



MRC  
Biostatistics  
Unit



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

*Lecture 1: Introduction to RA design and analysis*

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February 28, 2024

# 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  $k$

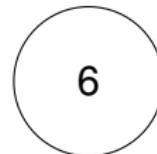
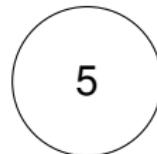
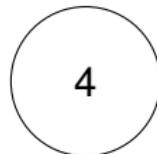
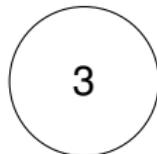
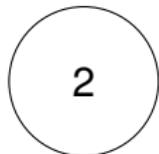
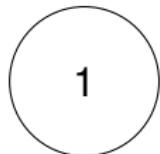
Treatment effect of interest denoted by  $\theta$ , e.g.  $\theta_k = p_k - p_0$

- 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)

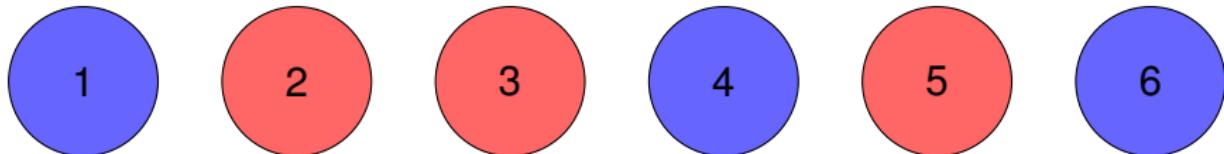


**Response-adaptive designs determine  $a_{k,i}$  based on data up to  $i$**

Before thinking of *adapting* assignment,

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

# Treatment assignment in clinical trials (CTs)



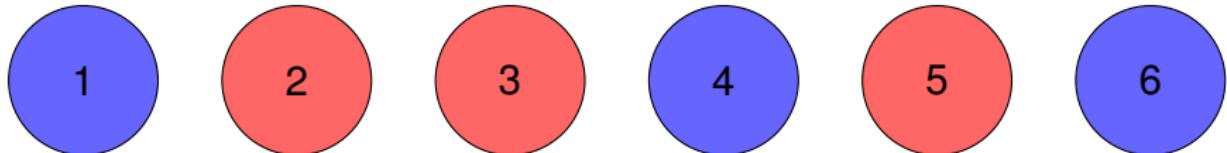
Assignment sequences (example)

$a_{0,i}$	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



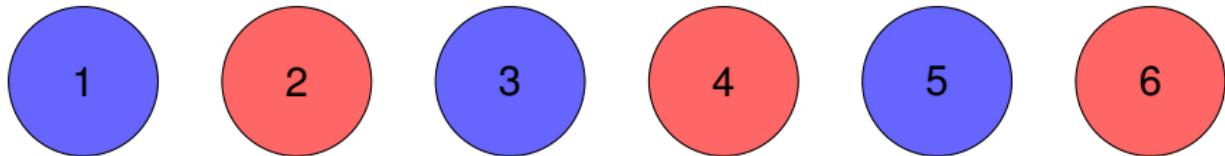
Assignment sequences (example 1)

$a_{0,i}$	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)

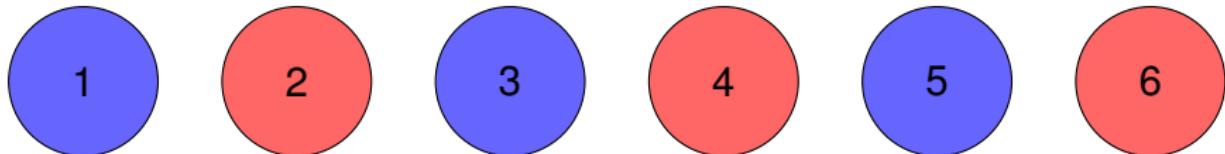
$a_{0,i}$	1	0	1	0	1	0
$a_{1,i}$	0	1	0	1	0	1

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

# Outline

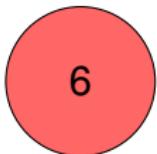
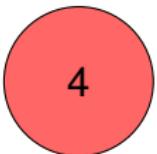
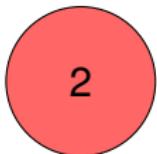
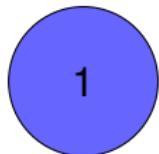
1. Introductory concepts

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# Responses to guide assignment



Assignment sequences (example 2)

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

- If the above changes for all  $i$  we have a **fully sequential** RA.  
Note, we 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  $n$ :

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

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

$\mathbb{1}_C$  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)].

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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.**

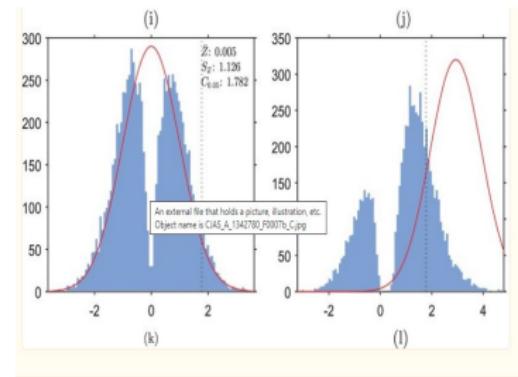
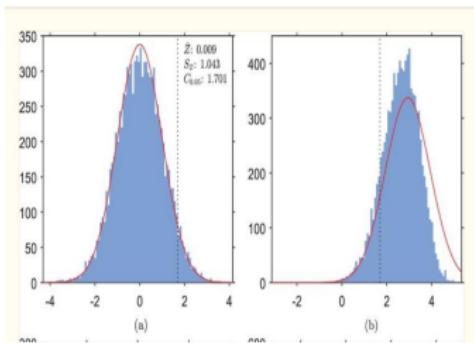
Optimistic sampling, larger/smaller point estimates lead to larger/smaller sample sizes even under the null. [See next slide]

- (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). (Both not covered by this lecture)

# Illustration of effect of RAR in test's distribution

Critical value for  $\alpha = 5\%$  is 1.645 for ER , 1.701 for BRAR and 1.782 for BRA. Test:  $Z = \frac{\mu_0 - \mu_1}{\sqrt{\frac{\sigma_0^2}{n_0} + \frac{\sigma_1^2}{n_1}}}$ . [Smith and Villar (2018)]

$$Z = \frac{\mu_0 - \mu_1}{\sqrt{\frac{\sigma_0^2}{n_0} + \frac{\sigma_1^2}{n_1}}}$$



**Figure:** Wald test for difference in means (L2) under BRAR (a) Null and (b) Alternative

**Figure:** Wald test for difference in means (L2) under BRA (C in Slide 11). Null/Alternative

# 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  $\mu$ : 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  $\mu_k$  (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:

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

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

# 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  $\theta$
  - 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	$\alpha$	$E(N_1)/n$	$(1 - R_0^*)$	$E(\sum_i^n Y_i)$
<i>Coin</i>	<b>0.049</b>	<b>0.500 (0.04)</b>	<b>0.5</b>	<b>44.33 (5.57)</b>
<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>	<b>0.805</b>	<b>0.500 (0.04)</b>	<b>0.500</b>	<b>59.25 (5.94)</b>
<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**
- 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 and 4. 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?

Off to Practical 1 (with some coffee/tea)