Influence of the ratio of the sample sizes between the two stages of an adaptive design: application for a population pharmacokinetic study in children

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CONTEXT

PHARMACOKINETIC (PK) STUDIES IN CHILDREN

- Conducted in patients
- Limitation on the blood volume which can be taken in children
- Mainly analysed by nonlinear mixed-effect models (NLMEM) [1,2]

CHOICE OF THE PHARMACOKINETIC (PK) DESIGN

- Balance between number of subjects and number of measures/subject, choice of sampling times
- Based on the calculation of the Fisher information matrix (M_F) and the optimization of its determinant (det(M_F)) [3,4]
  - Implemented in several software as PFIM in R [5,6]
  - Depends on the model and parameters for NLMEM

ADAPTIVE DESIGN FOR NLMEM

- Local design often used: based on *a priori* values of parameters

Alternatives:

- Robust design: based on *a priori* distribution of parameters [7]
- Adaptive design [8,9]: data accumulated during the trial are used to possibly modify the aspects of the study

➡ Two-stage design seems to be a good compromise for designing PK studies in children and is easier to conduct in clinical trials

OBJECTIVES

1) To study, by a simulation approach, the impact of two-stage designs on the precision of parameter estimation, when children true parameters are different from *a priori* ones
2) To investigate, by a simulation approach, the influence of the sample size ratio of each stage, when the true and the *a priori* PK parameters differ

METHODS

TWO-STAGE DESIGN

- Assumption: same elementary design (ξ) for all subjects in a cohort
- Notations
  - Ψ_0: *a priori* parameters
  - Ψ^*: true parameters
  - ξ_1: optimized design obtained with parameters Ψ_0 for N_1 subjects
  - Ψ_1: estimated parameters from data Y_1 with design ξ_1 and N_1 subjects
  - ξ_2: optimized design obtained with estimated parameters Ψ_1 for N_2 subjects
  - Ψ_2: estimated parameters from data Y_2, obtained with design ξ_2 for N_2 subjects, and data Y_1

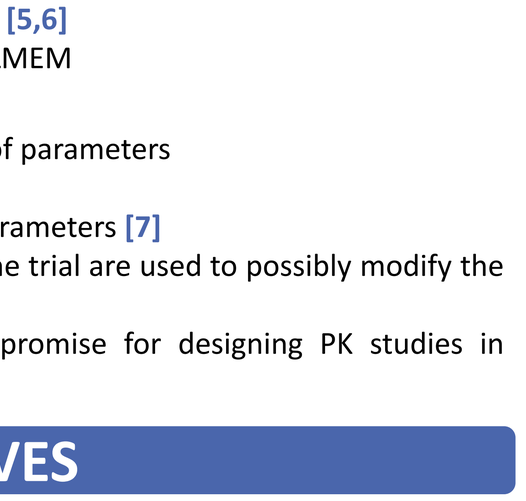

Figure 1: *Two-stage design*

- M_F for a two-stage design

First stage: ξ_1 is the design which maximizes determinant of

$$M_F(\Psi_0, N_1\xi) = N_1 M_F(\Psi_0, \xi)$$

Second stage: using estimated Ψ_1, ξ_2 is the design which maximizes determinant of

$$M_F(\Psi_1, N_1 \xi_1 + N_2 \xi) = N_1 M_F(\Psi_1, \xi_1) + N_2 M_F(\Psi_1, \xi)$$

PK EXAMPLE

- Two-compartment PK model with first-order absorption, exponential random effects and proportional error model
- Two vectors of parameters Ψ_0 (*a priori*) and Ψ^* (true)

-Same variance for all parameters ($\omega^2 = 0.3$)
-Same proportional error ($\sigma = 0.2$)

- N= $N_1 + N_2$ = 60 children and 5 sampling times per child

Parameters	Ψ_0	Ψ^*
k_a (h^{-1})	3.0	14
CL ($L.h^{-1}.kg^{-1}$)	1.5	1.0
V_1 ($L.kg^{-1}$)	2.0	1.0
Q ($L.h^{-1}.kg^{-1}$)	1.0	2.0
V_2 ($L.kg^{-1}$)	1.5	2.0

