Adaptive Methods in Clinical Research

Practical 4: Response-Adaptive Designs

In this practical we consider the re-design of the CALISTO trial (Decousus et al., 2010), a randomised study comparing a new drug (Arixtra) for treating patients with acute symptomatic thrombophlebitis of the lower limbs against Placebo. The primary efficacy outcome was a composite of events at day 47: death from any cause, symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis. A treatment success in this case is the absence of all of these events at day 47. Observed success probabilities were $p_0 = 0.941$ in placebo arm and $p_1 = 0.991$ in the Arixtra arm.
A well designed response adaptive design could be beneficial for trials like these because of their potential to increase the number of successes on average (given the nature of what a *failure* entails). Ideally, we would like to achieve this while preserving (or even increasing) power of treatment comparison. There are additional reasons to consider the use of a response-adaptive design in this kind of settings. (Tehranisa and Meurer, 2014).
Using the estimated success rates as if they were the underlying expected rates of the future trial, we will compare here the following response-adaptive designs:

(1) Randomised play the winner (as described in the lecture slides).

Using the results given in the slides, check that the limiting allocation proportions for this parameter values would be: $R_1^* = 0.8676$

(2) Play the winner rule: (or the non-randomised procedure version of the randomised play the winner rule). The first patient[1] is allocated to an arm randomly. If the outcome of that patient is a success the next patient will be allocated to the same arm. If it is a failure the next patient will be allocated to the other arm. $R_1^* = 0.8676$

(3) Optimal proportions (see appendix below for an explanation)

(3.1) Optimal proportion 1: Neyman proportion. minimise sample size for a given power level (for test in absolute difference in incidence of events)

$$R_1^* \to \frac{\sqrt{p_1(1-p_1)}}{\sqrt{p_0(1-p_0)} + \sqrt{p_1(1-p_1)}} = 0.2861 \tag{1}$$

(3.2) Optimal proportion 2: Minimise expected failures given minimum power (for test in absolute difference in incidence of events)

$$R_1^* \to \frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}} = 0.5065 \tag{2}$$

[1] Or patients if the *burn-in* is bigger than 1.

(3.3) Optimal proportion 3: Maximise the expected mean response given minimum power (for test in difference of means)

$$R_1^* \to \frac{\sqrt{1-p_0}}{\sqrt{1-p_0}+\sqrt{1-p_1}} = 0.7191 \tag{3}$$

(4) Bayesian response-adaptive RAR design with no tuning as in the Slides. Compute the limiting allocation by simulation.

You are asked for advice on which of the above designs should be considered for trial design in a very similar setting.[2] Assume the maximum trial size $n_{\max}$ was chosen to achieve 80% power in a design using equal randomisation. To implement and compare the aforementioned options we need to decide the size of the initial phase of the trial where allocation probabilities are fixed before adapting based on data accumulation. This initial phase is called a *burn-in* period. Please allocate a burn-in phase of 2, 40, 125 patients per arm using ER before starting with the RAR procedure. This leads to burn-in periods of 4, 80, 250 out of $n_{max} = 366$ patients.

Use the code provided to answer the questions below and compute relevant operating characteristics reported in Table 1.

1. Familiarise yourself with the provided Code. We left three methods for you to complete. (HINT: Look at play-the-winner rule to complete randomised-play-the-winner rule and the optimal proportion that minimises failures to complete the code for Neyman and maximising the mean response).

2. With the completed code you should be able to estimate in simulations the limiting mean allocation to the new arm (arm 1) for trial replicates (under the observed rates in the CALISTO trial). Compare the simulated value to the theoretical values provided before. Fill them into column 4 of Table 1. How do they compare to the theoretical values above?

3. Please fill the gaps for power and expected mean responses (EMR) in Table 1.

4. Engage in a discussion with others to determine the design you would recommend. If your design incorporates a burn-in period what is the optimal burn-in period to recommend?

5. Does your recommendation change if you consider the provided type-I error rates for $p_0 = p_1 = 0.941$ (no treatment difference) from Table 2?

Bonus Question: How would your conclusions change for a trial much larger?

[2]For example, Trials comparing therapies for acute myocardial infarction, these trials yield around 93%-95% non-failure rate and commonly use a 30-day mortality binary primary endpoint.

Table 1: Run 10,000 Simulations for each Scenario (1000 if it takes to long) and report the Power of the Z-test, which percentage of the patients gets assigned to the superior arm and what the expected mean response is. For the last two metrics we are also interested in their variance across simulations.

