

Pain: an Adaptive Dose Selection Phase II Trial

Goal: To apply Bayesian modeling and adaptive dose selection in order to identify the minimum efficacious dose.

Background: This is a pain trial adapted from Patel et al (2006). It involves 120 patients, in cohorts of size 12. Each cohort has 4 placebos and 8 active. The pain response is analysed after each cohort with a 4-parameter logistic regression model for normal data. The dose allocation to the next cohort is adapted in order to estimate precisely a minimum efficacious dose (MED).

Bayesian Model: Response was assumed to be normally distributed with constant error. Mean RO was modeled as a function of the drug dose using a 4-parameter logistic model (4PL):

$$\text{Mean} = B + (T - B) / (1 + \exp(-\text{int} - \text{slope} * \text{dose})),$$

where B is the lower asymptotic response, T is the maximum change, int is a function of the placebo response and slope is the response change with dose on a logit scale.

Priors were weakly informative in order to insure convergence of the MCMC estimator:

$$B, \text{int}, \text{slope} \sim \text{Normal}(0, 1000), T \sim \text{Normal}(1, 1000), \\ \text{and } \tau \sim \text{Gamma}(0.001, 0.001)$$

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

Adaptive design: Eight dose levels: 0, 1, 2, 3, 4, 5, 6, and 7 were available. Each cohort included 12 subjects: two placebos, and 8 actives. There was at least one patient receiving the top dose (7mg) in each cohort. In the first cohort, 2 subjects were assigned to the highest dose of 7mg, and one to each of the remaining dose levels. Treatment allocation in the next cohort was decided adaptively for the 7 patients who were flexibly randomized. To do so, the 4PL model was fitted and the probability that each dose level is the MED was calculated. The MED is defined as the minimum dose at which response exceeds 75% of the maximum response:

$$\text{Mean} \geq B + (T - B) * 0.75.$$

The ED75% is thus :

$$\text{ED75} = [-\text{int} - \logit(0.75)] / \text{slope}.$$

Patients were then allocated to doses proportionally to $\text{PR}[\text{dose} = \text{MED}]$, using the CRM/cum70pc allocation method in Decimaker.

Decision: Study was not terminated early and no decision was taken. To assess the performance of the adaptive design, the following statistics were calculated:

- Accuracy in ED75 estimation: $\Pr[5 < ED75 < 7]$.
- Variance of ED75 estimate: $CV(ED75) < 20\%$
- Significant dose response: $\Pr[\text{slope} > 0] > 95\%$.

Simulation: The performance of the adaptive allocator in identifying the ED75 was evaluated based on simulations in which the dose response was as follows:

Dose	Mean	Std
0	5.001	9
1	5.005	9
2	5.037	9
3	5.27	9
4	6.788	9
5	12.5	9
6	18.21	9
7	19.73	9

Results: One thousand studies were simulated. Results from the simulations are presented below.

As expected, more patients were allocated to the target doses of 5 and 6mg and fewer patients to the lower doses, where the dose-response profile was flat. At study end, a minimum of 11 patients were fixed at the 7mg dose by design. The actual mean number of patients at that dose was 17.86.

