



MRC
Biostatistics
Unit



UNIVERSITY OF
CAMBRIDGE

Short course on Response-Adaptive Methods for Clinical Trials

*Lecture 2: Considerations for implementing and
targeting optimal RAR designs*

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Outline

1. Motivation
2. Deriving two-armed optimal proportion
3. Measures of Interest
4. Estimating and targeting proportions
5. Multiple Treatments
6. Trial Example
7. Burn-In
8. Conclusion

Motivation

- **Equal Randomisation (ER):** Patients are allocated with equal probability to each arm. Often we additionally enforce equal allocation at the end.
- **Fixed Unbalanced Allocation:** Clinical trials for rare diseases, pediatric conditions, or diseases with limited treatment options use fixed unbalanced allocation, ensuring that more patients receive the potentially beneficial new therapy.
- **Response-Adaptive Randomization:** Adjusts randomization probabilities based on the emerging data, favoring the treatment showing better performance or increasing efficacy.

Taxonomy of RAR

- **Frequentist** vs. Bayesian
- **Parametric** vs. Nonparametric
- **Optimal** vs. Design-driven

→ **Optimal** allocation proportions, given **parametric** assumptions,
targeted in a **frequentist** way

(Caution: other classes of RAR exist)

Notation

- Multi-armed trial: 0,...,K different treatments
- Fix number of patients in the trial: $n = \sum_{k=0}^K n_k$
 - ▶ n_k is the number of patients on arm k
- Potential outcomes: random response variables $Y_{ki} \stackrel{\text{iid}}{\sim} F_k$
- Binary indicator a_{ki} s.t. $\sum_{k=0}^K a_{ki} = 1 \forall i$
- Assume that patients arrive sequentially and outcomes are immediately observable (both assumptions can be relaxed)
- Response-adaptive-randomization: $P(a_{ki} = 1 | a^{(i-1)}, Y^{(i-1)})$

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Choice of final statistical test

Wald test for difference in means

$$Z = \frac{\hat{\mu}_0 - \hat{\mu}_1}{\sqrt{\frac{\hat{\sigma}_0^2}{n_0} + \frac{\hat{\sigma}_1^2}{n_1}}}. \quad (1)$$

for normally distributed endpoints. Binary endpoint possible if CLT yields good enough approximation.

- Later other measures of interest
 - ▶ Relative risk
 - ▶ Odds ratio
- One could consider other inference methods such as nonparametric tests or randomisation based inference but have not been considered yet

Neyman Proportion I

- **Goal:** Minimizing variance of the Wald test statistic for a fixed sample size.
- **Optimization Problem:**

$$\min_{\rho} n_0 + n_1 \quad \text{s.t.} \quad s_T^2 \leq C,$$

where $(1 - \rho) \cdot n = n_0$, $\rho \cdot n = n_1$, $C \in \mathbb{R}^+$ and

$$s_T^2 = \frac{\sigma_0^2}{n_0} + \frac{\sigma_1^2}{n_1}. \tag{2}$$

- **Idea:** maximizing power = minimizing the variance of the test statistic s_T^2 .

Neyman Proportion II

- **Solution:**

$$\rho_N = \frac{\sigma_1}{\sigma_0 + \sigma_1} \quad (3)$$

- **Example:** $X_0 \sim Bern(0.3)$, $X_1 \sim Bern(0.8)$

$$\rho_N = \frac{\sigma_1}{\sigma_0 + \sigma_1} = \frac{\sqrt{p_1(1 - p_1)}}{\sqrt{p_0(1 - p_0)} + \sqrt{p_1(1 - p_1)}} = 0.466$$

- ▶ if CLT holds
- **Critique:** It is possible that more patients get allocated to the inferior arm.

Rosenberger et al. (2001) Proportion

- **Goal:** For a fixed sample size and power minimize treatment failures in a trial with binary responses.
- **Optimization Problem:**

$$\min_{\rho} n_0(1 - p_0) + n_1(1 - p_1) \quad \text{s.t.} \quad s_T^2 \leq C,$$

where $(1 - \rho) \cdot n = n_0$, $\rho \cdot n = n_1$ and $C \in \mathbb{R}^+$.

