A Bayesian decision-theoretic approach to incorporating pre-clinical information into phase I clinical trials

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Motivation

FDA (2005), Sharma and McNeill (2009), Reigner and Blesch (2002)

Current approaches that use pre-clinical data in early drug development centre around the allometric scaling:

- a maximum recommended starting dose for humans is determined using allometry, which can produce inaccurate predictions
- pre-clinical data are not formally incorporated into conduct/interpretation of the phase I trial

Formal incorporation of pre-clinical data in phase I trials should be considered:

- represent the information in a prior for parameters of the dose-toxicity model
- discount it quickly if a prior-data conflict emerges anytime during the trial

Model-based dose-escalation procedures: the BLRM

Whitehead and Williamson (1998), Neuenschwander et al. (2008)

Bayesian logistic regression model (BLRM)

- Doses $d_1, \ldots, d_J$ are available for testing
- Binary endpoint: Dose-limiting toxicity (DLT) versus no-DLT
- Aim: to estimate the TDπ, the dose associated with risk of DLT at level π
- The dose-toxicity model: $\log\left\{\frac{p(d)}{1-p(d)}\right\} = \theta_1 + \exp(\theta_2)\log d$
  - Dose-escalation decision making relies on the probabilistic inference with the risk of DLT $p(d)$
- A bivariate normal prior for $\boldsymbol{\theta} = (\theta_1, \theta_2)$
  - operational priors: calibrated to ensure dose-escalation scheme has favourable operating characteristics
  - informative prior: formulated using pre-clinical data

Incorporating pre-clinical toxicology data

Adopt mixture prior for $\boldsymbol{\theta}$

$$f(\boldsymbol{\theta}) = \omega \times \underbrace{g(\boldsymbol{\theta})}_{\text{pre-clinical data}} + (1-\omega) \times \underbrace{h(\boldsymbol{\theta})}_{\text{operational prior}},$$

Deriving the informative component $g(\boldsymbol{\theta})$:

1. Summarise pre-clinical information as pseudo-data on the lowest and highest doses d_{-1} and d_0
2. This specifies independent beta distributions for $p(d_{-1})$ and $p(d_0)$
3. Given $\text{logit}\{p(d)\} = \theta_1 + \exp(\theta_2)\log d$, derive the priors for $p(d_j), j = 1, \ldots, J$ and their $2.5^{\text{th}}, 50^{\text{th}}$ and 97.5^{th} percentiles
4. Find the bivariate normal prior for $\boldsymbol{\theta} = (\theta_1, \theta_2)$, which is calibrated to agree with the exact summaries

Choosing the mixture weight ω

Challenge: difficult to test the prior-data conflict and to quantify the degree of commensurability, since phase I trials are typically small

Our mixture prior for θ at stage k is

$$f_k(\theta) = \omega_k \times \underbrace{g(\theta)}_{\text{pre-clinical data}} + (1-\omega_k) \times \underbrace{h(\theta)}_{\text{operational prior}},$$

- ω_k is dynamically determined at each interim analysis
  - smaller weight when evidenced by prior-data conflict
  - larger weight when animal and human data appear commensurate
- We develop a Bayesian decision-theoretic approach to measuring the commensurability
  - How accurate are predictions of human responses based on pre-clinical data?
  - Penalise the pre-clinical data harshly when they underestimate the risk of DLT in humans

Measuring the prior-data conflict

Fouskakis and Draper (2002), Vehtari and Ojanen (2012)

Let Y denote the response of a human patient receiving a specific dose.

1. Derive prior predictive distributions $\mathcal{P}\{Y = \tilde{y}\}$ from animal data
2. Derive optimal prediction for Y as

$$\hat{\eta} = \arg \max_{\eta \in \{0,1\}} \sum_{\tilde{y}} u(\tilde{y}, \eta) \mathcal{P}\{Y = \tilde{y}\},\ \tilde{y} \in \{0, 1\}$$

where $u(\tilde{y}, \eta)$ is the utility function that rewards predictions of $\tilde{y}$ as η:

$$u(\tilde{y}, \eta) = \begin{cases} 0, & \text{if } \eta = 0 \text{ while } \tilde{y} = 1 \text{ (incorrectly predict as no-DLT)} \\ c, & \text{if } \eta = 1 \text{ while } \tilde{y} = 0 \text{ (incorrectly predict as DLT)} \\ 1, & \eta = \tilde{y} \text{ (correct prediction)} \end{cases}$$

Note that $0 < c < 1$.

