Information Theory in Dose-Finding: Improving Safety of the CRM

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Motivation

Consider a dose-finding trial with binary responses and two doses: $d_1, d_2$

Goal is to find the maximum tolerated dose (MTD): $\gamma = 0.30$.

10 patients were assigned to each dose, 2 and 4 toxicities observed

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

2. $\hat{p}_2 = 0.4$ is an unacceptably high toxicity.
It is usually of interest to balance both aims in a Phase I clinical trial.
Current solutions

**Safety:**

Escalation with Overdose Control (EWOC) design (Babb et al., 1998):

\[
\mathbb{E} \left( \alpha (\gamma - P_i)^+ + (1 - \alpha) (P_i - \gamma)^+ \right)
\]  

+ Low average number of DLTs
- Underestimation of the MTD

**Modifications:** \(\alpha_n\) by Tighiouart et al. (2010) and Wheeler et al. (2017)
Current solutions

Safety:
Escalation with Overdose Control (EWOC) design (Babb et al., 1998):

\[ \mathbb{E} (\alpha (\gamma - P_i)^+ + (1 - \alpha) (P_i - \gamma)^+) \]  \hspace{1cm} (2)

- Low average number of DLTs
- Underestimation of the MTD
- Modifications: \( \alpha_n \) by Tighiouart et al. (2010) and Wheeler et al. (2017)

Safety & Uncertainty
Bayesian Logistic Regression Model (BLRM, Neuenschwander et al., 2008). uses the distribution of DLT probabilities. For example, for \( \gamma = 0.33 \)

\[ L = \begin{cases} 
1 & \text{if } p \in (0.00, 0.26); \\
0 & \text{if } p \in (0.26, 0.41); \\
1 & \text{if } p \in (0.41, 0.66); \\
2 & \text{if } p \in (0.66, 1.00) 
\end{cases} \]
Goal

We propose a new criterion for selecting doses in dose-escalation trials that accounts for

1. Uncertainty in the estimates
2. Ethical constraints

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We propose a new criterion for selecting doses in dose-escalation trials that accounts for

1. Uncertainty in the estimates
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and requires only one additional parameter to be specified.

We incorporate the proposed criterion to the one-parameter Bayesian continual reassessment method (O’Quigley et al., 1990, CRM)
Novel Criterion

The main object of estimation is the probability of DLT \( p_i \in (0, 1) \)
Squared distance is not a reliable measure for objects on the unit interval (Aitchison, 1992).

\[ \delta(p, \gamma) = (p - \gamma)^2 p(1 - p) \]

\( \delta(\hat{p}, \gamma) = 0 \) at \( p = \gamma \)
\( \delta(\hat{p}) \to \infty \) as \( p \to 0 \) or \( p \to 1 \)

The variance in denominator (Criterion 3 is a score statistic)

In the illustration example above
\( \delta(\hat{p}_1 = 0.2, \gamma = 0.3) = 1/16 \) and
\( \delta(\hat{p}_2 = 0.4, \gamma = 0.3) = 1/24 \)

(1)
Single point estimate summarizes the information about uncertainty.
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Instead, we propose a distance satisfying the desirable properties

$$
\delta(p, \gamma) = \frac{(p - \gamma)^2}{p(1 - p)}. \tag{3}
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\delta(\hat{p}_1 = 0.2, \gamma = 0.3) = 1/16 \quad \text{and} \quad \delta(\hat{p}_2 = 0.4, \gamma = 0.3) = 1/24
\]

(!) Single point estimate summarizes the information about uncertainty.
Introducing safety compound

The target toxicity $\gamma$ is always less than 0.5.
Then for estimates $\hat{p}_1 = \gamma - \theta$ and $\hat{p}_2 = \gamma + \theta$, symmetric criterion favours $\hat{p}_2$. 

We introduce an asymmetry parameter $\delta$: 

$$
\delta(p, \gamma) = (p - \gamma)^2 p^a (1 - p)^2 - a.
$$

(4)

$0 < a < 1$ implies more severe penalty for more toxic doses. (!)
Selection of under toxic doses remain to be undesirable as well.
In the illustration example above, for $a = 0.5, \delta(\hat{p}_1 = 0.2, \gamma = 0.3, a = 0.5) < \delta(\hat{p}_2 = 0.4, \gamma = 0.3, a = 0.5)$. 

