Multi-objective dose-finding

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Dose escalation

- Limited prior knowledge about toxicities in humans
- Range of $m$ regimes (doses, combinations, schedules)
- $n$ patients

Goal:

- Find the maximum tolerated regime that corresponds to a controlled level of toxicity, usually $\gamma \in (0.2, 0.35)$ in oncology trials
Assume that a 20% risk of toxicity is an acceptable risk to pay for a chance of benefit.
**General (Bayesian) approach**

1. Make assumptions about the form of $p(d)$
2. Impose a prior distribution for the parameters that determine $p(d)$
3. Choose next dose to optimise some form of expected gain
4. Stop once target dose level can be estimated accurately enough
Bayesian continual reassessment method

1. \( p(d_i) = d_i^{\exp(\beta)} \)

2. \( \beta \sim N(0, 1.34) \)

3. \( d^* = \min_i \mathbb{E} \left( (p(d_i) - \gamma)^2 \right) \)

4. Stop after \( N \) patients have been recruited
## Single agent dose-escalation designs

<table>
<thead>
<tr>
<th>Model-based methods</th>
<th>Algorithm based methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM</td>
<td>‘3+3’ design</td>
</tr>
<tr>
<td>EWOC</td>
<td>Biased Coin Design</td>
</tr>
</tbody>
</table>

Fundamental assumption: a **monotonic** dose-response relationship

*Cannot be applied to:*

- Combination trials with many treatments
- Scheduling of drugs
- Non-monotonic dose-toxicity relations
Unknown ordering problem. Example (I)

Let us consider drugs combination dose-escalation trial with

- 3 dose levels of drug A: $A_1, A_2, A_3$
- 3 dose levels of drug B: $B_1, B_2, B_3$

<table>
<thead>
<tr>
<th></th>
<th>$(A_1; B_3)$</th>
<th>$(A_2; B_3)$</th>
<th>$(A_3; B_3)$</th>
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</table>

Even assuming monotonicity one drug being fixed, we cannot order

$(A_1; B_2)$ and $(A_2; B_1)$;

$(A_1; B_3)$ and $(A_2; B_1)$;

$(A_1; B_3)$ and $(A_3; B_1)$ and so on...
Unknown ordering problem. Example (II)
Unknown ordering problem. Example (III)
Method for drug combinations

- **Six-parameter model** *(Thall P. et al, 2003)*
- **Up-and-down design** *(Ivanova A, Kim S., 2009)*
  Using the T-statistic
- **Copula regression** *(G.Yin, Y.Yuan, 2009)*
  Parametrization of drug-drug interactive effect
- **POCRM** *(N.Wages, M. Conoway, J. O‘Quigley, 2011)*
  Choose several ordering and randomize between them during the trial

General restrictions:
- Strong model assumptions are usually needed
- No diagonal switching is allowed
- Synergistic effect is usually assumed
- Only two combinations only
To propose an escalation procedure that **does not require any parametric assumptions** (including monotonicity between regimes).
Problem formulation

- Toxicity probabilities $Z_1, \ldots, Z_m$ are random variables with Beta prior $B(\nu_j + 1, \beta_j - \nu_j + 1)$, $\nu_j > 0, \beta_j > 0$

- $n_j$ patients assigned to the regime $j$ and $x_j$ toxicities observed

- Beta posterior $f_{n_j} \cdot B(x_j + \nu_j + 1, n_j - x_j + \beta_j - \nu_j + 1)$

- Let $0 < \alpha_j < 1$ be the unknown parameter in the neighbourhood of which the probability of toxicity is concentrated

- Target toxicity $\gamma$
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

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

with the convention \( 0 \log 0 = 0 \).
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

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

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

It shows the amount of information needed to answer the question

What is the toxicity probability?
Weighted information

Consider a two-fold experiment:

(i) what is the toxicity probability

(ii) is the probability of toxicity close to a target, $\gamma$
Weighted information

Consider a two-fold experiment:

(i) what is the toxicity probability
(ii) is the probability of toxicity close to a target, \( \gamma \)

A: The \textit{weighted Shannon information}

\[
h_\phi(f) = - \int_{\mathbb{R}} \phi(z) f(z) \log f(z) dz.
\]
The Beta-form weight function

\[ \phi_n(p) = \Lambda(\gamma, x, n) p^{\gamma \sqrt{n}} (1 - p)^{(1 - \gamma) \sqrt{n}}. \]
Theorem

