MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Short course on Response-Adaptive Methods for Clinical Trials

Lecture 4: Trial examples using Response Adaptive Randomisation

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Overview

Introduce and **discuss** key features of two trials that used RAR:

- The ARREST trial
- Ketamine in LL-TRD trial

We will see how **RAR trials** are run in practice and what needs to be **considered** along with some of the **limitations**.

Disclaimer: *These examples have been selected for illustrative purposes and they should be taken as such and neither is used as a good nor bad example.*

Lecture plan - Part 1

- The Advanced REperfusion STrategies for Refractory Cardiac (ARREST) trial.
  - The Condition and Motivation.
  - Treatments and Primary Objective.
  - Hypotheses.
  - Priors and Posteriors.
  - Early Stopping.
  - Response Adaptive Randomisation.
  - Type I Error and Power.
  - Operating Characteristics.
- Discussion based around ARREST trial.

The ARREST Trial - The Condition and Motivation

- More than **350,000 people** in the United States **die** from out-of-hospital cardiac arrest (**OHCA**) each year.
- Patients with refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) OHCA have one of the worst prognosis (**85-90% mortality**), however the **underlying cause** of cardiac arrest is likely to be **reversible**.
- Adult patients (18-75 years old) with VF and VT who are transferred by emergency medical services (EMS) will receive one of the **2 standards of care practiced**.

The ARREST Trial - Treatments and Primary Objective

- Phase II, single center, partially blinded, intention to treat, safety and efficacy clinical trial to compare the results of
  - Extracorporeal membrane oxygenation facilitated resuscitation **(ECMO) (Treatment** 1**)** (Same intervention as in [Bartlett 1985]).
  - Standard advanced cardiac life support resuscitation **(ACLS) (Treatment** 0**)**.
- The primary objective: **Survival to hospital discharge**.
- The primary endpoint is a **binary endpoint**.

The ARREST Trial - Hypotheses

- The **primary study hypotheses** are

$$H_0 : p_1 = p_0 \text{ vs } H_A : p_1 \neq p_0.$$

  - p_1 the **probability** of a **positive response** in the target population under ECMO.
  - p_0 the **probability** of a **positive response** in the target population under ACLS.

- We are **interested in**
$P(p_1 > p_0 | \mathbf{A}^{(i)}, Y^{(i)}) = 1 - P(p_1 < p_0 | \mathbf{A}^{(i)}, Y^{(i)})$.

The ARREST Trial - Priors and Posteriors

- $Beta(1,1)$ **prior distributions** for p_1 and p_0.
- $Beta(x_1+1, n_1-x_1+1)$ **posterior distribution** for p_1.
- $Beta(x_0+1, n_0-x_0+1)$ **posterior distribution** for p_0.
  - n_1, n_0 denotes the number of participants assigned to treatment 1 and 0.
  - x_1, x_0 denotes the number of positive responses observed in treatment 1 and 0.
- We then calculate

$$P(p_1 > p_0 | \mathbf{A}^{(i)}, Y^{(i)})$$

The ARREST Trial - Early Stopping

- Interim analyses are **conducted after every 30 patients**.
- The trial will stop for **efficacy** if:

$$P(p_1 > p_0 | \mathbf{A}^{(i)}, Y^{(i)}) \geq \xi.$$

  - ξ is the level needed to reject the **null hypothesis**.

- The trial will stop for **inferiority** if:

$$P(p_1 < p_0 | \mathbf{A}^{(i)}, Y^{(i)}) \geq \xi.$$

The ARREST Trial - Bayesian Response Adaptive Randomisation

- The initial **burn-in is size 30** with equal allocation.
- If the trial does not stop, a form of **Thompson sampling** (or BRAR) is used with the next group randomized to ECMO with probability $P(p_1 > p_0 | \mathbf{A}^{(i)}, Y^{(i)})$.
- An additional restriction is the **randomization probability may not exceed 75%** in either direction.

The ARREST Trial - Type I Error and Power

- **Type 1 error** rate of 5% two sided.
- There is an **interim after 30 patients**, so $\xi = 0.986$ if there are up to **5 analyses** for Type 1 error rate of 5%.
- Aim was **power** of 90%, assuming success rates of 12% vs. 37% in the 2 groups.
- The **expected required sample size** is N = 148.
- Inflated to N = 174 for **15% expected drop out**.
- Only the **first 150 patients** are evaluated.

The ARREST Trial - Operating Characteristics

Scenario	Prob reject null	$E(N)$	$E(N_1)$	$E(N_0)$
Null	0.048	148.5	74.2	74.3
Alternative	0.905	81.6	52.5	29.2

Table: Simulated operating characteristics of the adaptive trial design as given in [Yannopoulos 2020a].

- $E(N)$ expected total sample size.
- $E(N_1)$ expected sample size for ECMO.
- $E(N_0)$ expected sample size for ACLS.