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Introducing safety compound

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

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$$\delta(\hat{p}_1 = 0.2, \gamma = 0.3, a = 0.5) < \delta(\hat{p}_2 = 0.4, \gamma = 0.3, a = 0.5).$$
Asymmetry parameter (I)

Parameter $a$ balances the trade-off between ethical concerns and uncertainty

How can $a$ be chosen?
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**How can $a$ be choosen?**

Value $a = 2\gamma$ leads to the same allocation as the squared distance $\rightarrow$

$a < 2\gamma$ leads to more conservative allocation of patients.
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**How can \( a \) be choosen?**

Value \( a = 2\gamma \) leads to the same allocation as the squared distance \( \rightarrow \)

\( a < 2\gamma \) leads to more conservative allocation of patients.

Let \((\gamma - \theta, \gamma + \theta)\) be an interval such that among two estimates standing on
the same squared distance from \( \gamma \), the lower estimate would be preferred

\[
a = 2 \times \left( 1 + \left( \log \frac{\gamma - \theta}{\gamma + \theta} \right) \bigg/ \left( \log \frac{1 - \gamma - \theta}{1 - \gamma + \theta} \right) \right)^{-1}
\]
Bayesian continual reassessment method

DLT probability has the functional form $\psi(d_i, \beta) = d_i^{\exp(\beta)}$.

$f_0(.)$ is prior distribution of $\beta$. After $j$ patients have already been assigned to doses $d(1), \ldots, d(j)$ and binary responses $\mathbb{Y}_j = [y_1, \ldots, y_j]^T$ were observed the posterior $f_j(\beta)$ is obtained.
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Then, the dose $d_k$ minimising

$$E\left( \frac{(\psi(d_i, \beta) - \gamma)^2}{\psi(d_i, \beta)^a(1 - \psi(d_i, \beta))^{2-a}} \right)$$

(5)

among all $d_1, \ldots, d_m$ is recommended for the next group of patients.
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Convex Infinite Bounds Penalization with parameter $a$ as CIBP($a$).
We revisit the Everolimus Trial in patients with HER2-overexpressing Metastatic Breast Cancer $\gamma = 0.3$. The study considers 3 regimens given together with Paclitaxel and Trastuzumab (PT):

1. Daily dosing of Everolimus 5mg plus PT ($d_1$)
2. Daily dosing of Everolimus 10mg plus PT ($d_2$)
3. Weekly dosing of Everolimus 30mg plus PT ($d_3$)

**Table: Aggregated data of the Everolimus trial**

<table>
<thead>
<tr>
<th>Dose</th>
<th>$d_1$</th>
<th>$d_2$</th>
<th>$d_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients assigned</td>
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<td>10</td>
</tr>
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We compare original CRM and CIBP (0.3) using the same prior parameters.
Illustration (II)

Individual trial (CRM)

Individual trial (CIBP)

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Illustration (II)

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Individual trial (CIBP)

- No Toxicity
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Illustration (II)

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Numerical Study

Setting by Wheeler et al. (2017).

- \( n = 40 \) patients; \( m = 6 \) doses; \( c = 1 \) cohort size; target \( \gamma = 0.33 \)
- \( \beta \sim \mathcal{N}(0, 1.34) \)
- \( a = \{0.5, 0.25, 0.10\} \).
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We study the performance of designs in terms of

(i) Accuracy

\[
A = 1 - m \frac{\sum_{i=1}^{m} (p_i - \gamma)^2 \pi_i}{\sum_{i=1}^{m} (p_i - \gamma)^2}
\]

(ii) mean number of toxic responses (DLTs) and focus on the mean performance.
Scenarios

1. Scenario 1
2. Scenario 2
3. Scenario 3
4. Scenario 4
5. Scenario 5
6. Scenario 6
7. Scenario 7
8. Scenario 8
9. Scenario 9
10. Scenario 10

Toxicity Probability vs. Dose

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Comparators

We compare the performance of the proposed approach to

- **EWOC**
- **TR** design by Tighiouart et al. (2010)
- Toxicity-dependent feasibility bound (**TDFB**) by Wheeler et al. (2017)
- **BLRM** by Neuenschwander et al. (2008)

We use the same prior distribution as Neuenschwander et al. (2008).
Results. Accuracy

<table>
<thead>
<tr>
<th>CIBP(0.5)</th>
<th>CIBP(0.25)</th>
<th>CIBP(0.1)</th>
<th>TDFB</th>
<th>EWOC</th>
<th>TR</th>
<th>BLRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Sc 1, Sc 2, Sc 3, Sc 4, Sc 5, Sc 6, Sc 7, Sc 8, Sc 9, Mean

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Results. Accuracy

Accuracy

CIBP(0.5) CIBP(0.25) CIBP(0.1) TDFB EWOC TR BLRM

Sc 1
Sc 2
Sc 3
Sc 4
Sc 5
Sc 6
Sc 7
Sc 8
Sc 9
Sc 10
Mean
Results. Accuracy

![Graph showing accuracy results for different conditions]