Let \( h(f_n) \) and \( h^{\phi_n}(f_n) \) be the DE and WDE corresponding to PDF \( f_n \) when \( x \sim \alpha n \) with the weight function \( \phi_n \) given in (15). Then

\[
\lim_{n \to \infty} (h^{\phi_n}(f_n) - h(f_n)) = \frac{(\alpha - \gamma)^2}{2\alpha(1 - \alpha)}
\]
Escalation criteria

Theorem

Let \( h(f_n) \) and \( h^{\phi_n}(f_n) \) be the DE and WDE corresponding to PDF \( f_n \) when \( x \sim \alpha n \) with the weight function \( \phi_n \) given in (15). Then

\[
\lim_{n \to \infty} (h^{\phi_n}(f_n) - h(f_n)) = \frac{(\alpha - \gamma)^2}{2\alpha(1 - \alpha)}
\]

Therefore, for a regimen \( d_j, j = 1, \ldots, m \), we obtained that

\[
\Delta_j \equiv \frac{(\alpha_j - \gamma)^2}{\alpha_j(1 - \alpha_j)}.
\]

Criteria:

\[
\Delta_j = \inf_{i=1,\ldots,m} \Delta_i.
\]
Consider the mode of the posterior distribution $f_{nj}$

$$\hat{p}_j^{(n)} = \frac{x_j + \nu_j}{n_j + \beta_j}.$$ 

Then the following "plug-in" estimator $\hat{\Delta}_j^{(n)}$ may be used

$$\hat{\Delta}_j^{(n)} = \frac{(\hat{p}_j^{(n)} - \gamma)^2}{\hat{p}_j^{(n)}(1 - \hat{p}_j^{(n)})}.$$
Let $d_j(i)$ be a regime $d_j$ 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 regime $k$ such that

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

We adopt regime $d_j(C + 1)$ as the final recommended regime.
Alternative angle

One can consider

$$\hat{\Delta}_j^{(n)} = \frac{(\hat{p}_j^{(n)} - \gamma)^2}{\hat{p}_j^{(n)}(1 - \hat{p}_j^{(n)})}$$

as a loss function for a parameter defined on $(0, 1)$.

- Loss function penalize $\hat{p}_j^{(n)}$ close to 0 to 1 and ‘pushes‘ the allocation away from bounds to the neighbourhood of $\gamma$
- Does not include any definition of safety $\rightarrow$ safety constraint is needed
Safety constraint

Considers regime $d_j$ as safe if at the moment $n$ its PDF satisfies

$$P(\text{regime is overly toxic}) = \int_{\gamma^*}^{1} f_{n_j}(p)dp \leq \theta_n$$

where

- $\gamma^*$ is some threshold after which all regimes above are declared to have excessive risk, $\gamma^* = \gamma + 0.2$
- $\theta_n$ is the level of probability that controls the overdosing
  - Note that this depends on $n$
Why is a time-varying SC is needed?

If $\beta = 1$ and $\theta_n = \theta = 0.50$ then regimes with prior mode $\geq 0.40$ will never be considered since

$$\int_{0.45}^{1} f_0(p|x = 0)dp = 0.5107 > 0.50$$

Requirements to the function $\theta_n$

- $\theta_n$ is a decreasing function of $n$
- $\theta_0 = 1$
- $\theta_N \leq 0.3$
- $\rightarrow \theta_n = 1 - rn$
## Choice of SC parameters

<table>
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<th>0.00</th>
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</table>

**Table:** Top row: Proportion of no recommendations for toxic scenario. Bottom row: Proportion of correct recommendations. $10^6$ simulations.
Simulations

For simulations below the following parameters were chosen:

- The cohort size $c = 1$
- Total sample size $N = 20$
- Number of regimes $m = 7$
- The target probability $\gamma = 0.25$
- Safety constraint

$$\theta_n = \begin{cases} 
1 - 0.035n, & \text{if } 0.035 \times n \leq 0.7; \\
0.3, & \text{otherwise.}
\end{cases}$$
Investigated scenarios

**Figure:** Considering response shapes. The TD is marked as triangle.
Specifying the prior

Assumptions:

- Vague beliefs about toxicity risk
- Prior belief: regimes have been correctly ordered monotonically
- A escalation to be started from \( d_1 \)

The prior for regime \( d_j \) \((1 \leq j \leq 7)\) is specified thought the mode \( \hat{p}_j^{(0)} = \frac{\nu_j}{\beta_j} \). Starting from the bottom: \( \hat{p}_1^{(0)} = \gamma \).

