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MODEL-BASED OPTIMAL DESIGN IN PHARMACOMETRICS USING ROBUST AND ADAPTIVE APPROACHES WITH APPLICATION IN ONCOLOGY

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Résumé

Choosing a good design in a clinical or preclinical trial is a crucial step as a poor design can lead to inconclusive studies. Approaches based on the Fisher information matrix (FIM) for nonlinear mixed effects models (NLMEM) have thus been developed for study designs evaluation and optimization in population pharmacokinetics (PK)/pharmacodynamics (PD), i.e. pharmacometrics. For a given design, the FIM is used for assessing the expected information and the predicted relative standard errors (pRSE) of all parameters of the NLMEM. Optimal design in pharmacometrics depends on prior information on models and parameters, which can be partially wrong. However, designs are often fixed throughout a trial with data only analyzed at the end.

Robust designs approaches have been developed for taking into account uncertainty on parameters by assigning prior distributions for the parameters. Alternative approaches are the adaptive designs (AD), which consist in designs that use accumulating information for modifying predefined aspects of the study after each new cohort of individuals. These two approaches were further evaluated in this PhD using a PKPD examples in oncology for continuous data and a new evaluation of the FIM for studies with discrete longitudinal data. Furthermore, optimal design was rarely applied to preclinical studies. In this PhD we used optimal design approach for the Simeoni tumor growth inhibition model to evaluate the importance of including measurements during the tumor regrowth phase of xenograft experiments for a better estimation of the model parameters.

In conclusion, this PhD project presents different contexts and use of optimal design strategies and it shows that these are powerful approaches which allow for improving the quality of a study, guarantying its reliability and a better precision of the acquired information.

Key words:

Adaptive design, Fisher information matrix, nonlinear mixed effects models, optimal design, pharmacokinetics/pharmacodynamics, robust design.