



MRC  
Biostatistics  
Unit



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# Designing Phase I Single Agent Dose-Escalation Studies

*Lecture 4: Model-assisted dose-escalation designs*

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- Model-based designs balance accuracy/safety trade-off, but...
- There is argument that they can be a “**black box**” for clinicians;
- And they might be time-consuming to set up.

Propose solution: **model-assisted design**.

- Up-and-down rules;
- Based on the statistical estimates of the toxicity risk at the **current** dose;
- Doses are modelled independently → quick to evaluate;
- All escalation/de-escalation decision could be summarised in **one table**;

# Model-Based Designs: general principles

- Use a set of decision rules based on the DLT probability estimated from a simple Bayesian model
- Use toxicity data of the most recently used dose level and does not borrow information from other dose levels
- Escalation/de-escalation rules imply the assumption of a monotonic ordering;

# Modified Toxicity Probability Interval (mTPI)

- **Equivalence interval** ( $TTL - \epsilon_1, TTL + \epsilon_2$ ),  $\epsilon_1, \epsilon_2 \geq 0$  covers the range of acceptable deviations from TTL.
- It divides the unit interval into **three subintervals**
  - ▶  $[0, TTL - \epsilon_1]$  [underdosing]
  - ▶  $[TTL - \epsilon_1, TTL + \epsilon_2]$  [target]
  - ▶  $(TTL + \epsilon_2, 1]$  [overdosing]
- Using vague priors on each toxicity risk and observing the patients on the current cohort, the posterior is updated;
- Decision are based on the **unit probability mass (UPM)** - ratio of the probability and length of the interval.
  - ▶ UPM for  $[0, TTL - \epsilon_1]$  is highest  $\rightarrow$  escalate;
  - ▶ UPM for  $[TTL - \epsilon_1, TTL + \epsilon_2]$  is highest  $\rightarrow$  stay;
  - ▶ UPM for  $(TTL + \epsilon_2, 1]$  is highest  $\rightarrow$  de-escalate.

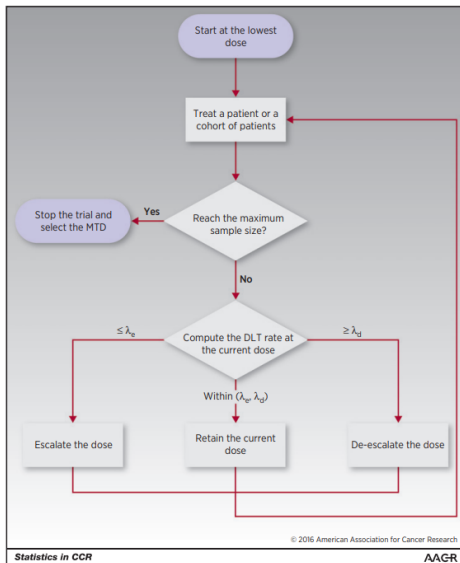
# Bayesian Optimal Interval (BOIN)

- Estimates the probability of toxicity at dose  $d_j$  using  $\hat{p}_j = y_j/n_j$ ;
- $\phi_1$  is the highest toxicity probability deemed subtherapeutic;
- $\phi_2$  is the lowest toxicity probability deemed overly toxic;
- Escalation process is defined by  $(\lambda_e, \lambda_d)$  chosen to **minimise the chance of incorrect escalation/de-escalation**

$$\lambda_e = \frac{\log\left(\frac{1-\phi_1}{1-TTL}\right)}{\log\left(\frac{TTL(1-\phi_1)}{\phi_1(1-TTL)}\right)} \quad \text{and} \quad \lambda_d = \frac{\log\left(\frac{1-TTL}{1-\phi_2}\right)}{\log\left(\frac{\phi_2(1-TTL)}{TTL(1-\phi_2)}\right)}$$

- ▶ If  $\hat{p}_j \leq \lambda_e \rightarrow$  escalate
- ▶ If  $\hat{p}_j \geq \lambda_d \rightarrow$  de-escalate
- ▶ If  $\lambda_e < \hat{p}_j < \lambda_d \rightarrow$  stay
- At the end, estimates  $p_j$  are calculated via isotonic regression.

# Bayesian Optimal Interval (BOIN)



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**Table 1.** Dose escalation and de-escalation boundaries

Boundary	Target toxicity rate for the MTD						
	0.1	0.15	0.2	0.25	0.3	0.35	0.4
$\lambda_e$ (escalation)	0.078	0.118	0.157	0.197	0.236	0.276	0.316
$\lambda_d$ (de-escalation)	0.119	0.179	0.238	0.298	0.358	0.419	0.479

**Table 2.** Dose escalation and de-escalation boundaries for target toxicity rate = 30%

Action	The number of patients treated at the current dose																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Escalate if no. of DLTs $\leq$	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4
De-escalate if no. of DLTs $\geq$	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6	6	7	7

- Result in **good accuracy** (slightly lower than the CRM), and good safety.
- Extended to various setting (dual endpoints, combinations);
- **Quick** to evaluate;
- Easy to use;



# Drawbacks

- Doses are modelled **independently**;
- High chance ( $\geq 75\%$ ) of **incoherent** recommendations;
- Cannot accommodate changes in the setting;
- The “intuitive” interval might be suboptimal (a challenge to convince HAs);
- Dose-skipping/backfill are not particularly meaningful;
- Overruling of recommendations can make the design completely **redundant**

# Challenges: Example

	Number of patients treated									
	3	6	9	12	15	18	21	24	27	30
Escalate if number of DLT $\leq$	0	1	2	2	3	4	5	5	6	7
De-escalate if number of DLT $\geq$	2	3	4	5	6	7	8	9	10	11
Eliminate if number of DLT $\geq$	3	4	5	7	8	9	10	11	12	14

- Doses: 1mg, 2mg, 3mg, 4mg, 5mg;
- Start at 2mg, 0/3 DLTs but the team decides to stay (sub-DLT);
- 1/3 DLTs, the design recommends escalating  $\rightarrow$  overrule;
- 1/3 DLTs, the design recommends escalating  $\rightarrow$  overrule

*Would your judgement on the escalation be different if there were 2/10 on 1 mg, or 0/10 at 1 mg?*