Response-Adaptive Randomisation

Practical 2: Implementing and Targeting Optimal Allocation Proportions

In this practical we continue to 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. Recall, that we observed success probabilities were $p_0 = 0.941$ in placebo arm and $p_1 = 0.991$ in the Arixtra arm.

As said before, 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.

We now want to take a closer look at the optimal allocation proportions introduced in Lecture 2. Compute the limiting values for each of the proportions below taking the observed values on the CALISTO trial as the ground truth.

(1) Neyman proportion maximizes power given a fixed sample size.

$$\rho_N \to \frac{\sqrt{p_1(1-p_1)}}{\sqrt{p_0(1-p_0)} + \sqrt{p_1(1-p_1)}} =? \tag{1}$$

(2) Optimal proportion ρ_{minF} minimises expected failures given minimum power.

$$\rho_{minF} \to \frac{\sqrt{p_1}}{\sqrt{p_0} + \sqrt{p_1}} =? \tag{2}$$

(3) Optimal proportion ρ_{AD}

$$\rho_{AD} \to \frac{p_1}{p_0 + p_1} =? \tag{3}$$

Compare these theoretical values to the simulated limiting proportion from Table 1 from practical 1. What differences are most interesting to you?

Because optimal allocation depends on the unknown parameters p_0, p_1, we cannot implement these in practice without estimating these parameters sequentially in a suitable way. In Lecture 3 we described the following methods

1. sequential maximum likelihood procedure (SMLE),
2. doubly adaptive biased coin design (DBCD),
3. efficient randomized-adaptive design (ERADE),

to target the estimated proportions. We now continue our investigation started in practical one. We want to compare the different optimal proportions and targeting methods to ER.

Exercise 1: Use the R shiny app compute relevant operating characteristics reported in Table 1. Choose SMLE as targeting method. Discuss the results with your neighbours. How do the theoretical proportions differ from the ones in Table 1?

Procedure	type-I error	$Power_Z$	% Arm1 (Var)	EMR (Var)
ER	5%	80%	0.5 (0)	0.966 (0.0001)
Neyman				
minF				
AD				

Table 1: Run 10,000 Simulations for each Scenario (1000 if it takes to long) and report type-I error ($p_0 = p_1 = 0.941$) and 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.

Exercise 2: Try SMLE and DBCD as targeting methods. Which one do you think performs best and why? Take some notes to report back to all at the end of the practical.

Exercise 3: You have now been told the the clinicians are interested in the log relative risk rather than the simple mean difference. Calculate the theoretical proportions (see lecture slides) and rerun the simulation with $n = 420$. Which design would you recommend now? Has the change of measure of interest affected your preferences? Take some notes to report back to all at the end of the practical.

Procedure	type-I error	$Power_Z$	% Arm1 (Var)	EMR (Var)
ER	5%	80%	0.5 (0)	0.966 (0.0001)
Neyman				
minF				

Table 2: Same analysis but for the log relative risk.

Exercise 4: Now try different burn-in periods for the designs you are considering. Try smaller and larger burn-in periods. Minimum burn-in is 2 patients per arm and maximum is $n/2$ patients per arm. What burn-in period would you recommend and why? Take some notes to report back.

Exercise 5: Consider different sample sizes. Which RAR design (procedure, sample size, burn-in period) would you recommend a clinician considering all designs and metrics discussed in the previous and current practical. Take some notes to report back.

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

Space for your own notes!

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.