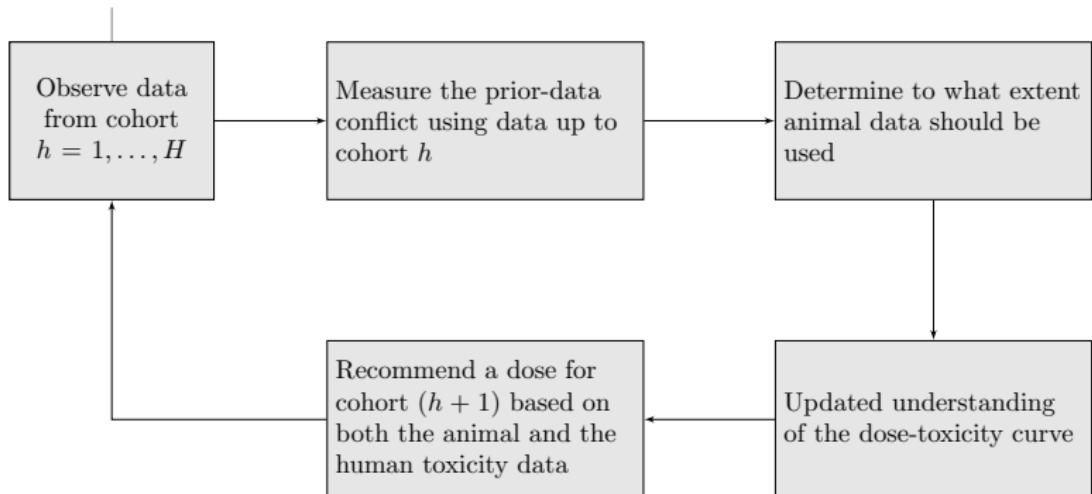
Potential prior-data conflict



Challenge: difficulty to quantify the prior-data conflict in small, sequential trials

Measure as you go

For analysing an ongoing phase I trial



Dynamic mixture priors

Our mixture prior for θ is

$$\pi^{(h)}(\theta | \mathbf{x}_{\mathcal{A}}) = w^{(h)} \times \underbrace{p(\theta | \mathbf{x}_{\mathcal{A}})}_{\text{preclinical data}} + (1 - w^{(h)}) \times \underbrace{m(\theta)}_{\text{operational prior}}$$

Here, $w^{(h)} \in [0, 1]$ is dynamically determined at each cohort h

- $w^{(h)} \rightarrow 0$: animal data completely discarded
- $w^{(h)} \rightarrow 1$: animal data fully used when perfectly commensurate

Predictive accuracy in sequential trials (I)

Let Y be the binary outcome

- Use animal data to obtain an optimal prediction of Y as $\hat{\eta}$
- Compare optimal prior predictions versus observed human responses, y , for each dose d_i at **every cohort h**

		Observation (y)		Counts	
		No toxicity	Toxicity		
Prior prediction ($\hat{\eta}$)	No toxicity	u_{00} (1)	u_{10} (0)	n_{00}	n_{10}
	Toxicity	u_{01} (c)	u_{11} (1)	n_{01}	n_{11}

Note that $0 < c < 1$.

- Derive the **predictive utility** of the animal data for the observed human toxicity data on dose d_i as

$$U_i^{(h)} = \sum_{\ell=0}^1 \sum_{s=0}^1 u_{\ell s} n_{\ell s}$$

Predictive accuracy in sequential trials (II)

- Measure the **predictive accuracy** at cohort h by

$$\bar{a}_h = \frac{1}{\mathcal{I}} \sum_{i=1}^{\mathcal{I}} \frac{U_i^{(h)}}{\sum_{\ell=0}^1 \sum_{s=0}^1 n_{\ell s}}$$

