MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Dose-escalation designs for combination & dose-schedule studies

Lecture 11: Phase I/II designs for monotherapy and combination trials

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Beyond single-agent binary toxicity data

- Non-binary toxicity
  - Ordinal (different toxicity grades): Lee *et al.* 2011
  - Continous: Wang and Ivanova (2015)
- Incorporate efficacy
  - Binary Efficacy: Bivariate CRM (Braun, 2002), Reducing to trivariate outcome (Thall & Russell, 1998)
  - Continuous Efficacy: Zhou *et al.* (2006), Latent variable model (Bekele & Shen, 2005), Bivariate normal model (Hirakawa, 2012)
- PK information in single-agent studies: Piantadosi & Liu (1996), Whitehead *et al.* (2007), Ursino *et al.* (2017)

Including continuous efficacy

General idea:

- Model toxicity
- Model efficacy (or biomarker of efficacy)
- Make escalation/de-escalation decisions based on a **“trade-off” function**

Model

- Dose levels $d_{(1)} < \cdots < d_{(k)}$
- Toxicity model

$$p(d_{(j)}) = \frac{\exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}}{1 + \exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}}$$

  for all $j = 1, ..., k$.

- Given no DLT, efficacy is modelled as

$$y_i = \beta_1 + \beta_2 \log\{\log(d_i)\} + \epsilon_i$$

- Specify priors using pseudo-patients data (as Approach 3 in Lecture 2)

Dose escalation

- Defined $y'_{(j)}$ as

$$y'_{(j)} = \begin{cases} y_{(j)} & \text{if no DLT is observed} \\ \kappa & \text{if a DLT is observed} \end{cases}$$

where $y_{(j)}$ is the response of a subject receiving dose j

- Define the gain at dose j as

$$G_{(j)} = E(y'_{(j)}) = \frac{y_{(j)}}{1 + \exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}} + \frac{\kappa \exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}}{1 + \exp\{\alpha_1 + \alpha_2 \log(d_{(j)})\}}$$

