An information-theoretic approach for selecting arms in clinical trials (with applications to Phase I/II)

Dr Pavel Mozgunov, Prof Thomas Jaki

Medical and Pharmaceutical Statistics Research Unit,
Department of Mathematics and Statistics, Lancaster University, UK

September 26, 2018

Acknowledgement: 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.

Motivating trial

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.

Motivating trial

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.

Regimen	R_1	R_2	$\mathbf{R_3}$	$\mathbf{R_4}$	$\mathbf{R_5}$	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

Motivating trial

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.

Regimen	R_1	R_2	$\mathbf{R_3}$	$\mathbf{R_4}$	$\mathbf{R_5}$	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

- **6** toxicity orderings;
- **48** efficacy orderings (due to a non-monotonic dose-efficacy for the MTA),

but only **36** patients are available.

Motivating trial

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.

Regimen	R_1	R_2	$\mathbf{R_3}$	$\mathbf{R_4}$	$\mathbf{R_5}$	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

- **6** toxicity orderings;
- **48** efficacy orderings (due to a non-monotonic dose-efficacy for the MTA),

but only **36** patients are available.

The aim: to find the **optimal** regimen (maximum efficacy, least toxicity)

Motivating trial

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.

Regimen	R_1	R_2	$\mathbf{R_3}$	$\mathbf{R_4}$	$\mathbf{R_5}$	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

- **6** toxicity orderings;
- **48** efficacy orderings (due to a non-monotonic dose-efficacy for the MTA),

but only **36** patients are available.

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

Current approaches

Two perspective 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 estimates.

- 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**

Derivation of selection criterion (I)

Finding a measure of uncertainty in a Phase I/II trial with 3 outcomes.

Outcome	Probability	Optimal characteristics
Efficacy + No Toxicity	θ_1	γ_1
No Efficacy + No Toxicity	θ_2	γ_2
Toxicity	$\theta_3 = 1 - \theta_1 - \theta_2$	$\gamma_3 = 1 - \gamma_1 - \gamma_2$

Derivation of selection criterion (I)

Finding a measure of uncertainty in a Phase I/II trial with 3 outcomes.

Outcome	Probability	Optimal characteristics
Efficacy + No Toxicity	θ_1	γ_1
No Efficacy + No Toxicity	θ_2	γ_2
Toxicity	$\theta_3 = 1 - \theta_1 - \theta_2$	$\gamma_3 = 1 - \gamma_1 - \gamma_2$

Consider a statistical experiment in which one would like to estimate (θ_1, θ_2). Let $f_n(\mathbf{p}|\mathbf{x})$ be a pdf corresponding to the vector of interest given the data.

The amount of information required in such experiment can be measured by the *Shannon information*

$$h(f_n) = -\int_{\mathbb{S}^2} f_n(\mathbf{p}|\mathbf{x}) \log f_n(\mathbf{p}|\mathbf{x}) \mathrm{d}\mathbf{p} \tag{1}$$

Derivation of selection criterion (I)

Finding a measure of uncertainty in a Phase I/II trial with 3 outcomes.

Outcome	Probability	Optimal characteristics
Efficacy + No Toxicity	θ_1	γ_1
No Efficacy + No Toxicity	θ_2	γ_2
Toxicity	$\theta_3 = 1 - \theta_1 - \theta_2$	$\gamma_3 = 1 - \gamma_1 - \gamma_2$

Consider a statistical experiment in which one would like to estimate (θ_1, θ_2). Let $f_n(\mathbf{p}|\mathbf{x})$ be a pdf corresponding to the vector of interest given the data.

The amount of information required in such experiment can be measured by the *Shannon information*

$$h(f_n) = -\int_{\mathbb{S}^2} f_n(\mathbf{p}|\mathbf{x}) \log f_n(\mathbf{p}|\mathbf{x}) \mathrm{d}\mathbf{p} \tag{1}$$

This measure **does not reflect** interest in the optimal regimen.

Derivation of selection criterion (II)

Consider an estimation experiment with "sensitive" area, i.e. the neighbourhood of (γ_1, γ_2).

The amount of information required can be measured by the *weighted Shannon information* (Belis and Guiasu, 1968; Kelbert and Mozgunov, 2017)

$$h^{\phi_n}(f_n) = -\int_{\mathbb{S}^2} \phi_n(\mathbf{p}) f_n(\mathbf{p}|\mathbf{x}) \log f_n(\mathbf{p}|\mathbf{x}) \mathrm{d}\mathbf{p}. \tag{2}$$

$\phi_n(\mathbf{p})$ says that the information about the probability vector which lies in the neighbourhood of (γ_1, γ_2) **is more valuable** in the experiment.

