Optimising the sample allocation across a multi-stage adaptive randomized clinical trial

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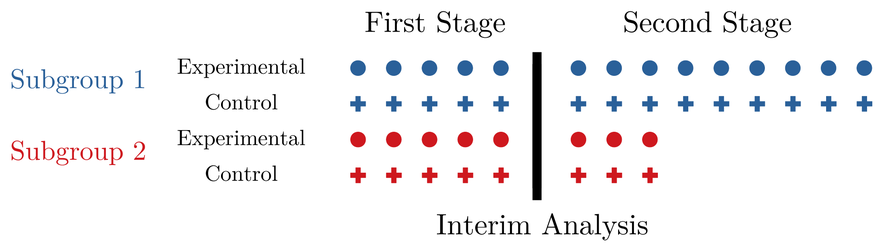
1. Objective

RCT with total fixed sample size to test efficacy in two disjoint sub-populations. Perform interim analyses to adapt:

- the sizes of the subgroups in the second stage
- the weights for the testing procedure.



2. Introduction

We design two-stage adaptive confirmatory clinical trials that make use of a Bayesian decision theoretic framework and a utility function which takes into account the prevalence of the subpopulations. Given the pre-specified utility function, our proposal allows altering the sample allocation and hypothesis testing weights at the interim analysis of the trial, ensuring efficient use of available resources to maximise the expected utility. This includes Adaptive Enrichment and single-stage designs as special cases. For each subgroup, we test the null hypotheses of no treatment effect and guarantee strong control of the Familywise Error Rate using the conditional error rate approach.

3. Methods

Adaptive closed test: Let θ_i be the treatment effect in subgroup i, we shall investigate $H_i : \theta_i \leq 0$ with statistic Z_i, $i = 1, 2$. To ensure strong control of the FWER at α we require level α tests of $H_1 : \theta_1 \leq 0$, $H_2 : \theta_2 \leq 0$ and $H_1 \cap H_2 : \{\theta_1 \leq 0\} \wedge \{\theta_2 \leq 0\}$.
We use the conditional error rate approach for a weighted Bonferroni test with weights ω_1 and ω_2, where at interim we use first stage Z-values, $z_i^{(1)}$, to calculate

$$A_i = \mathbb{P}_{H_i}\left(Z_i > \Phi^{-1}(1-\alpha) | z_i^{(1)}\right), \text{ and}$$

$$A_{12} = \mathbb{P}_{H_1 \cap H_2}\left(Z_1 > \Phi^{-1}\left(1-\alpha\omega_1^{(1)}\right) \text{ or } Z_2 > \Phi^{-1}\left(1-\alpha\omega_2^{(1)}\right) | z_1^{(1)}, z_2^{(1)}\right).$$

Using second stage Z-values, $z_i^{(2)}$, we reject an elementary null hypothesis H_i if both

- $z_i^{(2)} > \Phi^{-1}(1-A_i)$;
- $z_1^{(2)} > \Phi^{-1}\left(1-\omega_1^{(2)} A_{12}\right)$ or $z_2^{(2)} > \Phi^{-1}\left(1-\omega_2^{(2)} A_{12}\right)$

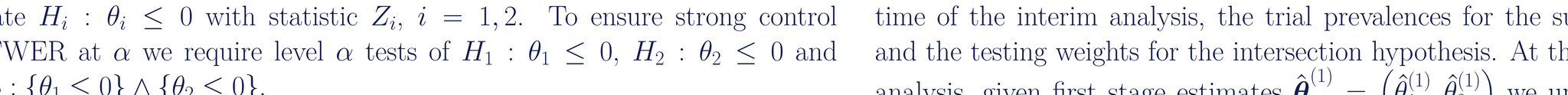
Bayesian optimization: For the first stage we may optimise the time of the interim analysis, the trial prevalences for the subgroups, and the testing weights for the intersection hypothesis. At the interim analysis, given first stage estimates $\hat{\boldsymbol{\theta}}^{(1)} = \left(\hat{\theta}_1^{(1)}, \hat{\theta}_2^{(1)}\right)$ we update the second stage parameters (subgroup prevalences and testing weights).
We define a prior distribution $\pi(\boldsymbol{\theta})$ for $\boldsymbol{\theta} = (\theta_1, \theta_2)$. Given $\boldsymbol{\theta}$ and the data observed during the trial, X say, we define a utility function, $\mathcal{U}(\boldsymbol{\theta}, X)$, giving a single measure of trial performance from possible trial outcomes. Our aim is to maximise the Bayes expected utility