Sc 1, Sc 2, Sc 3, Sc 4, Sc 5, Sc 6, Sc 7, Sc 8, Sc 9, Sc 10, Mean

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# Results

## Accuracy

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy</th>
<th>Sc 1</th>
<th>Sc 2</th>
<th>Sc 3</th>
<th>Sc 4</th>
<th>Sc 5</th>
<th>Sc 6</th>
<th>Sc 7</th>
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<th>Sc 9</th>
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<th>Mean</th>
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<tbody>
<tr>
<td>CIBP(0.5)</td>
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Results. DLTs

- Average DLTs

<table>
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<tr>
<th>Sc 1</th>
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Sc 1, Sc 2, Sc 3, Sc 4, Sc 5, Sc 6, Sc 7, Sc 8, Sc 9, Sc 10, Mean

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Results. DLTs

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Mean

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Conclusions

- The novel criterion requires **one additional parameter only**.
- The criterion incorporated into the one-parameter CRM method is found to result in
  1. **Similar** accuracy, but **fewer** mean number of DLTS.
  2. **Greater** accuracy, but **similar** mean number of DLTs.
- The new criterion allows to make model-based design **more ethical** as it does not lead to any decrease in accuracy.
- Criterion can be motivated by information theory and used by itself (Mozgunov and Jaki, 2018)


1) A statistical experiment of estimation of a toxicity probability. The Shannon differential entropy (DE) $h(f_n)$ of the PDF $f_n$ is defined as

$$h(f_n) = -\int_0^1 f_n(p) \log f_n(p) \, dp$$  \hspace{1cm} (6)$$

with the convention $0 \log 0 = 0$. 

Information theory

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$$h(f_n) = -\int_0^1 f_n(p) \log f_n(p) \, dp$$

(6)

with the convention $0 \log 0 = 0$.

2) A statistical experiment of a sensitive estimation. The weighted Shannon differential entropy (WDE), $h^{\phi_n}(f_n)$, of the RV $Z^{(n)}$ with positive weight function $\phi_n(p) \equiv \phi_n(p, \alpha, \gamma)$ is defined as

$$h^{\phi_n}(f_n) = -\int_0^1 \phi_n(p) f_n(p) \log f_n(p) \, dp.$$  

(7)
The Beta-form weight function

\[ \phi_n(p) = \Lambda(\gamma, x, n)p^{\gamma\sqrt{n}}(1 - p)^{(1-\gamma)\sqrt{n}}. \] (8)
Additional information for sensitive estimation

\[ h_{\phi n}(f_n) - h(f_n) \cong \frac{(\alpha - \gamma)^2}{\alpha (1 - \alpha)} \]
Additional information for sensitive estimation

\[ h^{\phi_n}(f_n) - h(f_n) \approx \frac{(\alpha - \gamma)^2}{\alpha(1 - \alpha)} \]

Can be estimated for each regimen \( j \)

\[ \hat{\Delta}_j = \frac{(\hat{p}_j - \gamma)^2}{\hat{p}_j(1 - \hat{p}_j)} \]
Let $d_j(i)$ be a regimen $d_j$ recommended for cohort $i$.

- The procedure starts from $\hat{\Delta}_j^{(0)}$
- $l$ cohorts were already assigned

The $(l+1)^{th}$ cohort of patients will be assigned to regimen $k$ such that

$$d_j(l+1) : \hat{\Delta}_k^{(l)} = \inf_{i=1,\ldots,m} \hat{\Delta}_i^{(l)}, \ l = 0, 1, 2, \ldots, C.$$ 

We adopt regimen $d_j(C+1)$ as the final recommended regimen.
Asymmetry parameter (II)
Comparators

We compare the performance of the proposed approach to

- **EWOC** design using fixed $\alpha = 0.25$
- **TR** design by Tighiouart et al. (2010) using $\alpha_2 = \ldots = \alpha_9 = 0.25$, $\alpha_n = \min(\alpha_{n-1} + 0.05, 0.50)$.
- Toxicity-dependent feasibility bound (**TDFB**) by Wheeler et al. (2017)
  \[
  \alpha_{n+1} = \min \left( 0.50, 0.25 + (0.50 - 0.25 \frac{n - 1 - \sum_{i=1}^{n} y_i}{12^{2/3}}) \right)
  \]
- **BLRM** by Neuenschwander et al. (2008)
  We use the same prior distribution as Neuenschwander et al. (2008).