



MRC
Biostatistics
Unit



UNIVERSITY OF
CAMBRIDGE

Short course on Response-Adaptive Methods for Clinical Trials

Lecture 1: Introduction to RA design and analysis

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Overview

- **What** class of designs fall under the “*response-adaptive*’ (RA) label? [Broad definition]
- **Why** to use them (or not)?
- **How** to perform inference (specifically, hypothesis testing) at the end of a RA design?
- **How** to investigate/decide if your RA design is a good design choice for a given setting?

Outline

1. Introductory concepts

2. Design

3. Analysis

4. Assessing RA Designs

General (starting) setting

Consider a clinical trial as an **experiment** where:

- K experimental treatments are compared against control ($k = 0$ control) in n patients recruited sequentially ($n \leq n_{max}$).
- For the i^{th} patient the efficacy outcome on treatment k : $Y_{k,i}$ is a random variable (RV), e.g., $Y_{k,i} \sim Bernoulli(p_k)$ for all k

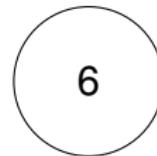
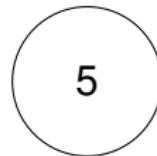
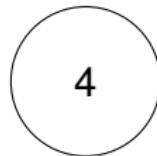
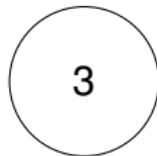
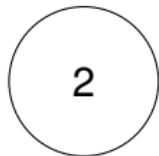
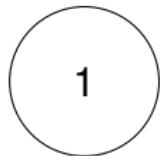
Treatment effect of interest denoted by θ , e.g. $\theta_k = p_k - p_0$

- Treatment assignments recorded as a binary variable $a_{k,i} = 1$ iff patient i receives treatment k and 0 otherwise.

- Assume only 1 treatment per patient $\sum_{k=0}^K a_{k,i} = 1$ for all i

Note: notation a initially stands for assignment but can later be seen as ***action*** or ***adaptive decision***.

Treatment assignment in clinical trials (CTs)

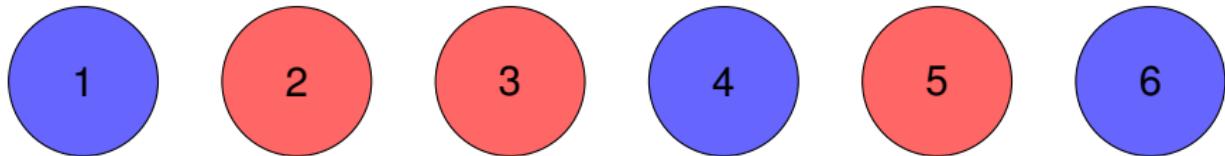


Response-adaptive designs determine $a_{k,i}$ based on data up to i

Before thinking of *adapting* assignment,

let's look closer to how assignment procedures work in CTs

Treatment assignment in clinical trials (CTs)



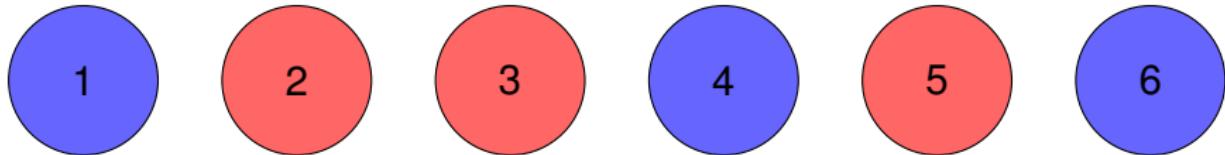
Assignment sequences (example)

$a_{0,i}$	1	0	0	1	0	1
$a_{1,i}$	0	1	1	0	1	0

How did we determine these specific treatment assignment sequences?

