



MRC  
Biostatistics  
Unit



UNIVERSITY OF  
CAMBRIDGE

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## **Short course on Response-Adaptive Methods for Clinical Trials**

*Lecture 6: Other applications of RAR: Backfill in  
dose finding and RAR for power*

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# Outline

## 1. Enhancing Statistical Power and Robustness to assumptions through Nonparametric Response Adaptive Randomisation

Introduction

Parametric Neyman Proportion

Nonparametric Neyman Proportion

Estimation and Targeting

Trial Example

Discussion

## 2. Implementing and assessing Bayesian response-adaptive randomisation for backfilling in dose-finding trials

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# 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:  $P(a_{ki} = 1 | a^{(i-1)}, Y^{(i-1)})$

# RAR Objectives

## 1. Increasing Power / Enhancing efficacy of the test

*Examples:* Neyman Proportion .....

## 2. Patient Benefit

*Examples:* Thompson Sampling, Randomised-Play-the-Winner

## 3. Combine both goals above and Balance them in a certain way

*Examples:* RSHIR Allocation, Jennison Allocation .....

## Derivation of parametric Neyman Proportion for two-armed trials

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# Wald 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, but binary endpoint possible if CLT yields good enough approximation.

# Derivation of Neyman Proportion I

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

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

# Derivation of Neyman Proportion II

- **Solution:**

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

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

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

- ▶ if CLT holds
- **Critique:** More patients can get allocated to inferior arm.
- **History:** Called Neyman Allocation but better attributed to Tschuprow (1923) and Robbins (1952)