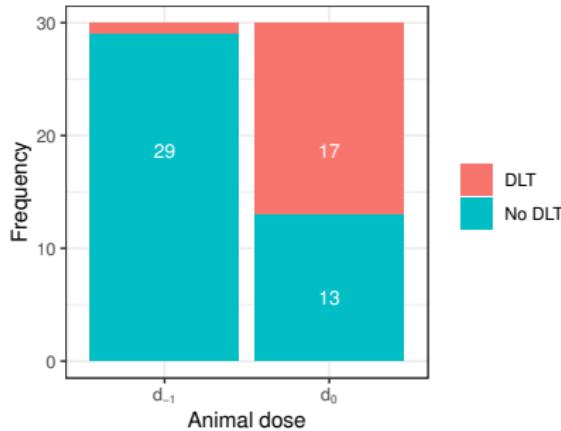
- Define

$$w^{(h)} = \bar{a}_h^{\lambda_h},$$

where λ_h can reflect the trial information time, e.g., $\sqrt{N_{\max}/n_h}$ with $1 \leq n_h \leq N_{\max}$

Application

Hypothetical nonclinical safety data from a dog study:



Suppose

$d_{A-1} = 0.1$ and $d_{A0} = 2.7$ mg/kg have been tested in 39 dogs each.

Use **allometric scaling** to find the human equivalent doses as

$$d_{-1} = 2 \quad \text{and} \quad d_0 = 54 \text{ mg/m}^2.$$

We can then find the animal prior as

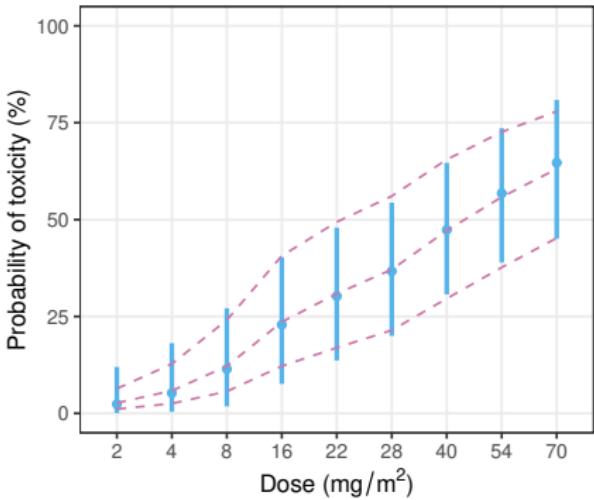
$$\theta | \mathbf{x}_A \sim \text{BVN} \left(\begin{pmatrix} -0.524 \\ 0.147 \end{pmatrix}, \begin{pmatrix} 0.151 & -0.008 \\ -0.008 & 0.001 \end{pmatrix} \right).$$

Safe starting dose

To estimate **TD25**, associated with the toxicity rate of 0.25.

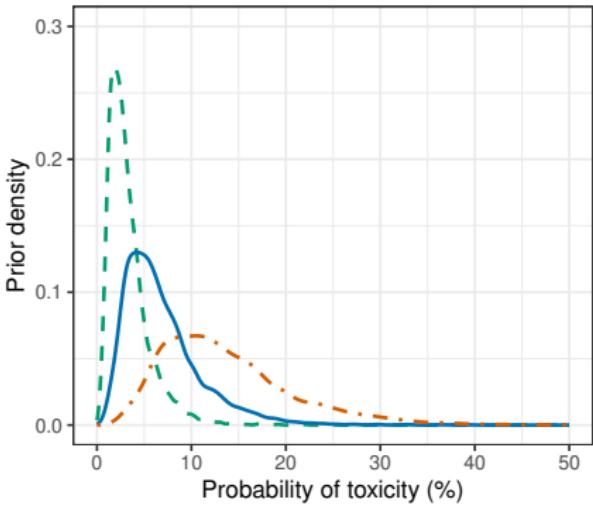
A

Animal priors



B

2 mg/m^2 4 mg/m^2 8 mg/m^2



Interim dose recommendations

Given the posteriors for toxicity rate, p_i , $i = 1, \dots, \mathcal{I}$,

- Overdose: toxicity rate > 0.33
- Target level: toxicity rate $\in (0.16, 0.33]$
- Underdose: toxicity rate < 0.16

