Improving Safety of the Continual Reassessment Method (CRM) via a Modified Allocation Rule

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Motivation

Consider a **Phase I dose-escalation clinical trial** with two doses, d_1, d_2:

- Binary endpoint, DLT or no DLT;
- **Goal:** to find the maximum tolerated dose (**MTD**), the target $\gamma = 0.30$.
- 10 patients were assigned to each dose
- 2 and 4 toxicities were observed for dose d_1 and d_2, respectively
- Probability of DLT are Beta RV and $\hat{p}_1 = 0.2$ and $\hat{p}_2 = 0.4$.

A typical question in a sequential trial is

"Which dose should be administered to the next patient?"

A common criterion (e.g used by the CRM) is the **squared distance** between the point estimate $\hat{p}_i$ and γ:

$$(\hat{p}_i - \gamma)^2 . \tag{1}$$

Following (1), the next patient **can be allocated to either of doses**. However **these doses are not "equal"** for at least two reasons:

1. The criterion (1) **ignores the randomness** of the estimates as

$$\mathbb{P}(p_2 \in (0.25, 0.35)) > \mathbb{P}(p_1 \in (0.25, 0.35)) . \tag{2}$$

2. The allocation of a patient to the dose corresponding to $\hat{p}_2 = 0.4$ **can be unethical** as it exposes a patient to unacceptably high toxicity.

Our proposal: a new allocation criterion to be used by CRM:

- The criterion takes **both the randomness** of the estimates and the **ethical concerns** of an investigator into account;
- requires only one additional parameter controlling the trade-off between them.

A novel allocation criterion

Step 1. Addressing the uncertainty.
It is argued by [1] that (1) **is not a reliable measure of distance** between objects defined on the unit interval, i.e. for $\hat{p}$ and γ. Instead, [2] proposed

$$\delta(p, \gamma) = \frac{(p-\gamma)^2}{p(1-p)}. \tag{3}$$

- Criterion (3) takes its minimum value $\delta(\cdot) = 0$ at $p = \gamma$;
- The denominator is the variance of the probability of a binary event;
- The criterion **"drives away"** the selection from the bounds to γ.

Applying (3) to the example, $\delta(\hat{p}_1 = 0.2, \gamma = 0.3) = 1/16$, $\delta(\hat{p}_2 = 0.4, \gamma = 0.3) = 1/24$. Single point estimate carries information about uncertainty.

Step 2. Addressing the ethical concerns.
The denominator in (3) implies that overly toxic and overly safe doses are equally penalised. Therefore, we include the **asymmetry parameter** a:

$$\delta(p, \gamma) = \frac{(p-\gamma)^2}{p^a(1-p)^{2-a}}. \tag{4}$$

Values $0 < a < 1 \rightarrow$ more severe penalty for more toxic doses.

Applying (4) to the example, $\delta(\hat{p}_1 = 0.2, \gamma = 0.3, a = 0.5) < \delta(\hat{p}_2 = 0.4, \gamma = 0.3, a = 0.5) \rightarrow d_1$ will be selected due to the safety penalty.

Step 3. Choosing the asymmetry parameter a**.**

1. "Plug-in" estimator of (4) using $a = 2\gamma$ is equivalent to (1) $\rightarrow a < 2\gamma$ is **more conservative choice**.

2. We require that given two point estimates belonging to interval $(\gamma - \theta, \gamma + \theta)$ and standing on the same squared distance from γ, **one should select the lower one.**

The value of a satisfying this condition can be found as

$$a = 2\left(1 + \left(\log\frac{\gamma-\theta}{\gamma+\theta}\right) / \left(\log\frac{1-\gamma-\theta}{1-\gamma+\theta}\right)\right)^{-1}$$

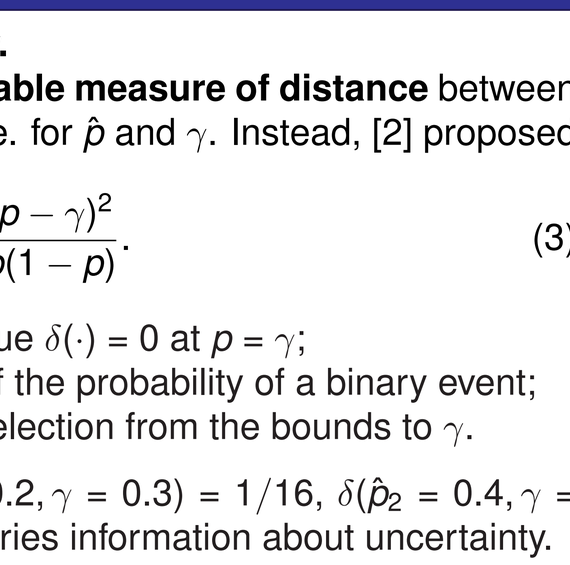

Fig. 1: Parameter a for $\gamma = 0.20$ (dashed-dotted) , $\gamma = 0.25$ (solid), $\gamma = 0.30$ (dashed), $\theta \in (0, 0.35)$.

CRM dose-finding design with novel criterion

Consider a Phase I clinical trial with m doses and n patients. Assume that

- The DLT probability has the form $\psi(d_i, \beta) = d_i^{\exp(\beta)}$, β is a parameter;
- $f_0(\cdot)$ is the prior distribution of β, j patients have already been assigned.

