# Simultaneous Optimization of Sampling Strategies for Parent and Metabolite Data Taking into Account a Body Weight Distribution: Applications to Paediatric Studies

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## OBJECTIVE

Population pharmacokinetic (PK) modeling of parent drug (PAR) and active metabolite(s) (MET) is important to understand the overall therapeutic effect.

The purpose of this project was to optimize the precision of PK parameters for a population PK model including PAR and MET data in a pediatric population with body weight distribution in the following age groups:

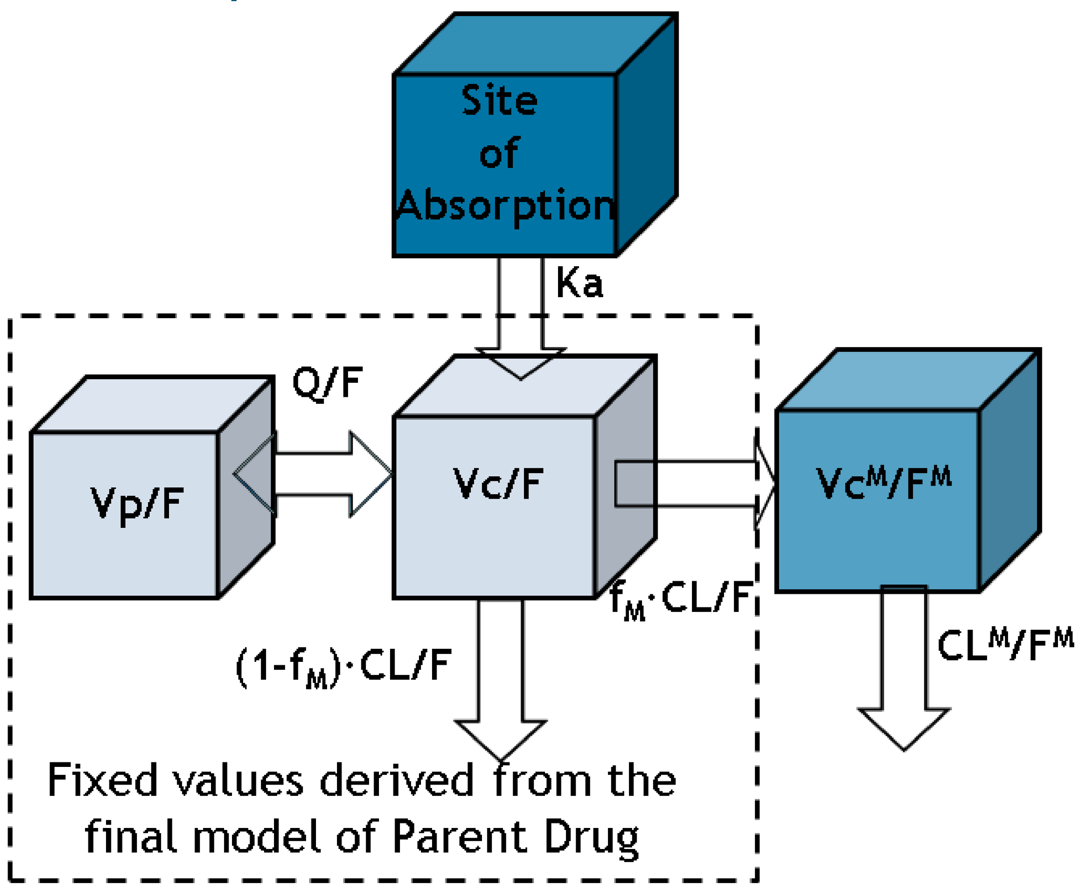
- 2 ≤ AGE< 5 years old
- 5 ≤ AGE < 13 years old
- 13 ≤ AGE < 18 years old

Fixed-doses were used in the above groups.

## METHODS

A sequential approach was used to develop a population PK model linking the parent drug (PAR) to its active metabolite (MET) with NONMEM version 7.2. The population PK model included an allometric function of weight (WT) on V, CL and Ka [i.e., $V_i = V \cdot (WT/75)^1$, $CL_i$= CL·(WT/75)0.75, $Ka_i = Ka \cdot (WT/75)^{-0.25}$].

