MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Designing Phase I Single Agent Dose-Escalation Studies

Lecture 4: Model-assisted dose-escalation designs

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Motivation

- 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 $\rightarrow$ 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)

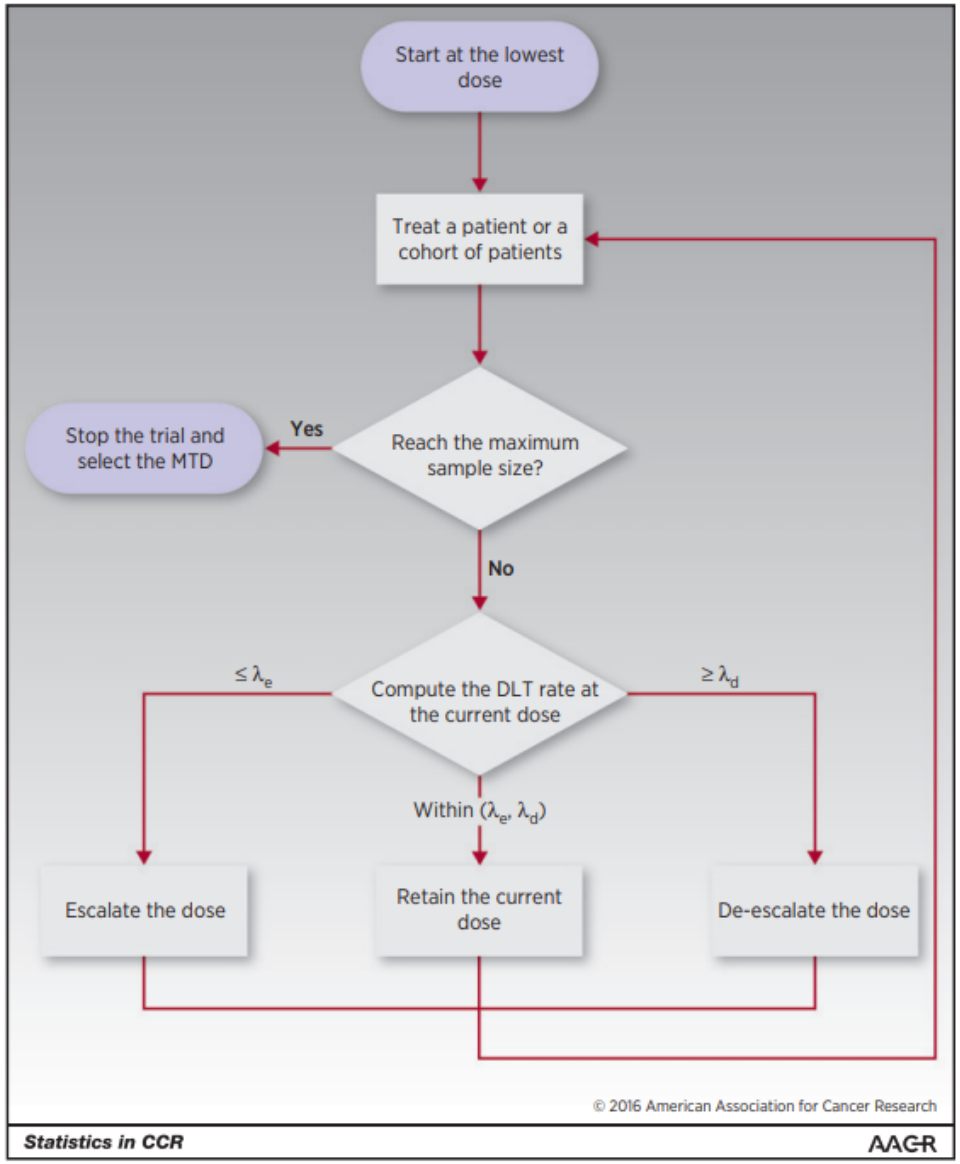
- Estimates the probability of toxicity at dose d_j using $\hat{p}_j = y_j/n_j$;
- ϕ_1 is the highest toxicity probability deemed subtherapeutic;
- ϕ_2 is the lowest toxicity probability deemed overly toxic;
- Escalation process is defined by (λ_e, λ_d) chosen to **minimise the chance of incorrect escalation/de-escalation**

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

  - 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)



Bayesian Optimal Interval (BOIN)

Table 1. Dose escalation and de-escalation boundaries

	Target toxicity rate for the MTD						
Boundary	**0.1**	**0.15**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**
λ_{e} (escalation)	0.078	0.118	0.157	0.197	0.236	0.276	0.316
λ_{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%

	The number of patients treated at the current dose																	
Action	**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

Benefits

- 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 <=	0	1	2	2	3	4	5	5	6	7
De-escalate if number of DLT >=	2	3	4	5	6	7	8	9	10	11
Eliminate if number of DLT >=	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?