Measuring the prior-data conflict (*Cont'd*)

$f_k(\theta) = \omega_k \times g(\theta) + (1 - \omega_k) \times p(\theta)$

3. Compare optimal prior predictions versus observed human responses for each dose d_j at interim analysis k

		Rewards and Penalties		Cell counts	
		Observation (y)			
		No-DLT	DLT		
Prior prediction ($\hat{\eta}$)	No-DLT	u_{00} (1)	u_{10} (0)	n_{00}	n_{10}
	DLT	u_{01} (c)	u_{11} (1)	n_{01}	n_{11}

4. Derive the predictive utility of the animal data for the observed human toxicity data on dose d_j as $U_j^k = \sum_{l=0}^{1} \sum_{m=0}^{1} u_{lm} n_{lm}$
5. Measure commensurability of animal and human data at stage k by taking average of predictive accuracy across doses used so far

$$\bar{a}_k = \frac{1}{J} \sum_{j=1}^{J} \frac{U_j^k}{\sum_{l=0}^{1} \sum_{m=0}^{1} n_{lm}}$$

6. Set ω_k as a function of $\bar{a}_k$ in relevance to the trial information time

$$\omega_k = \bar{a}_k \sqrt{N/n}$$

Interim dose recommendations

Whitehead and Williamson (1998), Babb et al. (1998)

At each interim anakysis, $k = 1, 2, \ldots, N-1$

- Compare prior animal data with human data to derive ω_k
- Update the mixture prior $f_k(\boldsymbol{\theta}) = \omega_k \times g(\boldsymbol{\theta}) + (1 - \omega_k) \times h(\boldsymbol{\theta})$ to derive posterior $f_k(\boldsymbol{\theta}|\boldsymbol{x}_k)$
- Use the accumulated data $\boldsymbol{x}_k$ to recommend a dose for the $(k+1)^{\text{th}}$ cohort according to the determinant gain criterion

$$\mathcal{G} = \int (\det \boldsymbol{I}(\boldsymbol{\theta}))^{-1} f_k(\boldsymbol{\theta}|\boldsymbol{x}_k) \mathrm{d}\boldsymbol{\theta}$$

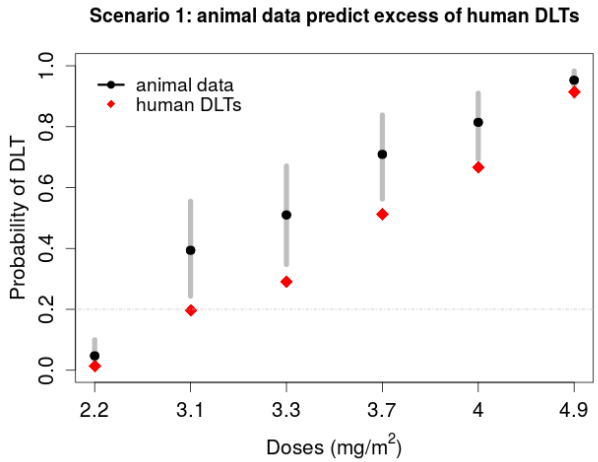
Safety constraint
Controlling the probability of excessive toxicity at level δ:

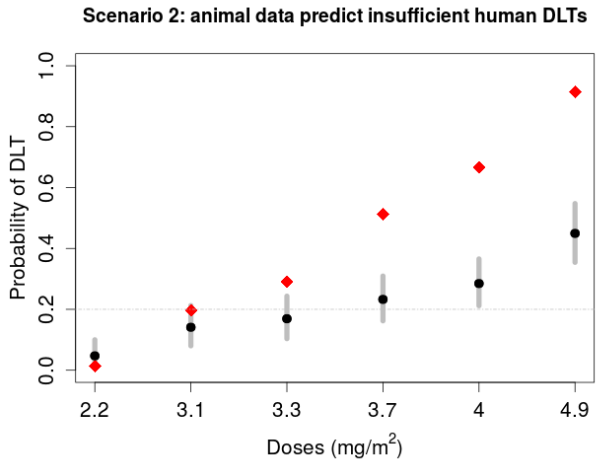
$$\int_{\gamma}^{1} g(p(d_j)) \mathrm{d}p(d_j) \leq \delta,$$