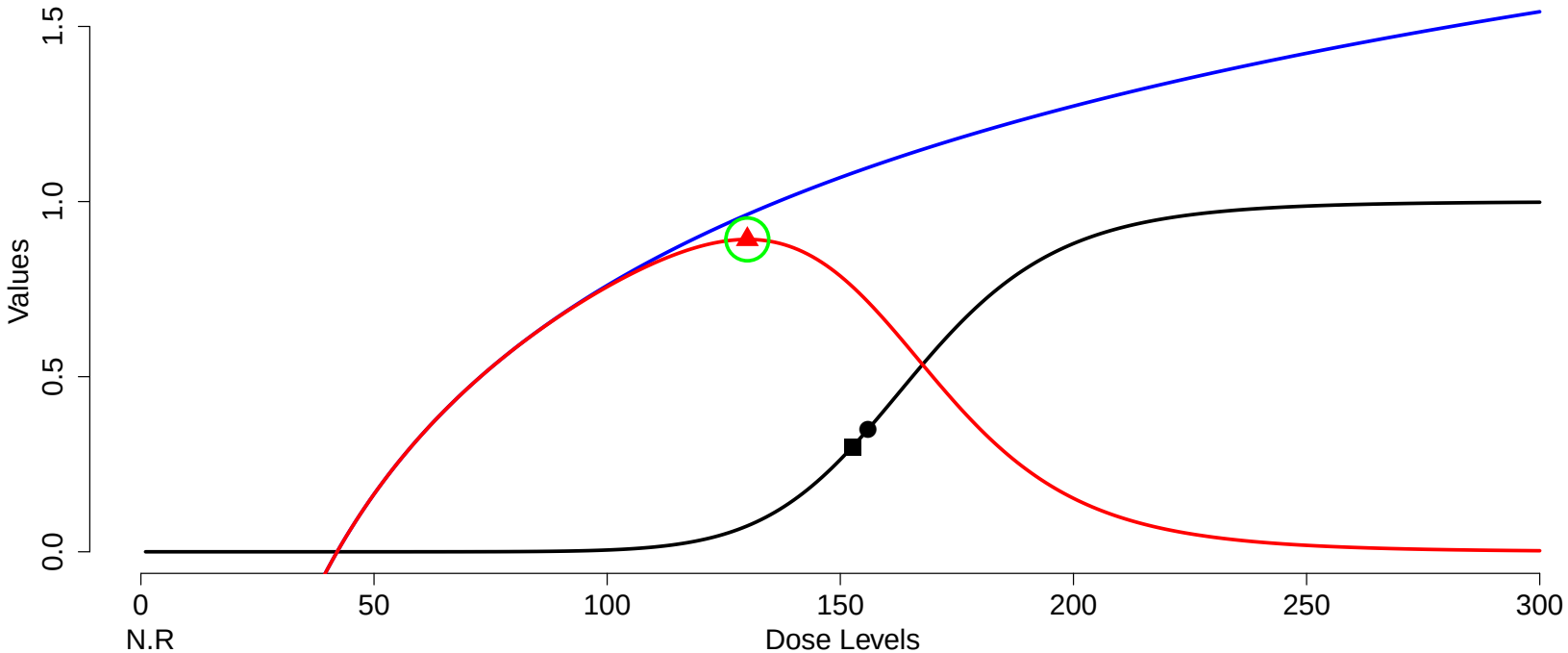
Dose escalation

Allocate next dose that