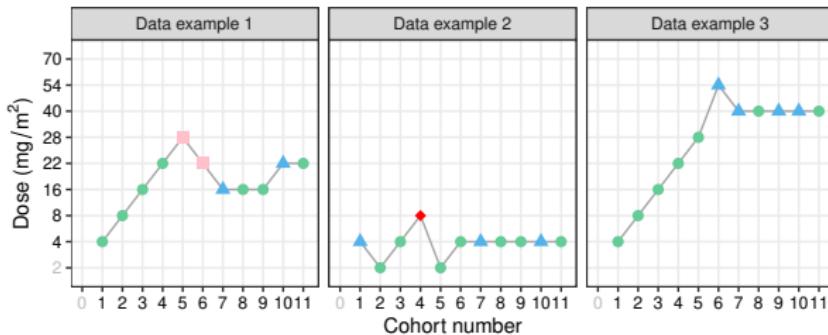
Overdose criterion: $\Pr(\text{toxicity rate} > 0.33 | \mathbf{x}_{\mathcal{A}}, \mathbf{x}_{\mathcal{H}}^{(h)}) > 0.25$

Recommend dose d_i , at which the toxicity is largely within the target level yet the overdose $\leq 25\%$.

Data examples

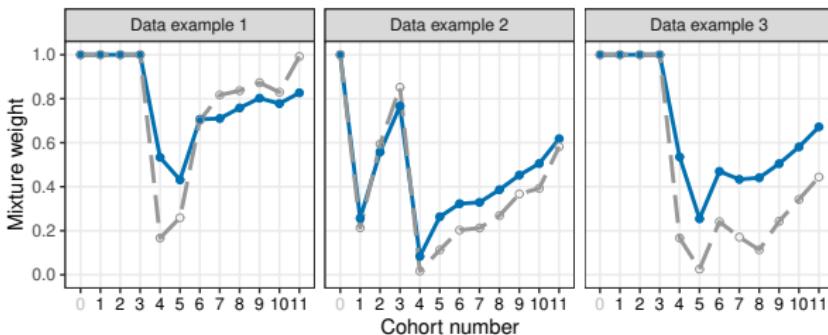
A

DLT data ● 0/3 ▲ 1/3 ■ 2/3 ◆ 3/3



B

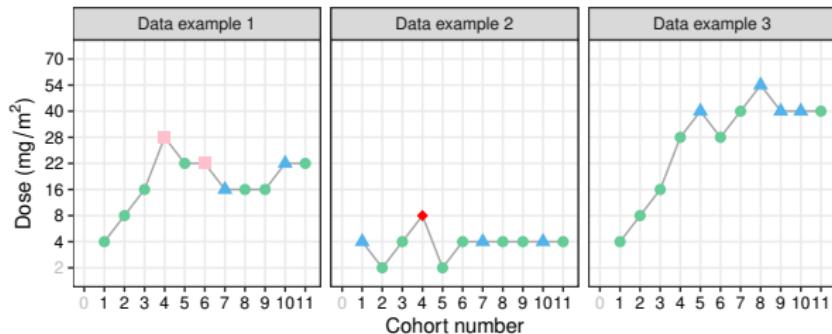
● Prior, $w^{(h)}$ —○— Posterior, $w_*^{(h)}$



