An information-theoretic Phase I/II design for molecularly targeted agents that does not require an assumption of monotonicity

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Motivating trial

Immunotherapy (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)
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- Current methods: model-based approaches

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- Alternative: a design **relaxing parametric/monotonicity assumptions**

Step 1: Quantify the uncertainty

Outcome	Probability	Optimal characteristics
Efficacy + No Toxicity	θ_1	γ_1
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Using information-theoretic arguments, the "information" about regimen is

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

$\delta(\boldsymbol{\theta}, \boldsymbol{\gamma}) = 0$ iff $\boldsymbol{\theta} = \boldsymbol{\gamma}$

Step 2: Re-parametrise

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

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

Step 3: Estimate and Randomise

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

Let $\hat{\delta}_i^{(n_i)}$ be the plug-in estimate of the trade-off for regimen i after n_i

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Randomisation between two "best" regimens

The next patient is allocated to regimen k with probability proportional to

$$1/\hat{\delta}_k^{(n_k)}$$

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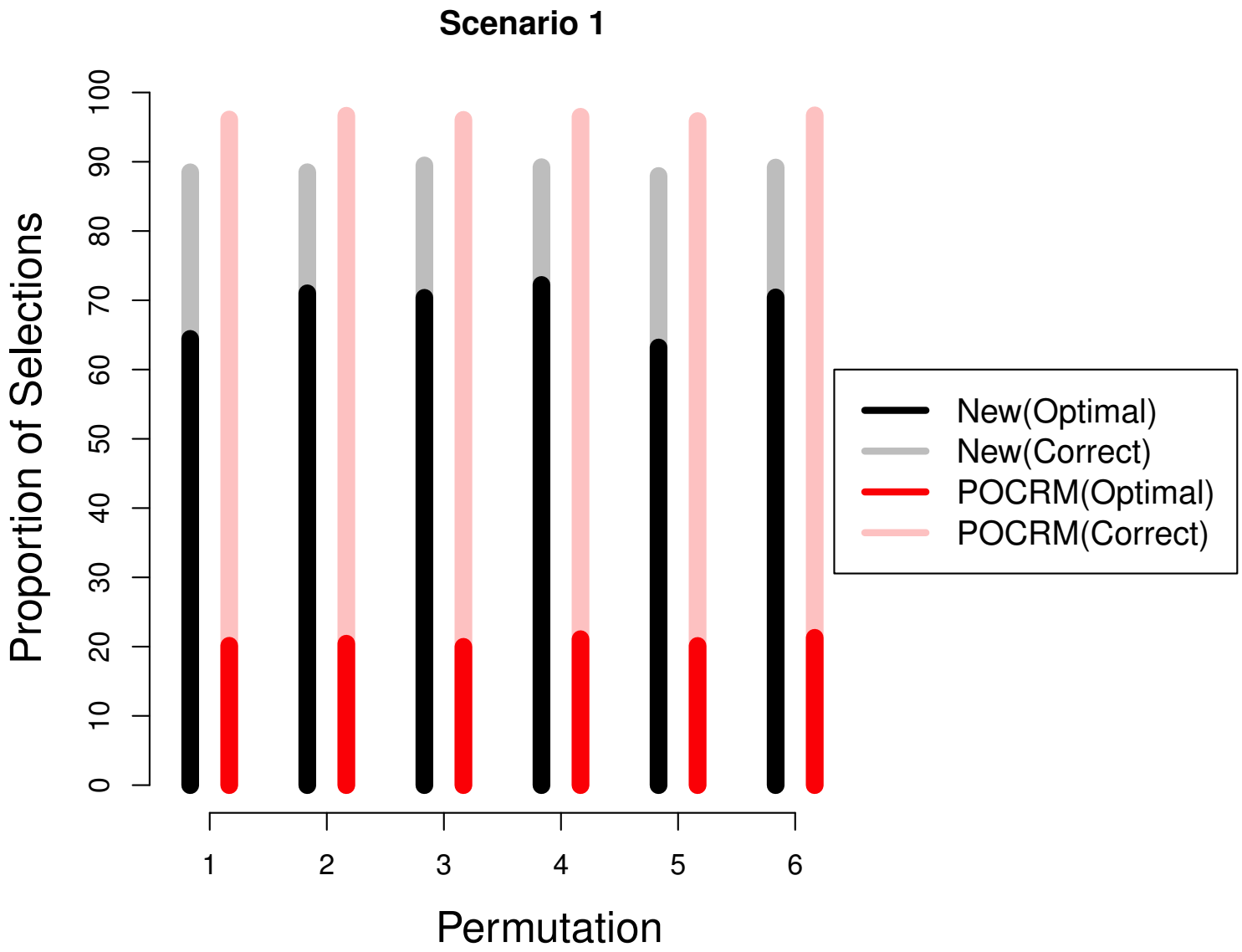
Comparator:

