

## Seamless: a Seamless Adaptive Phase II/III Trial

**Goal:** To design a seamless phase II/III trial with one interim look for dose selection or futility stop after an initial dose-ranging study part.

**Background:** Seamless phase II/III trials are cost-effective solutions to combine phase II dose ranging and phase III confirmatory assessments in a single trial. Here, we consider a 3-dose trial versus placebo in pain indication. One interim analysis is planned after 20 patients have been enrolled per arm. Futility may be concluded if the maximum mean response under treatment is not superior to the placebo mean with some insurance to be determined. If the study is not stopped, then a second study part (phase III) is initiated. One dose level is kept in part 2, versus placebo. It is the minimum dose having the largest mean response among the 3 dose levels of Part 1. Sample size for Part 2 is also 20/arm. At the interim and final look, the superior efficacy of any dose level is tested against placebo.

We run a simulation study in order to assess the operational characteristics of the proposed design and to define the futility and efficacy thresholds that are suitable to maintain type I error rate to 5%. The power is also assessed.

**Bayesian Model:** Pain response is analysed with a one-way ANOVA using constant error.

Vague priors are chosen for the 4 mean:  $\mu_0$  (pbo),  $\mu_1$  (dose 1),  $\mu_2$  (dose 2),  $\mu_3$  (dose 3) and inverse variance  $\tau$ :

$$\mu_i \sim \text{Normal}(0, 1E9), \text{ and } \tau \sim \text{Gamma}(0.001, 0.001)$$

where  $\text{Normal}(\mu, \sigma^2)$  is the Normal distribution with mean  $\mu$  and variance  $\sigma^2$ ,  $\text{Gamma}(a, b)$  is the gamma distribution and  $\tau = 1/\sigma^2$  is the inverse variance.

**Adaptive design:** The first cohort counts 80 patients, equally randomized to Pbo, doses 1, 2 and 3. If the study is pursued after the interim analysis, the second cohort has  $N=40$  patients, among which 20 receive a placebo and 20 receive the target dose.

The target dose is defined (using the CRM/best allocation in Decimaker) as the dose having the largest probability to be minimum dose with the maximum response mean among all treatment arms.

**Decision:** The study may be stopped for futility when the posterior distribution  $\Pr[\text{Futility}] = \Pr[\max(\mu_1, \mu_2, \mu_3) \leq \mu_0]$

exceeds a futility margin  $\theta$ .

Any dose level  $i$  will be declared superior to placebo when the posterior distribution

$$\Pr[\mu_i > \mu_0] > \delta.$$

**Simulation:** The values of  $\theta$  and  $\delta$  will be determined using simulations in order to control type I & type II error rates.

We first simulate under  $H_0$ , when all means are equal to 5 and residual std=10.  
We also report simulations for one alternative hypothesis of interest, being:

Dose	Mean
0	5
1	5
2	15
3	10

Dose 1 is equal to placebo, dose 2 and 3 are superior and dose 2 has the larger mean.

**Results:** Five thousand studies were simulated in the 2 scenarios. Results from the simulations are presented below.

Under  $H_0$ , the type I error rate for the pairwise comparisons to placebo is preserved around 5% when  $\delta$  equals 95% at the interim and final analyses.

Choosing a value of  $\theta=0.45$  will insure with 80% power that the study will be stop for futility at the interim under  $H_0$ .