Derivation of selection criterion (III)

In an actual studies, the question is

Which arm has an associated probability vector closest to (γ_1, γ_2).

The information gain from considering the experiment with sensitive area:

$$\delta(\cdot) = h(f_n) - h^{\phi_n}(f_n). \tag{3}$$

$\delta(\cdot)$ is the average amount of statistical information required when considering **the context-dependent estimation problem instead of the traditional.**

Applying to Phase I/II, f_n is Dirichlet distribution, ϕ_n is Dirichlet form weight

$$\delta(\boldsymbol{\theta}, \boldsymbol{\gamma}) := \frac{\gamma_1^2}{\theta_1} + \frac{\gamma_2^2}{\theta_2} + \frac{(1-\gamma_1-\gamma_2)^2}{1-\theta_1-\theta_2} - 1. \tag{4}$$

We propose to use the criterion to govern the regimen selection.

Re-parametrisation

The goal of Phase I/II clinical trials is conventionally formulated in terms of toxicity (p_t) and efficacy (p_e) probabilities.

Efficacy + No Toxicity

$$\begin{aligned} \theta_1 &= p_e(1-p_t) \\ \gamma_1 &= \gamma_e(1-\gamma_t) \end{aligned}$$

No Efficacy + No Toxicity

$$\begin{aligned} \theta_2 &= (1-p_e)(1-p_t) \\ \gamma_2 &= (1-\gamma_e)(1-\gamma_t) \end{aligned}$$

We would refer to $\delta(\boldsymbol{\theta}, \boldsymbol{\gamma})$ as to the **trade-off function**.