The vector of modes \( \hat{p} \) for all regimes is defined as

\[
\hat{p} = [0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55]^T.
\]

Vague prior \( \rightarrow \beta_j = \beta = 1 \) for \( j = 1, \ldots, m \).

Is there a unique set of prior parameters that lead to the equivalent performance?
Choice of prior

**Figure:** Proportion of correct recommendations: \( \beta = \text{number of patients and difference between the risk of toxicity on lowest and highest dose across six scenarios.} \)
Alternative methods

We have also investigated

- Continual reassessment method (CRM)
- Partial ordering continual reassessment method (POCRM)
  All correct orderings used in simulation are incorporated in the model.
- Escalation with overdose control (EWOC)
  A target 25\textsuperscript{th} percentile is used.
- Non-parametric optimal benchmark
Simulation results. Ordering is correctly specified
Simulation results. Ordering is wrongly specified.

<table>
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<tr>
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<th>$d_1$</th>
<th>$d_2$</th>
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Simulation results. Highly toxic scenarios.

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<td><strong>83.71</strong></td>
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Conclusions - toxicity only

The WDE-based method

- performs comparably to the model-based methods when the ordering is specified correctly scenarios
- outperform them in wrongly specified setting

However, WDE-based method

- experience problems in scenarios with no safe doses or with sharp jump in toxicity probability at the bottom.
- The time-varying safety constrain in the proposed form can overcome overdosing problems and increase the accuracy of the original method
Motivating trial - Dual endpoint

Immunotherapy (Molecularly Targeted Agent, MTA) + Chemotherapy:

- 2/3 days immunotherapy AFTER chemotherapy ($S_1/S_2$),
- 4 days immunotherapy OVERLAP chemotherapy for 1/2 days ($S_3/S_4$);
- binary toxicity and efficacy endpoints.

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<tr>
<td>Cycle 2</td>
<td>$S_1$</td>
<td>$S_2$</td>
<td>$S_2$</td>
<td>$S_3$</td>
<td>$S_4$</td>
<td>$S_4$</td>
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</tbody>
</table>
Motivating trial - Dual endpoint

Immunotherapy (Molecularly Targeted Agent, MTA) + Chemotherapy:

- 2/3 days immunotherapy AFTER chemotherapy ($S_1/S_2$),
- 4 days immunotherapy OVERLAP chemotherapy for 1/2 days ($S_3/S_4$);
- binary toxicity and efficacy endpoints.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R_4$</th>
<th>$R_5$</th>
<th>$R_6$</th>
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<td>$S_1$</td>
<td>$S_2$</td>
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</table>

The aim: to find the **optimal** regimen (maximum efficacy, least toxicity) and the **correct** regimen (maximum efficacy, acceptable toxicity).
Current approaches

Two perspectives for model-based designs:

- to include parameters for each term (agent, cycle, interaction)
  see e.g. Riviere et al (2016) for a Phase I/II single-agent design.

  **Challenge:** many parameters to be estimated.

- to include all possible orderings of regimens according to toxicity/efficacy
  see e.g. Wages and Tait (2015) for a Phase I/II single-agent design.

  **Challenge:** many orderings to be considered.

Alternative: a design *relaxing parametric/monotonicity assumptions*
Finding a measure of uncertainty in a Phase I/II trial with 3 outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Probability</th>
<th>Optimal characteristics</th>
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</thead>
<tbody>
<tr>
<td>Efficacy + No Toxicity</td>
<td>$\theta_1$</td>
<td>$\gamma_1$</td>
</tr>
<tr>
<td>No Efficacy + No Toxicity</td>
<td>$\theta_2$</td>
<td>$\gamma_2$</td>
</tr>
<tr>
<td>Toxicity</td>
<td>$\theta_3 = 1 - \theta_1 - \theta_2$</td>
<td>$\gamma_3 = 1 - \gamma_1 - \gamma_2$</td>
</tr>
</tbody>
</table>
Derivation of selection criterion

