An ethical non-parametric design for selecting arms in a multi-arm clinical trial

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Motivation (I)

Consider a trial with **two arms** and **binary outcomes** which aims to find the **superior arm**.

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We would like to

- make a reliable recommendation (high statistical power)
- maximize the proportion of the population on the superior arm

"Earn vs Learn" trade-off

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   Challenges:

   - Unethical (low number of treated patients)

Current approaches

- Fixed randomization
- Randomized play the winner
- Current belief (maximum point estimate)
- Optimal multi-arm bandit (MAB) and the dynamic programming

Back to information measures

The Shannon information (entropy)

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In the example above,

$$h(\text{arm 1}) = h(\text{arm 2}).$$

This information **does not reflect** our specific interest in the **superior arm**

It shows the amount of information needed to answer the question

What is the success probability?

Weighted information

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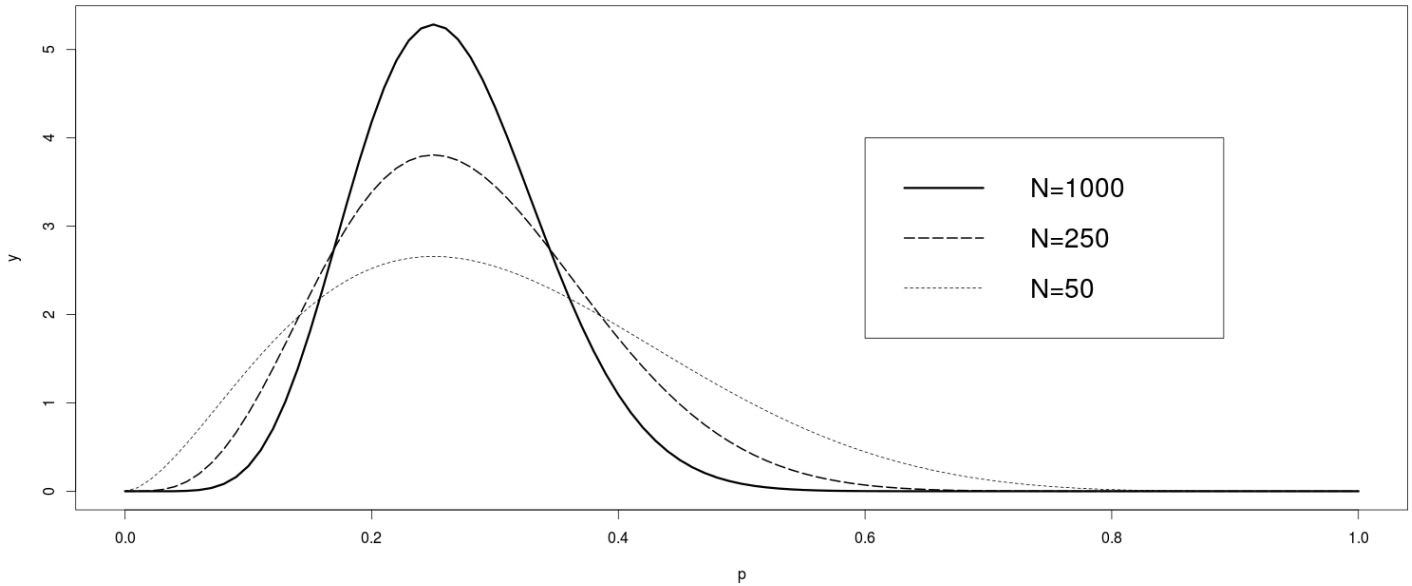
A: The *weighted Shannon information*

$$h_\phi(f) = -\int_{\mathbb{R}} \phi(z) f(z) \log f(z) \mathrm{d}z.$$

Weight Function

The Beta-form weight function

$$\phi_n(p) = \Lambda(\gamma, x, n) p^{\gamma\sqrt{n}} (1-p)^{(1-\gamma)\sqrt{n}}. \tag{1}$$



Methods

- Model probability of success with a Beta distribution
- α is the true probability of success
- γ is the target probability (for instance, $\gamma = 0.999$)

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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Design

$$\hat{\delta}_{n_j}^{(\kappa)} = \frac{(\hat{p}_{n_j} - \gamma)^2}{\hat{p}_{n_j}(1 - \hat{p}_{n_j})} n_j^{2\kappa - 1}$$

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.

Note: Randomize in case of tie.

Illustration. Two arms trial

Consider the trial with $m = 2$ arms ($\alpha_1 = 0.5$ and $\alpha_2 = 0.7$), $n = 75$ patients