**Figure 1- Structural Population PK Model of the Parent and Metabolite**

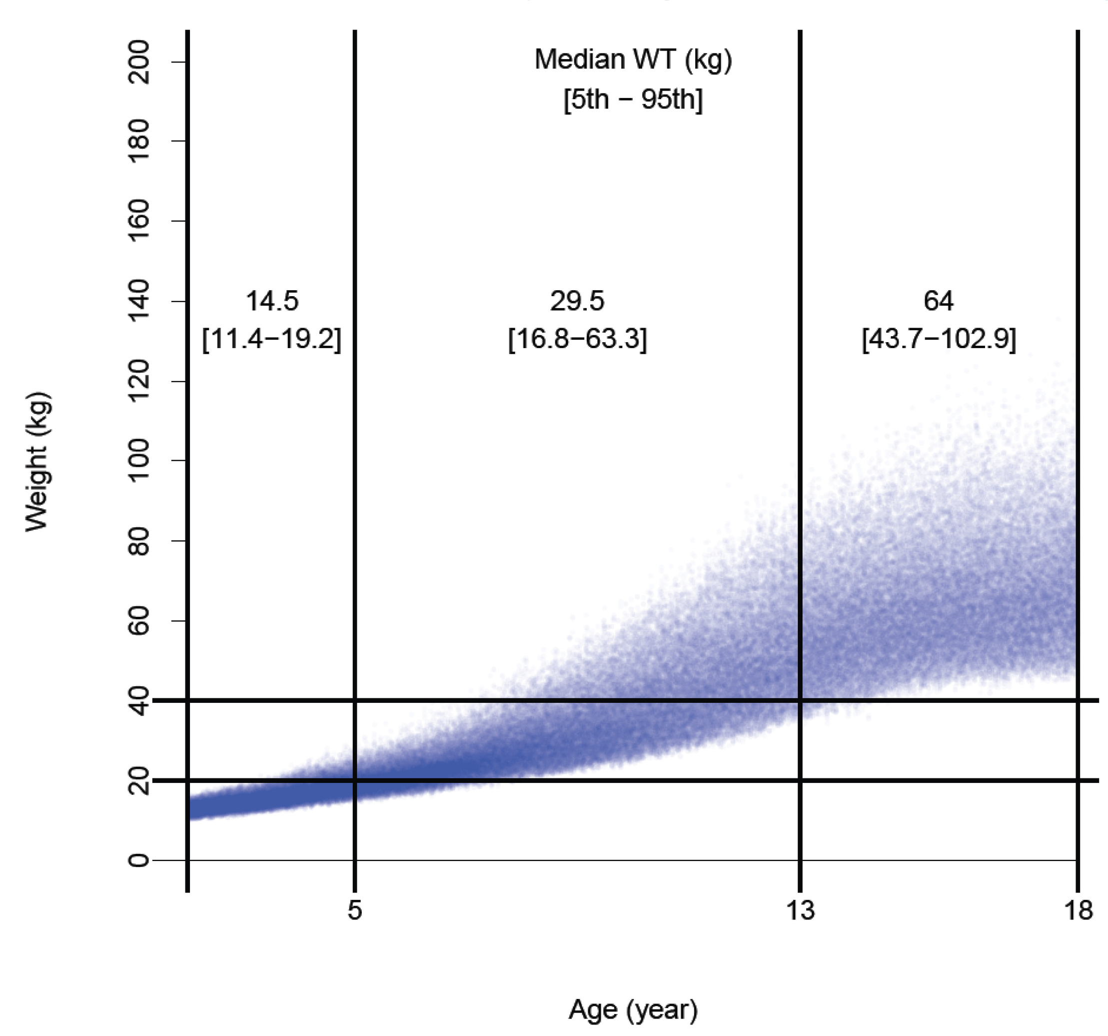



The apparent clearance (CL/F) of PAR and MET were markedly different and thus different sampling timepoints were tested to optimize the PK precision of both products according to the body weight distribution in various pediatric age groups.

To account for the complexities of the PAR-MET model and the body weight distribution, a simulation/re-estimation approach (SIM-RE) was deemed the most appropriate. To reduce the number of the scenarios and iterations, the initial sampling schedule for PAR was determined based on the optimization of population Fisher information matrix in WinPOPT using the mean WT values for each age group. Simulations were first performed to determine the last sampling time with PAR and MET concentrations above the limit of quantitation.