Using the same arguments as before we base our criterion on

\[ \delta(\cdot) = \lim_{n \to \infty} h^{\phi_n}(f_n) - h(f_n) \]

which, for a Dirichlet distribution \( f_n \), and a Dirichlet form weight \( \phi_n \) yields

\[ \delta(\theta, \gamma) := \frac{\gamma_1^2}{\theta_1} + \frac{\gamma_2^2}{\theta_2} + \frac{(1 - \gamma_1 - \gamma_2)^2}{1 - \theta_1 - \theta_2} - 1. \]
Trade-off function

Figure: $\gamma_t = 0.01$, $\gamma_e = 0.99$
Regimen-finding design

As before but with randomization between best two regimens with probabilities proportional to

\[ \frac{1}{\delta_i^{(k)}} \quad l = i, j \]
Application to the motivating trial

$M = 6$ regimens and $N = 36$ patients

We study

1. the proportion of **optimal** selections (maximum efficacy, least toxicity)
2. the proportion of **correct** selections (maximum efficacy, acceptable T)
Application to the motivating trial

\[ M = 6 \] regimens and \[ N = 36 \] patients

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**Scenarios:**

8 scenarios for single-MTA studies \( \rightarrow \) **six permutations** wrt toxicity orderings.

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<td>(.05;.50)</td>
<td><strong>(.10;.80)</strong></td>
<td>(.15;.80)</td>
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\[
\begin{array}{ccccccc}
1 & 2 & 3 & 4 & 5 & 6 \\
1.1 (.005;.01) & (.01;.10) & (.02;.30) & (.05;.50) & (.10;.80) & (.15;.80) \\
1.2 (.005;.01) & (.01;.10) & (.02;.30) & (\textbf{.10;.80}) & (.05;.50) & (.15;.80) \\
\end{array}
\]
Application to the motivating trial

\( M = 6 \) regimens and \( N = 36 \) patients

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Practical considerations

- Delayed efficacy response
  e.g. toxicity is evaluated in 1st cycle and efficacy in a 2nd

- Missing efficacy response
  no efficacy data for patients with toxic response

- Coherence principles
  Escalation/De-escalation restrictions

**Comparator:**
Partial Ordering CRM with 6 toxicity and 48 efficacy orderings.
Results

Scenario 1

Permutation
Proportion of Selections
1 2 3 4 5 6
0 10 20 30 40 50 60 70 80 90 100
New(Optimal)
New(Correct)
POCRM(Optimal)
POCRM(Correct)
Results

Scenario 1

Scenario 2

Scenario 3

Scenario 4

Scenario 5

Scenario 6

Scenario 7

Scenario 8

- New (Optimal)
- New (Correct)
- POCRM (Optimal)
- POCRM (Correct)
Conclusions - dual endpoint

- The intuitively **clear** and **simple** trade-off function
- Performs **comparably or better** than model-based alternatives in majority of scenarios
- **Robust** to true ordering

- Results in **fewer** toxicities and **comparable** number of efficacies
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

Q: Which dose should be administered to the next patient?
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$$(\hat{p}_i - \gamma)^2$$

The next patient can be assigned to either of doses, but one can argue that doses are not ‘equal‘ for two reasons.
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$$(\hat{p}_i - \gamma)^2$$

The next patient can be assigned to either of doses, but one can argue that doses are not ‘equal’ for two reasons.

1. The squared distance ignores the randomness of the estimates.

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

2. $\hat{p}_2 = 0.4$ is an unacceptably high toxicity.
Motivation

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):

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

- 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 (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

and requires only one additional parameter to be specified.
Goal

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

1. Uncertainty in the estimates
2. Ethical constraints

and requires only **one additional parameter** to be specified.

We incorporate the proposed criterion to the one-parameter Bayesian continual reassessment method.
The main object of estimation is the probability of DLT \( p_i \in (0, 1) \).

