MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 4: Introduction to Response-Adaptive 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

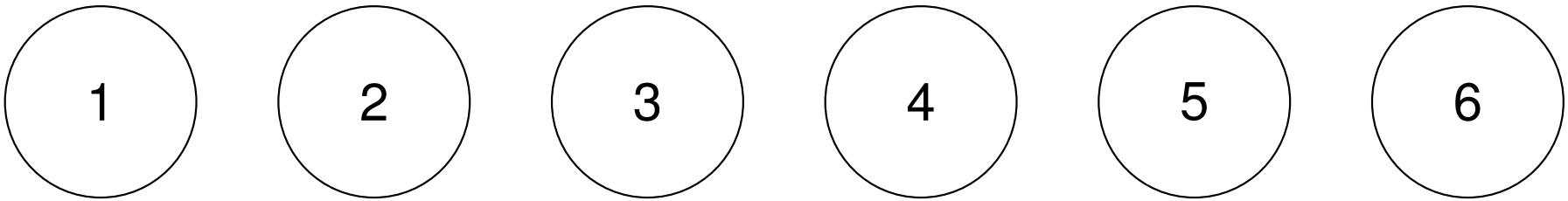
Consider a clinical trial as an **experiment** where:

- 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., $Y_{k,i} \sim Bernouilli(p_k)$ 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)

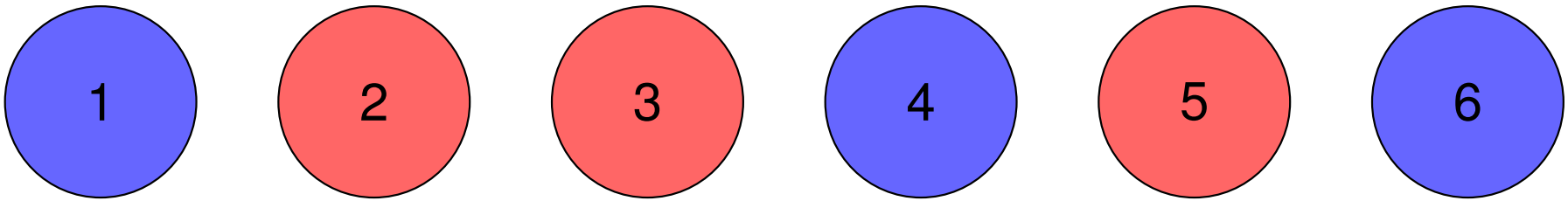


Response-adaptive designs determine $a_{k,i}$ based on data up to i

Before thinking of *adapting* assignment,

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

Treatment assignment in clinical trials (CTs)



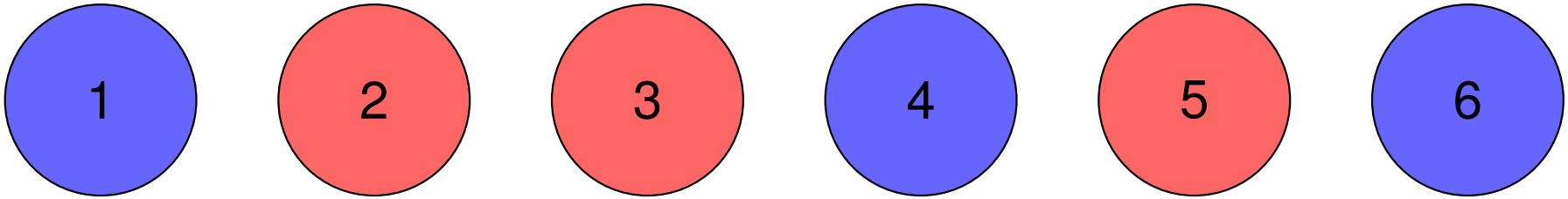
Assignment sequences (example)

$a_{0,i}$	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



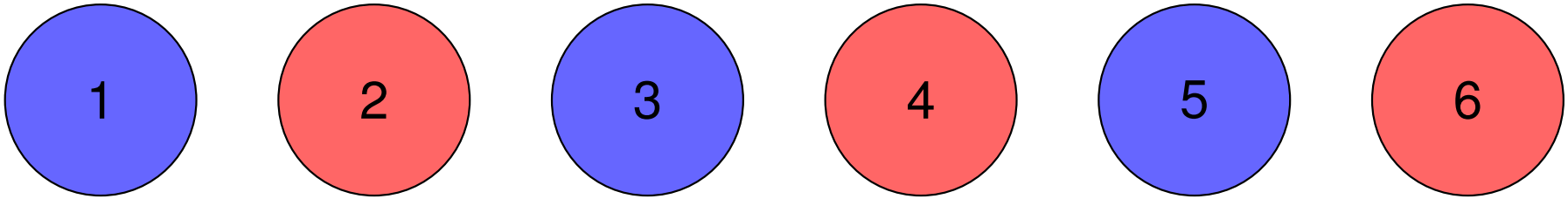
Assignment sequences (example 1)