Table 1: *Population PK parameter values*

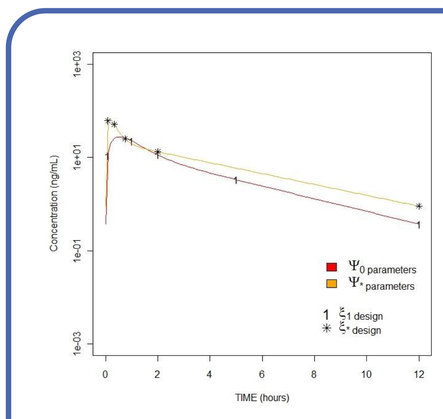

Figure 2: *Mean profiles in semi-log scale*

- Optimal design:

For Ψ_0 : ξ_1 = 0.083; 1; 2; 5; 12

For Ψ^*: ξ^*= 0.083; 0.33; 0.75; 2; 12

SIMULATION STUDY

- Parameters for simulation: Ψ^*
- Estimation of parameters using SAEMIX [10] in R
- Design optimization with PFIM in R
- Fixed design:

Simulation of 100 trials with design ξ_1 and 100 with design ξ^* for N = 60 children

- Two-stage design
  - 10 simulations of the first cohort with N_1 children
  - 10 simulations with N_2 children (N = $N_1 + N_2$ = 60 children) for each design ξ_2 → 100 trials
  - varying N_1 and N_2 (30-30, 10-50 and 50-10)

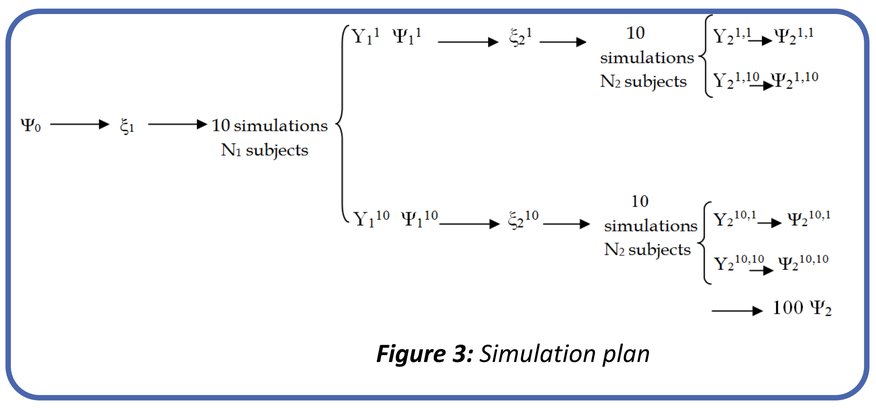

Figure 3: *Simulation plan*

EVALUATION

- Relative root mean square errors (RRMSE) for each design and each parameter
- Standardized RRMSE for each design and each parameter: ratio of the RRMSE and the RRMSE of ξ^*
- Mean standardized RRMSE for each design

RESULTS

IMPACT OF THE TWO-STAGE DESIGN

Optimal designs for the second stage (with $N_1 = N_2 = 30$ children)

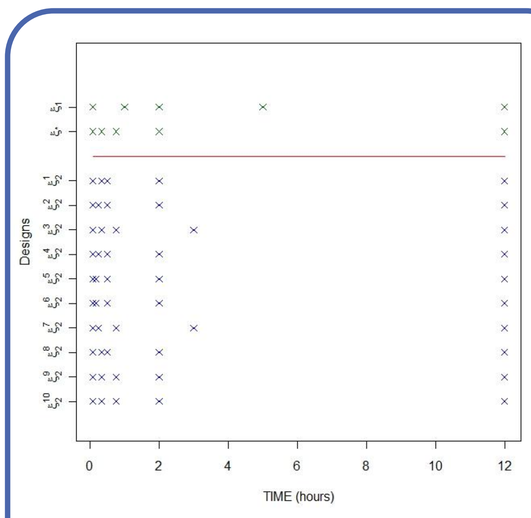

Figure 4: *The ten second-stage designs (ξ_2) optimized from the ten estimated Ψ_1*