$$n_0 = \sum_{i=1}^6 a_{0,i} = 3 \text{ and } n_1 = \sum_{i=1}^6 a_{1,i} = 3$$

Randomisation



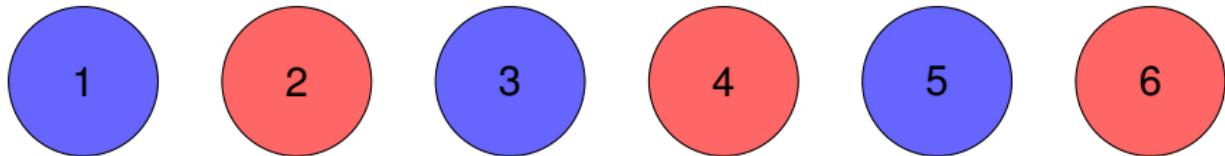
Assignment sequences (example 1)

$a_{0,i}$	1	0	0	1	0	1
$a_{1,i}$	0	1	1	0	1	0

In a confirmatory setting (Phase III trials):

$a_{k,i}$ sequences *should* have an element of **randomness**

Simple randomisation: *coin toss*



Assignment sequences (example 2)

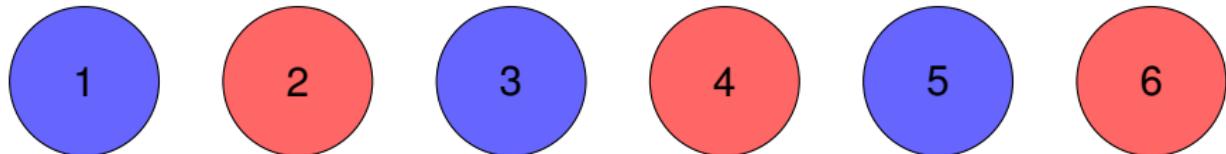
$a_{0,i}$	1	0	1	0	1	0
$a_{1,i}$	0	1	0	1	0	1

Defining $P(a_{k,i} = 1) = c$ (where $c = 1/2$ for all k,i)

It achieves (**on average**) equal sample sizes $E(N_0) = E(N_1)$

Note: Randomness can be introduced in many ways!

Deterministic assignment: *round robin*



Assignment sequences (example 2')

$a_{0,i}$	1	0	1	0	1	0
$a_{1,i}$	0	1	0	1	0	1

With $P(a_{0,i} = 1) = \mathbb{1}_O$, $O \stackrel{\text{def}}{=} \{i = 1, 3, 5\}$; $P(a_{1,i} = 1) = 1 - P(a_{0,i} = 1)$
It achieves (**exactly**) equal sample sizes $n_0 = n_1$

Note: Randomness and balance can be introduced in many ways!

Key points

- The procedure to determine treatment assignment during a trial is a key **design** element (even when the trial is not response-adaptive and $K = 1$) [Berger et al (2021)].
- The degree of *randomness* and *predictability* a procedure has impacts how to (best) analyze trial data!

Example 1 (*coin toss*) is **fully randomised**

Example 2 (*round robin*) is **fully deterministic**

- More importantly, both of these are independent of outcome
[RA designs alter this feature]

In Example 1, it holds $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = P(a_{k,i} = 1)$

where $\mathbf{A}^{(i-1)} = [a_0^{(i-1)}; a_1^{(i-1)}; \dots; a_k^{(i-1)}]$

$a_k^{(i-1)} = \{a_{k,1}, \dots, a_{k,(i-1)}\}$ and $Y^{(i-1)} = \{Y_1, \dots, Y_{(i-1)}\}$

Key take aways and more resources

- Every trial where more than one treatment/dose needs to be assigned to patients will have a unique allocation sequence (the one observed).
- An identical sequence can be generated in many different ways. The way in which this was generated affects integrity (bias protection) and can impact analysis considerably.

Useful resource: randomizeR (R package) to generate randomization lists and assess randomization procedures. The package implements 15 randomization procedures and 6 assessment criteria. [Uschner et al (2018)]

Caveat and caution note

Allocation probabilities in principle could depend on various data types (where $\mathbf{X}^{(i)}$ is a set of covariates):

$$P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, \mathbf{X}^{(i)}, Y^{(i-1)})$$

- RAR requires outcome and allocation data (unblinded data):
 $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)})$
- CARA(R) requires covariate, outcome and allocation data (unblinded data): $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, \mathbf{X}^{(i)}, Y^{(i-1)})$
treatment interactions, best treatment for covariate profile)
- CAR requires allocation (and possibly covariate) data (unblinded data): $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, X^{(i-1)})$
to achieve balance between the treatment groups with respect to baseline covariates (e.g., minimisation)