Trade-off function

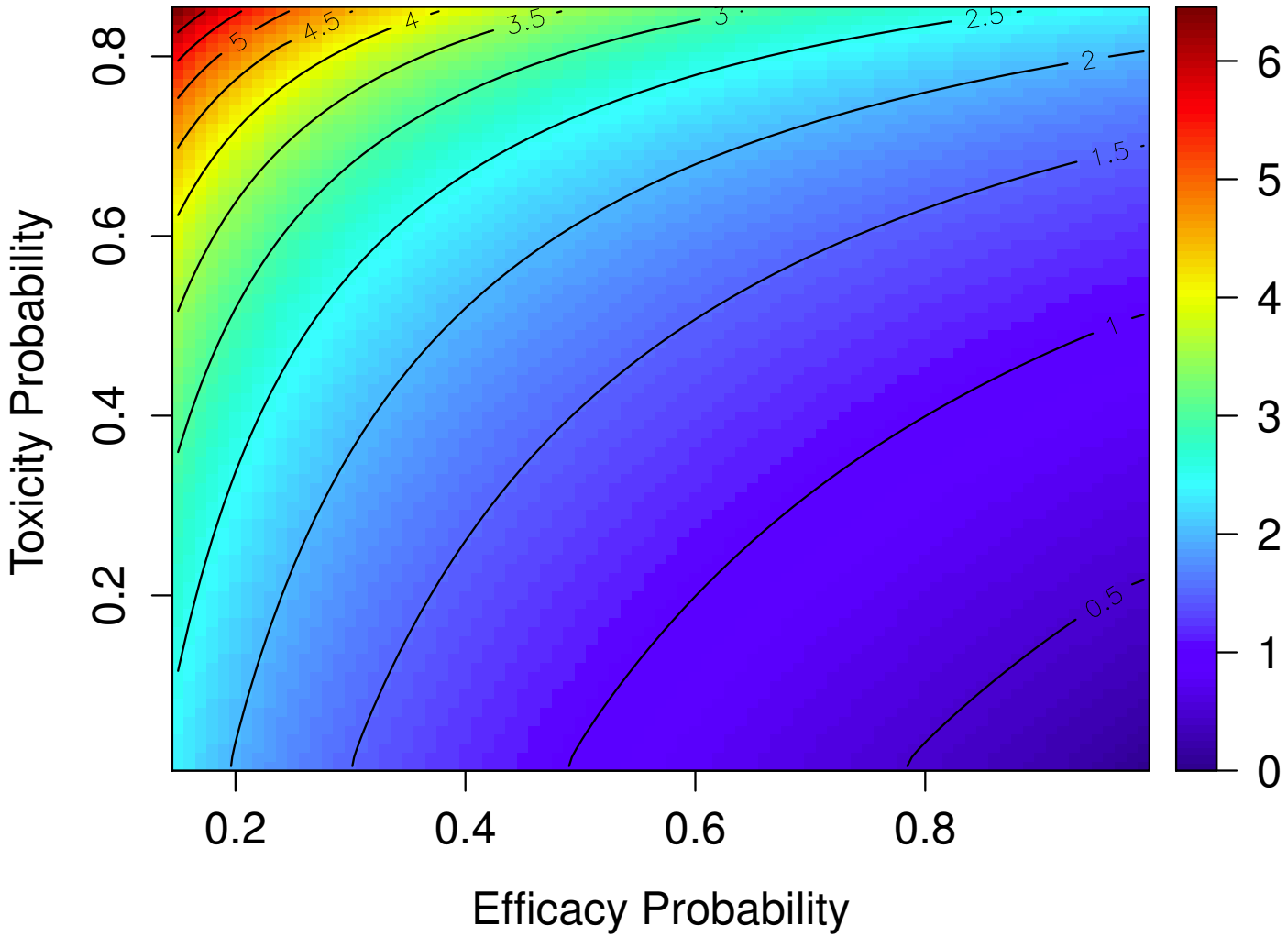


Figure : $\gamma_t = 0.01$, $\gamma_e = 0.99$

Dose-finding design

Estimates:

$$\hat{p}_t^{(n)} = \frac{x_t}{n}, \qquad \hat{p}_e^{(n)} = \frac{x_e}{n}. \tag{5}$$

and 'plug-in' in the trade-off function

$$\hat{\delta}_j^{(k)} = \delta(\hat{p}_t^{(n)}, \hat{p}_e^{(n)}, \gamma_t, \gamma_e).$$

Dose-finding design

Estimates:

$$\hat{p}_t^{(n)} = \frac{x_t}{n}, \qquad \hat{p}_e^{(n)} = \frac{x_e}{n}. \tag{5}$$

and 'plug-in' in the trade-off function

$$\hat{\delta}_j^{(k)} = \delta(\hat{p}_t^{(n)}, \hat{p}_e^{(n)}, \gamma_t, \gamma_e).$$

Randomization

$(k+1)^{th}$ cohort is randomized between 'two best' regimens j and i with probabilities proportional to

$$1/\hat{\delta}_l^{(k)} \quad l = i, j$$

Application to the motivating trial

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

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

We study

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

Scenarios:

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

	1	2	3	4	5	6
1.1	(.005;.01)	(.01;.10)	(.02;.30)	(.05;.50)	**(.10;.80)**	(.15;.80)

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)

Scenarios:

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

	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)	**(.10;.80)**	(.05;.50)	(.15;.80)

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)

Scenarios:

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

	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)	**(.10;.80)**	(.05;.50)	(.15;.80)
1.3	(.005;.01)	(.01;.10)	(.05;.50)	(.02;.30)	**(.10;.80)**	(.15;.80)
1.4	(.005;.01)	(.01;.10)	**(.10;.80)**	(.02;.30)	(.05;.50)	(.15;.80)
1.5	(.005;.01)	(.01;.10)	(.05;.50)	**(.10;.80)**	(.02;.30)	(.15;.80)
1.6	(.005;.01)	(.01;.10)	**(.10;.80)**	(.05;.50)	(.02;.30)	(.15;.80)

