A Modelling and Simulations Framework to Optimize Paediatric Studies and Facilitate Decision-Making

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OBJECTIVE

Paediatric drug development is challenging and unique in several aspects. FDA recently provided new recommendations for designing optimal paediatric studies [relative standard error (RSE) and 90% confidence intervals <20%]. A modelling and simulations framework was developed to simultaneously determine an optimal pharmacokinetic (PK) sampling strategy and sample size of paediatric subjects that would result in robust PK parameters and ultimately identify a dose level that would result in drug exposure within the targeted range of efficacy and safety of the product.

METHODS

1- Perform simulations using a population PK model (Trial Simulator®) to determine dose levels that would result in exposure within the targeted range in different age groups

A previously developed population PK model including an allometric function with fixed body weight effect was used to assess PK in paediatric patients.

Exposure of candidate dose levels in paediatric patients was compared to those observed in adults.

The following age cohorts were considered in a first step:

- 1 - < 2 years
- 2 - < 4 years
- 4 - < 6 years
- 6 - < 8 years
- 8 - ≤ 12 years

2- Optimize sample size of patients and PK sampling using WinPOPT®

Optimal sample size and sparse PK sampling strategies were identified based on the population PK model using WinPOPT® to maximize the robustness of PK parameters while minimizing the number of samples in paediatric patients.

3- Confirm the best study design using a simulation-fitting approach

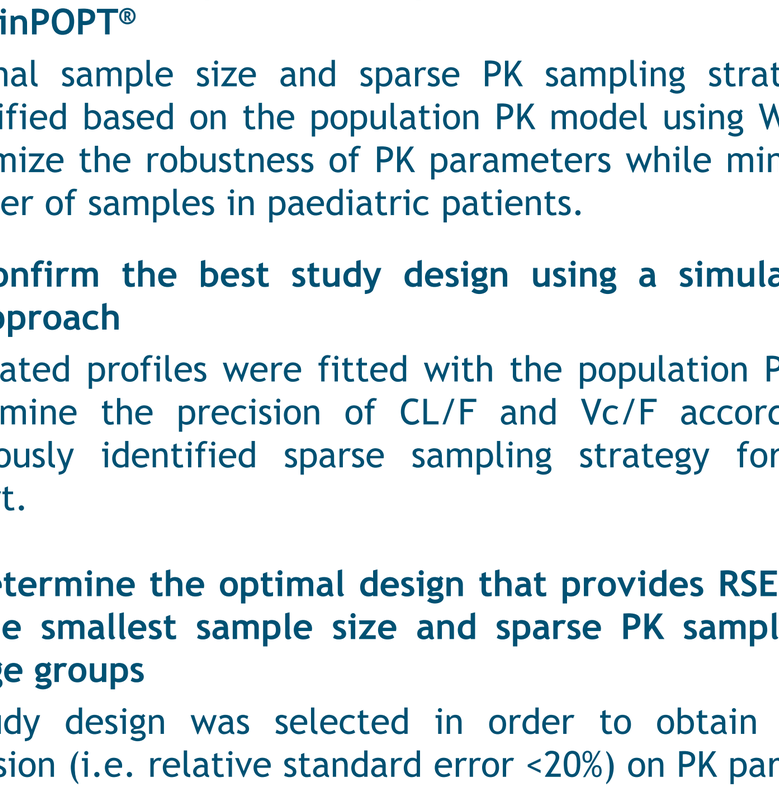
Simulated profiles were fitted with the population PK model to determine the precision of CL/F and Vc/F according to the previously identified sparse sampling strategy for each age cohort.

4- Determine the optimal design that provides RSE <20% with the smallest sample size and sparse PK samplings across age groups

A study design was selected in order to obtain an optimal precision (i.e. relative standard error <20%) on PK parameters.

A hypothetical population of 20000 paediatric patients (1 to 12 years) was generated using the body weight distribution provided by CDC (i.e., 1000 children for each age and treatment group)

Figure 1 - Simulated Body Weight Values in Paediatric Patients



RESULTS

The previously developed population PK model was implemented in WinPOPT® to derive the optimal sampling times using mean weight values for each age group.

Optimal sampling time points were first derived with WINPOPT and converted into sampling time points that would be considered clinically feasible.

Table 1: Optimal Sampling Strategies Estimated with WinPOPT® (N=25 subjects/group)

	1 < 2 years old		2 < 4 years old		4 < 6 years old		6 < 8 years old		8 ≤ 12 years old	
Samples	3	2	3	2	3	2	3	2	3	2
Sampling time (h)	0.9, 4.9, 5.7 h	0.9, 5.3 h	0.9, 4.9, 6.2 h	1.1, 5.7 h	1.1, 5.3, 6.7 h	1.2, 6.2 h	1.2, 5.7, 6.7 h	1.4, 6.7 h	1.4, 6.7, 7.2 h	1.4, 7.2 h
RSE~CL	7.5	8.2	7.1	8.2	7.5	8.2	7.7	8.5	7.7	8.6
RSE~Vc	14.5	14.6	13.6	14.6	14.5	14.6	14.8	14.8	14.8	14.9

Overall, the following sparse sampling strategies were explored across all age cohorts.