Useful resource: Tutorial paper: [Coart et al (2023)]

A note on minimisation

Example from [Coart et al (2023)]. 60-year-old woman in center XYZ is ready to be randomized into the trial that has the following status (Table 1):

- The goal of minimization is to minimize the total imbalance on some scale. E.g., the *range* method minimizes the sum of the absolute values of the imbalances. B is preferred as $7 > 5$

TABLE 1. Illustrative example of the range and variance implementation of minimization, showing current status of a two-arm trial and imbalances if next patient is assigned to arm A or arm B.

Number of patients already allocated to	A	B	Imbalance if next patient allocated to A	Imbalance if next patient allocated to B
Age: ≤65	23	22	2 (24–22)	0 (23–23)
Gender: Female	55	54	2 (56–54)	0 (55–55)
Center: XYZ	16	20	3 (17–20)	5 (16–21)
	94 (T_A)	96 (T_B)	7 (δ_A)	5 (δ_B)

Note: T_A/T_B : sum of number of patients assigned to treatment A/B corresponding to factor levels of the next patient. Note that T_A/T_B are not the total number of patients randomized to A/B due to overlap between the rows.

Outline

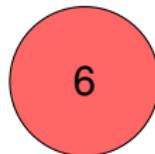
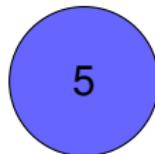
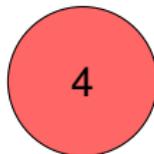
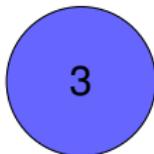
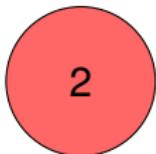
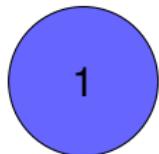
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Responses to guide assignment



Assignment sequences (example 2)

$a_{0,i}$	1	0	1	0	1	0
-----------	---	---	---	---	---	---

$a_{1,i}$	0	1	0	1	0	1
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Y_i	1	1	0	0	0	1
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Assign next patient(s) with $P(a_{k,i=7} = 1 | \mathbf{A}^{(6)}, Y^{(6)})$

How to response-adapt (and why)?

More generally, $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) \quad \forall k, i = 1, \dots, n$

- **How?** If the above changes for all i we have a **fully sequential** RA. Assume n is fixed (for now). An important distinction is:

Response-adaptive and **strictly randomised** for all i in n :

$$P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) \in [l, u] \quad \forall i, k \quad \text{and } l >> 0 \text{ and } u << 1$$

Response-adaptive but **not strictly randomised** for all i in n :

$$P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) \in [0, 1] \quad \forall i, k$$

E.g., $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) \stackrel{\text{def}}{=} \mathbb{1}_C,$

$\mathbb{1}_C$ is an indicator function and C is a condition of interest given past data such as $C \stackrel{\text{def}}{=} (\hat{p}_1^{(i-1)} > \hat{p}_0^{(i-1)})$ (*Myopic/greedy*)

- **Why?** Improve efficiency (e.g., of a final test $T(Y^{(n)}, \mathbf{A}^{(n)})$) or improve patient outcome (measured as a function of either $Y^{(n)}$ or $\mathbf{A}^{(n)}$) or a combination of both!

Example I: Randomised Play the Winner

- **RPTW Design:** An urn contains b_0 blue ($k=0$) and r_0 red ($k=1$) balls. Draw a ball at random, assign treatment k to patient i and replace the ball. If $Y_i = 1$, add 1 ball to the urn of the colour k , otherwise add 1 of the other. Repeat for all patients in n .
- **Why?** To assign on average more patients to the superior [Wei and Durham (1978)].
- $B^{(i)}$ and $R^{(i)}$ are RVs defining a stochastic process with transition probabilities depending on p_0, p_1
- Let $\mathbf{C}^{(i)} = (b^{(i)}, r^{(i)})$ be the urn composition after treating patient i , where the initial urn: $\mathbf{C}^{(0)} \stackrel{\text{def}}{=} (b^{(0)} = e, r^{(0)} = e) \quad e \geq 1$ (Equipoise) and where $\|\mathbf{C}^{(i)}\| \stackrel{\text{def}}{=} b^{(i)} + r^{(i)}$