- **Solution:**

$$\rho_{minF} = \frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}} \tag{4}$$

- **Example:** $X_0 \sim Bern(0.3)$, $X_1 \sim Bern(0.8)$

$$\rho_{minF} = \frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}} = 0.62$$

- **Goal:** Allocation for which *no alternative proportion* can reduce the expected number of failures without also diminishing power, or enhance the power without increasing the expected number of failures *for any possible combinations of* (p_0, p_1) .
- **Solution:**

$$\rho_{AD} = \frac{p_1}{p_0 + p_1}, \quad (5)$$

- Does NOT solve analogous optimization problem
- **Example:** $X_0 \sim Bern(0.3)$, $X_1 \sim Bern(0.8)$

$$\rho_{AD} = \frac{p_1}{p_0 + p_1} = 0.73$$

Comparison: Binary I

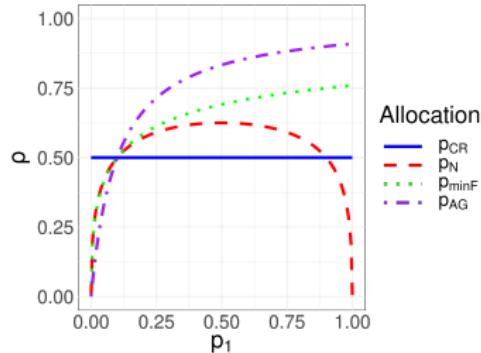


Figure: $p_0 = 0.1$

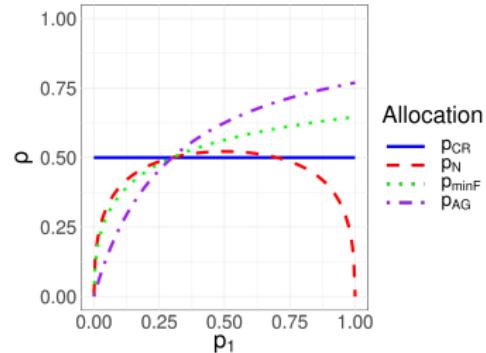


Figure: $p_0 = 0.3$

Comparison: Binary II

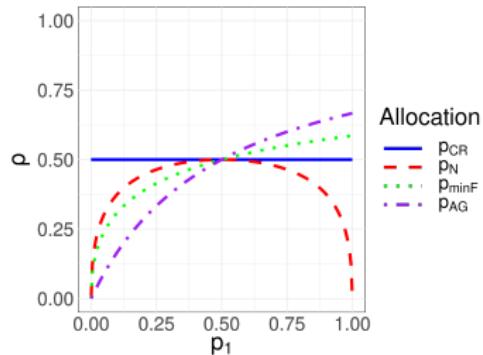


Figure: $p_0 = 0.5$

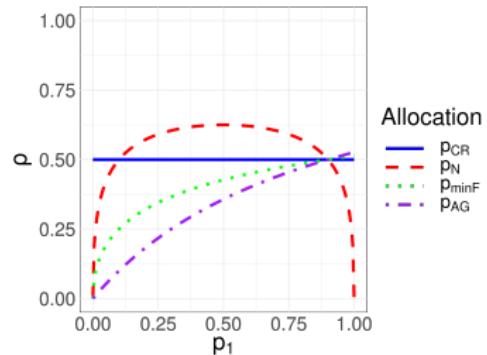


Figure: $p_0 = 0.9$

Comparison: Binary III

1. Equal Randomisation only optimal when
 $p_0(1 - p_0) = p_1(1 - p_1)$ (homoscedasticity)
2. In certain regions possible to have efficacy and patient benefit gains by using unequal proportion
3. In other regions goals of efficacy and patient benefit are in conflict

minTR Allocation

- **Goal:** For a fixed sample size and power minimize the expected total response (smaller responses are desirable) (Zhang and Rosenberger, 2006).
- **Optimization Problem:**

$$\min_{\rho} n_0 \mu_0 + n_1 \mu_1 \quad \text{s.t.} \quad s_T^2 \leq C,$$

where $(1 - \rho) \cdot n = n_0$, $\rho \cdot n = n_1$ and $C \in \mathbb{R}^+$.