- 3 blood samples: 1, 4 and 6 h
- 2 blood samples: 1 and 6 h

Typical population PK parameters were re-estimated based on the above optimal blood sampling strategies across the 5 age cohorts.
A total of 25, 30, 40 and 50 paediatric subjects between 1 and 12 years (equal number per age group, sex) were randomly selected.
The above steps were performed 50 times and RSE of PK parameters were computed.

Figure 2 Distributions of Relative Standard Error of PK Parameters Estimated with NONMEM (N=25, 30, 40 and 50 subjects) - 3 Blood Samples

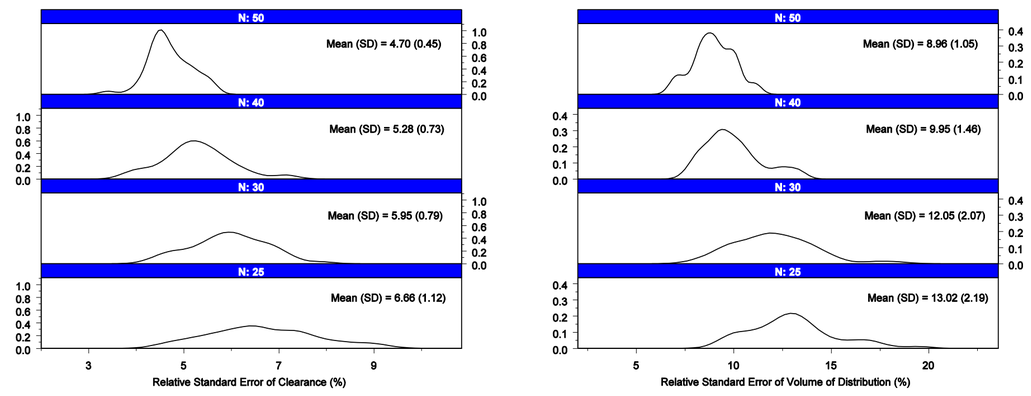


Figure 3 Distributions of Relative Standard Error of PK Parameters Estimated with NONMEM (N=25, 30, 40 and 50 subjects) - 2 Blood Samples

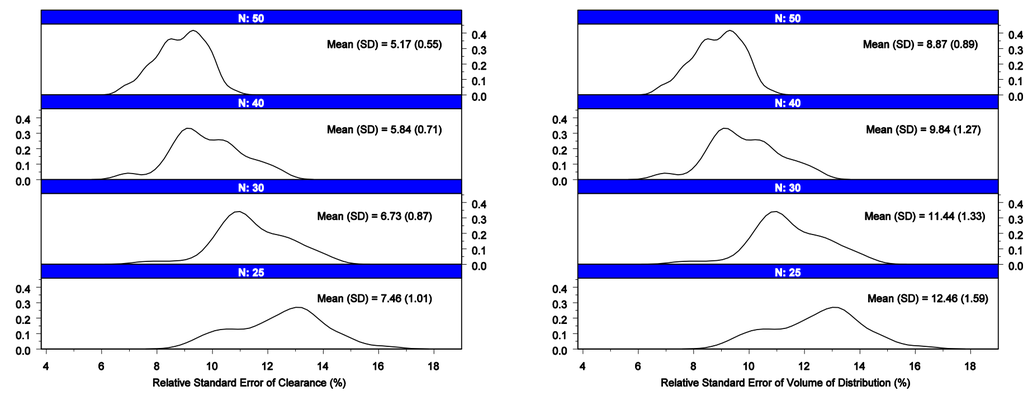


Table 2: Descriptive Statistics of Relative Standard Error Estimated with NONMEM (N=25)

PK Parameters	Mean RSE (CV%) Median [Min-Max]	
	3 Blood Samples	2 Blood Samples
CL/F (L/h)	6.66 (16.89%) 6.6 [4.6 - 9.1]	7.46 (13.57%) 7.1 [5.3 - 10.6]
Vc/F (L)	13.02 (16.85%) 12.9 [9.6 - 19.4]	12.46 (12.79%) 12.7 [9.2 - 16.2]

Overall, sparse sampling strategy with 2 or 3 samples resulted in good precision of PK parameters, with distributions of mean RSE values of CL/F and Vc/F for all total number of subjects lower than 20%.

CONCLUSIONS

A modelling and simulations framework was developed to rapidly identify optimal study designs in paediatrics patients and allowed a precise estimation of RSE to ensure robustness of PK parameters and meet FDA's requirements for clinical studies in paediatrics. Although EMA did not provide regulatory requirements to define the level of robustness required in paediatric studies, the above modelling and simulations framework may be considered for optimizing paediatric studies in Europe and to facilitate decision-making.