Extended POCRM design by Wages and Tait (2015)

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)

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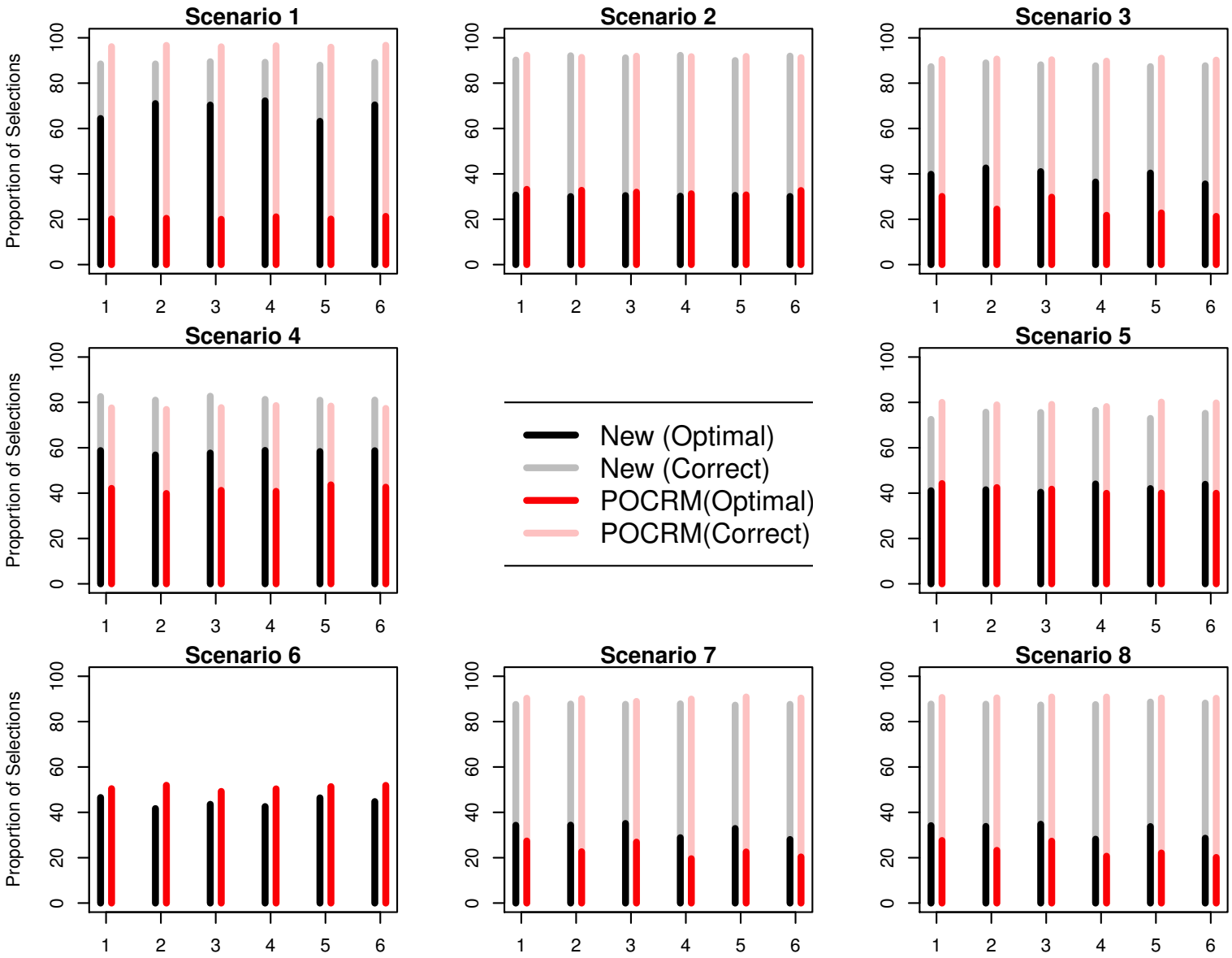
Scenario 1
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Scenario 4
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Scenario 6
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Conclusions

- Performs **comparably or better** than model-based alternatives in majority of scenarios
- **Robust** to true ordering
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- **Robust** to true ordering
- Results in **fewer** toxicities and **comparable** number of efficacies
- Further developments: **Continuous** efficacy (toxicity) endpoint

References

Mozgunov, P. and Jaki, T. (2018) An information-theoretic phase i/ii design for molecularly targeted agents that does not require an assumption of monotonicity. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, **68**, 1–24, Epub.

Riviere, M.-K., Yuan, Y., Jourdan, J.-H., Dubois, F. and Zohar, S. (2016) Phase i/ii dose-finding design for molecularly targeted agent: Plateau determination using adaptive randomization. *Statistical Methods in Medical Research*, **27**, 466–479.

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.

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**