- **Solution:**

$$\rho_{minTR} = \begin{cases} \frac{\sigma_1 \sqrt{\mu_0}}{\sigma_0 \sqrt{\mu_1} + \sigma_1 \sqrt{\mu_0}} & \text{if } s = 1, \\ \frac{1}{2} & \text{otherwise,} \end{cases} \quad (6)$$

where s is equal to 1 if at least one mean is larger than 0 and neither of the two means is smaller than 0.

minTR Allocation II

- **Example:** $X_0 \sim \mathcal{N}(1, 1)$, $X_1 \sim \mathcal{N}(3, 4)$

$$\rho_{minTR} = \frac{\sigma_1 \sqrt{\mu_0}}{\sigma_0 \sqrt{\mu_1} + \sigma_1 \sqrt{\mu_0}} = \frac{2 \cdot 1}{1 \cdot \sqrt{3} + 2} = 0.536$$

Comparison: Normal Distributions I

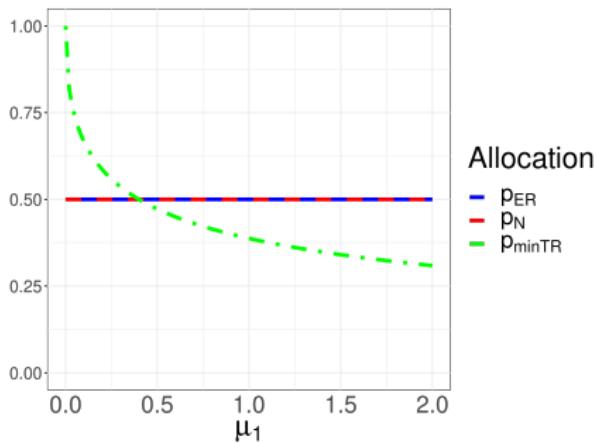


Figure: $\mu_0 = 0.4$

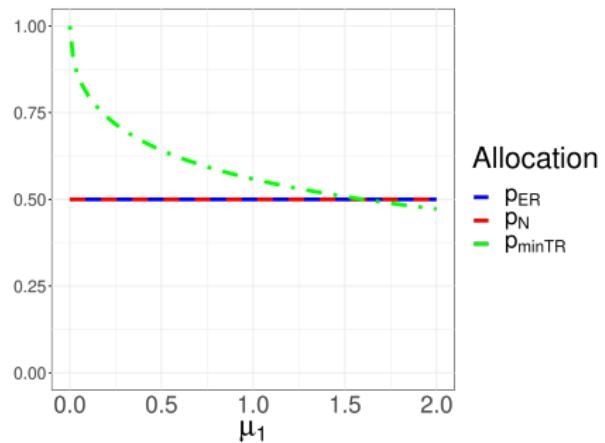


Figure: $\mu_0 = 1.2$

Comparison: Normal Distributions II

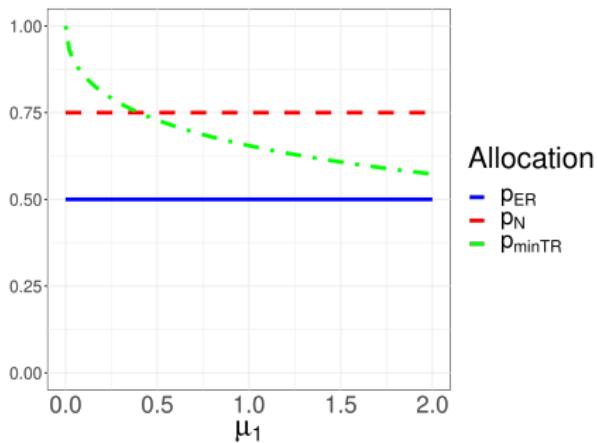


Figure: $\mu_0 = 0.4$

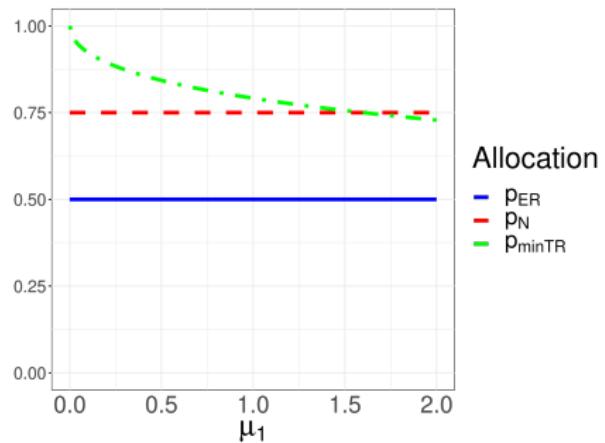


Figure: $\mu_0 = 1.2$

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Other Measures of Interest I