The precisions of PK parameters of PAR and MET derived from this optimal design were re-assessed using a simulations/re-estimation approach in NONMEM using 200 replicates for each scenario. Realistic WT-age distribution were incorporated into the simulated data for patients 2 to 18 years using a generalized additive model for location scale and shape (GAMLSS) as presented in Figure 2.[1] The asymptotic RSE derived from NONMEM covariance step of the 200 replicates were summarized. This procedure was tested for several possible N to determine the minimum number of subjects that would meet the desired precision.

**Figure 2- Distribution of Body Weight in Pediatric Population**




## RESULTS

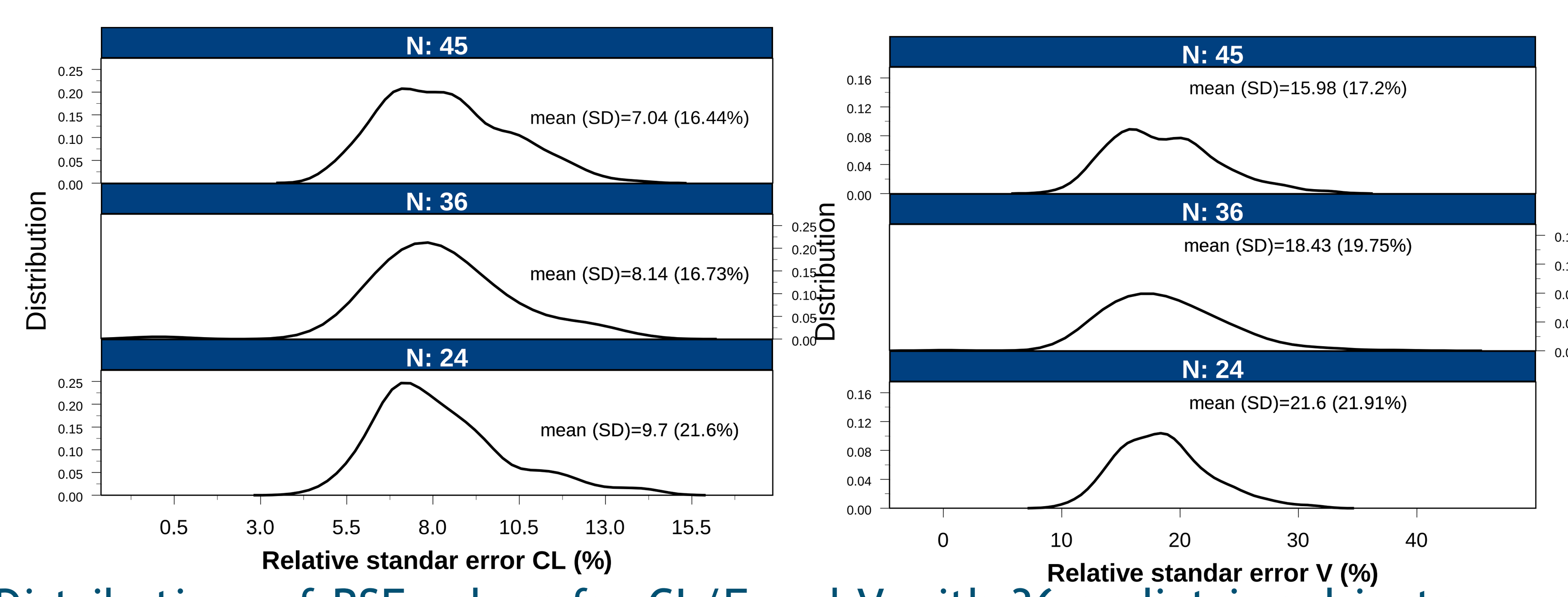
The PAR model was implemented in WinPOPT to derive the optimal sampling times for each of age groups (with N=25/group). Relative standard errors were re-estimated using more appropriate sampling time as presented in Table 1.