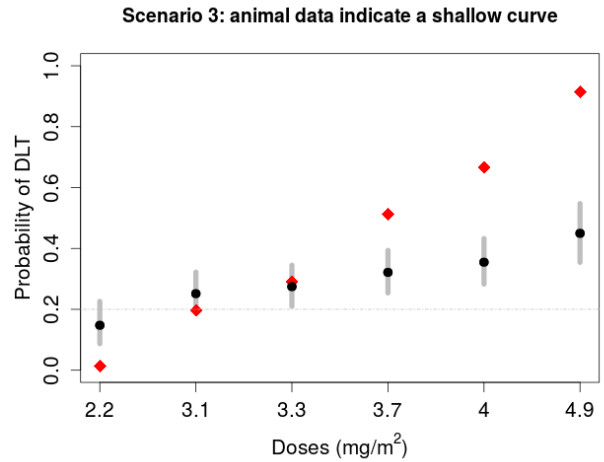
where γ is some threshold above which the risk of toxicity is considered excessively high. In our simulations, we set $\gamma = 0.50$ and $\delta = 0.25$.

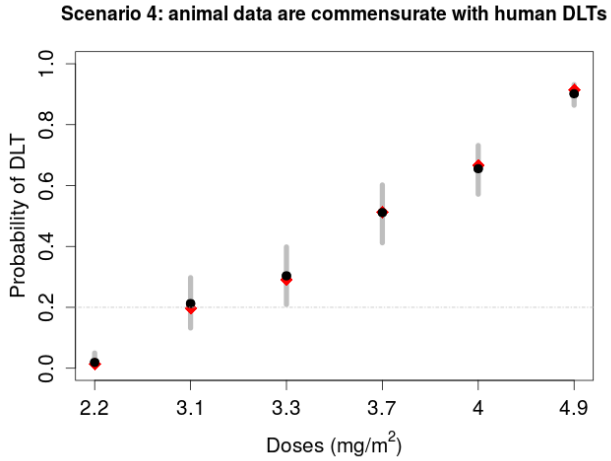
Simulation scenarios

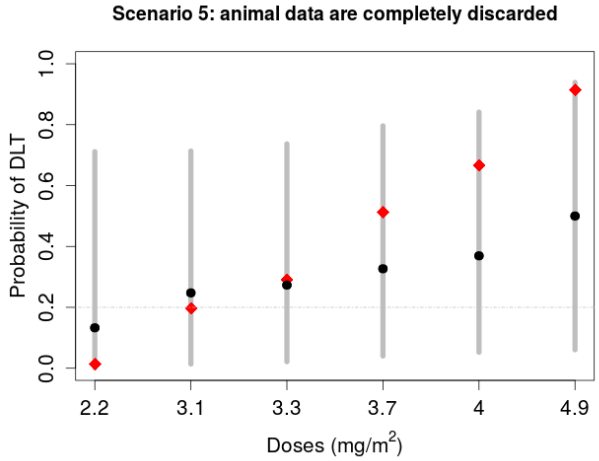
- Re-design the lurtotecan trial (N=24, c=1) reported by Giles et al. (2004) by incorporating pre-clinical information - **5 hypothetical prior scenarios**
- Early stopping for accuracy is not considered