$a_{0,i}$	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)

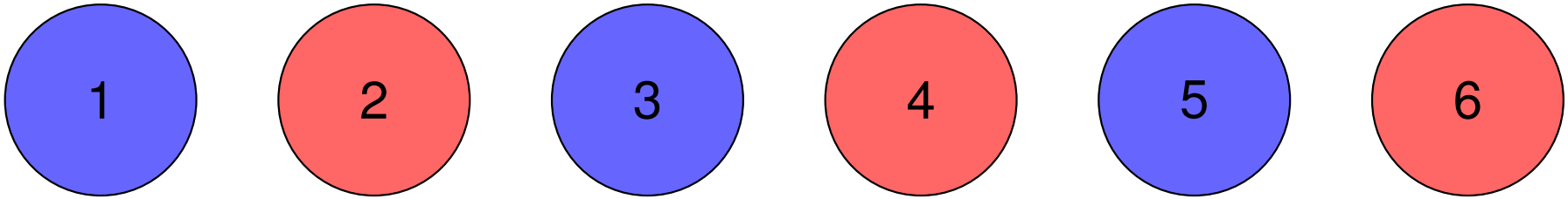
$a_{0,i}$	1	0	1	0	1	0
$a_{1,i}$	0	1	0	1	0	1

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

It achieves (**on average**) equal sample sizes $\mathrm{E}(N_0) = \mathrm{E}(N_1)$

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 (ADs typically) 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 $\mathbf{A}^{(i-1)} = [a_0^{(i-1)}; a_1^{(i-1)}; \ldots; a_k^{(i-1)}]$
  $a_k^{(i-1)} = \{a_{k,1}, \ldots, a_{k,(i-1)}\}$ and $Y^{(i-1)} = \{Y_1, \ldots, Y_{(i-1)}\}$

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 difference 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 (unlblinded data):
$P(a_{k,i} = 1|\mathbf{A}^{(i-1)}, Y^{(i-1)})$

- CARA(R) requires covariate, outcome and allocation data (unlblinded data): $P(a_{k,i} = 1|\mathbf{A}^{(i-1)}, \mathbf{X}^{(i)}, Y^{(i-1)})$
treatment interactions, best treatemnt for covariate profile)

- CAR requires allocation (and possibly coveriate) data (unlblinded 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., *minimsation*)

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.

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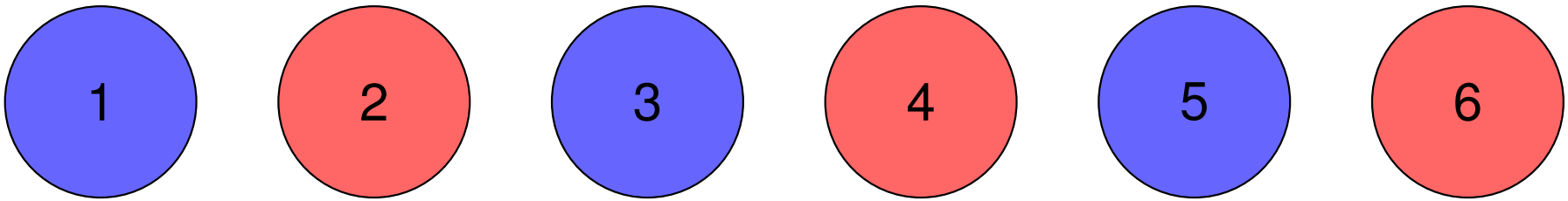
Responses to guide assignment



Assignment sequences (example 2)

$a_{0,i}$	1	0	1	0	1	0
$a_{1,i}$	0	1	0	1	0	1
	Outcome history					
Y_i	1	1	0	0	0	1

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

How to response-adapt (and why)?

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

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

  Response-adaptive but not strictly randomised for all i in n:
  $P(a_{k,i} = 1|\mathbf{A}^{(i-1)}, Y^{(i-1)}) \in [0, 1] \ \forall i, k$
  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:

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

Example I: Randomised Play the Winner (contd)

- Thinking of the urn composition as a Markovian process, recursively compute the probability as in (1) (Slide 15), 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:

$$D(Y_i = 1) = \begin{array}{c} \\ b \\ r \end{array} \begin{array}{c} \begin{array}{cc} b & r \end{array} \\ \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \end{array} \quad D(Y_i = 0) = \begin{array}{c} \\ b \\ r \end{array} \begin{array}{c} \begin{array}{cc} b & r \end{array} \\ \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix} \end{array}$$

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

Example I: Randomised Play the Winner (contd)

- For RPTW it is intuitive that: $\mathrm{E}(\mathbf{D}) = \begin{array}{c} \\ b \\ r \end{array} \begin{array}{c} \begin{array}{cc} b & r \end{array} \\ \begin{pmatrix} p_0 & (1-p_0) \\ (1-p_1) & p_1 \end{pmatrix} \end{array}$

- If the design runs *indefinitely* (or $n \to \infty$), where would the limiting assignment proportion go?