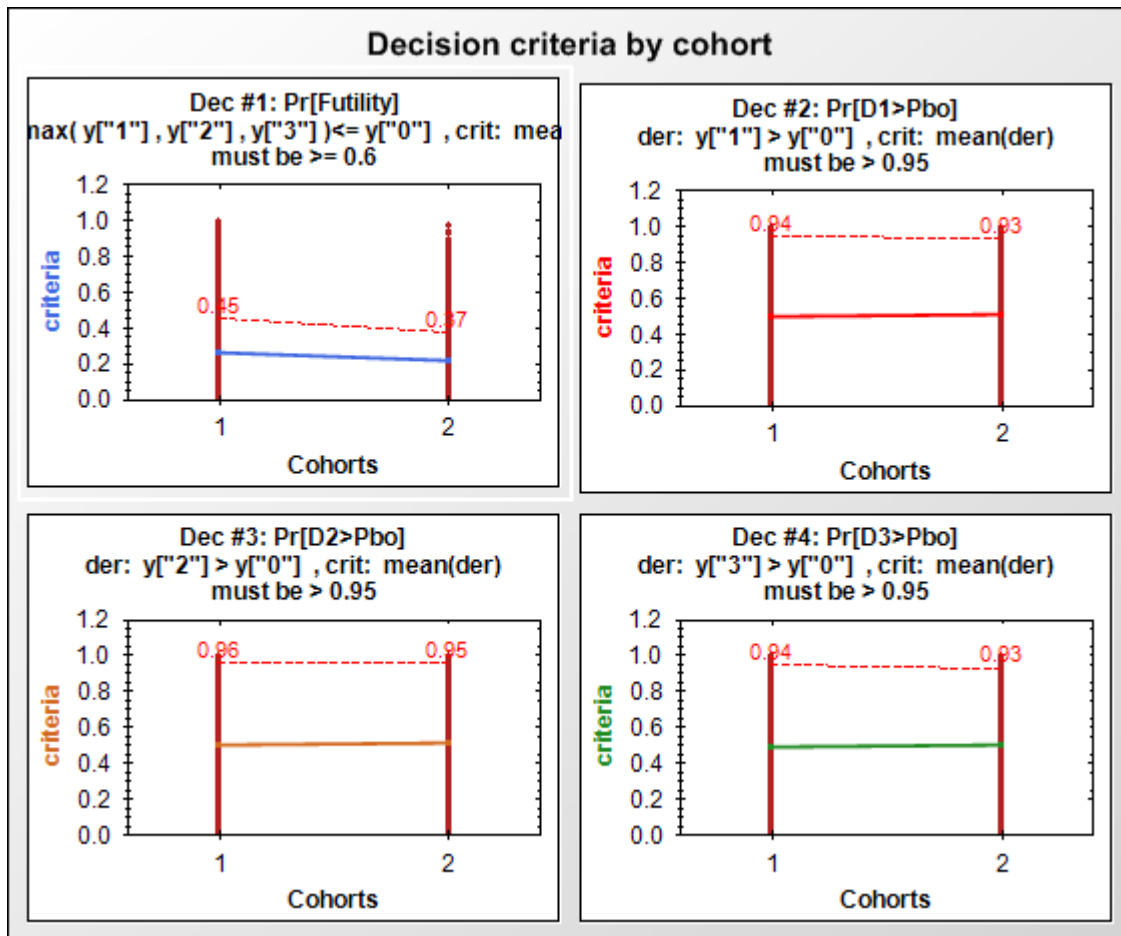


Figure 1. Simulated posterior probabilities of futility and dose effects under H0. Means are displayed as colour lines. Red dotted lines join the 80% percentile of Pr[Futility] and the 95% percentiles of the Pr[D<sub>i</sub>>Pbo].

Under the H<sub>a</sub> scenario, there is minimal risk of futility stop. The type I error rate for D1 is also controlled below 5%. The study has high power (92%) to declare superiority of D2 at the interim and 99% at study end.

Power Table	Cohort1	Cohort2
Pr[Futility]	0.001	0.000
Pr[D1>Pbo]	0.035	0.040
Pr[D2>Pbo]	0.922	0.990
Pr[D3>Pbo]	0.457	0.564

In most cases where the study was pursued after the interim, D2 was rightly selected as the phase III dose level.