Table: Overview of measures of interest with respective allocation proportions that minimize failures p_{minF} or maximize power p_N (Pin et al. 2024).

	Simple difference	Relative Risk	Odds ratio	Log relative risk	Log odds ratio
θ	$p_0 - p_1$	q_1/q_0	$\frac{p_0}{q_0} / \frac{p_1}{q_1}$	$\log(q_1/q_0)$	$\log\left(\frac{p_0}{q_0} / \frac{p_1}{q_1}\right)$
p_{minF}^*	$\frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}}$	$\frac{\sqrt{p_1}q_0}{\sqrt{p_0}q_1 + \sqrt{p_1}q_0}$	$\frac{\sqrt{p_0}q_0 + \sqrt{p_1}q_1}{\sqrt{p_0}q_0}$	$\frac{\sqrt{p_1}q_0}{\sqrt{p_0}q_1 + \sqrt{p_1}q_0}$	$\frac{\sqrt{p_0}q_0 + \sqrt{p_1}q_1}{\sqrt{p_0}q_0}$
p_N^*	$\frac{\sqrt{p_1}}{\sqrt{p_0}q_0 + \sqrt{p_1}q_1}$	$\frac{\sqrt{p_1}q_0}{\sqrt{p_0}q_1 + \sqrt{p_1}q_0}$	$\frac{\sqrt{p_0}q_0 + \sqrt{p_1}q_1}{\sqrt{p_0}q_0 + \sqrt{p_1}q_1}$	$\frac{\sqrt{p_0}q_1}{\sqrt{p_0}q_1 + \sqrt{p_1}q_0}$	$\frac{\sqrt{p_0}q_1}{\sqrt{p_0}q_0 + \sqrt{p_1}q_1}$