The allocation probability for patient i for this RPTW design is:

$$P(a_{k,i}) = P(a_{k,i} | \mathbf{A}^{(i-1)}, \mathbf{Y}^{(i-1)}) = \left(\frac{\mathbf{C}^{(i-1)}}{\|\mathbf{C}^{(i-1)}\|} \right)' \quad (1)$$

Example I: Randomised Play the Winner (contd)

- Thinking of the urn composition as a Markovian process, recursively compute the probability as in (1) (Slide 12), from the urn's composition result below:
[Wei and Durham (1978), Hu and Rosenberger (2006)]:
- Recursive formula: $\mathbf{C}^{(i)} = \mathbf{C}^{(i-1)} + a_i \mathbf{D}(Y_i)$

Design matrix for all i :

$$D(Y_i = 1) = \begin{matrix} b & r \\ r & 1 \end{matrix} \quad D(Y_i = 0) = \begin{matrix} b & r \\ r & 0 \end{matrix}$$

Rows: colour drawn; Columns: balls to add to the colour

Example I: Randomised Play the Winner (contd)

- For RPTW it is intuitive that: $E(\mathbf{D}) = \begin{pmatrix} b & r \\ r & (1-p_0) \end{pmatrix} \begin{pmatrix} p_0 & (1-p_0) \\ (1-p_1) & p_1 \end{pmatrix}$
- If the design runs *indefinitely* (or $n \rightarrow \infty$), where would the limiting assignment proportion go?
- Asymptotic urn behavior - e.g., in terms of $E(N_k^{(i)})$ for all k - depends on $E(\mathbf{D})$ and thus on p_0, p_1
It holds that as $n \rightarrow \infty$:

$$E\left(\frac{N_1^{(n)}}{n}\right) \xrightarrow{\text{a.s.}} \frac{(1-p_0)}{(1-p_0)+(1-p_1)}$$

Example II: Bayesian RAR

- **BRAR design:** use a posterior probability of interest to determine assignment **probabilities** (at start and then sequentially). [Thompson (1933)]
- BRAR allocation probability (example):
 $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = P(p_1 > p_0 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = q^{(i-1)}$
- If $n \rightarrow \infty$) where would the limiting allocation ratio go?
Asymptotic behavior depends on p_0, p_1 in this case
For $p_1 > p_0$ it holds that: $n \rightarrow \infty: E\left(\frac{N_1^{(i)}}{n}\right) \rightarrow 1$
- First proof of the asymptotic optimality (of TS) for Bernoulli outcomes [Kaufmann et al (2012)].
- BRAR *tuned* (down): [Thall and Wathen (2007)]
 $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) \propto (q^{(i-1)})^c$ where $c = (i-1)/n$. This gives $P(a_{k,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = 1/(K+1)$ for $i = 1$

Example III: Bayesian RA

- *Tuning* dilutes the adaptation (towards an equal probabilities) making *tuned* BRAR a fully randomised procedure for $n \ll \infty$. A similar result can be achieved by a *burn-in* stage (Lecture 2).
- On an opposite direction to *tuning*, could consider defining

$$P(a_{1,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = \mathbb{1}_{q^{(i-1)} > 1/2}$$
$$P(a_{0,i} = 1 | \mathbf{A}^{(i-1)}, Y^{(i-1)}) = \mathbb{1}_{q^{(i-1)} \leq 1/2}$$

- The above RA design would allocate every patient to the current *best* arm with probability 1 [How do you think this would behave for $i = 1$?]
- This is an example of a ‘not fully randomised’ RA design. Most *optimal* RA designs have this property [Villar et al (2015)].

Key take aways and more resources

- Multiple RAR procedures exist. These define the probability of allocation based on outcome and allocation data in different ways.
- Urn models are model free. Bayesian RAR needs a posterior probability (and model assumptions).
- There is a plethora of RAR algorithms and it is hard to classify them. [Robertson et al (2023)]

Useful resource: Review paper by our group
[Robertson et al (2023)]

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Valid inference after RA designs

- Q If we collected data using a RA design, what inferential tests are **valid** (and how do we define them/compute them)?