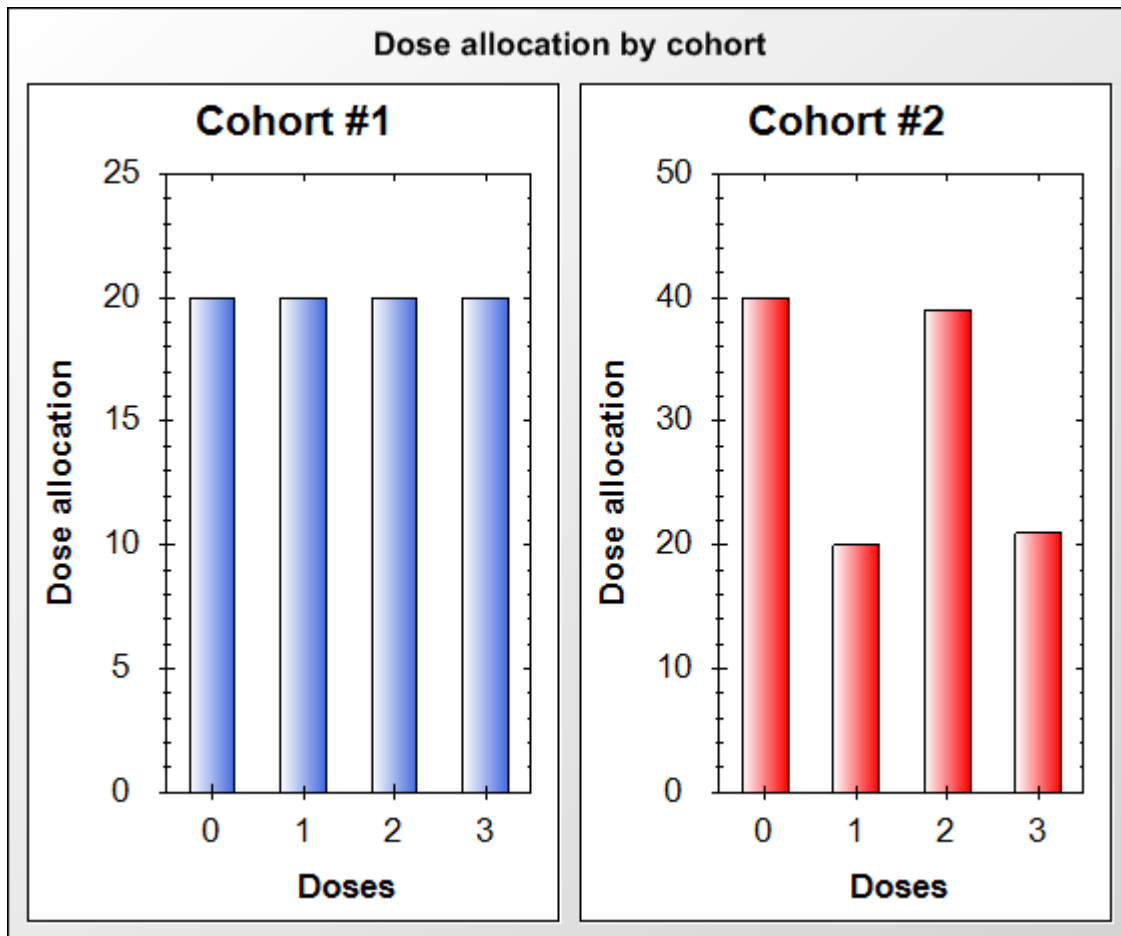


Figure 2. Dose allocation before and after the interim analysis.

**Decimaker:** The corresponding Decimaker study project for  $H_0$  may be found [here](#) and for  $H_a$  [here](#).

### References:

- Inoue LYT, Thall PF, Berry D. Seamlessly expanding a randomized Phase II trial to Phase III. *Biometrics*. 2002; 58: 823-831.
- Frank Bretz, Heinz Schmidli, Franz König, Amy Racine, Willi Maurer. Confirmatory Seamless Phase II/III Clinical Trials with Hypotheses Selection at Interim: General Concepts *Biometrical Journal* 2006; 48: 623 – 634.