Other Measures of Interest - Neyman

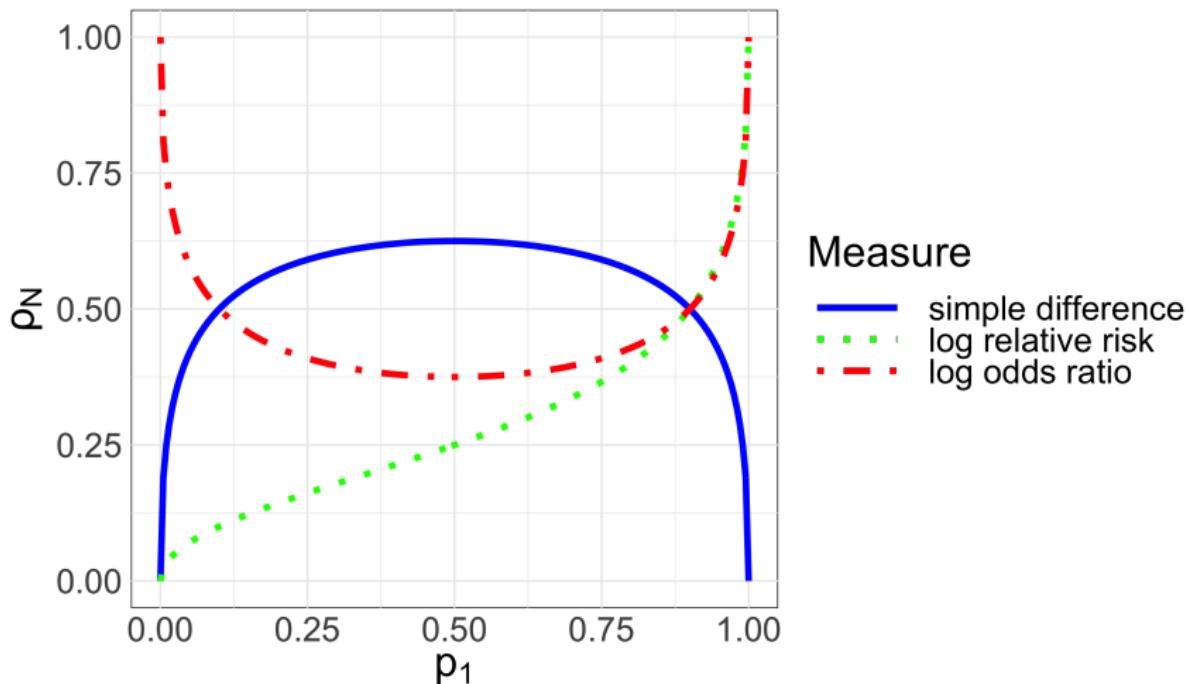


Figure: $p_0 = 0.9$

Other Measures of Interest - minF

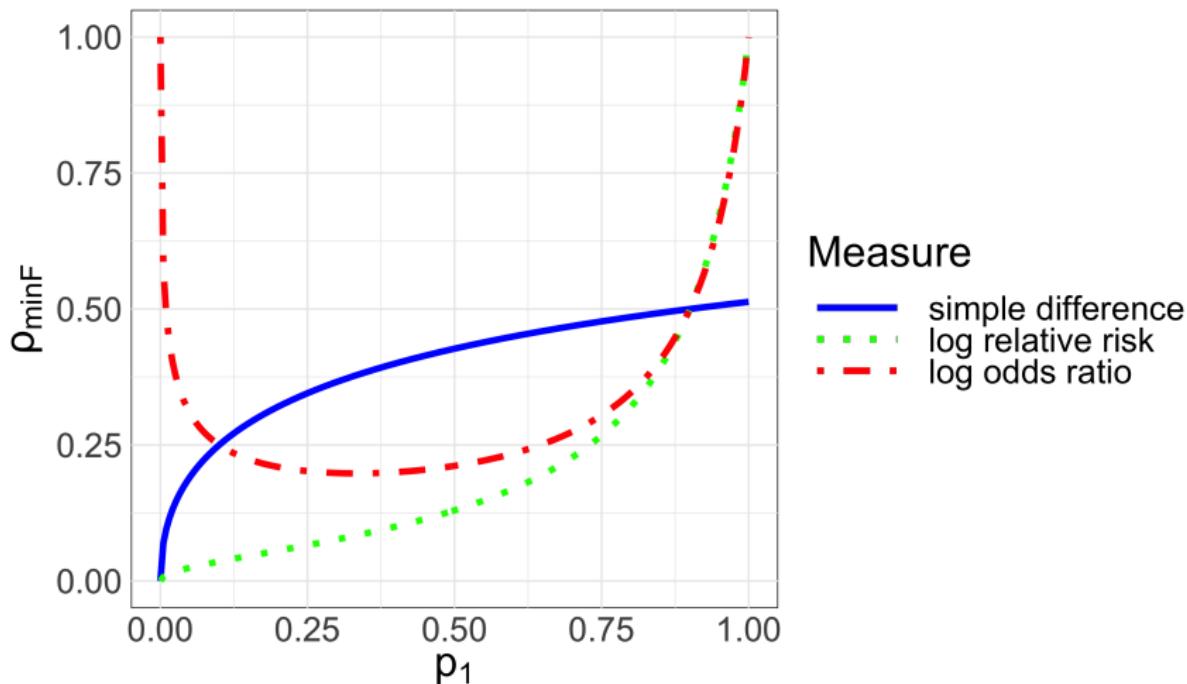


Figure: $p_0 = 0.9$

Other measure of interest - Conclusion

1. ER still only optimal when $p_0 = p_1$ or $p_0 = 1 - p_1$
2. Areas where efficacy and patient benefit conflict change
3. Areas where specific optimal RAR could be useful depends on measure of interest and parameter region of interest.