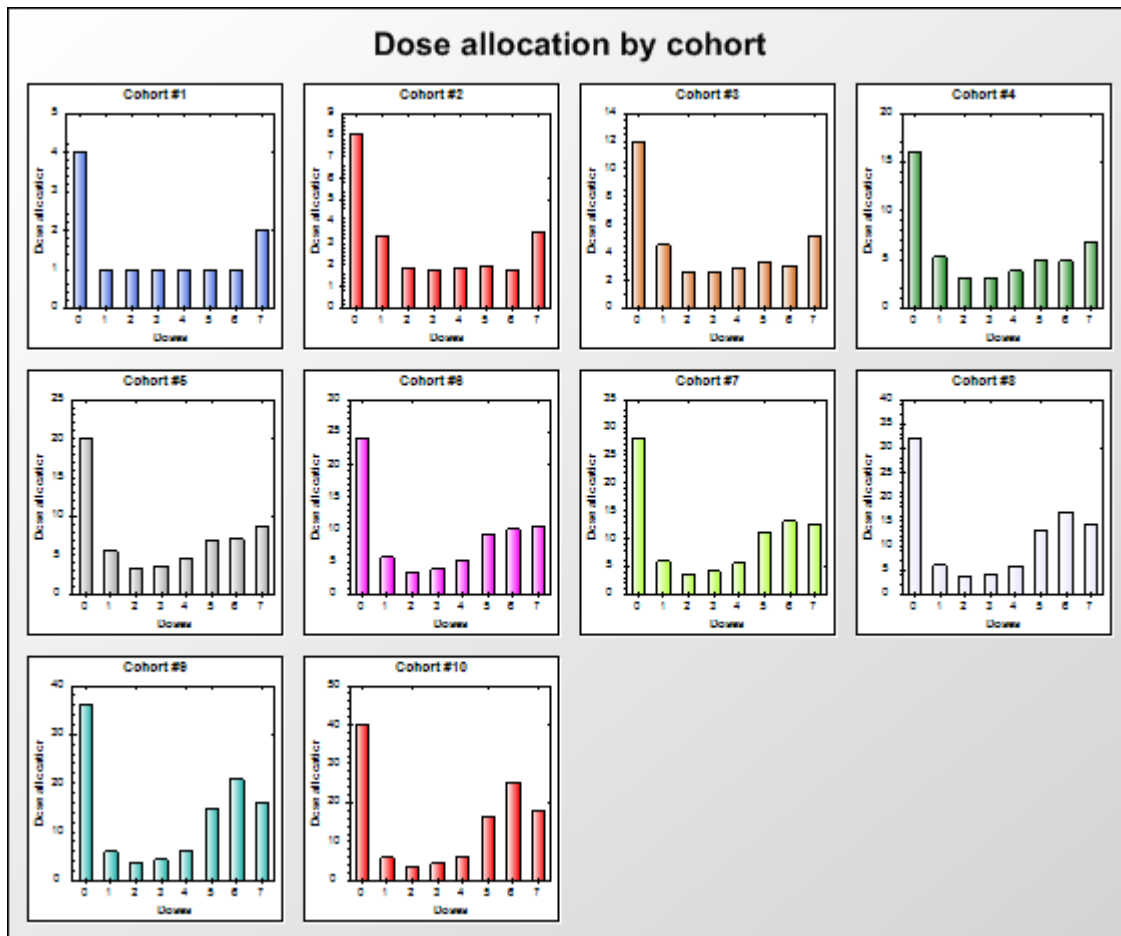


Figure 1. Mean dose allocation by cohort.

From cohort 6 (N=72), the study had 83% power to detect a significant dose-response relationship. Power increases to 99% at cohort 10 (N=120). At study end, there is a 80% chance that the ED75 will be accurately estimated within the 5-7mg dose range. There is 77% chances that CV(ED75) be below 20%.

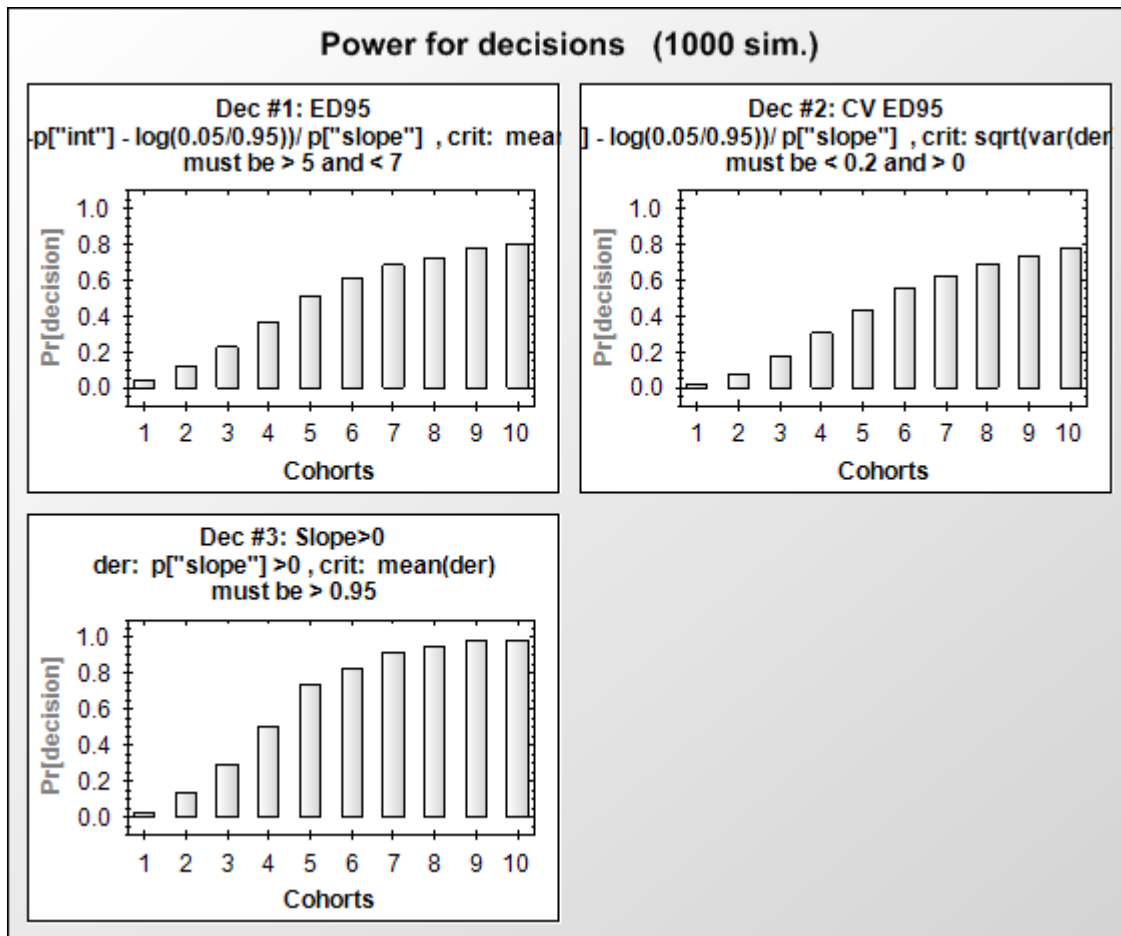


Figure 2. Power for accuracy of ED75 (ED75), precision of ED75 (CV(ED75)) and dose-response test (slope).

Decimaker: The corresponding Decimaker study project may be found [here](#). It includes the simulation results as presented above.

References:

- Nitin Patel, James Bolognese, Inna Perevozskaya. Bayesian Adaptive Designs for Phase 2a Proof-of-Concept Clinical Trials . A featured talk at CBI's "Adaptive Dose Finding Trials Conference" Feb 26, 2007 - Philadelphia, PA