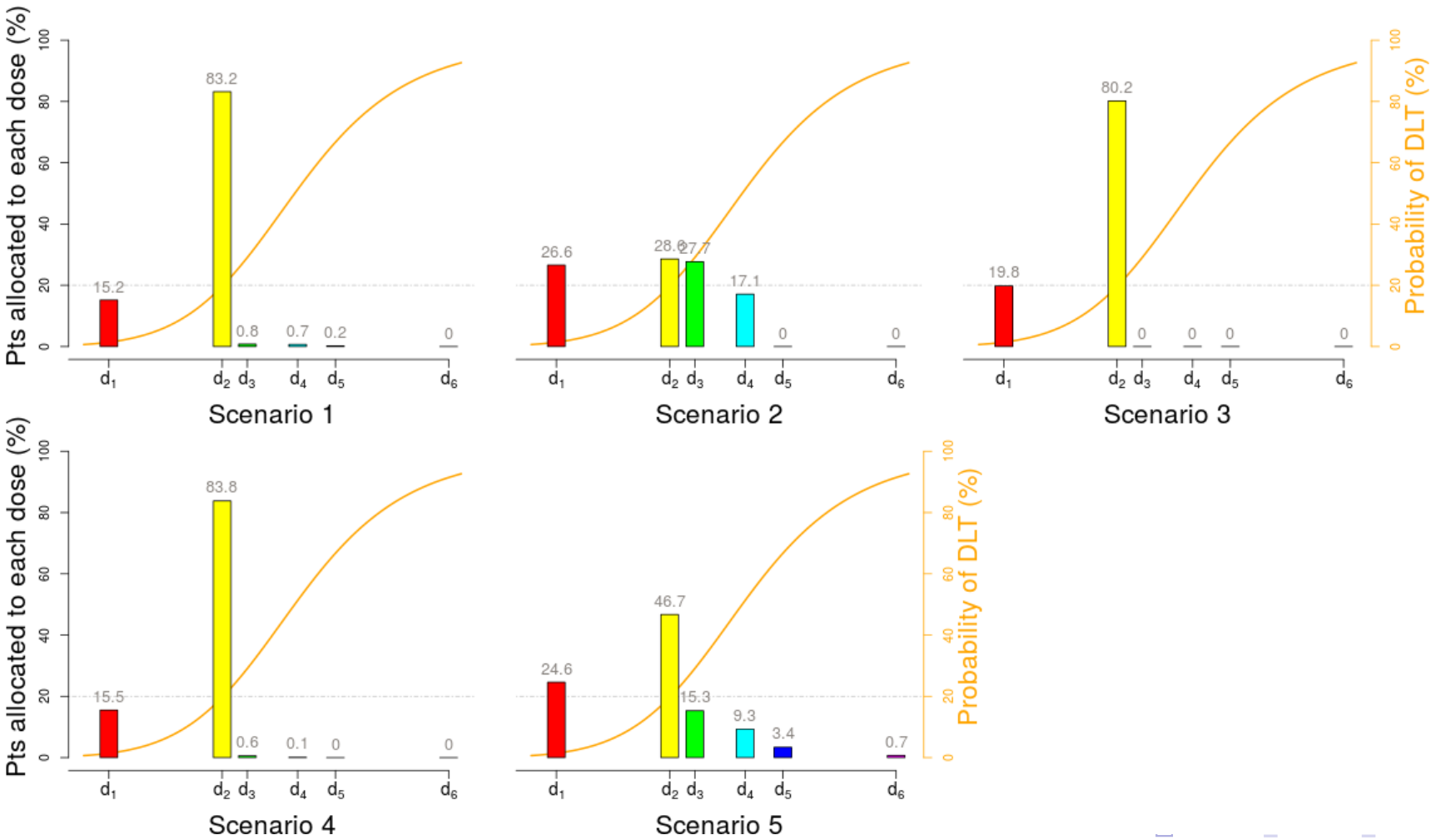




Simulation results (1)

Results based on 1000 simulated dose-escalation studies (N=24, c=1)

