

# Flat: Type I Error Rate Estimation in Bayesian Adaptive Dose Selection Trial

**Goal:** To assess Type I error rate for posterior probability decision in GADA adaptive dose selection trial.

**Background:** This is one case study coming from PhRMA adaptive design working group white paper. It includes 9 dose levels from 0 to 8 in a total of 144 patients. A flat dose-response was simulated to quantify type I error rate under the null hypothesis. The Bayesian adaptive dose allocation procedure (GADA) was implemented.

**Bayesian Model:** The response was assumed to be normally distributed with constant error. Dose-response relationship was fitted using a Normal Dynamic Linear Model (NDLM).

Priors were vague on the placebo response (intercept), initial slope (from 0 to 1mg) and residual error:

int  $\sim$ Normal(0,10E9), slope Normal(5,10E9), and tau $\sim$ Gamma(0.0001,0.0001).

Vague priors were also taken on the variance inflation factors for the intercept and slope:  
Wdelta  $\sim$ uniform(0.0001, 100), and Wtheta  $\sim$ uniform(0.0001, 100).

**Adaptive design:** Although the adaptive allocation method may be implemented after each subject (ie, by choosing a cohort size =1 in Decimaker), we have limited the number of interim dose adjustments to 3, using cohorts of size 36 each. The initial cohort counted 4 subjects per dose. The number of placebos in the next cohorts was fixed to 4, while the 32 remaining subjects were adaptively assigned across the 8 dose levels, using the Quantile Weighted Variance (QWV) allocator targeting the clinically relevant response of -1.3.

**Decision:** At the interim and final analyses, the following posterior probabilities were computed:

- Pr[DR]: Probability to detect a decreasing ordinal trend in dose-response:  
$$\Pr[ (4Y_0+3Y_1+2Y_2+Y_3+0Y_4-Y_5-2Y_6-3Y_7-4Y_8) > 0 ]$$
- Pr[Dose]: Probability to identify a clinically relevant dose where mean response  $\leq -1.3$ :  
$$\Pr[Y_1 \leq -1.3 \mid Y_2 \leq -1.3 \mid Y_3 \leq -1.3 \mid Y_4 \leq -1.3 \mid Y_5 \leq -1.3 \mid Y_6 \leq -1.3 \mid Y_7 \leq -1.3 \mid Y_8 \leq -1.3]$$

Whenever it exists, the minimum administered dose (0,...,8) where response was  $\leq -1.3$  (DTarget) was also estimated.

**Simulation:** A flat dose-response pattern with mean =0 and residual standard error equal to 2.25 was simulated to evaluate the type I error rate of the Pr[DR] test.

The distribution of Pr[Dose] and DTarget responses was also quantified.

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

The mean dose-response profile remains flat, as expected.

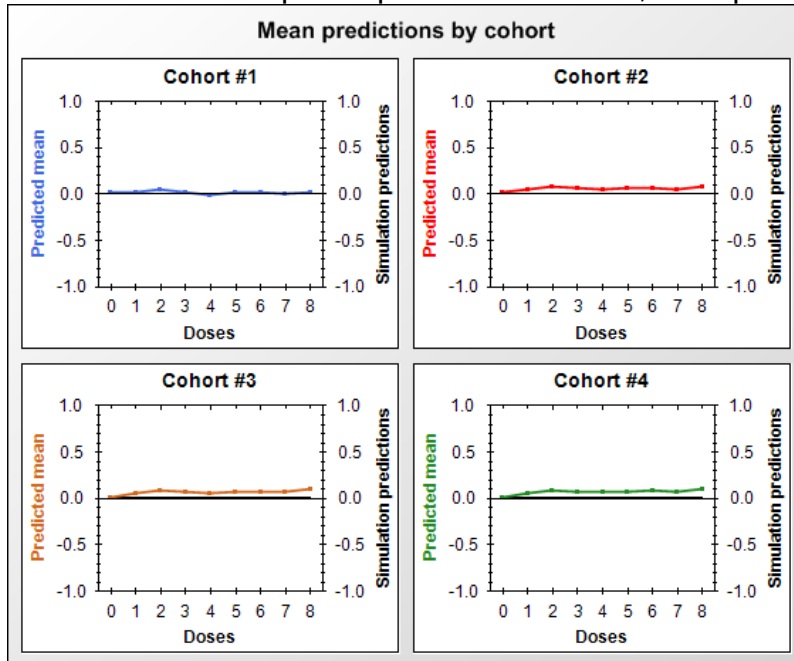


Figure 1. Mean dose-response predictions after each cohort.

Under H0, the mean Pr[DR] at final analysis is close to 50% and the 95% percentile is 95%. Thus, type I error rate for the dose-response decision:

$$\Pr[\text{DR}] > 95\%$$

is 5%.

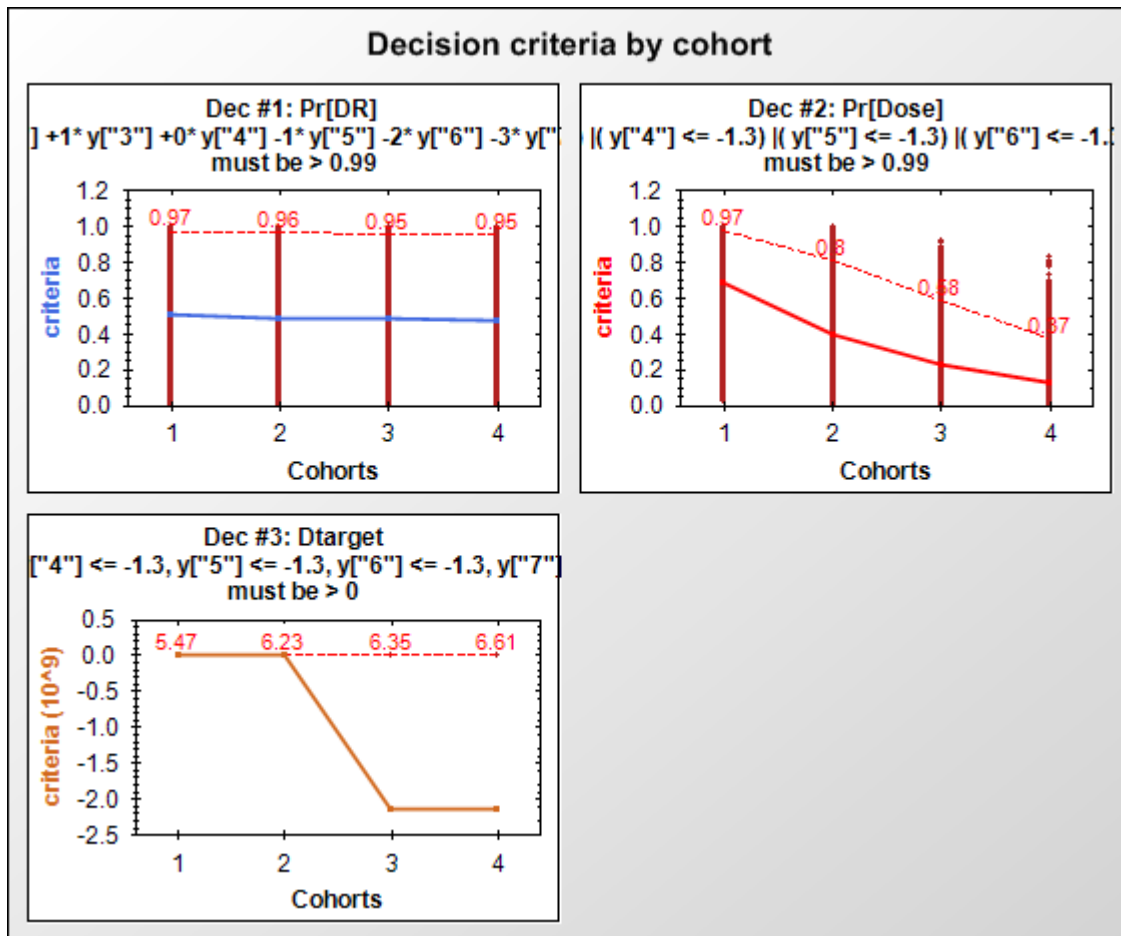


Figure 2. Simulated posterior results Pr[DR], Pr[Dose] and Dtarget at interim and final analyses with means (colour lines) and 95% quantile (dotted red line showing values)

**Decimaker:** The Decimaker study project may be found [here](#). It is a rather big file (10MB), as it contains large-scale simulation results.

### References:

- Paul Gallo, Michael Krams. PhRMA Working Group on Adaptive Designs: Introduction to the Full White Paper. Drug Information Journal. 2006; 40: 421-423.
- Vladimir Dragalin. Adaptive Designs: Terminology and Classification. Drug Information Journal. 2006; 40: 425-435.
- Judith Quinlan, Michael Krams. Implementing adaptive designs: logistical and operational considerations. Drug Information Journal 2006; 40: 437-444.
- Paul Gallo. Confidentiality and Trial Integrity Issues for Adaptive Designs. Drug Information Journal. 2006; 40: 445-450.
- Brenda Gaydos, Michael Krams, Inna Perevozskaya, Frank Bretz, Qing Liu, Paul Gallo, Don Berry, Christy Chuang-Stein, Jose Pinheiro, Alun Bedding. Adaptive Dose-Response Studies. Drug Information Journal. 2006; 40: 451-461.

- Jeff Maca, Suman Bhattacharya, Vladimir Dragalin, Paul Gallo, Michael Krams. Adaptive Seamless Phase II/II Designs-Background, Operational Aspects, and Examples. *Drug Information Journal*. 2006; 40: 463-473.
- Christy Chuang-Stein, Keaven Anderson, Paul Gallo, Sylva Collins. Sample Size Reestimation: A Review and Recommendations. *Drug Information Journal*. 2006; 40: 475-484.
- Paul Gallo, Christy Chuang-Stein, Vladimir Dragalin, Brenda Gaydos, Michael Krams, José Pinheiro. Executive Summary of the PhRMA Working Group on Adaptive Designs in Clinical Drug Development. *Journal of Biopharmaceutical Statistics*. 2006; 16: 275-283.