We propose a distance satisfying the desirable properties

\[
\delta(p, \gamma) = \frac{(p - \gamma)^2}{p(1 - p)}.
\]

- \( \delta(\cdot) = 0 \) at \( p = \gamma \)
- \( \delta(\cdot) \to \infty \) as \( p \to 0 \) or \( p \to 1 \)
- The variance in denominator (Criterion is a score statistic)
Novel Criterion

The main object of estimation is the probability of DLT $p_i \in (0, 1)$

We propose a distance satisfying the desirable properties

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

- $\delta(\cdot) = 0$ at $p = \gamma$
- $\delta(\cdot) \to \infty$ as $p \to 0$ or $p \to 1$
- The variance in denominator (Criterion is a score statistic)

In the illustration example above

$$\delta(\hat{p}_1 = 0.2, \gamma = 0.3) = 1/16 \quad \text{and} \quad \delta(\hat{p}_2 = 0.4, \gamma = 0.3) = 1/24$$

(!) 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 $\delta$:

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

$0 < a < 1$ 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 $a = 0.5$, $\delta(\hat{p}_1 = 0.2, \gamma = 0.3, a = 0.5) < \delta(\hat{p}_2 = 0.4, \gamma = 0.3, a = 0.5)$. 

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 $a$:

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

$0 < a < 1$ 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 $a = 0.5$

$$\delta(\hat{p}_1 = 0.2, \gamma = 0.3, a = 0.5) < \delta(\hat{p}_2 = 0.4, \gamma = 0.3, a = 0.5).$$
Bayesian continual reassessment method

- DLT probability modelled as $p(d_i) = d_i^{\exp(\beta)}$

- $\beta \sim N(0, 1.34)$

- Then, the dose $d_k$ minimising

$$\mathbb{E} \left( \frac{(p(d_i) - \gamma)^2}{p(d_i)^a(1 - p(d_i))^{2-a}} \right)$$

among all $d_1, \ldots, d_m$ is recommended for the next group of patients.
Bayesian continual reassessment method

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*Convex Infinite Bounds Penalization* with parameter $a$ as CIBP($a$).
Numerical Study


- $n = 40$ patients; $m = 6$ doses; $c = 1$ cohort size; target $\gamma = 0.33$
- $\beta \sim \mathcal{N}(0, 1.34)$
- $a = \{0.5, 0.25, 0.10\}$.

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.
Comparators

We compare the performance of the proposed approach to

- **EWOC**
- **TR** design by Tighiouart et al. (2010)
- Toxicity-dependent feasibility bound (\textbf{TDFB}) by Wheeler et al. (2017)
- **BLRM** by Neuenschwander et al. (2008)
Results. Accuracy

accuracy

<table>
<thead>
<tr>
<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>
<th>Sc 8</th>
<th>Sc 9</th>
<th>Sc 10</th>
<th>Mean</th>
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CIBP(0.5) CIBP(0.25) CIBP(0.1) TDFB EWOC TR BLRM

Thomas Jaki (Lancaster University) | Multi-objective dose-finding
Results. Accuracy

Accuracy

CIBP(0.5)  CIBP(0.25)  CIBP(0.1)  TDFB  EWOC  TR  BLRM
0.3  0.4  0.5  0.6  0.7  0.8  0.9  1

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

Accuracy

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

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Mean
Results. Accuracy

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Thomas Jaki (Lancaster University)
Multi-objective dose-finding
Results. DLTs

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<th>CIBP(0.5)</th>
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Sc 9
Sc 10

Mean

Thomas Jaki (Lancaster University)
Multi-objective dose-finding
Results: DLTs

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Average DLTs
CIBP(0.5)  CIBP(0.25)  CIBP(0.1)  TDFB  EWOC  TR  BLRM
Results. DLTs

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Sc 1: CIBP(0.5) CIBP(0.25) CIBP(0.1) TDFB EWOC TR BLRM

Thomas Jaki (Lancaster University)
## Results: DLTs

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- **TDFB**: Dose-finding by-targets approach
- **EWOC**: Early withdrawal from ongoing clinical trial
- **TR**: Toxicity response
- **BLRM**: Bayesian linear regression model

---

**Graphical representation**

The graph shows the average DLTs for different scenarios (Sc 1 to Sc 10) across various models (CIBP(0.5), CIBP(0.25), CIBP(0.1), TDFB, EWOC, TR, BLRM). Each scenario is represented by a different marker, and the mean is indicated by a cross. The x-axis represents the models, while the y-axis shows the average DLTs.
Conclusions - Safety

- 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.
Discussion

- Information theory can be useful in dose-finding
- Coherent framework with little tuning necessary
- Useful in itself or in combination with traditional model based ideas
References