# Comparison: Normal Distributions - Homoscedastic Variances $\sigma_0 = \sigma_1$

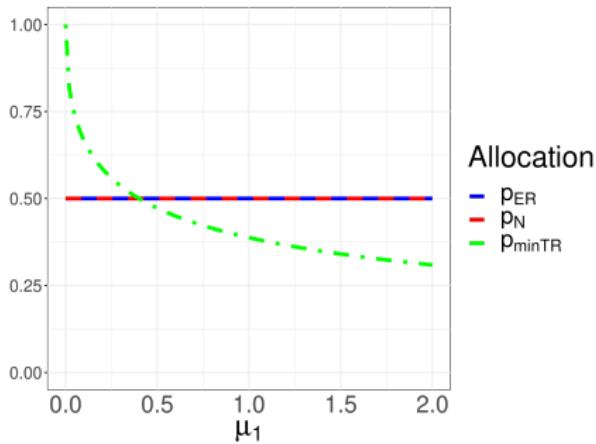


Figure:  $\mu_0 = 0.4$

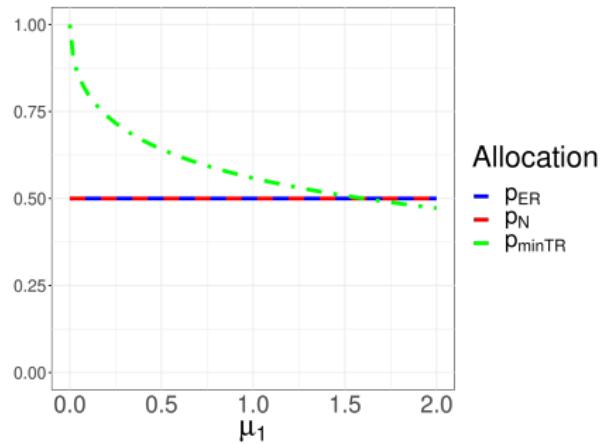


Figure:  $\mu_0 = 1.2$

# Comparison: Normal Distributions - Heterscedastic Variances $3\sigma_0 = \sigma_1$

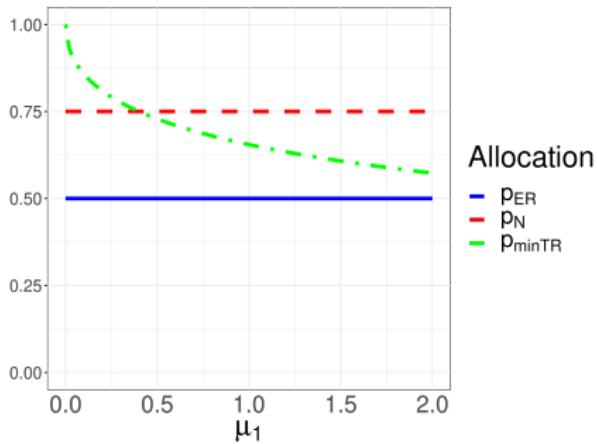


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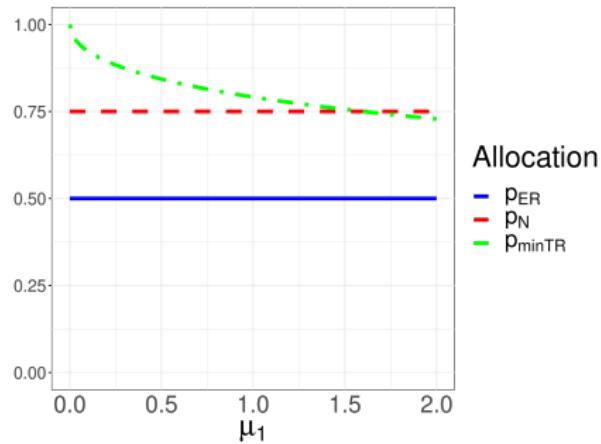


Figure:  $\mu_0 = 1.2$

# Comparison: Binary I

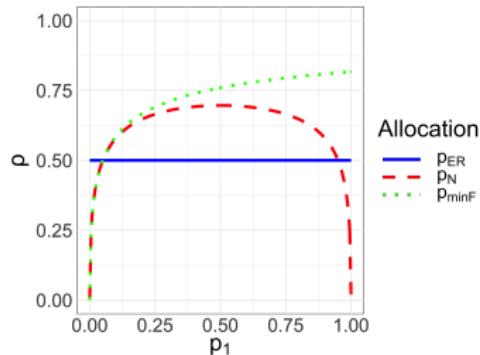


Figure:  $p_0 = 0.05$

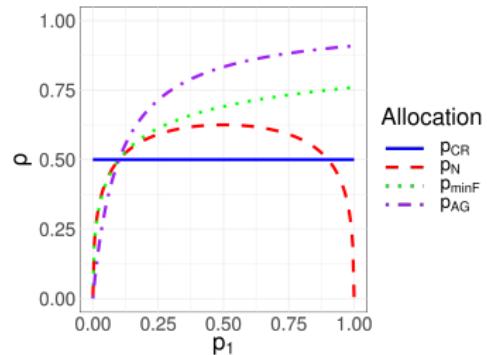


Figure:  $p_0 = 0.3$

# Summary

1. Homoscedasticity  $\sigma_0 = \sigma_1 \rightarrow$  Equal Randomisation optimal
2. In certain regions possible to have efficacy and patient benefit gains by using unequal proportion (given test and endpoint).
3. Goals of efficacy and patient benefit generally in conflict.

Parametric → Nonparametric

Nonparametric Proportion that  
maximizes Power of a  
Nonparametric Test

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# Nonparametric Power Proportion

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- Null-Hypothesis  $H_0 : \theta = 0.5$ 
  - ▶ Based on Mann-Whitney test (1947) but corrected for discrete endpoints and allowing for CI construction
  - ▶ Nonparametric relative effect

$$\theta_{01} := P(Y_{01} < Y_{11}) + \frac{1}{2}P(Y_{01} = Y_{11}) \quad (4)$$

# Nonparametric Power Proportion

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$$\theta_{01} := P(Y_{01} < Y_{11}) + \frac{1}{2}P(Y_{01} = Y_{11}) \quad (4)$$

- The test statistic is

$$BM = \frac{\theta - 0.5}{\sqrt{\frac{\tau_0^2}{n_0} + \frac{\tau_1^2}{n_1}}}, \quad (5)$$

where  $\tau_0^2 := \text{Var}(F_1(Y_{01}))$  and  $\tau_1^2 := \text{Var}(F_0(Y_{11}))$ .