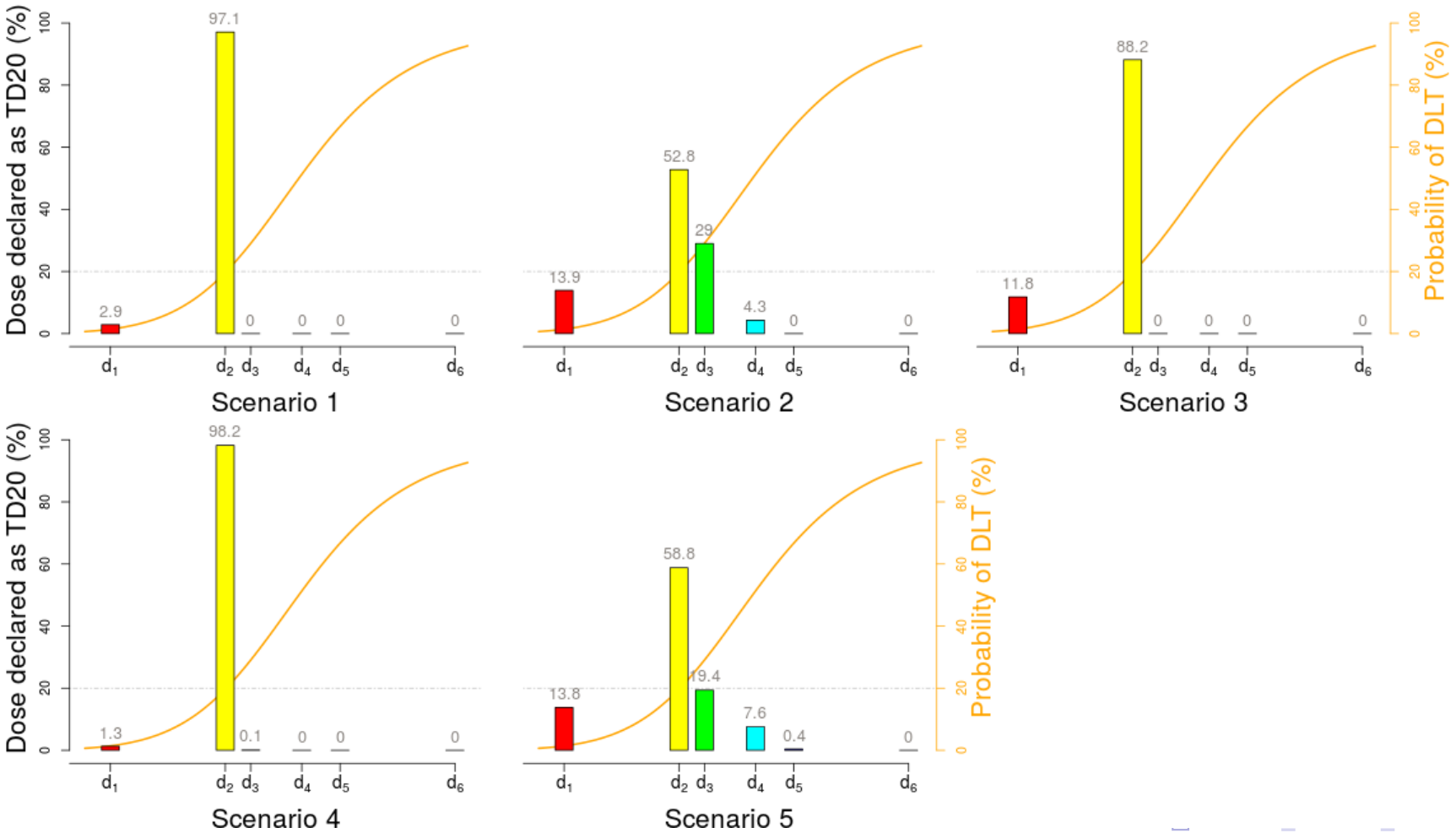
- Average proportion of allocating patients to each dose



Simulation results (2)

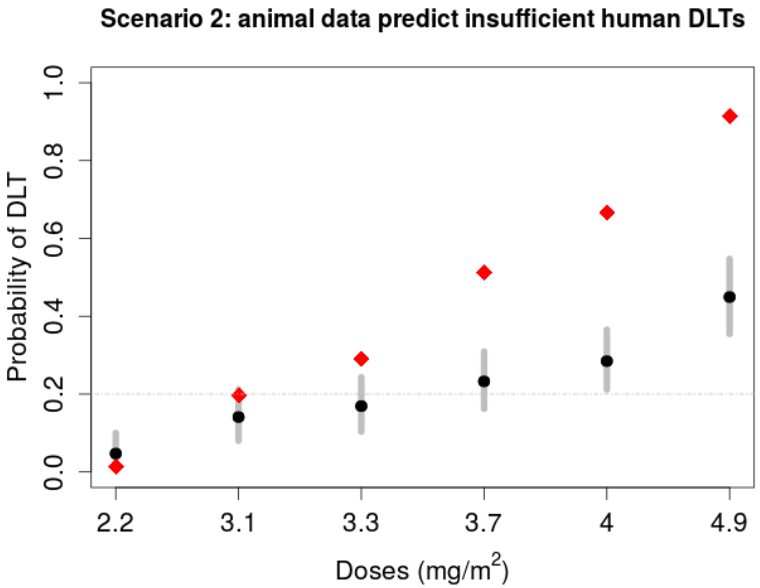
Results based on 1000 simulated dose-escalation studies (N=24, c=1)

