A flexible non-parametric dose-finding design for Phase II clinical trials

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"Earn vs Learn" trade-off

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   Challenges:

   - Unethical (low number of treated patients)

Current approaches

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  Low statistical power, **high variance** of the expected number of success
- Optimal multi-arm bandit (MAB) and the dynamic programming
  Low statistical power

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<u>What is the success probability?</u>

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Q: Can we quantify this interest in the information measure?

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Due to ethical constraints we concentrate on the question (ii) alone and on the corresponding measure of the information

$$h_{\phi}(f) - h(f)$$

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$$\phi_n(\mathbf{p}) = C(x, \gamma, n) p^{\gamma n^{\kappa}} (1-p)^{(1-\gamma) n^{\kappa}}$$

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Theorem

Let $h(f_n)$ and $h^{\phi_n}(f_n)$ be the standard and weighted differential entropies. Then,

$$\lim_{n\to\infty}\left(\left[h^{\phi_n}(f_n)-h(f_n)\right]-\frac{1}{2}\left(\frac{(\alpha-\gamma)^2}{\alpha(1-\alpha)}\right)n^{2\kappa-1}+\omega\right)=0$$

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Arm selection algorithm:

1. Start from $\hat{\delta}_{\beta_i}^{(\kappa)}$, $i = 1, \ldots, m$
2. Observed n_i and x_i outcomes for the arm A_i, $i = 1, \ldots, m$
3. Arm A_j is selected if it satisfies

$$\hat{\delta}_{n_j}^{(\kappa)} = \inf_{i=1,\ldots,m} \hat{\delta}_{n_i}^{(\kappa)}.$$

4. Repeat 2-3 until the total number of patients is reached.

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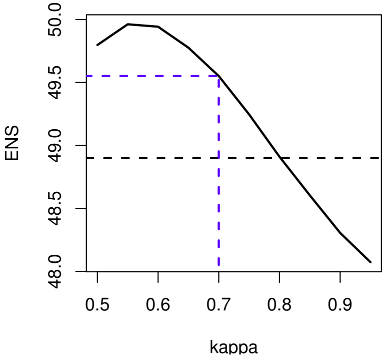

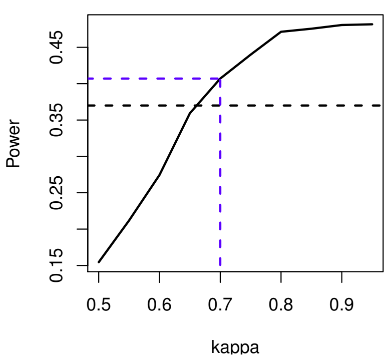

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Comparators:

- MAB approach based on the Gittins index
- Fixed randomization

Numerical study. Results

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Method	$H_0 : p_0 = p_1 = p_2 = p_3 = 0.3$			$H_1 : p_0 = p_1 = p_2 = 0.3, p_3 = 0.5$		
	α	$p^*(s.e)$	ENS(s.e.)	$(1-\eta)$	$p^*(s.e.)$	ENS (s.e.)
MAB	0.05	0.25 (0.18)	126.7 (9.4)	0.43	0.83 (0.10)	198.3 (13.7)
WE ($\kappa = 0.55$)	0.05	0.22 (0.20)	126.9 (9.4)	0.55	0.83 (0.18)	197.1 (17.8)

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MAB	0.00	0.25 (0.13)	24.0 (4.10)	0.00	0.49 (0.21)	41.6 (5.4)
WE ($\kappa = 0.55$)	0.01	0.20 (0.15)	24.0 (4.10)	0.11	0.50 (0.27)	40.7 (5.9)

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- Can be applied to any trial with the target $\gamma \in (0, 1)$
- Theoretical result: the design is consistent
- The criterion can be generalized for multinomial outcomes