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Estimating

- **Problem:**
 - ▶ In practice, parameters (success probabilities, means, variances) are unknown
 - ▶ potentially even distribution class unknown
- **Solution:** Maximum Likelihood Estimation

→ Sequential Maximum Likelihood Procedure (SMLE)

But: High Variance! → Targeting Methods

Doubly Adaptive Biased Coin Design (DBCD)

- **Goal:** Reduce variability of sequential procedure (Eisele, 1994)
- Notation:
 - ▶ $\hat{p}(j)$ is estimated allocation probability to treatment 1 for patient j
 - ▶ $n_1(j)$ is the number of patients allocated to arm 1 after the j -th patient has been allocated
- **Solution:** For $\gamma \geq 0$ the probability with which we sample patient $j + 1$ towards treatment 1 is defined as

$$p_1(n(j), \hat{p}(j)) = \frac{\hat{p}(j) \left(\frac{\hat{p}(j)}{\frac{n_1(j)}{j}} \right)^\gamma}{(1 - \hat{p}(j)) \left(\frac{(1 - \hat{p}(j))}{\frac{n_0(j)}{j}} \right)^\gamma + \hat{p}(j) \left(\frac{\hat{p}(j)}{\frac{n_1(j)}{j}} \right)^\gamma}. \quad (7)$$

Example DBCD

- $\gamma = 2$
- $n_0(9) = 4$ and $n_1(9) = 5$
- $p_0(9) = 25\%$ and $p_1(9) = 60\%$
- $p_{minF}(9) = \frac{\sqrt{0.6}}{\sqrt{0.25} + \sqrt{0.6}} = 0.608$

$$p_1(n(9), \hat{p}(9)) = \frac{0.608 \left(\frac{9 \cdot 0.608}{5}\right)}{(1 - 0.608) \left(\frac{9 \cdot (1 - 0.608)}{4}\right) + 0.608 \left(\frac{9 \cdot 0.608}{5}\right)} = 0.704$$

Efficient Randomized-Adaptive Design (ERADE)

Hu et al. (2009) proposed discretized version of DBCD. For a parameter $\alpha \in (0, 1)$, we sample patient $j + 1$ towards treatment 1 with probability

$$p_1(n_1(j), \rho(j)) = \begin{cases} \alpha\rho(j), & \text{if } n_1(j)/j > \rho(j), \\ \rho(j), & \text{if } n_1(j)/j = \rho(j), \\ 1 - \alpha(1 - \rho(j)), & \text{if } n_1(j)/j < \rho(j). \end{cases}$$

Example ERADE

- $\alpha = 0.5$
- $n_0(9) = 4$ and $n_1(9) = 5$
- $p_0(9) = 25\%$ and $p_1(9) = 60\%$
- $p_{minF}(9) = p_{minF} = \frac{\sqrt{0.6}}{\sqrt{0.25} + \sqrt{0.6}} = 0.608$
- $n_1(j)/j = 5/9 = 0.55$
- $p_1(n(9), \hat{p}(9)) = 1 - 0.5 \cdot (1 - 0.608) = 0.804$
- **Recall:** SMLE $p_1 = 0.608$ and DBCD $p_1 = 0.704$

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Multiple Treatments - Neyman