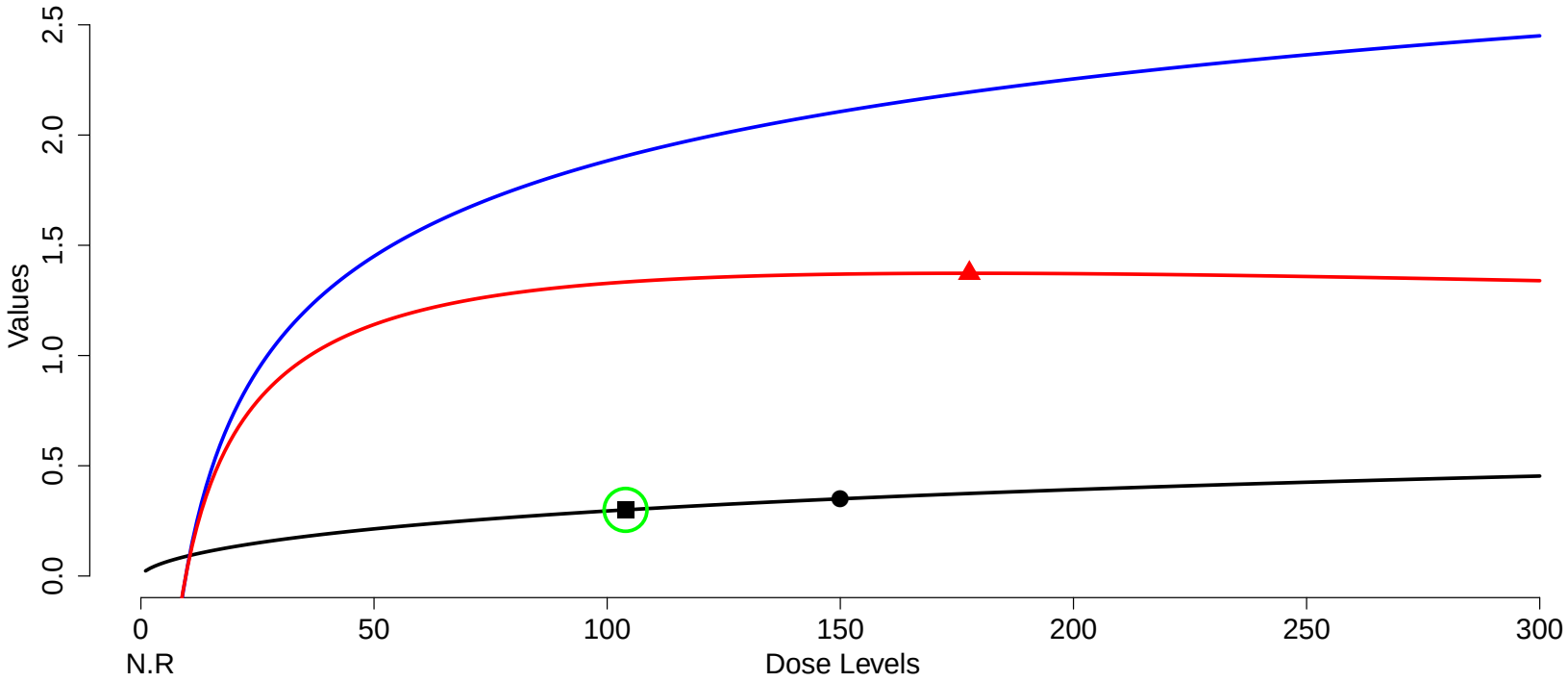
- maximizes gain
- provided it is less than estimated TDθ.