- Asymptotic urn behavior - e.g., in terms of $\mathrm{E}(N_k^{(i)})$ for all k - depends on $\mathrm{E}(\mathbf{D})$ and thus on p_0, p_1
  It holds that as $n \to \infty$:

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

Thus, $\mathrm{E}\left(\frac{N_1^{(n)}}{n}\right) \xrightarrow{a.s.} c$ with $c \in (0.5, 1)$ if $p_1 > p_0$.

Example II: Bayesian RAR

- **BRAR design**: use a posterior probability of interest to determine assignment **probabilities** (at the 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 $n \to \infty$ 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: $n \to \infty$: $\mathrm{E}\left(\frac{N_1^{(i)}}{n}\right) \to 1$
- First proof of the asymptotic/regret optimality (of TS) for Bernoulli outcomes [Kaufmann et al (2012)].
- BRAR *tuned* (down): [Thall and Wathen (2007)]
  $P(a_{k,i} = 1|\mathbf{A}^{(i-1)}, Y^{(i-1)}) \propto \left(q^{(i-1)}\right)^c$ 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 $n << \infty$. A similar result can be achieved by a *burn-in* stage.

- 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 $i = 1$? and for $i = n - 1$?]

- 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 **very** different ways.
- Urn models are model free. Bayesian RAR needs a prior and posterior probability (and model assumptions).
- There is a plethora of RAR algorithms, hard to classify them.

  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) Special cases where standard frequentist inferential tests remain **asymptotically** valid [Specific RAR + large n Slide 20]

(2) For all other cases:

(2.1) Estimate (frequentist) operating characteristics of a decision rule/test statistic by **simulation** studies

(2.2) For RAR, **randomization-based inference** is valid in finite samples [Simon and Simon (2011)]. Exact tests ([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 trial allocations.

  Assume no effect at all (all outcome remains fixed/unaffected by allocation) - *sharp null*

  All variability comes from randomisation. - *known by design*

  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 $n \to \infty$ then $\frac{N_k^{(n)}}{n} \xrightarrow{a.s.} \rho_k(\mu)$ with $\rho(\mu) \in (0,1)^{K+1}$ for $k = 0, \ldots, K$ 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 $\mathbf{I}(\mu) = diag\{\rho_k \mathbf{I}_1(\mu_k)\}$ $k = 0, \ldots, K$ 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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$$\sqrt{n}(\hat{p}_1 - p_1) \xrightarrow{d} N(0, v) \quad \text{with } v = \frac{p_1(1-p_1)[(2-p_0-p_1]}{(1-p_0)}$$

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 μ

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 $\alpha = P(\textit{reject } H_0 | H_0 \textit{ true})$ and power $(1 - \beta) = P(\textit{reject } H_0 | H_1 \textit{ true})$
  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.

Simulation results: illustration

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

$n = 148$	$H_0 : p_0 = p_1 = 0.3$			
5000 trials	α	$E(N_1)/n$	$(1 - R_0^*)$	$E(\sum_i^n Y_i)$
Coin	**0.049**	**0.500 (0.04)**	**0.5**	**44.33 (5.57)**
RPTW	0.048	0.503 (0.28)	*0.5*	44.43 (5.48)
BRAR (tuned)	0.066	0.499 (0.10)	*?*	44.39 (5.58)
BRA	0.046	0.528 (0.44)	*?*	44.34 (5.55)
$n * p_1$				44.40 (0.00)
$n = 148$	$H_1 : p_0 = 0.3\ p_1 = 0.5$			
5000 trials	$(1 - \beta)$	$E(N_1)/n$	$(1 - R_0^*)$	$E(\sum_i^n Y_i)$
Coin	**0.805**	**0.500 (0.04)**	**0.500**	**59.25 (5.94)**
RPTW	0.659	0.592 (0.25)	*0.583*	62.10 (9.40)
BRAR (tuned)	0.795	0.685 (0.09)	*1*	64.85 (6.62)
BRA	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 29) in context are key to decide.

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!

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)**. RAR can be used in combination with early stopping.
- They are also most useful at specific ranges of the parametric space for binary endpoints.
- 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.**
- RA for Multi-armed trials also more likely to result in superior designs to ER ones (accounting for multiplicity and suitable power definition). Particularly those in which control allocation is *protected*.
- RA will result in **biased MLE estimates** in finite samples (L3)

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Thank you for your attention!

Any questions?