- Among the ten second-stage designs, six are different and the other are identical
- Designs ξ_2 : closer to ξ^* than to ξ_1

Comparison between fixed and two-stage designs

Parameters	RRMSE (%) (standardized RRMSE)		
	ξ_1	ξ^*	$\xi_{30\text{-}30}$
ka (h^{-1})	**160** (7.05)	22.7	27.3 (1.20)
CL ($L.h^{-1}$)	7.17 (1.07)	6.73	5.77 (0.857)
V1 (L)	25.2 (1.65)	15.3	23.7 (1.55)
Q ($L.h^{-1}$)	27.1 (1.67)	16.2	18.8 (1.16)
V2 (L)	11.4 (1.00)	11.4	9.73 (0.854)
ω^2_{ka}	**100** (1.21)	**82.4**	**90.4** (1.10)
ω^2_{CL}	17.0 (0.950)	17.9	18.3 (1.02)
ω^2_{V1}	48.0 (1.33)	36.0	38.3 (1.06)
ω^2_{Q}	**89.9** (1.50)	**59.9**	**71.5** (1.19)
ω^2_{V2}	36.4 (1.17)	31.2	26.6 (0.853)
σ_{slope}	10.4 (0.765)	13.6	10.8 (0.794)
Mean standardized RRMSE	1.76	1.00	1.06

Table 2: *Relative RMSE for the extremum designs and for the two-stage design (30-30)*

- Poor results (large RRMSE) for ξ_1 compared to these of ξ^*
- Much better results for two-stage design than *a priori* design (ξ_1)
- Results of two-stage design close to fixed optimal design with true parameters (ξ^*)

INFLUENCE OF THE SAMPLE SIZE RATIO BETWEEN THE TWO STAGES

Parameters	RRMSE (%) (standardized RRMSE)		
	$\xi_{10\text{-}50}$	$\xi_{30\text{-}30}$	$\xi_{50\text{-}10}$
ka (h^{-1})	**30.3** (1.33)	27.3 (1.20)	**32.8** (1.44)
CL ($L.h^{-1}$)	7.07 (1.05)	5.77 (0.857)	4.88 (0.725)
V1 (L)	19.3 (1.26)	23.7 (1.55)	21.1 (1.38)
Q ($L.h^{-1}$)	21.2 (1.31)	18.8 (1.16)	19.2 (1.19)
V2 (L)	12.3 (1.08)	9.73 (0.854)	11.4 (1.00)
ω^2_{ka}	**86.3** (1.05)	**90.4** (1.10)	**82.6** (1.00)
ω^2_{CL}	30.6 (1.71)	18.3 (1.02)	21.4 (1.20)
ω^2_{V1}	23.5 (0.653)	38.3 (1.06)	37.1 (1.03)
ω^2_{Q}	**78.2** (1.31)	**71.5** (1.19)	**68.0** (1.14)
ω^2_{V2}	34.1 (1.09)	26.6 (0.853)	34.3 (1.10)
σ_{slope}	11.0 (0.809)	10.8 (0.794)	8.14 (0.599)
Mean standardized RRMSE	1.15	1.06	1.07

Table 3: *Relative RMSE for three two-stage designs studied (10-50, 30-30, 50-10)*

- Satisfactory results in terms of RRMSE for the three two-stage designs studied
- Results globally similar for the three cases studied

CONCLUSION

- Two-stage designs are a good approach for PK study: the results are satisfactory even if the *a priori* parameters are wrong (involving a poor design and therefore poor results)
- Two-stage designs are easier to conduct and could be more efficient than fully adaptive design
- No clear influence of the ratio of sample sizes between cohorts: more extreme cases should be studied

- Perspectives:
  - To create an automatic connection between SAEMIX and PFIM
  - To increase the number of simulations
  - To apply this methodology for other examples

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