Example

$$G(j) = \frac{\beta_1 + \beta_2 log\{log(d_{(j)})\}}{1 + \exp\{\alpha_1 + \alpha_2 log(d_{(j)})\}}$$



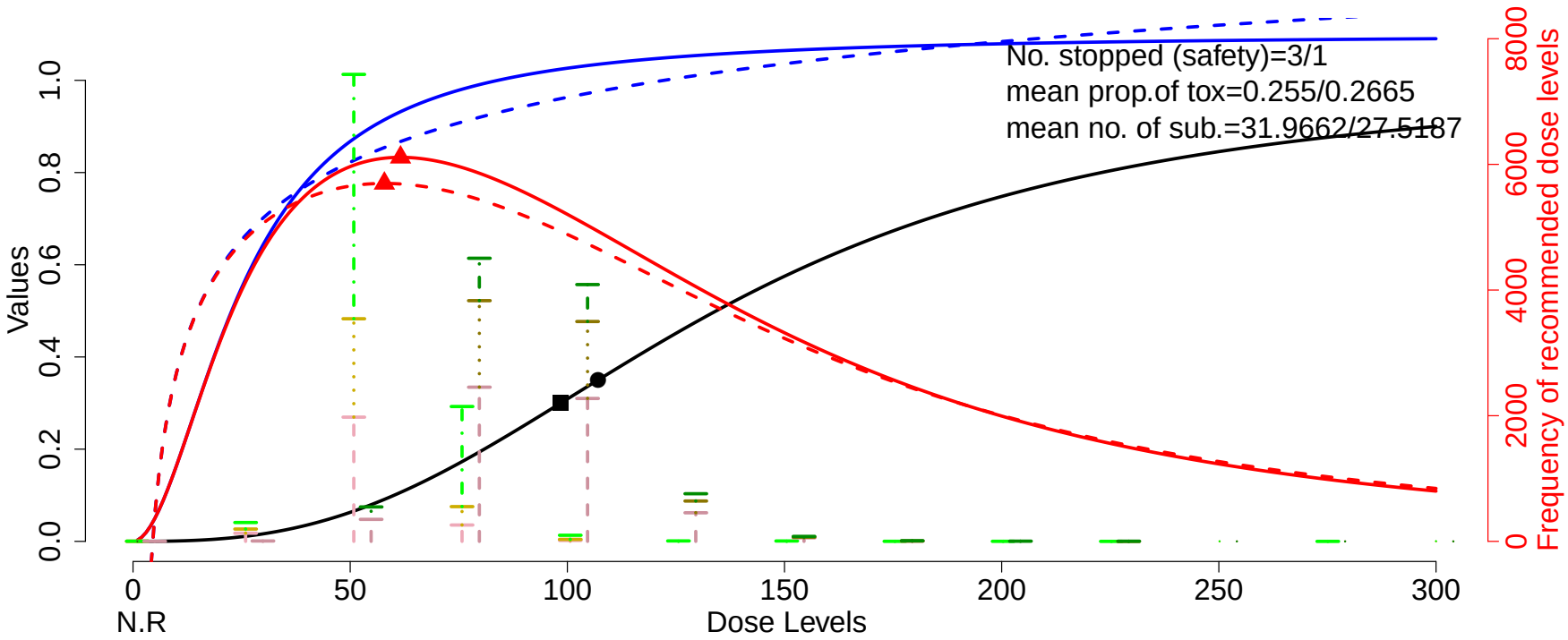
Example



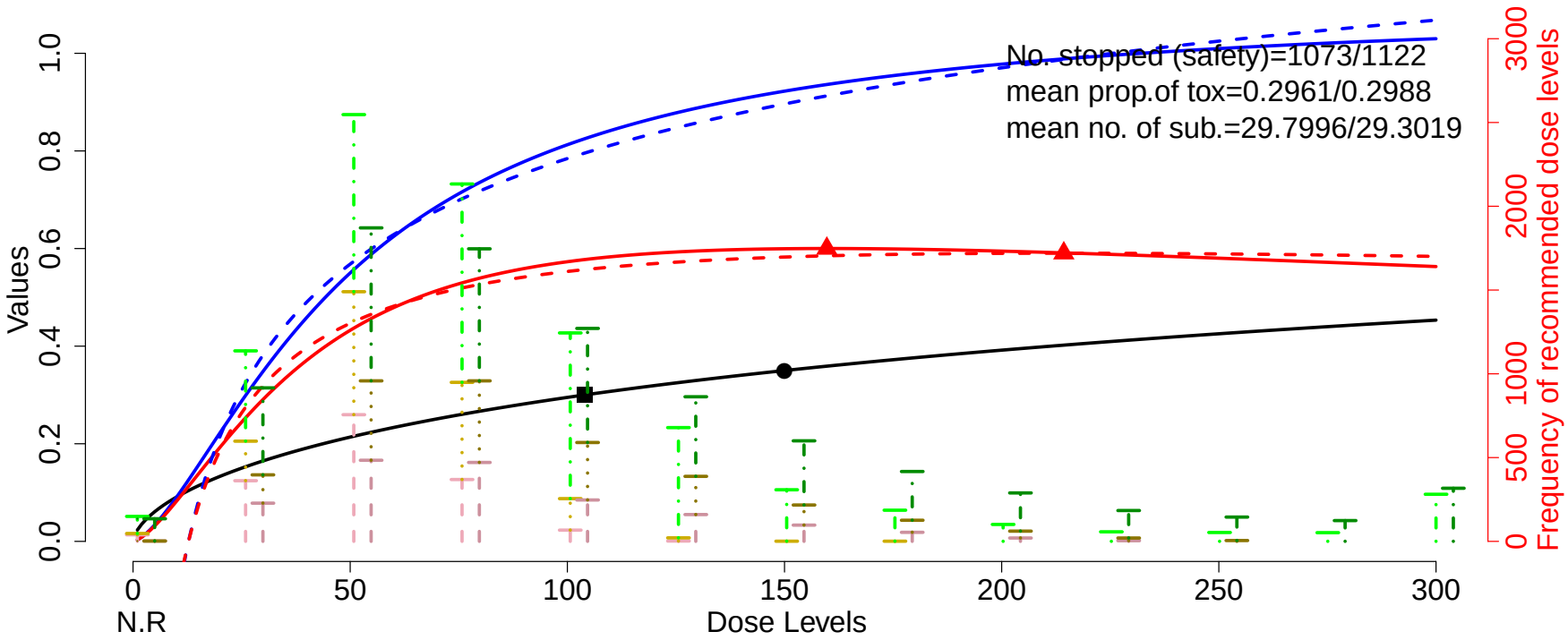
Stopping escalation

- When maximum number of patients has been recruited
- When we can estimate “optimal dose” accurately enough
  - Determine current “optimal dose”
  - Find corresponding 95% credibility interval
  - Stop if the ratio of the upper and lower bound ¡ 5