$$\text{Prior}: \qquad \hat{p} = (0.99, 0.99); \quad \beta = (2, 2)$$

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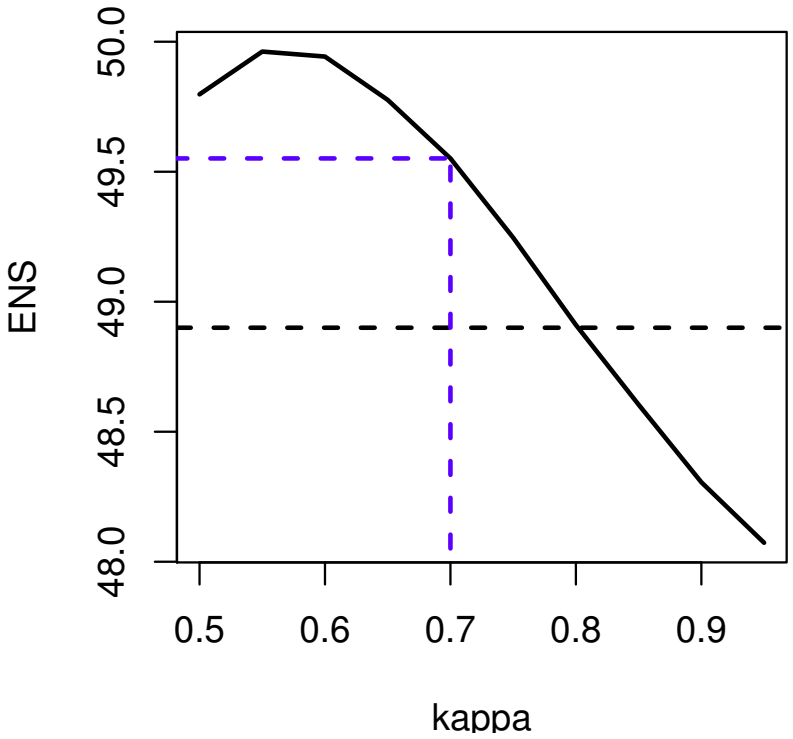

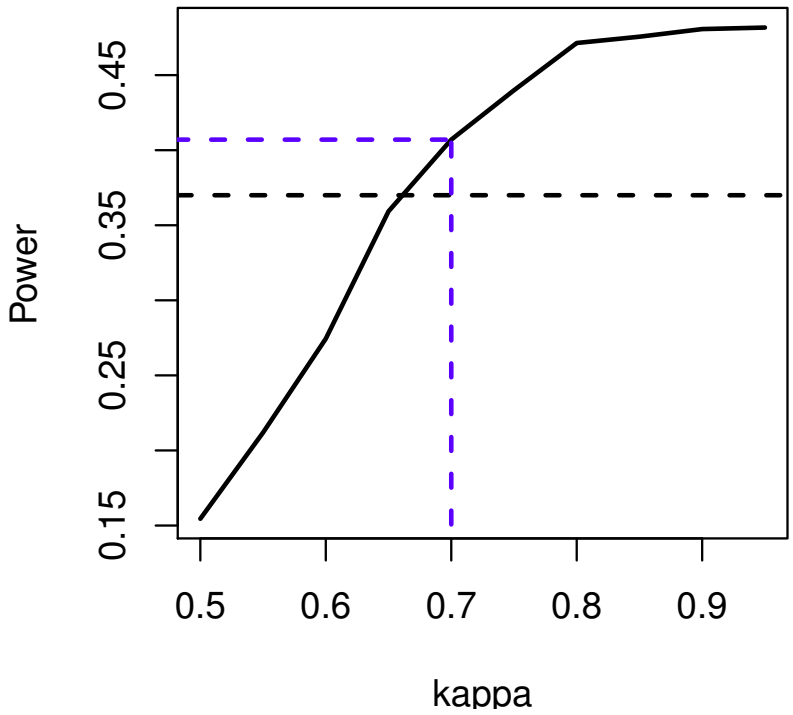

Numerical study

We consider two trials with $m = 4$ treatments (Villar et.al, 2015)

Trial 1: $N_1 = 423$, $p = [0.3, 0.3, 0.3, 0.5]^{\mathrm{T}}$

Trial 2: $N_2 = 80$, $p = [0.3, 0.4, 0.5, 0.6]^{\mathrm{T}}$.

$$\text{Hypothesis} \quad H_0 : \; p_0 \geq p_i \text{ for } i = 1, 2, 3$$

with the family-wise error rate calculated at $p_0 = \ldots = p_3 = 0.3$

$$\text{Prior :} \qquad \hat{p} = (0.99, 0.99, 0.99, 0.99); \quad \beta = (5, 2, 2, 2)$$

We study:

- the type-I error rate (α)
- statistical power ($1 - \eta$)
- expected number of successes (ENS)

Comparators:

- MAB approach based on the Gittins index
- Fixed randomization

Numerical study. Results

Trial 1

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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FR	0.05	0.25 (0.02)	126.9 (9.4)	0.82	0.25 (0.02)	147.9 (9.6)
WE ($\kappa = 0.65$)	0.05	0.23 (0.13)	126.9 (9.4)	0.87	0.74 (0.10)	189.3 (13.7)

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Trial 2

Method	$H_0 : p_0 = p_1 = p_2 = p_3 = 0.3$			$H_1 : p_0 = 0.3, p_1 = 0.4, p_2 = 0.5, p_3 = 0.6$		
	α	$p^*(s.e)$	ENS(s.e.)	$(1-\eta)$	$p^*(s.e.)$	ENS (s.e.)
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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Trial 2

Method	$H_0 : p_0 = p_1 = p_2 = p_3 = 0.3$			$H_1 : p_0 = 0.3, p_1 = 0.4, p_2 = 0.5, p_3 = 0.6$		
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FR	0.05	0.25 (0.04)	24.0 (4.10)	0.50	0.25 (0.04)	36.0 (4.3)
WE ($\kappa = 0.65$)	0.05	0.24 (0.07)	24.0 (4.05)	0.52	0.47 (0.21)	40.2 (4.8)

Conclusion

- Simple, intuitively clear, can be computed by non-statisticians
- Penalty parameter κ reflects the trade-off between ENS and Power
- Performs better than currently used approaches

	MAB	FR
Power	higher	same
ENS	same	higher

- 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