Practical considerations

- Delayed efficacy response

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

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

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

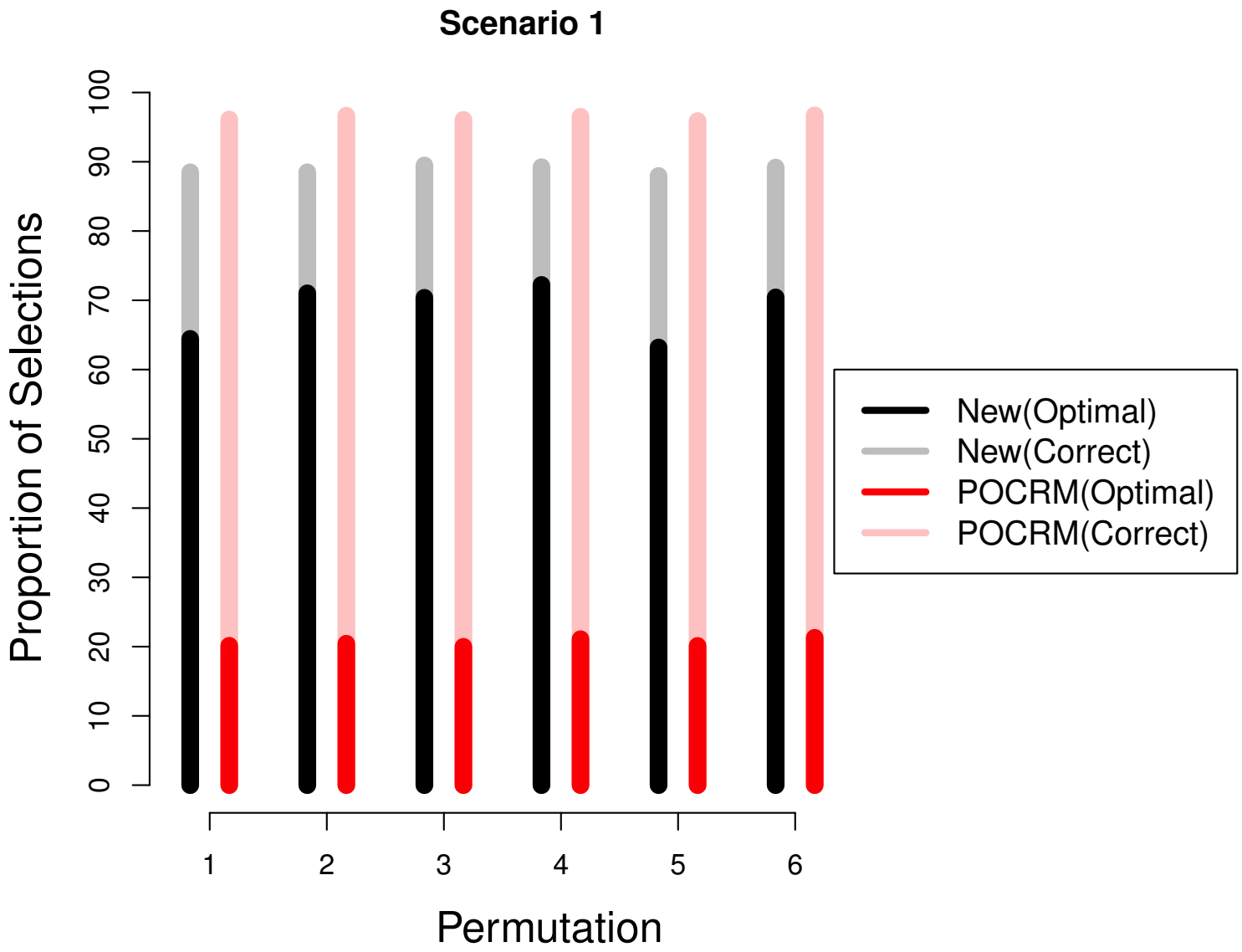
Practical considerations

- 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

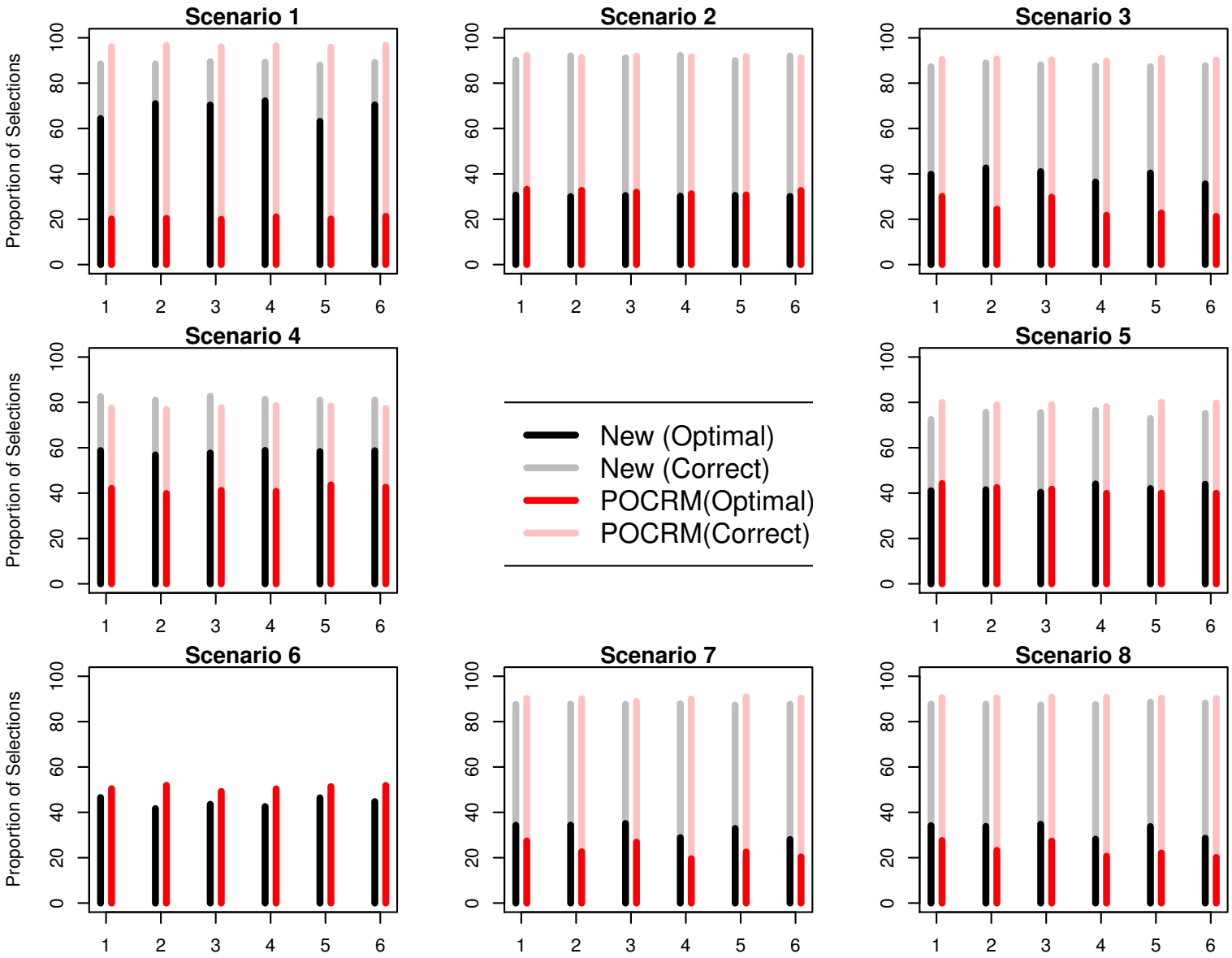
Comparator:

Partial Ordering CRM with 6 toxicity and 48 efficacy orderings.

Results


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

Conclusions of the Phase I/II application

- 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

Generalisations and Extensions

1) Application of the information-theoretic design (Mozgunov and Jaki, 2018c)
   Phase I clinical trials (binary toxicity + unknown order of toxicities)
   Phase II clinical trials (binary efficacy & two co-primary efficacy endpoints)
   $\rightarrow$ higher statistical power and similar average number of treated patients

Generalisations and Extensions

1) Application of the information-theoretic design (Mozgunov and Jaki, 2018c)
   Phase I clinical trials (binary toxicity + unknown order of toxicities)
   Phase II clinical trials (binary efficacy & two co-primary efficacy endpoints)