Discussion

- What is the effect of the average time to observe the outcome in a RAR design?
- What do you think about the restriction for the randomization probability?
- What would the effect of having more interims be?
- What could be the advantage and disadvantages to also using lack of benefit boundaries?

Additional questions

- What is the effect of using a RAR design on blinding in the Arrest trial?
- What is the effect of different lengths of time between outcome measures for each patient in a RAR design?
- What could the effect of time trends be?
- What approaches can be used to do the randomisation?

References for the ARREST Trial

Yannopoulos, D and others (2020)

Advanced REperfusion STrategies for Refractory Cardiac Arrest (The ARREST Trial) Protocol version 1.4 (2020a)

Yannopoulos, D and others (2020b)

Rationale and methods of the Advanced R2Eperfusion STrategies for refractory cardiac arrest (ARREST) trial.

American Heart Journal. 229 29–39.

Yannopoulos, D and others (2020c)

Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial.

The lancet. 396 1807–1816.

Bartlett, R and others (1985)

Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study.

Pediatrics Journal. 76(4) 479–487.

Lecture plan - Part 2

- Ketamine for late-life treatment-resistant depression (LL-TRD) trial.
  - The Condition and Motivation.
  - Treatments and Primary Objective.
  - Multiple Arm Allocation.
  - Response Adaptive Randomisation.
  - Early Stopping.
  - Type I Error and Power.
  - Operating Characteristics.
- Discussion based around Ketamine in LL-TRD trial.

Ketamine in LL-TRD trial - The Condition and Motivation

- Late-life depression (LLD) is a common, disabling condition that affects up to **20% of older veterans**.
- LLD is associated with a variety of medical comorbidities and negative health outcomes including **functional impairment and mortality**.
- Up to **one-third** of older adults show **resistance** to available first-line treatments due to a more complex clinical picture and a **greater risk of side effects** associated with increased age.

Ketamine in LL-TRD trial - Treatments and Primary Objective

- Early Phase, double-blind, placebo-controlled, response adaptive randomization trial to examine the efficacy, safety and tolerability of:
  - **Three different doses** of intravenous ketamine (0.1, 0.25 or 0.5 mg/kg).
  - Active placebo **midazolam** (0.03 mg/kg).
- The primary objective: $\geq$ 50% **decrease** from the baseline Montgomery-Asberg Depression Rating Scale (MADRS) score, 7 days post-infusion.
- The primary endpoint is **dichotomous** so is a **binary endpoint**.

Ketamine in LL-TRD trial - Multiple Arm Allocation

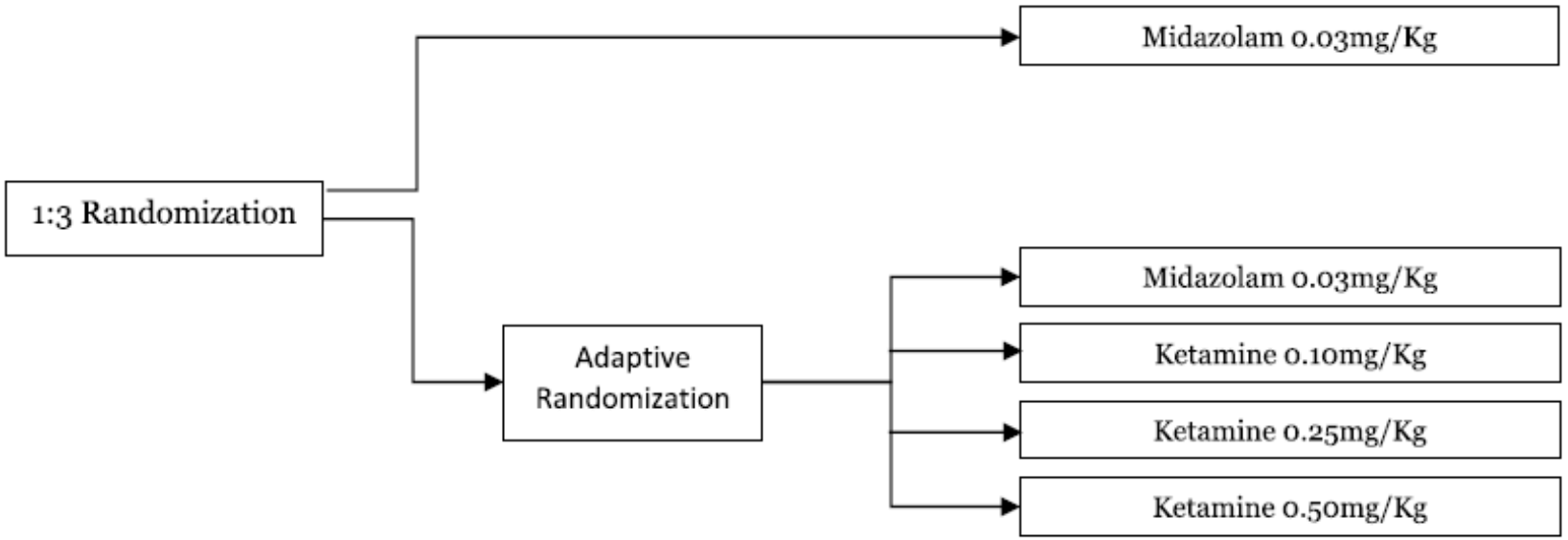

Figure: Schematic of Ketamine in LL-TRD randomization design from [O'Brien 2019].