$$\mathbb{E}_{\pi(\boldsymbol{\theta})}(\mathcal{U}(\boldsymbol{\theta}, X)).$$

For this work we use $\mathcal{U}(\boldsymbol{\theta}, X) = \lambda \mathbb{I}(\text{Reject } H_1) + (1-\lambda)\mathbb{I}(\text{Reject } H_2)$, where λ is the true prevalence for subgroup 1.

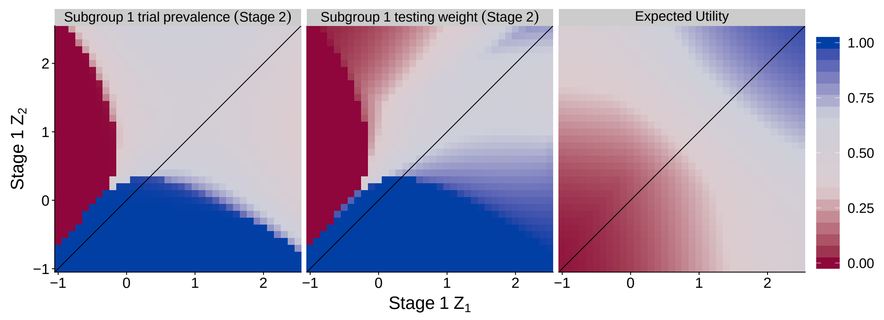
4. Optimized design parameters and adaptation rules

Optimizing second stage parameters



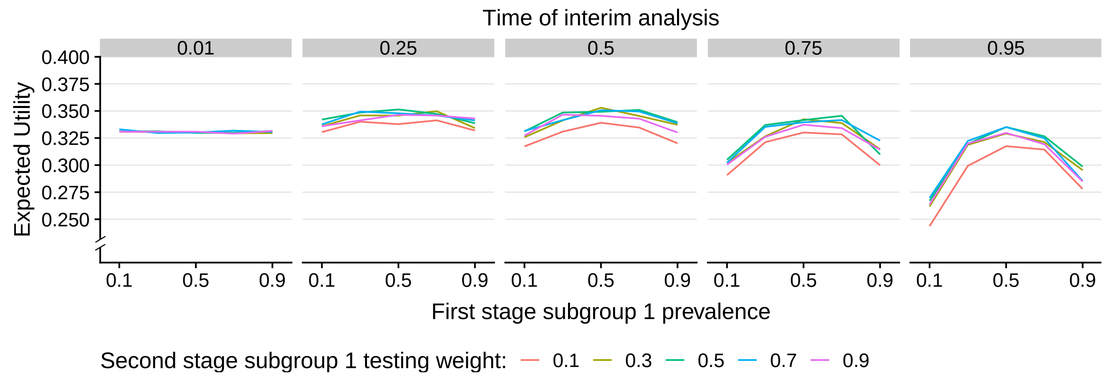
Operating characteristics for trials with equal first stage prevalence and weights (0.5). We assume a Normal prior distribution with means 0.1 and 0, variances of 0.1 and correlation 0.5. The total sample size is 700, subgroup 1 true prevalence $\lambda = 0.5$ and true effect in subgroup 1 $\theta_1 = 0.3$. Line colours correspond to varying true effects θ_2 in subgroup 2

Optimal adaptation rule at interim analysis



Example of decision at interim analysis when the it is performed with 30% of the subjects. For each combination of first stage Z-values we calculate the subgroup prevalences and testing weights that lead to the maximum expected utility.

Optimizing first stage parameters



Example of optimisation of first stage parameters. We calculate the expected utility for each combination of first stage prevalences, testing weights, and time for interim analysis assuming a Normal prior distribution with means 0.1 and 0, variances of 0.1 and a correlation of 0.5.

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