- It follows

$$\rho_P = \frac{\tau_1}{\tau_0 + \tau_1}. \quad (6)$$

# Properties of Nonparametric Power Proportion

1. Nonparametric → Robust to type of endpoint: discrete vs. continuous, symmetric vs. skewed
2. Valid for small samples
3. Converges to parametric Neyman if parametric assumptions are fulfilled:  $\rho_P \xrightarrow{N \rightarrow \infty} \rho_N$

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# Estimation

In practice true variances  $\sigma_i$  and  $\tau_i$  unknown. Use maximum-likelihood estimators (MLEs)  $\hat{\sigma}_i$  or rank-based estimators

$$\hat{\tau}_k^2(j) = \frac{S_k^2(j)}{(N - n_k(j))^2}, \quad (7)$$

where

$$S_k^2(j) = \frac{1}{n_k(j) - 1} \sum_{i=1}^{n_k(j)} \left( R_{ki}(j) - R_{ki}^{(k)}(j) - \bar{R}_{k\cdot}(j) + \frac{n_k(j) + 1}{2} \right). \quad (8)$$

# Targeting

- Sequential-Estimation (SE) Procedure
  - ▶ sequentially estimate  $\hat{\tau}_k^2(j)$  to estimate  $\hat{\rho}_P$  and then sample accordingly
  - ▶ similar to sequential-Maximum-Likelihood-Estimation (SMLE) for  $\hat{\rho}_N$

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- Targeting Methods to *target* proportion and *reduce variance*
  - ▶ Doubly adaptive biased coin design (DBCD)
  - ▶ Efficient randomized-adaptive design (ERADE)

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# Simulated Trial

**Table:**  $p_0 = 0.05$ ,  $p_1 = 0.3$  achieving at least 80% power (Z-test) when using ER, given  $n = 60$  patients and burn-in of 5 patients per arm. We ran  $5 \cdot 10^4$  simulations for each scenario. The bias of the proportion is defined using the proportion that was estimated for the  $n$ -th patient. Monte Carlo error for power < 0.18%.

Procedure	$Power_Z$	$Power_{BM}$	% sup Arm (Var)	Proportion (Bias)	EMR
ER	80.16%	78.23%	50% (0)	0.5 (0)	0.1753
$\rho_N$ -DBCD	91.08%	90.67%	80.72 % (447)	0.8155 (0.0462)	0.2519
$\rho_P$ -DBCD	<b>92.52%</b>	<b>92.37%</b>	<b>82.38% (696)</b>	0.8155 (0.0453)	0.2561

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# Summary

1. The nonparametric proportion achieves higher power than the parametric Neyman proportion for all three targeting methods and both tests
2. Better estimation for small samples
3. Power gain of more than 12% compared to ER
4. Superiority of BM- over Z-test is seen when we sample from skewed distributions
5. In this trial also improved patient-benefit

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# Final Thoughts

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4. Nonparametric Proportion asymptotically equivalent to original Neyman Proportion
5. Nonparametric Proportion achieves higher power, is more robust, valid for small samples
6. Future Research: Multi-Armed Proportions

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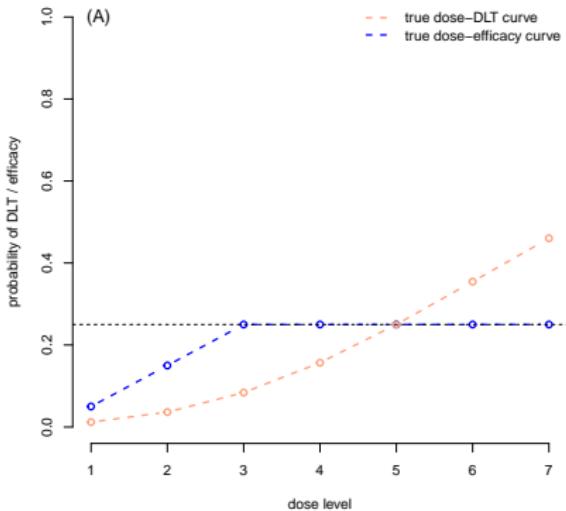
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# Motivation