Ketamine in LL-TRD trial - Bayesian Response Adaptive Randomisation

- The initial cohort are randomized with equal probability within the RAR group for a **burn-in** of the **first 20 patients** (so 25 patients in total) out of a **maximum of 66 participants**.
- Then the RAR is based on the probability that each arm is the best arm using a form of **Thompson sampling** (or BRAR).
- This is calculated **after every patient** response.
- Using beta posterior distributions with the following **priors** per arm based on **extant data and clinical experience**:
  - $Beta(1.797, 17.743)$ for midazolam **(mean effect 0.09)**.
  - $Beta(10.849, 46.329)$ for ketamine 0.10 mg/kg **(mean effect 0.20)**.
  - $Beta(12.607, 24.268)$ for ketamine 0.25 mg/kg **(mean effect 0.30)**.
  - $Beta(11.260, 11.260)$ for ketamine 0.50 mg/kg **(mean effect 0.50)**.

Ketamine in LL-TRD trial - Early Stopping

- The trial stops for **superiority** if the best performing treatment has the **posterior probability** of > 0.975, that it is better than the next best treatment.
- A treatment stops for **inferiority** if < 0.025 posterior probability is that it is better than the best performing treatment.
- A treatment stops for **lack of benefit** if there $< 10\%$ chance of a positive response at day 7 has a posterior probability > 0.95.
- **After allocation of all participants** a treatment will be declared superior, if the posterior probability that its response rate exceeds that of the next best performing treatment is > 0.75.

Ketamine in LL-TRD trial - Type I error and Power

- **Type I error rate:** Setting the **probability of response to 0.09** for all treatments simulations indicated that the trial would identify a treatment as **best 3.96% of the time**.
- **Power:** Assuming the effects and previously specified prior distributions simulations indicated that the trial would **identify the best treatment 95%** of the time.

Ketamine in LL-TRD trial - Operating Characteristics

Scenario	$n_{\max}$	$E(N)$	$E(N_0)$	$E(N_1)$	$E(N_2)$	$E(N_3)$
Null	49	48.89	5.07	5.42	13.8	24.6
Alternative	49	42	5	5	8	24

Table: Simulated operating characteristics of the adaptive trial design as given in [O'Brien 2019]

- $n_{\max}$ and $E(N)$ are the maximum and expected total sample size of the trial's adaptive component.
- $E(N_k)$ expected sample size for treatment k of adaptive component with $k = 0$ for midazolam, ..., $k = 3$ for ketamine 0.5mg/kg.

Discussion

- Why do you think they used the “randomization ratio split” approach discussed on slide 16?
- What are the advantages and disadvantages to using informative priors?
- How much gains do we think comes from the RAR and how much from the prior?
- What do you think of their definitions of the type I error rate and power of the trial?

Additional questions

- How could the design allow for the addition of more arms and what complications might this bring?
- Should we stop arms based on their relationship to the control or their relationship to all the treatments and how might this differ in a non-dose finding setting?
- Should we be considering sharing information across doses?

References for Ketamine in LL-TRD trial

O'Brien, B and others (2019)

Rationale and methods of the Advanced R2Eperfusion STrategies for refractory cardiac arrest (ARREST) trial.

Contemporary Clinical Trials Communications. 16.

Lijffijt, M and others (2022)

Identification of an optimal dose of intravenous ketamine for late-life treatment-resistant depression: a Bayesian adaptive randomization trial

Neuropsychopharmacology. 47 1088–1095.

Any Questions

Any questions on Lecture 4?

Thank you for coming

Any final questions on anything we have covered today and please let us know!

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Any final questions on anything we have covered today and please let us know!

We welcome your feedback and thoughts, so please complete the feedback form if you can to help us improve this course.

Appendix 1: The ARREST Trial - Allocation Method

Modified permuted block design

- Block size (b=10) and $P(p_E < p_C|data) = 0.5$,
  - 100% of 5:5 allocation.
- Block size (b=10) and $P(p_E < p_C|data) = 0.65$,
  - 50% of 6:4 allocation.
  - 50% of 7:3 allocation.
- Block size (b=10) and $P(p_E < p_C|data) = 0.62$,
  - 80% of 6:4 allocation.
  - 20% of 7:3 allocation.