Data examples with a run-in period

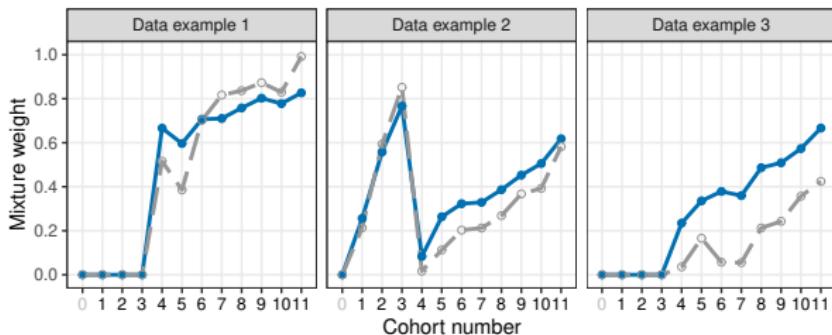
A

DLT data • 0/3 ▲ 1/3 ■ 2/3 ◆ 3/3



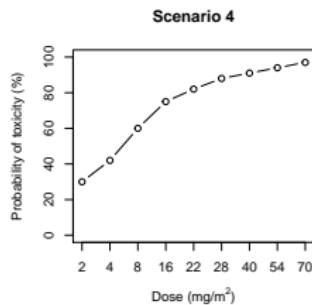
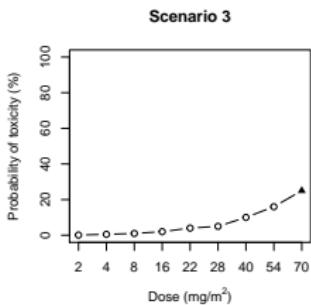
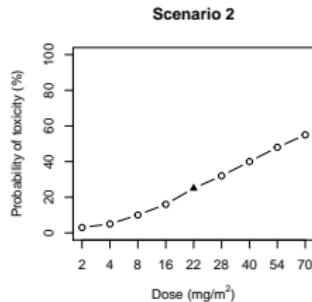
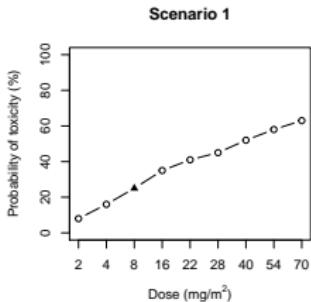
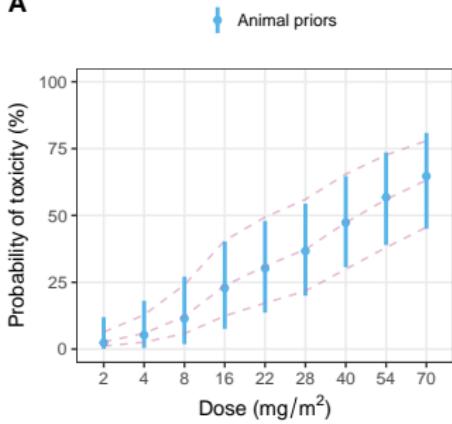
B

◆ Prior, $w^{(h)}$ —○— Posterior, $w_*^{(h)}$



Simulation settings

A

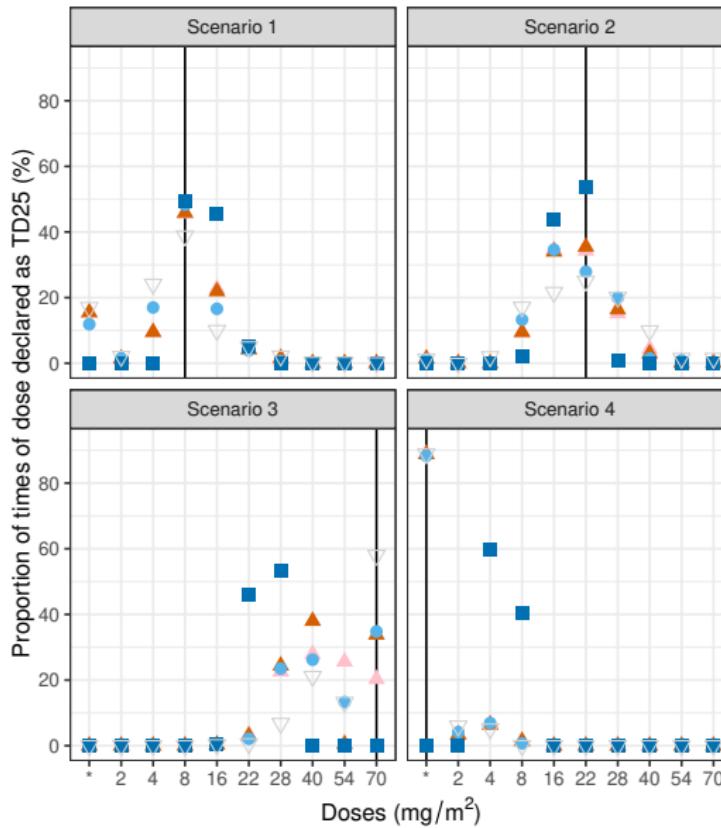


- Simulate 1,000 phase I dose-escalation trials
(15 cohorts of 3 patients per trial)
- Stop the trial if d_1 is found overly toxic, otherwise until N_{\max}

