



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):** Fair coin toss. Patients are allocated with equal probability to each arm. Mirrors the state of equipoise.
- **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

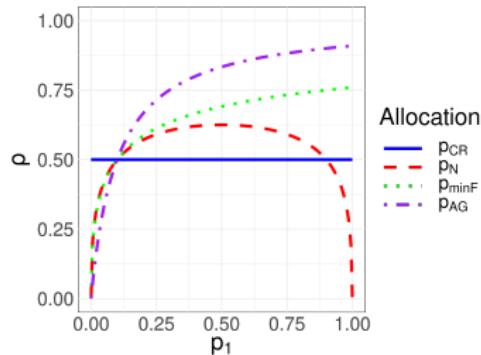


Figure: $p_0 = 0.1$

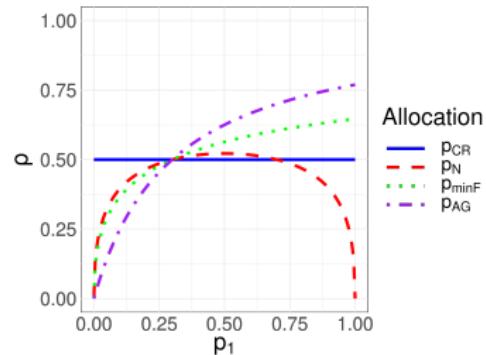


Figure: $p_0 = 0.3$

Comparison: Binary II

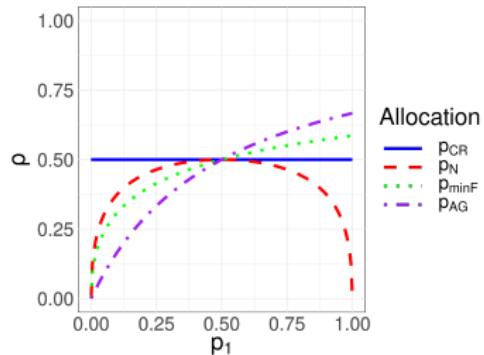


Figure: $p_0 = 0.5$

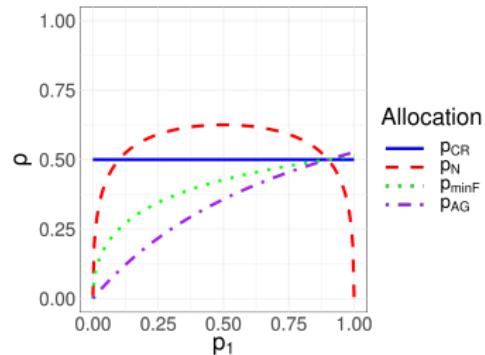


Figure: $p_0 = 0.9$

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

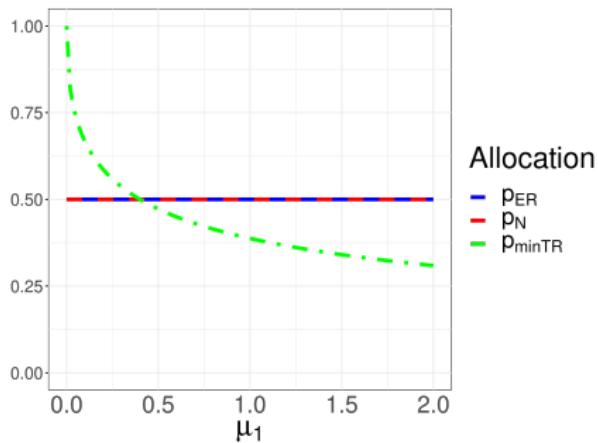


Figure: $\mu_0 = 0.4$

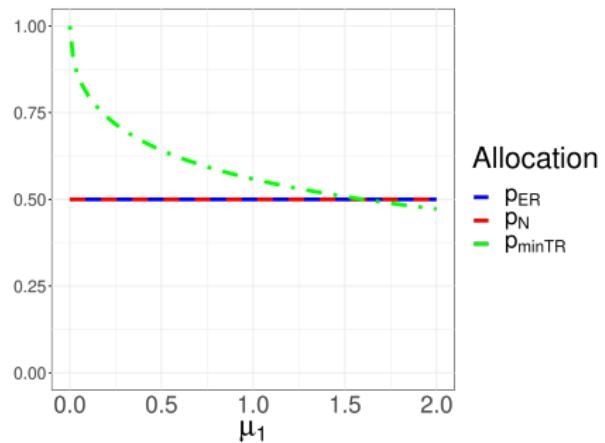


Figure: $\mu_0 = 1.2$

Comparison: Normal Distributions II

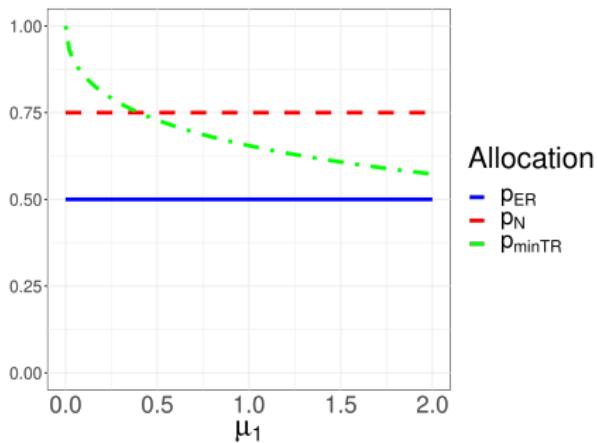


Figure: $\mu_0 = 0.4$