[Why do we ask?] Independent sampling assumption no longer holds due to outcome-induced correlation in the sampling.

Optimistic sampling, larger/smaller point estimates lead to larger/smaller sample sizes even under the null. [See next slide]

- (1) Cases where standard frequentist inferential tests remain **asymptotically** valid [Specific RAR and large n Slide 20]
- (2) For all other cases:
 - (2.1) Estimate (frequentist) operating characteristics of a decision rule/test statistic by **simulation**
 - (2.2) For RAR, **randomization-based inference** is valid in finite samples [Simon and Simon (2011)]. Exact tests (under development [Baas et al (2024)] [Wei et al (1990)][Yi (2013)]

Finite sample valid procedures

- **Randomisation-based inference (RBI):** based on the randomisation procedure used to generate allocations in the trial.

Assume no effect at all (all outcome remains fixed/unaffected by allocation)

All variability comes from randomisation.

For any final test of choice $T(Y^{(n)}, \mathbf{A}^{(n)})$, find the randomisation induced distribution. Select cut-off from there.

- For **exact tests**, we need to write the (sequential) likelihood of the data $(Y^{(n)}, \mathbf{A}^{(n)})$ induced by the RAR. With this one, derive the exact distribution for a given test $T(Y^{(n)}, \mathbf{A}^{(n)})$.

This will require a model for the outcomes. More general null hypothesis than in RBI.

Asymptotic-based inference after RAR rules

- Q If we use RAR within a trial design, when can we apply **standard inferential tests** (and how do we define then)?[Hu and Rosenberger (2006)]

For some parameter vector μ : If as $n \rightarrow \infty$ then $\frac{N_k^{(n)}}{n} \xrightarrow{\text{a.s.}} \rho_k(\mu)$ with $\rho(\mu) \in (0, 1)^{K+1}$ for $k = 0, \dots, K$ then:

- (1) $\hat{\mu}_k$ strongly consistent estimator of μ_k (converges in prob.) $\forall k$;
- (2) $\sqrt{n}(\hat{\mu}_k - \mu_k) \xrightarrow{d} N(\mathbf{0}, \mathbf{I}^{-1}(\mu))$ with $\mathbf{I}(\mu) = \text{diag}\{\rho_k \mathbf{I}_1(\mu_k)\}$
 $k = 0, \dots, K$ and $\mathbf{I}_1(\mu_k)$ is the Fisher's information for a single observation on treatment k .

E.g: for RPTW with $K = 2$ it holds that:

$$\rho_1(p_0, p_1) = \frac{(1-p_0)}{(1-p_0)+(1-p_1)}$$

$$\sqrt{n}(\hat{p}_1 - p_1) \xrightarrow{d} N(0, v) \quad \text{with } v = \frac{p_1(1-p_1)[(2-p_0-p_1)]}{(1-p_0)}$$

Asymptotic-based inference after RAR rules

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Simulation-based inference after RAR rules

- Q If we perform RAR within a trial and asymptotic inference is not suitable, how can we analyse it in that case?
- 1) Pick a statistical test (or any other decision rule) to be used at the end of the study $T(Y^{(n)}, \mathbf{A}^{(n)})$
 - 2) Simulate a large number of trial replications of the RA design for a *good* range of interest of the parameter space θ
 - 3) Find critical values or threshold for $T(Y^{(n)}, \mathbf{A}^{(n)})$ that ensure desirable target performance of the RA design.

Additional simulations if there are specific design parameters to *tune*. Repeat 1)-3) until targets are met.

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Comparing RAR

- What are the relevant dimensions (for RA clinical trials)?

