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Influence of the size of the cohorts in adaptive design for nonlinear mixed effect models: an evaluation by simulation for a pharmacokinetic (PK) and pharmacodynamic (PD) model in oncology.

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Objectives: Optimal design in population PKPD is based on prior information on the models and parameters. Adaptive designs [1, 2] are a promising alternative to local or robust designs [3]. Two-stage designs are easier to implement than fully adaptive designs and can be as efficient [4]. Here, we compared by simulation several one-stage designs and two-, three- and five-stage adaptive designs.

Methods: We used the PKPD model of a drug in development in oncology [5] and we assumed that the model is known. We defined two sets of population parameters: wrong "prior" parameters Ψ^0[6], and "true" parameters, Ψ^*.We evaluated several designs of N=50 patients by clinical trial simulation.

We first defined two 'reference' one-stage designs ξ^0 and ξ^*optimized with Ψ^0 and Ψ^*, as the worst and best designs, respectively. Two-stage designs are composed of a first cohort of N_1 patients with design ξ^0 and a second cohort of N_2 patients with design ξ_2, ξ_2 being optimized using parameter estimates from data collected after first stage. Various two-stage designs with different cohort sizes at each stage ($N_1+N_2=50$) were studied. We finally compared one two-stage adaptive design with 2 three- and 1 five-stage adaptive designs, with $N_1=10$ patients in the first cohort.

Design optimization was performed using determinant of the Fisher Information Matrix (FIM) within PFIM 4.0 [7]. For the adaptive designs, prior information obtained after each stage was incorporated in the evaluation of FIM [2]. We simulated 100 datasets for each scenario using true parameters Ψ^*. Parameters were then estimated using the SAEM algorithm in MONOLIX 4.3. Relative Bias (RB) and Relative Root Mean Square Error (RRMSE) were used to compare the various designs.

Results: Estimation results with two-stage designs were close to those with the optimal design ξ^* and much better than those with the prior design ξ^0. The balanced two-stage design ($N_1=N_2=25$) performed better than unbalanced two-stage designs. The three- and five-stage designs were better than the two-stage adaptive design with a small first cohort ($N_1=10$), but not better than the balanced two-stage design.

Conclusions: Two-stage designs improve the design after the first cohort and are therefore useful when prior information on parameters is not reliable. In this study we found that the balanced two-stage design was the best. In case of small first cohort, more adaptive steps are needed, but these designs are more complex to implement.

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