**Table 1: Optimal Sampling Strategies with the Residual Standard Errors estimated with WinPOPT (N=25 subjects/group)**

| PK Parameters of Parent Drug | Relative Standard Error (%) 2 ≤ AGE< 5 years old | 5 ≤ AGE < 13 years old | 13 ≤ AGE < 18 years old |
|---|---|---|---|
| Sampling time (hr) | Pre-dose, 5 min, 15 min, 3 and 6 h | Pre-dose, 5 min, 30 min, 1, 2 and 6 h | Pre-dose, 5 min, 30 min, 2 h, 3 h, 8 h |
| CL | 11.9 | 12.1 | 11.9 |
| Vc | 29.9 | 23.4 | 19.4 |
| Vp | 16.1 | 14.6 | 14.1 |
| Q | 11.8 | 15.7 | 11.9 |
| Ka | 15.6 | 14.7 | 13.2 |

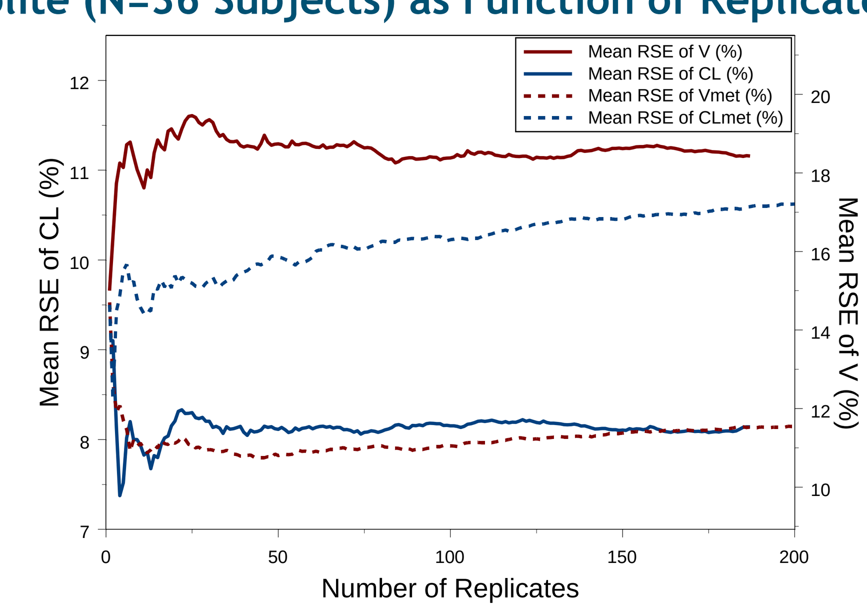
The population PK model was used to simulate PAR and MET concentrations at different sampling times for 24, 36 and 45 pediatric subjects with WT data generated based on the GAMLSS model.[1] Typical PK parameters with the respective standard errors were re-estimated using NONMEM.

**Figure 3: Distributions of Relative Standard Error of PK Parameters for the Parent Drug Estimated with NONMEM (N=24, 36, 45 subjects)**




Distributions of RSE values for CL/F and V with 36 pediatric subjects were acceptable, with mean values slightly lower than 20% (FDA's requirements for clinical pediatric studies). Figure 4 suggests that after 100 replicates the RSE mean values are stable for CL/F and V/F of Parent Drug but for the metabolite the RSE values continue to increase.

**Figure 4: Mean Relative Standard Error (RSE%) of CL/F and V/F for the Parent Drug and Metabolite (N=36 Subjects) as Function of Replicates**




RSE values of PK parameters for MET that were re-estimated with NONMEM in presented in Table 2.

**Table 2- Descriptive Statistics of Relative Standard Error Estimated with NONMEM (200 Replicates with 36 Subjects)**

| PK Parameters | RSE% Mean (CV%) Parent | Metabolite |
|---|---|---|
| CL/F(L/h) | 8.14 (16.73%) | 10.62 (12.3%) |
| Vc/F (L) | 18.43 (19.75%) | 11.34 (15.38%) |
| BSV on CL/F(%) | 23.33 (18.08%) | 23.33 (17.4%) |
| BSV on Vc/F (%) | 25.3 (16.31%) | 29.01 (19.38%) |

Overall, the sparse sampling strategy for PAR and MET resulted in a good precision of PK parameters (RSE<20% for CL and V).

## CONCLUSIONS

The optimization of population Fisher information matrix in combination with a simulation/re-estimation approach allowed a rapid assessment of optimal study designs and sparse sampling strategies. This approach accelerated the assessment of precision of PK parameters for parent and metabolite data in sub-populations of paediatric patients with different body weight distributions.

## REFERENCE

1) Mouksassi et al. Clin Pharmacol Ther. 2009;86(6):667-71.
2) 2000 CDC Growth Charts for the United States: Methods and Development. Centers for Disease Control and Prevention, Department of Health and Human Services, May 2002.