Modelling approaches in dose finding clinical trial: Simulation-based study comparing predictive performances of model averaging and model selection.

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Objectives: In dose-finding clinical trials, modeling-based approaches require selection of the model (MS) that best describes the data. However, MS ignores model uncertainty which could impair predictive performance [1,2]. To overcome this limit, model averaging (MA) might be used and has recently been applied to NLMEs [3]. MA allows taking into account the uncertainty across all candidate models by weighting them in function of an information criterion (IC). We aimed at comparing predictive performances of MA and MS based on a predefined set of NLMEs with similar disease progression model and different dose-effect relationships.

Methods: Clinical trial simulations were based on a simplified version of a disease model characterizing the time course of visual acuity (VA) of age-related macular degeneration patients. For each trial, parameters of four candidate models (emax, sigmoid emax, log-linear and linear) were estimated using importance sampling and several IC were investigated to select a model or compute weights. Estimation of minimal effective dose (MED) and Kullback-Leibler divergence (D_{KL}) between true and predicted distributions of VA change from baseline were used as performance criteria to compare MS and MA.

Results: The overall predictive performance of the MED was better for MA than MS (up to 10% RMSE reduction). When looking at the entire dose response profile, mean D_{KL} was reduced (up to 50%) when using MA compared to MS. Finally, regardless of modelling approach, AIC outperformed others IC.

Conclusions: By estimating weights on a predefine set of NLMEs, MA adequately described the data and showed better predictive performance than MS increasing the likelihood to accurately characterize the optimal dose.

References: