

## GADA: PhRMA Adaptive Design Working Group GADA Trial

**Goal:** To replicate the Bayesian adaptive dose allocation procedure GADA in a phase II trial and assess its performance using simulations.

**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. An Emax dose-response relationship was simulated in which the clinically relevant dose was 2mg. The Bayesian adaptive dose allocation procedure (GADA) was implemented to optimize the selection of that dose.

**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:

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

Vague priors were also taken on the variance inflation factor for the slope and intercept:  
 $W_{\text{delta}} \sim \text{uniform}(0.0001, 100)$ , and  $W_{\text{theta}} \sim \text{uniform}(0.0001, 100)$ .

**Adaptive design:** Although the GADA may be applied after each subject (cohort size =1), we chose to perform interim dose adjustment in cohorts of 9 subjects. The initial cohort counted 36 subjects (4 per dose). There was 1 placebo fixed in any subsequent cohort plus 8 subjects that were adaptively assigned across the 8 dose levels. The adaptive allocation used the Quantile Weighted Variance (QWV) allocator targeting the clinically relevant response of -1.3.

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

- Pr[DR]: Probability to detect decreasing dose-response relationship using ordinal trend test:

$$\text{Pr}[4Y_0 + 3Y_1 + 2Y_2 + Y_3 + 0Y_4 - Y_5 - 2Y_6 - 3Y_7 - 4Y_8 > 0]$$

- Pr[Dose]: Probability to identify a clinically relevant dose where mean response  $\leq -1.3$ :

$$\text{Pr}[Y_1 \leq -1.3 \mid Y_2 \leq -1.3 \mid Y_3 \leq -1.3 \mid Y_4 \leq -1.3 \mid Y_5 \leq -1.3 \mid Y_6 \leq -1.3 \mid Y_7 \leq -1.3 \mid Y_8 \leq -1.3]$$

Dose-response was concluded at final analysis when  $\text{Pr}[\text{DR}] \geq 95\%$ . The study was not stopped early.

Whenever it existed, the minimum administered dose (1,...,8) where response was  $\leq -1.3$  (DTarget) was also estimated after each cohort.

**Simulation:** A Emax dose-response pattern was simulated where  

$$\text{mean} = -1.81 \text{ dose} / (0.79 + \text{dose})$$

and residual standard error was equal to 2.25.

The power for the posterior decision rules:

$$\Pr[\text{DR}] \geq 95\% \text{ and } \Pr[\text{Dose}] \geq 95\%$$

was evaluated after each interim but the study was not stopped early in case of positive results.

We also estimated the predicted Dtarget and compared it to the expected value of 2.01mg.

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

The NDLM model predictions were in line with the Emax model. On average, a few more subjects were allocated to the 2 and 3mg doses and fewer to the highest dose of 8mg.

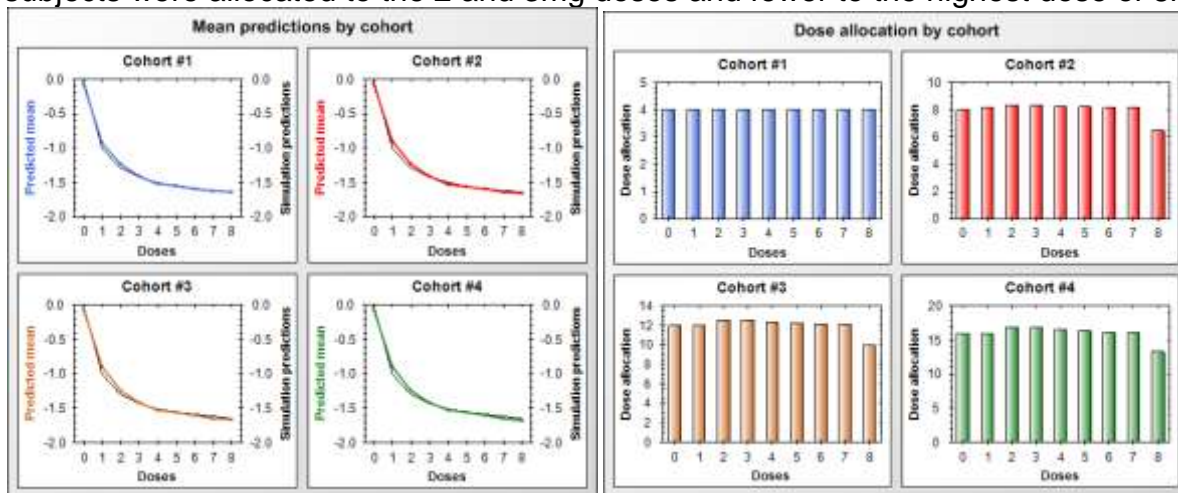


Figure 1. Mean dose response profile and dose allocation after each cohort.

After N=144 patients enrolled, there is a 70% chance to detect a significant dose-response.

Table 1. Interim and Final Power Results

Decision rule	Cohort 1 N=36	Cohort 2 N=72	Cohort 3 N=108	Cohort 4 N=144
Pr[DR] $\geq 95\%$	0.32	0.47	0.60	0.70
Pr[Dose] $\geq 95\%$	0.96	0.97	0.98	0.98

The final discrete DTarget estimate (mean = 2.41mg) was close to the nominal value of 2.01mg. Across all simulations, the DTarget estimate didn't reach a value below 1.09 mg or above 4.09mg with 95% confidence.

Table 2. DTarget distribution after each cohort.

Summary	Cohort 1 N=36	Cohort 2 N=72	Cohort 3 N=108	Cohort 4 N=144
Mean	1.93	2.19	2.32	2.41
2.5%	0.38	0.65	0.96	1.09
97.5%	3.92	4.03	4.04	4.05

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

### References:

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