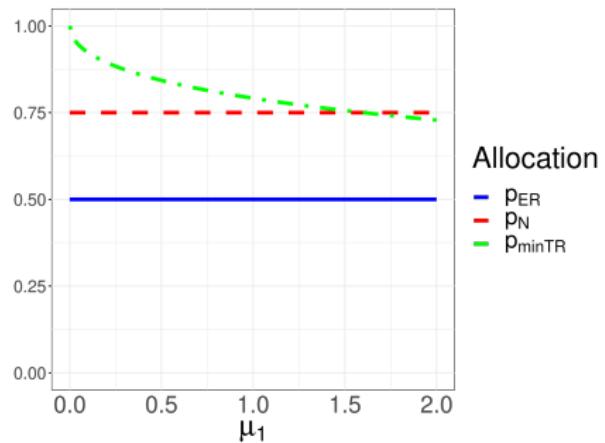


Figure: $\mu_0 = 1.2$

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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}	$\frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}}$	$\frac{\sqrt{q_0^3 p_1}}{\sqrt{p_0} + \sqrt{q_0^3 p_1}}$	$\frac{q_0^2 \sqrt{p_1}}{\sqrt{p_0} q_1^2 + q_0^2 \sqrt{p_1}}$	$\frac{q_0 \sqrt{p_1}}{\sqrt{p_0} q_1 + q_0 \sqrt{p_1}}$	$\frac{\sqrt{p_0} q_0}{\sqrt{p_0} q_0 + \sqrt{p_1} q_1}$
p_N	$\frac{\sqrt{p_1 q_1}}{\sqrt{p_0 q_0} + \sqrt{p_1 q_1}}$	$\frac{\sqrt{q_0^3 p_1 q_1}}{\sqrt{p_0} + \sqrt{q_0^3 p_1 q_1}}$	$\frac{\sqrt{q_0^3 p_1 q_1^3}}{\sqrt{p_0} + \sqrt{q_0^3 p_1 q_1^3}}$	$\frac{\sqrt{q_0 p_1}}{\sqrt{p_0} q_1 + \sqrt{q_0} p_1}$	$\frac{\sqrt{p_0 q_0}}{\sqrt{p_0} q_0 + \sqrt{p_1} q_1}$