- Phase-II Dose-Finding Study
- Efficacy Plateau
  - ▶ in oncology with targeted agents or immunotherapy
- **Identify** the lowest dose level that maximises efficacy whilst remaining tolerable and **allocating** patients close to that dose level
  - ▶ Backfill + RAR



# Previous Work

- Continual Reassessment Method (CRM) to identify *Maximum Tolerated Dose (MTD)* [O'Quigley et al (1990)]
- Backfill with Equal Randomization (ER) under MTD to identify *Recommended Phase 2 Dose (RP2D)* [Dehbi et al (2021)]
- Backfill with Response Adaptive Randomization (RAR) under MTD to identify RP2D and allocated patients better [Pin et al (2024)]

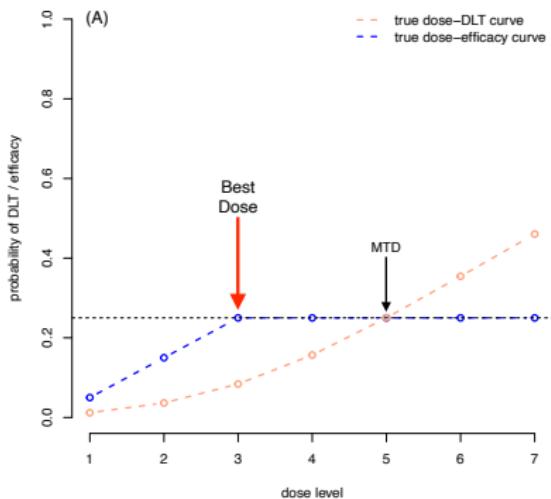


Figure: Dose 3 (RP2D) < Dose 5 (MTD)

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# Notation

- Multi-armed trial: 1,...,K different dose levels
- Fix number of patients in the trial:  $n = \sum_{k=1}^K n_k$ 
  - ▶  $n_k$  is the number of patients on dose level k
- Potential efficacy outcomes:  $Y_{ki} \stackrel{\text{iid}}{\sim} Bern(p_k)$ 
  - ▶  $p_k$  is success probability
- Binary indicator  $a_{ki}$  s.t.  $\sum_{k=1}^K a_{ki} = 1 \forall i$
- Response-adaptive-randomization:  $P(a_{ki} = 1 | a^{(i-1)}, Y^{(i-1)})$

# How does Backfill work?

**Algorithm** backfill( $n = 57, c = 3$ )

$MTD \leftarrow 1$

**while**  $MTD = 1$  **do**

    allocate  $c$  patients to dose level 1

$MTD \leftarrow$  update through CRM

**end while**

**while** Number of allocated patients  $< n$   
**do**

    allocate  $c$  patients to MTD

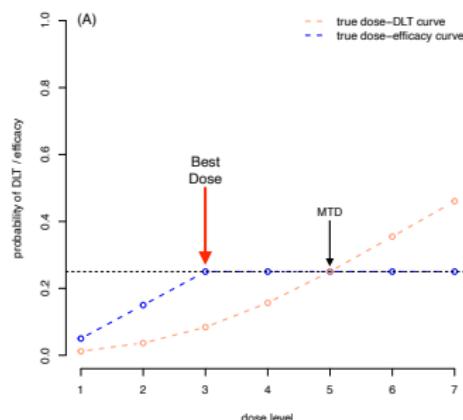
    randomise  $c$  backfill-patients with ER or RAR to dose levels 1, ...,  $MTD - 1$