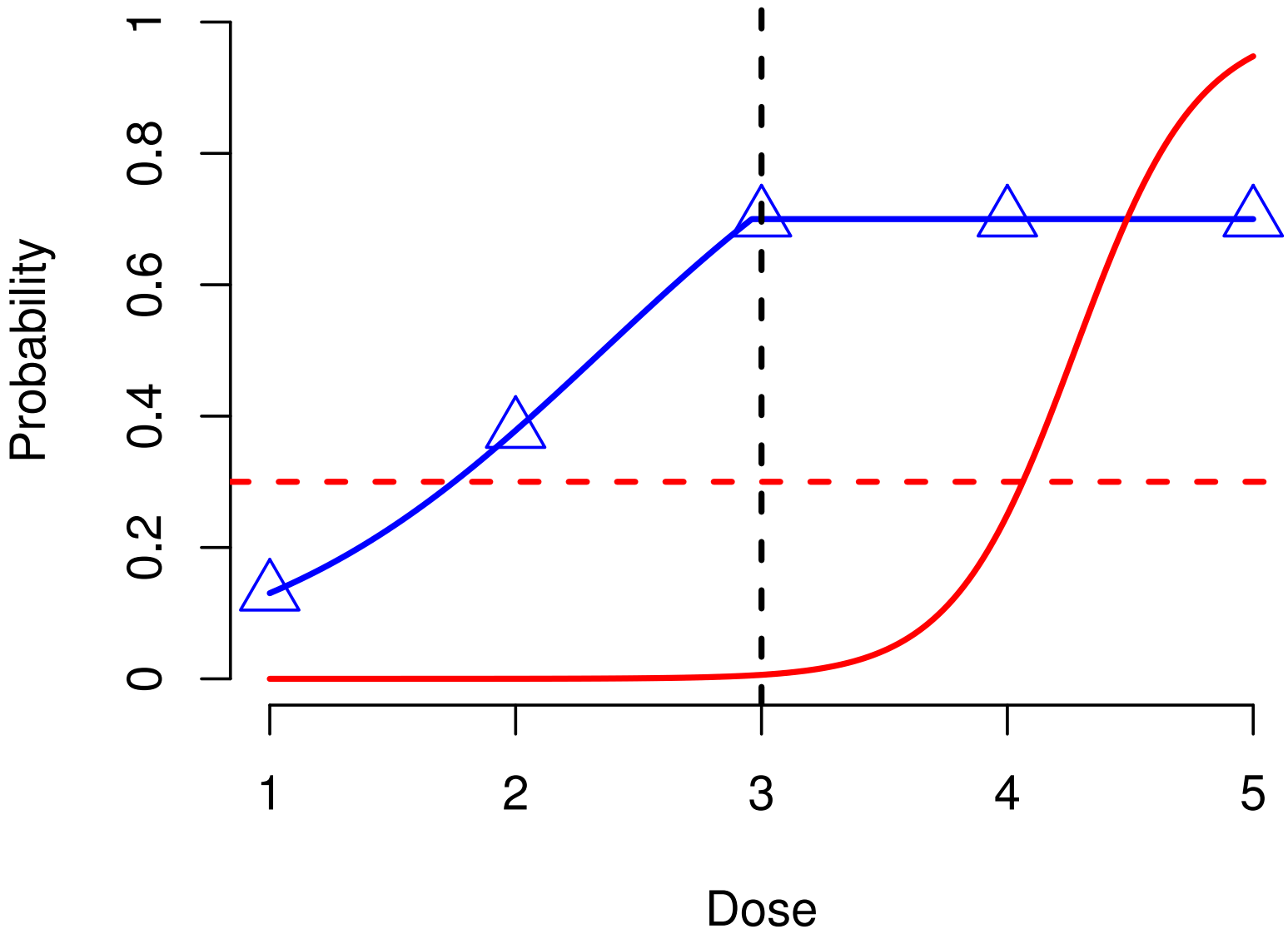
Simulations



Simulations



Single-agent trial for MTA



BLRM extension for the single-agent MTA

Modified **two-parameter logistic model**

- Dose-toxicity:

$$\text{logit} p_{t_j} = \beta_0 + \beta_1 \tilde{d}_j$$

- Dose-efficacy:

$$\text{logit} p_{e_j} = \gamma_0 + \gamma_1 \left(\bar{d}_j I_{j<\tau} + \nu_\tau I_{j \geq \tau} \right)$$

- Randomization between plateau locations

POCRM extension for the single-agent MTA

In addition to toxicity model, define the dose-efficacy model

$$p_{im}^{(eff)} = \lambda_{im}^{exp(\beta_m)}, \text{ where } \lambda \text{ is skeleton}$$

- Define efficacy orderings (might be different from toxicity ones)
- Estimate both α_m and β_m for each ordering
- Choose the toxicity and efficacy orderings that data indicates to be **the most likely** ones ($m^\star$ and m')
- Update estimates of probabilities within these orderings

$$\hat{p}_{im^\star} = \pi_{im^\star}^{\hat{\alpha}_{m^\star}}; \quad \hat{p}_{im'}^{(eff)} = \lambda_{im'}^{\hat{\beta}_{m'}}$$

- The next cohort is assigned using the pre-specified decision criterion, e.g.

$$\arg\max \hat{p}_{im'}^{(eff)} \text{ such that } \hat{p}_{im^\star} < \theta.$$

Alternative approaches incorporating efficacy

Essentially, regardless of the type of outcome (binary, ordinal, continous), all model-based designs follow a similar scheme:

1. Specify parametric models for the dose-response relationships given the type of data
2. Use prior distribution to start the trial
3. Update the estimate of the parameters cohort-by-cohort
4. Add safety constraints and stopping rules
5. Assign the next cohort according to the chosen criterion

Discussion

- Efficacy endpoint needs to be **quickly observable**
  - but does not require both DLT and efficacy endpoint to be available at the same time
  - The evaluation window for each endpoint should be taken into account when planning/designing the trial;
- Form of gain function/model/orderings need to be context specific