Other Measures of Interest - Neyman

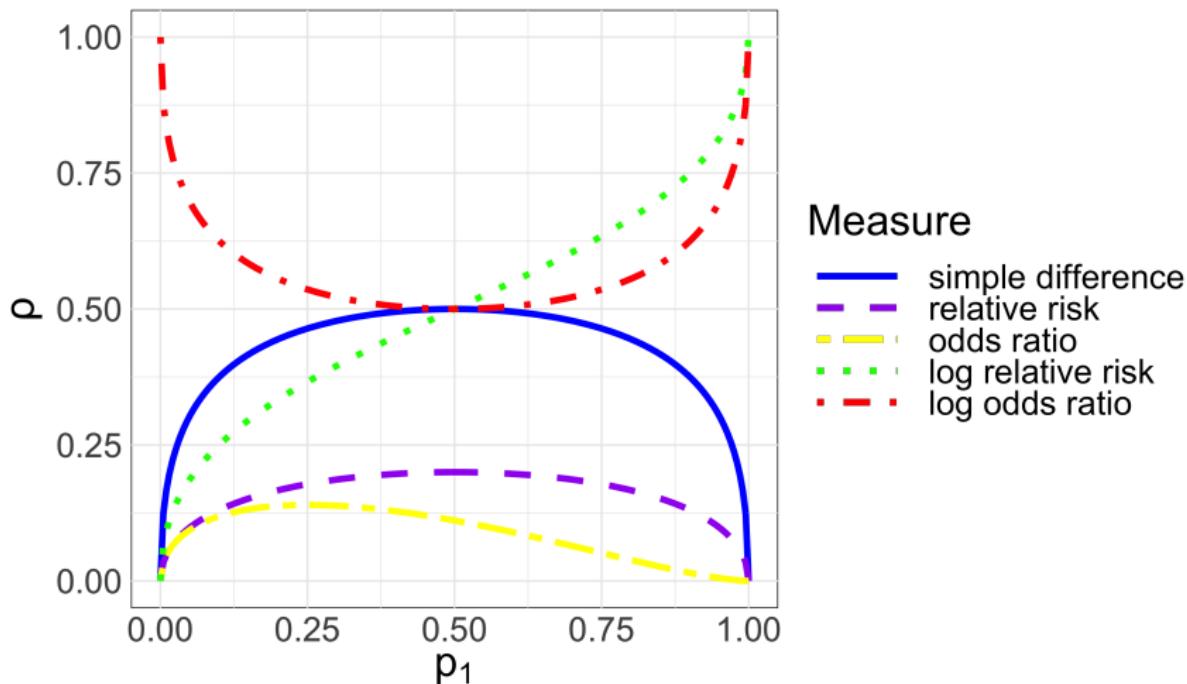


Figure: $p_0 = 0.5$

Other Measures of Interest - minF

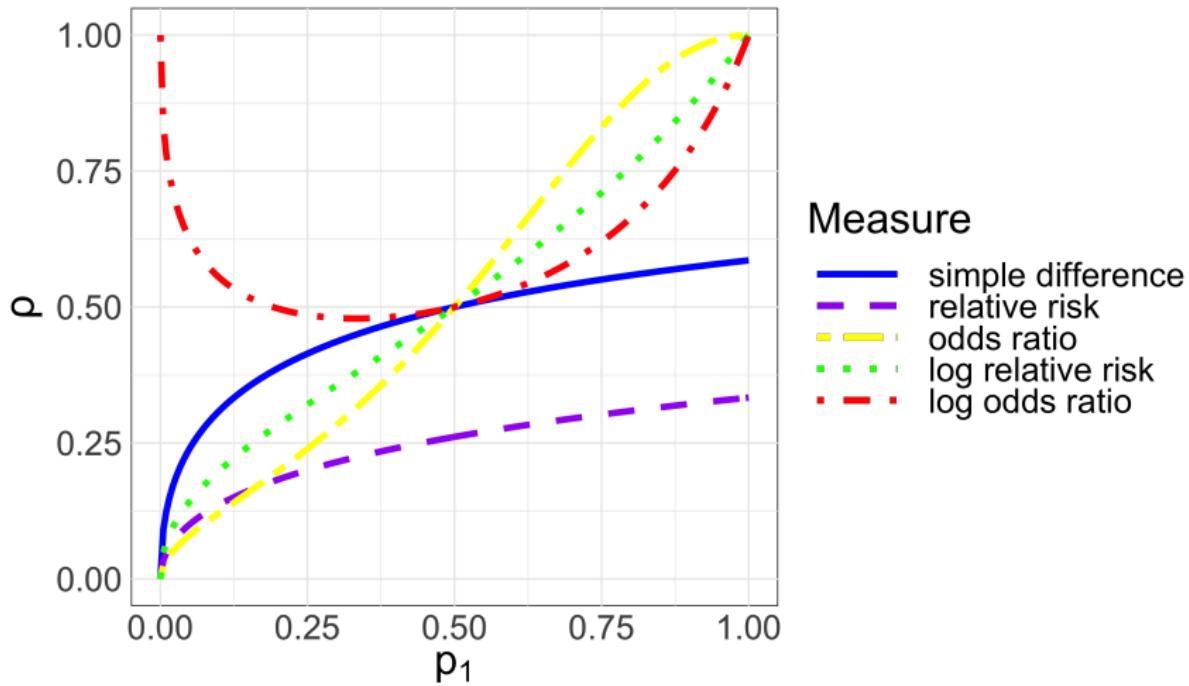


Figure: $p_0 = 0.5$

Other measure of interest - Conclusion

1. ER still only optimal when $p_0 = p_1$
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

- Stabilizes estimation of the relevant parameters (p_0, p_1)
 - No optimal Burn-In period, depends on
 - ▶ RAR design (aggressiveness)
 - ▶ sample size
 - ▶ true treatment effect
 - The size of the burn-in period affects expected patient allocation, power, type-I error
 - More important for confirmatory trials
- More research needed (currently investigated at the BSU)

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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
2. Inference methods
3. Optimal proportions for multiple arms
4. Proportions for different distribution classes
5. Burn-in period
6. Targeting parameters

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The End

Thank you for your attention!

Any questions?

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