   $\rightarrow$ higher statistical power and similar average number of treated patients

2) The criterion as an allocation criterion in the CRM (Mozgunov and Jaki, 2018b)
   $\rightarrow$ improving safety without compromising the accuracy

3) The criterion considered as a loss function in a Bayesian framework
   $\rightarrow$ applied to estimation in restricted parameter spaces (Mozgunov et al., 2018a).
   $\rightarrow$ considered as a utility score in Benefit-Risk Analysis (Saint-Hilary et al., 2018)

4) Extended for trials with continuous outcomes (Mozgunov and Jaki, 2018a)
   $\rightarrow$ higher accuracy compared to model-based designs (Mozgunov et al., 2018b)

References

Belis, M. and Guiasu, S. (1968) A quantitative-qualitative measure of information in cybernetic systems. *IEEE Trans. on Information Theory*, **14**, 593–594.

Kelbert, M. and Mozgunov, P. (2017) Generalization of cramér-rao inequality for the weighted covariance matrix. *Math. Comm.*, 25–40.

Mozgunov, P. and Jaki, T. (2018a) A flexible design for advanced phase i/ii clinical trials with continuous efficacy endpoints. *Preprint*.

— (2018b) Improving a safety of the crm via a modified allocation rule. *Preprint, arXiv:1807.05781 (Under Review)*.