$MTD \leftarrow$  update through CRM

**end while**

Choose Model with(out) Plateau

**return** RP2D



# ER vs. RAR

- **Equal randomisation (ER)** allocated backfill patients with equal probability ( $1/(\text{size of backfill set})$ ) to one of the dose level in the backfill set
- **Bayesian RAR (BRAR)** adjusts probabilities based on efficacy data from dose-escalation and backfill patients
  - ▶ BRAR design: use a posterior probability of interest to determine assignment **probabilities** [Thompson (1933)].
  - ▶ BRAR allocation probability:  $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = P(\max_{1 \leq h \leq MTD-1} p_h = p_k | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = q^{(i-1)}$

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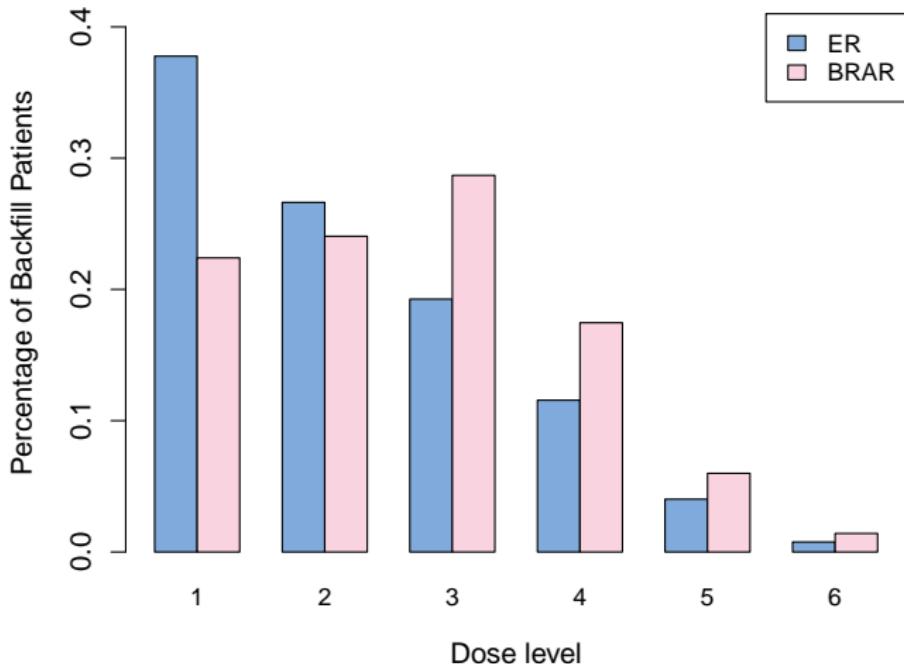
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# Allocation of Backfill Patients

Scenario A



# Recommendation of Dose Level

**Scenario A: % of recommendations per dose**

Dose Level	CRM	Backfill & ER	Backfill & BRAR
1	0%	0%	0%
2	0%	0.3%	0.1%
3	0.2%	27.3%	30.8%
4	15.7%	43.7%	44.7%
5	62.0%	19.4%	16.9%
6	20.7%	7.3%	5.9%
7	1.4%	2.0%	1.6%
RP2D	0.2%	27.3%	30.8%
[RP2D, MTD)	15.9%	70.9%	75.5%
[RP2D, MTD]	78.0%	90.4%	92.4%
(MTD , 7]	22.1%	9.3%	7.5%

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# Final Thoughts

1. Whether backfill is beneficial depends on true DLT and Efficacy curves (7 other scenarios in [Pin et al (2024)]).
2. If Backfill is beneficial, using BRAR leads to *allocating more patients close to RP2D and an increased probability of recommending the correct dose level at the end of the trial.*
3. Future Research
  - 3.1 Impact of different cohort sizes on the design
  - 3.2 Other dose-escalation methods: 2-parameter CRM, BOIN
  - 3.3 Continuous endpoints → nonparametric RAR

# References I

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The End

Thank you for your attention!

Any questions?

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