Dose-escalation procedures

Evaluate the operating characteristics of phase I trials using:

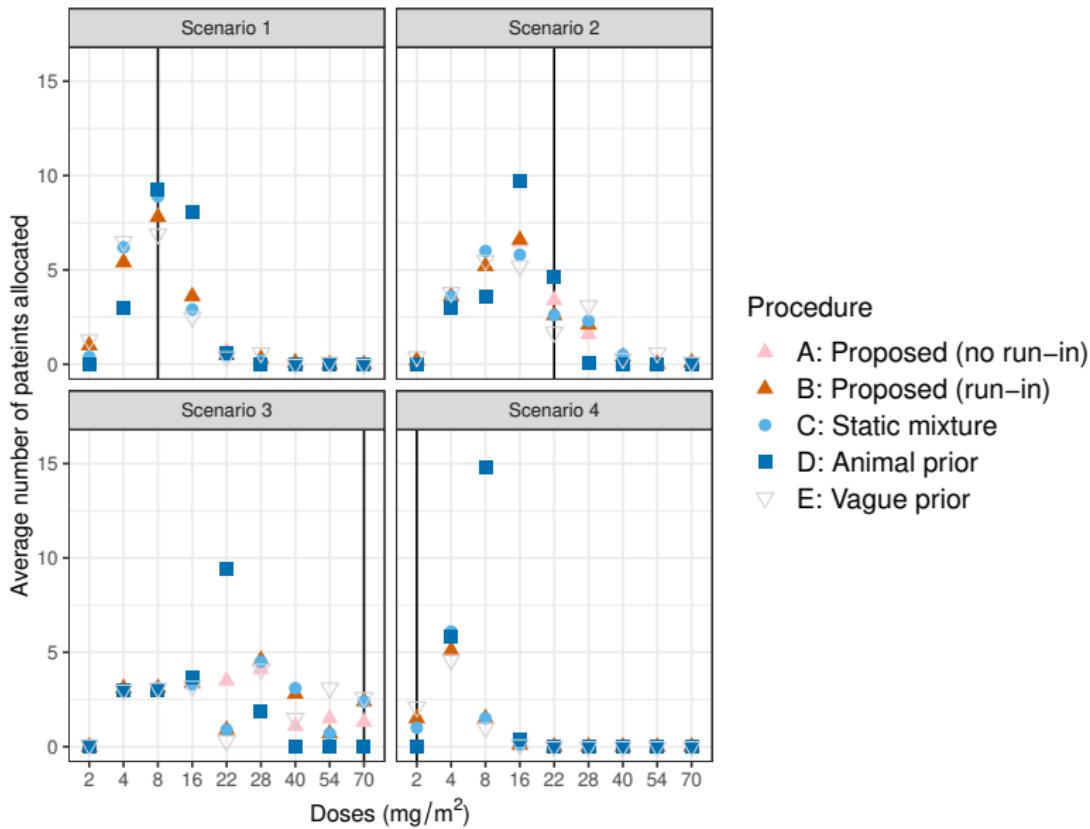
- Procedure A: **proposed** approach without a run-in period
- Procedure B: **proposed** approach with a run-in period
- Procedure C: Bayesian mixture prior with all $w_h = 0.5$
- Procedure D: Animal prior only, no dynamic discounting
- Procedure E: Vague prior, no use of animal data at all



Procedure

- A: Proposed (no run-in)
- B: Proposed (run-in)
- C: Static mixture
- D: Animal prior
- E: Vague prior

Patient allocation



Summary

- Dynamic mixture priors can handle prior-data conflict
- Other measures may be viable to quantify the prior-data conflict
- Preclinical data were assumed from the same species
- When animal data are from multiple species, meta-analytic approaches are recommended (Zheng et al., 2020; 2021)

Summary

- Dynamic mixture priors can handle prior-data conflict
- Other measures may be viable to quantify the prior-data conflict
- Preclinical data were assumed from the same species
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**“How may preclinical studies be designed
to better bridge the gap?”**

Some thoughts

- Include more animal doses for evaluation
- Choice of those doses
- Uncertainty in the interspecies translation (Zheng et al., 2020; 2021)
- Go optimal or adaptive for the design of animal studies?

References (I)

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