Procedure	Burn-in	$Power_Z$	% Arm1 (Var)	EMR (Var)
ER	-	80%	0.5 (0)	0.966 (0.0001)
PW	4			
RPW	4			
RPW	80			
RPW	250			
Neyman	4			
Neyman	80			
Neyman	250			
minF	4			
minF	80			
minF	250			
maxMR	4			
maxMR	80			
maxMR	250			
BRAR	4			
BRAR	80			
BRAR	250			

Table 2: Type-I error rates for $p_0 = p_1 = 0.941$ for $n = 366$ (10,000 Simulations for each Scenario).

Procedure	Burn-in	Type-I Error Z-test
ER	-	5%
PW	-	2.7%
RPW	4	4.9%
RPW	80	4.9%
RPW	250	5%
Neyman	4	81.3%
Neyman	80	20.6%
Neyman	250	5.9%
minF	4	5.1%
minF	80	5%
minF	250	5%
maxMR	4	3.6%
maxMR	80	4.3%
maxMR	250	4.4%
BRAR	4	53.5%
BRAR	80	3.6%
BRAR	250	3.2%

Appendix to Practical. Optimal proportions: derivation and implementation

- Wald Test: $Z = \frac{\hat{p}_0 - \hat{p}_1}{\sqrt{s^2_{\Delta\hat{p}}(n_0,n_1)}}$ $s^2_{\Delta\hat{p}}(n) = \frac{\hat{p}_0(1-\hat{p}_0)}{n_0} + \frac{\hat{p}_1(1-\hat{p}_1}{n_1}$.

  Fora two-armed setting maximising power = minimising $s_{\Delta\hat{p}}(n_0, n_1)$

  Optimal proportions are derived from an optimisation problem. Imagine we know p_0 and $-p_1$. Below an example:

Q What is **the minimum sample size** $n = n_A + n_B$ given a power constraint (or a fixed variance level)? Note, that this question is equivalent to the question: What is the **maximal power** given a fixed sample size?

$\min_R n_0 + n_1 \quad$ s. t. $\sigma^2_{\Delta\hat{p}}(n_0, n_1) = C$

Solution (a.k.a., Neyman allocation):

$$R^*(p_0, p_1) = \frac{\sqrt{p_0(1-p_1)}}{\sqrt{p_0(1-p_0)} + \sqrt{p_1(1-p_1)}} \tag{4}$$

- Assigning patients by letting: $R^*(\hat{p}_0, \hat{p}_1)$ and $\hat{p}_0, \hat{p}_1$ be MLEs of p_0, p_1 (e.g. if $\hat{p_0} = 0.3$, $\hat{p_1} = 0.5$ $R = 0.478$, $1 - R = 0.522$). Similarly, for the other proportions in the practical you would change the objective function to:

Q How to minimise failures given a power constraint (or a fixed variance level)?

$\min_R n_0 q_0 + n_1 q_1 \quad$ s. t. $\sigma^2_{\Delta\hat{p}}(n_0, n_1) = C$

Solution (minF):

$$R^*(p_0, p_1) = \frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}} \tag{5}$$

Q How to maximise the expected mean response given a power constraint (or a fixed variance level)?

$\max_R n_0 p_0 + n_1 p_1 \quad$ s. t. $\sigma^2_{\Delta\hat{p}}(n_0, n_1) = C$

Solution (maxMR):

$$R^*(p_0, p_1) = \frac{\sqrt{1-p_0}}{\sqrt{1-p_0} + \sqrt{1-p_1}} \tag{6}$$

If you have further questions, you can ask the RAR experts present in the room. Just ask!

Because optimal allocation depends on the unknown parameters p_0, p_1, we cannot implement these in practice without estimating these parameters sequentially. In the R-code provided the optimal proportion designs have been implemented using the sequential maximum likelihood procedure (SMLE). If you want to read more on this please see Rosenberger and Lachin (2016).

References

H. Decousus, P. Prandoni, P. Mismetti, R. M. Bauersachs, Z. Boda, B. Brenner, S. Laporte, L. Matyas, S. Middeldorp, G. Sokurenko, and others. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *New England Journal of Medicine*, 363(13):1222–1232, 2010.

W. F. Rosenberger and J. M. Lachin. *Randomization in Clinical Trials*. John Wiley & Sons, Inc, Hoboken, NJ, USA, 1 2016. ISBN 9781118742112. doi: 10.1002/9781118742112.

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