— (2018c) An information-theoretic approach for selecting arms in clinical trials. *Preprint, arXiv:1708.02426 (Under Review)*.

— (2018d) An information-theoretic phase i/ii design for molecularly targeted agents that does not require an assumption of monotonicity. *JRSS C (Applied Statistics)*, **68**, 1–24, Epub.

Mozgunov, P., Jaki, T. and Gasparini, M. (2018a) Loss functions in restricted parameter spaces and their bayesian applications. *Preprint, arXiv:1706.02104 (Under Review)*.

Mozgunov, P., Jaki, T. and Paoletti, X. (2018b) A benchmark for dose finding studies with continuous outcomes. *Biostatistics*, kxy045.

Riviere, M.-K., Yuan, Y., Jourdan, J.-H., Dubois, F. and Zohar, S. (2016) Phase i/ii dose-finding design for mta: Plateau determination. *Stat. Meth. in Medical Research*, **27**, 466–479.

Saint-Hilary, G., Robert, V., Jaki, T., Gasparini, M. and Mozgunov, P. (2018) A novel measure of drug benefit-risk assessment based on scale loss score (slos). *Stat. Methods in Medical Research*.

Wages, N. A. and Tait, C. (2015) Seamless phase i/ii adaptive design for oncology trials of molecularly targeted agents. *Journal of Biopharmaceutical Statistics*, **25**, 903–920.

Acknowledgements

I wish to thank Prof Thomas Jaki for providing a tremendous help and advice during my period of research and for broadening my mind.

I would also like to thank Dr Xavier Paoletti, Prof Mauro Gasparini and Dr Alun Bedding for many useful discussions and for fruitful collaborations which resulted in several joint works.

Results (II)

Scenario	1	2	3	4	5	6	7	8	9
				Toxicity responses					
Proposed	**2.5**	6.4	**3.2**	**4.4**	**7.0**	**7.7**	**5.0**	**5.1**	**3.9**
CRM	4.1	**5.0**	4.5	7.1	7.9	8.7	5.9	6.0	**3.3**
				Efficacy responses					
Proposed	**23.7**	**14.4**	**20.8**	**19.9**	**18.4**	12.5	**22.7**	**22.8**	**15.4**
CRM	**24.5**	**14.4**	**21.0**	**21.4**	**19.0**	**13.8**	**23.4**	**23.5**	**15.8**

Generalisation

Consider a discrete random variable taking one of **d values** and corresponding random probability vector with a Dirichlet distribution

$$f_n(\mathbf{p}|\mathbf{x}) = \frac{1}{B(\mathbf{x}+\mathbf{v}+\mathbf{J})} \prod_{i=1}^{d} \left(p^{(i)}\right)^{x^{(i)}+v^{(i)}}, \tag{6}$$

where $\mathbf{p} = \left[p^{(1)}, \ldots, p^{(d)}\right]^{\mathrm{T}}$, $\mathbf{x} = \left[x^{(1)}, \ldots, x^{(d)}\right]$, $\sum_{i=1}^{d} x^{(i)} = n$, $0 < p^{(i)} < 1$.

$\boldsymbol{\theta} = \left[\theta^{(1)}, \ldots, \theta^{(d)}\right]^{\mathrm{T}}$ is the vector to be estimated
$\boldsymbol{\gamma} = \left[\gamma^{(1)}, \ldots, \gamma^{(d)}\right]^{\mathrm{T}}$ is the vector corresponding to the target regimen.

$$\phi_n(\mathbf{p}) = C(\mathbf{x}, \boldsymbol{\gamma}, n) \prod_{i=1}^{d} \left(p^{(i)}\right)^{\gamma^{(i)} n^{\kappa}} \tag{7}$$

Important case: Binary outcomes, $d = 2$

θ is the probability of outcome (e.g. toxicity)

γ is the target probability (e.g. MTD)

$$f_n(p|x) = \frac{p^{x+v}(1-p)^{n-x+\beta}}{B(x+v+1)}, \quad \phi_n(p) = \frac{p^{\gamma\sqrt{n}}(1-p)^{(1-\gamma)\sqrt{n}}}{C(x,\gamma,n)}$$

Following the same information-theoretic concept,

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

Further work

- Explore further application of the criterion in Phase II clinical trials
- Other applications of the novel information-theoretic criterion
- Derivation of the information-theoretic criterion for continuous and mixed outcomes
- Alternative methods of estimation of the information-theoretic measure
- Accommodating delayed and missing outcomes