One updates the distribution of β obtaining $f_j(\beta)$. The dose d_k minimising

$$\mathbb{E}_{f_j(\beta)}\left(\frac{(\psi(d_i, \beta) - \gamma)^2}{\psi(d_i, \beta)^a(1 - \psi(d_i, \beta))^{2-a}}\right), \text{ is selected for the next patient.}$$

Numerical Study

We consider scenarios by [3] with $n = 40$ patients, $m = 6$ doses, $\gamma = 0.33$.

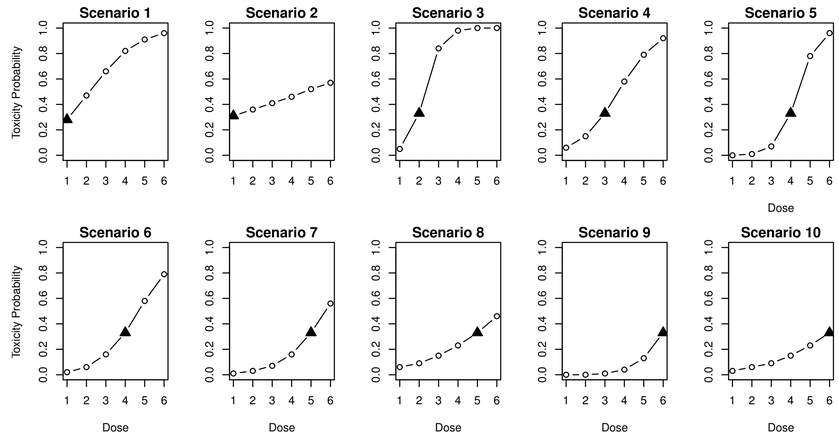

Fig. 2: Dose-toxicity scenarios. The MTD is marked by a black triangle.

- **Accuracy** $\mathcal{A} = 1 - m\frac{\left(\sum_{i=1}^m (p_i-\gamma)^2 \pi_i\right)}{\left(\sum_{i=1}^m (p_i-\gamma)^2\right)}$ and Mean number of **DLTs**.

Comparators: EWOC, **Toxicity-dependent feasibility bound design** (TDFB) by [3], **Bayesian Logistic Regression Model** (BLRM) by [4].

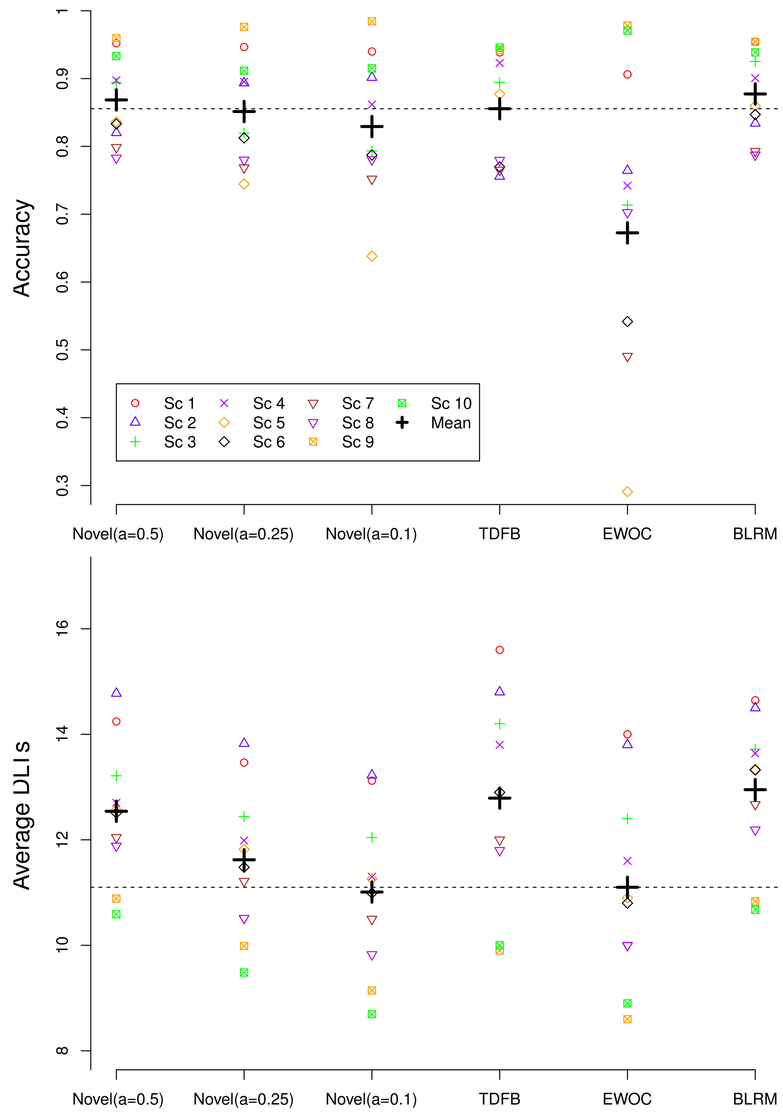

Fig. 3: Accuracy indices, mean DLTs for the proposed method and comparators.

Conclusions

The new criterion allows to make model-based design **more ethical**:

- **Similar** accuracy, but **fewer** mean number of DLTS.
- **Greater** accuracy, but **similar** mean number of DLTs.

References and Acknowledgement

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.