Tymofyeyev et al. (2007), discuss the contrast test of homogeneity for $K - 1$ comparisons versus a control

$$H_0 : p_0 = p_1 = \dots = p_K$$

and obtain multi-armed Neyman solution

$$\begin{aligned} p_0^* &= \dots = p_s^* = \frac{\sqrt{p_0(1-p_0)}}{(s+1)(\sqrt{p_0(1-p_0)} + \sqrt{p_K(1-p_K)})}, \\ p_{s+1}^* &= \dots = p_{K-g}^* = 0, \\ p_{K-g+1}^* &= \dots = p_K^* = \frac{\sqrt{p_K(1-p_K)}}{g(\sqrt{p_0(1-p_0)} + \sqrt{p_K(1-p_K)})}. \end{aligned} \tag{8}$$

Multiple Treatments - Dunnett

Earlier Dunnett et al. derived a similar allocation

$$p_0^* = \frac{1}{1 + \sqrt{K}}, \quad (9)$$
$$p_1^* = \dots = p_K^* = \frac{1}{K + \sqrt{K}},$$

for the t -test assuming a homogeneous variance across all experimental treatments.

Multiple Treatments - Biswas

Biswas et al. provide a closed form solution for a very specific hypothesis

$$H_0 : p_1 - p_0 = p_2 - p_0 = \dots = p_K - p_0 = 0,$$

against the alternative

$$H_1 : \text{At least one of the differences } p_j - p_0 \neq 0 \text{ for } j = 1, \dots, K.$$

Solution:

$$p_0^* = \frac{\sqrt{p_0} \sqrt{\sum_{i=1}^K p_i(1-p_i)^2}}{\sqrt{p_0} \sqrt{\sum_{i=1}^K p_i(1-p_i)^2 + p_1(1-p_1) + \dots + p_K(1-p_K)}}, \quad (10)$$

$$p_j^* = \frac{p_j(1-p_j)}{\sqrt{p_0} \sqrt{\sum_{i=1}^K p_i(1-p_i)^2 + p_1(1-p_1) + \dots + p_K(1-p_K)}} \quad (11)$$

Multiple Treatments Conclusion

- No closed form solutions available (software needed)
- Solutions are not very useful because they solve very specific hypothesis or do not allocate patients in an intuitive way.
- More research for multi-armed proportions needed?
 - ▶ Which hypothesis do we want to test?
 - ▶ Which test should we use?
- Targeting: DBCD can be extended!

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Trial Example

Table: $n = 120$, $p_0 = 0.1$, $p_1 = 0.3$, Number of simulations 10^4 , Burn-In 10 patients per arm. The variance of the percentage of patients allocated to the treatment arm is given in percent as well.

Proportion	Targeting	$Power_Z$	% Arm1 (Var)	# Failures
ER	-	80.6%	50% (0)	96
Neyman	SMLE	84.6%	67.8% (304)	92
Neyman	DBCD	86.8%	69.9% (327)	91
Neyman	ERADE	85.1%	69.2% (304)	91
minF	SMLE	85.2%	69.5% (304)	91
minF	DBCD	86.2%	71.5% (297)	91
minF	ERADE	85.8%	71.2% (271)	91
AD	SMLE	84.8%	74.8% (241)	90
AD	DBCD	85.6%	77.5% (233)	89
AD	ERADE	85.5%	77.2% (218)	89

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Burn-In Considerations [Pin et al.(2025)]

- Stabilizes estimation of the relevant parameters (p_0, p_1) and
- the size of the burn-in period affects expected patient allocation, power, type-I error [Pin et al.(2025)]
- Burn-In period, depends on
 - ▶ RAR design (reactiveness and error)
 - ▶ sample size
 - ▶ true treatment effect

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Conclusion

1. Optimal allocation proportion can be used to implement response-adaptive designs that increase patient benefit and/or enhance statistical power.
2. Implications for the use of optimal proportions differ depending on the measure of interest and true parameters / expected region of effect.
3. The choice of an appropriate targeting method is crucial to reduce variance.

Discussion

1. Measures of Interest - Estimands
2. Inference methods - Score Test or Nonparametric
3. Optimal proportions for multiple arms
4. Burn-in period
5. Targeting parameters

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The End

Thank you for your attention!

Any questions?

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