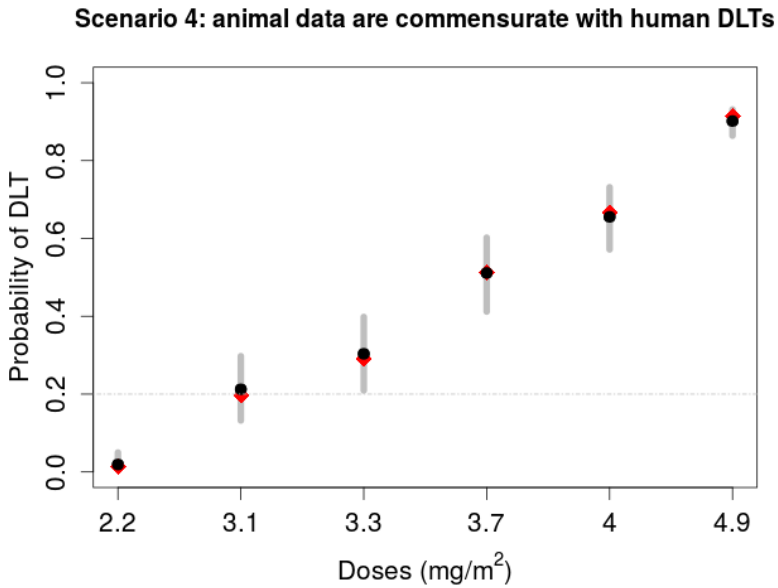
- Average proportion of declaring a dose as TD20

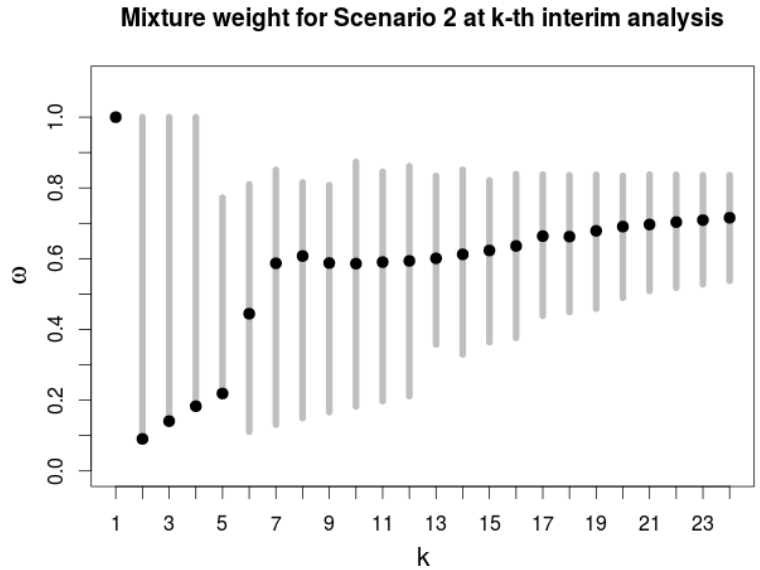


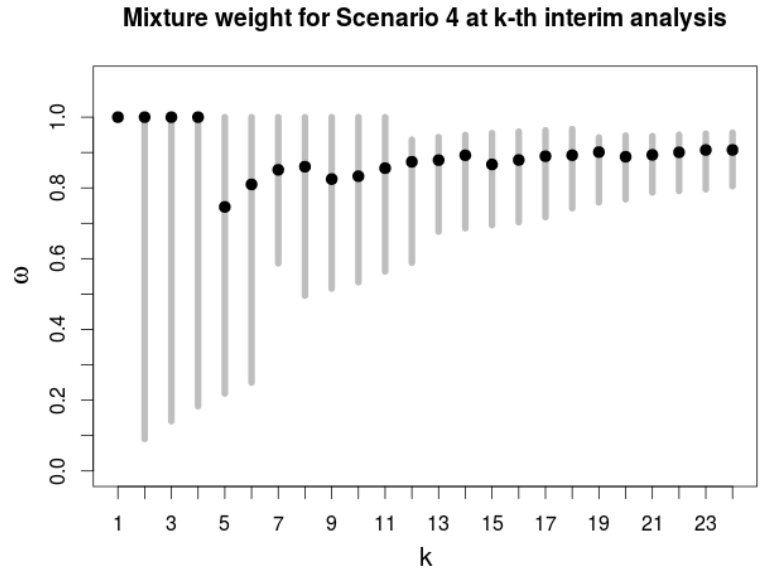
Simulation results (3)

Results based on 1000 simulated dose-escalation studies (N=24, c=1)









Conclusions

- Incorporating pre-clinical data will potentially lead to more efficient escalation decision making and greater estimation precision
  - Patients have enhanced possibility to receive the target dose
  - Dose recommendations are robust and sensible to different type of prior from animal data
- Our approach can essentially discount the pre-clinical information if prior-data conflict emerges anytime during the trial

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