For simplicity, let's do this when $K = 1$ (two-arm study) with $H_0 : p_0 = p_1$ (null) and (some alternative) $H_1 : p_0 \neq p_1$

- Many metrics can be put forward. Focus on 3 main classes.
 - 1 **Testing metrics:** type I error $\alpha = P(\text{reject } H_0 | H_0 \text{ true})$ and power $(1 - \beta) = P(\text{reject } H_0 | H_1 \text{ true})$
 - 2 **Estimation metrics:** mean bias $= E(\hat{p}_k) - p_k$, variance of estimator $= V(\hat{p}_k)$ or the mean squared error of an estimator $= E[(\hat{p}_k - p_k)^2]$
 - 3 **Patient benefit metrics:** the expected proportion of patients allocated to the best arm $E(\rho^*)$ with $\rho^* = \frac{N_{k^*}}{n}$ (and k^* is the best arm. Under H_0 , $k^* = 0$)
 - 4 **Other metrics:** sample size (minimum n to achieve power and control type I error), variability of resulting assignments.

How to consider the use of RAR?

How to decide on a RA trial design (without early stopping)

1. Start by creating a fixed sample size design with equal allocation ratio. Report all (1)-(4) for it [Slide 22].
2. Consider which are the dimension(s) most relevant to improve on for that fixed sample design (as well as which ones should not considerably get worse)
3. Consider what n_{\max} is, how often you can feasibly update randomisation probabilities (and how to implement it!)
4. Search for a (practically feasible) RAR procedure that achieves the design objective from step 2.
5. Compare the '*best*' RAR design with other adaptive designs in terms of that metric of interest
6. Choose the simplest design that achieves the goal!

Simulation results: illustration

Wald Test: $Z = \frac{\hat{p}_0 - \hat{p}_1}{\sqrt{s_T}} \quad s_T^n = \frac{\hat{p}_0(1-\hat{p}_0)}{n_0} + \frac{\hat{p}_1(1-\hat{p}_1)}{n_1}$.

$n = 148$	$H_0 : p_0 = p_1 = 0.3$			
5000 trials	α	$E(N_1)/n$	$(1 - R_0^*)$	$E(\sum_i^n Y_i)$
<i>Coin</i>	0.049	0.500 (0.04)	0.5	44.33 (5.57)
<i>RPTW</i>	0.048	0.503 (0.28)	0.5	44.43 (5.48)
<i>BRAR (tuned)</i>	0.066	0.499 (0.10)	?	44.39 (5.58)
<i>BRA</i>	0.046	0.528 (0.44)	?	44.34 (5.55)
np_1				44.40 (0.00)
$n = 148$	$H_1 : p_0 = 0.3 \quad p_1 = 0.5$			
5000 trials	$(1 - \beta)$	$E(N_1)/n$	$(1 - R_0^*)$	$E(\sum_i^n Y_i)$
<i>Coin</i>	0.805	0.500 (0.04)	0.500	59.25 (5.94)
<i>RPTW</i>	0.659	0.592 (0.25)	0.583	62.10 (9.40)
<i>BRAR (tuned)</i>	0.795	0.685 (0.09)	1	64.85 (6.62)
<i>BRA</i>	0.228	0.782 (0.35)	1	67.75 (12.0)
$n * p_1$				74.00 (0.00)

Comparing designs in practice: trade-offs

The baseline design (*coin*) achieves 5% type I error with 80% power and assigns 50% patients to best arm when it exits.

- RPTW achieves 5% type I error, assigns 59% patients to best arm when it exits but with 66% power
- BRAR(tuned) Assigns 68.5% patients to best arm when it exits with 0.795 power but 6.6% type I error.
- BRA Assigns 78.5% patients to best arm when it exits with 4.6% type I error but 0.228 power and variability of allocations almost 9 times larger than coin.

Which design is superior? Steps 3) and 5) (Slide 24) key to decide.

Discussion

- RA designs are most useful in situations where allocation probabilities can be updated easily and often and at a pace aligned with that of observing responses (**fully sequential RAR**) to be relaxed in Lecture 3 and 4.
- They are also most useful at specific ranges of the parametric space (to be discussed in Lecture 2).
- RA most known to be used so as to increase expected within patient outcome but not the only one. **Efficiency or composite objectives can also be targeted. Lecture 2 and Lecture 6**
- RA for Multi-armed trials also more likely to result in superior designs to ER ones (accounting for multiplicity and suitable power definition). Lecture 2, 4 and 5. Particularly those in which control allocation is *protected*.
- RA will result in **biased MLE estimates** in finite samples (L3)

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The End

Thank you for your attention!

Any questions?

On to Practical 1 (coffee/tea refill)