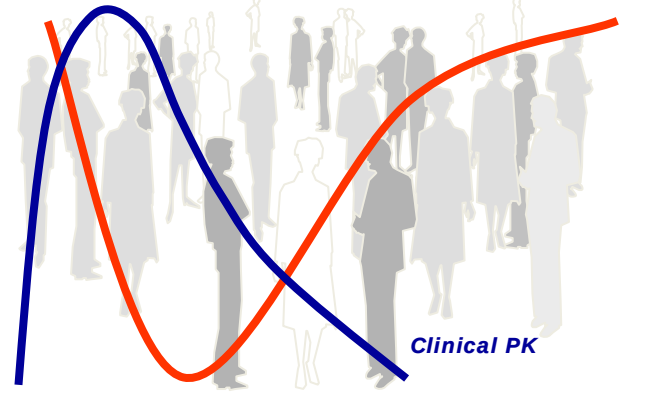


Using optimal design methods to help to design a paediatric pharmacokinetic study



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Context

- Pharmacokinetic (PK) studies in children
 - Conducted in patients
 - Limitation on the blood volume which can be taken in children → few PK samples per patient
 - Use of nonlinear mixed effects models (NLMEM) to analyse PK data from such studies
- Choice of the PK sampling design
 - Impact on the study results (precision of parameter estimates, power of test)
 - Balance between number of patients and number of samples/patient, choice of sampling times
- Evaluation/optimisation of PK sampling designs for NLMEM
 - Require hypotheses
 - On the model (and its parameter values) describing the PK profile
 - On the distribution of covariate(s), e.g. bodyweight (BW)
 - Methods
 - Based on simulations: cumbersome method, very time consuming
 - Based on the calculation of the Fisher information matrix (M_F) [1]

Objectives: 1. To help to design a paediatric study assessing the PK of drug S, in development at Servier, using M_F approach
2. To evaluate the influence of the number of subjects and the bodyweight distribution on the precision of parameter estimates

Methods

1. NLMEM

- Notations: $i=1, \dots, N$ subjects, $j=1, \dots, n$ samples/subject, $l=1, \dots, L$ model parameters
- Structural model: two-compartment model with first-order absorption and elimination
- Statistical model
 - Individual parameters: $\phi_{il} = \mu_l \times \left(\frac{BW}{70}\right)^{\theta_{il}} \times \exp(\eta_{il})$ with $\eta_{il} \sim \mathcal{N}(0, \omega_l)$
 - Proportional residual error: $y_{ij} = f(t, \phi_i) \times (1 + b \times \varepsilon_{ij})$ with $\varepsilon_{ij} \sim \mathcal{N}(0, 1)$

Table 1: NLMEM parameter values used in the analysis

μ_{k_a}	μ_{CL}	μ_{V_1}	μ_Q	μ_{V_2}	θ_{CL}	θ_{V_1}	θ_Q	θ_{V_2}	$\omega_{k_a}^2$	ω_{CL}^2	$\omega_{V_1}^2$	ω_Q^2	$\omega_{V_2}^2$	b^2
0.1	0.132	2.6	0.644	2.9	1	1	1	1	0.14	0.2	0.5	0	0.5	0.01

2. PK design evaluation

- Use of the optimal design software POPDES 4.0 implemented in MATLAB [2]
 - D-optimality: higher the M_F determinant ($\det(M_F)$), “better” the PK sampling design
 - Computation of the relative standard error (RSE) for $N=20, 30, 40$ children
 - Computation of the number of subjects needed (NSN) to allow
 - RSE of the fixed effects parameters (μ and θ) below 30%: $NSN_{RSE, f}$
 - RSE of the variance parameters (ω^2 and b^2) below 50%: $NSN_{RSE, v}$
- Study Design
 - Two age groups (requirement from regulatory agency) of $N/2$ children: $[2; 11[$ and $[11; 18[$ years
 - One drug S administration every 28 days, 4 administrations
 - Evaluated sampling designs
 - Rich: 38 samples/patient (with most of the samples during the 1st drug S administration)
 - Sparse: 6 samples/patient

3. Distribution of the bodyweight

- Uniform with BW between 5 and 75 kg
 - With categorization of the distribution assuming seven categories (U_C)
 - Without categorization (U_U)
- Non-uniform assuming
 - Inclusion of children between 2 and 18 years (N_A)
 - Inclusion of the “oldest” children in both age groups: $[9; 11[$ and $[16; 18[$ years (N_{OO})
 - Inclusion of the “youngest” children in both age groups: $[2; 4[$ and $[11; 13[$ years (N_{YY})

4. Wald test on the BW effect

- Hypotheses: $H_0: \theta = \Delta$ versus $H_1: \theta \neq \Delta$, with $\Delta=(0,0,0,0)$
- Wald statistic
 - $T = (\hat{\theta} - \Delta)^T \hat{V}^{-1} (\hat{\theta} - \Delta)$, with $T \sim \chi^2(4)$ and $\hat{V} = M_F^{-1}(\theta_{CL}, \theta_{V_1}, \theta_Q, \theta_{V_2})$
 - Under H_1 assuming $\Delta=Y$, $T \sim \chi^2(4, \lambda)$, with $\lambda = (Y - \Delta)^T \hat{V}^{-1} (Y - \Delta)$
- Computation of the NSN to detect a BW effect on all disposition parameters (NSN_{power}) assuming a type I error of 5%, a power of 80% and $Y=(1,1,1,1)$ or $Y=(0.75,1,0.75,1)$

Figure 1: Typical PK profile for a BW of 70kg

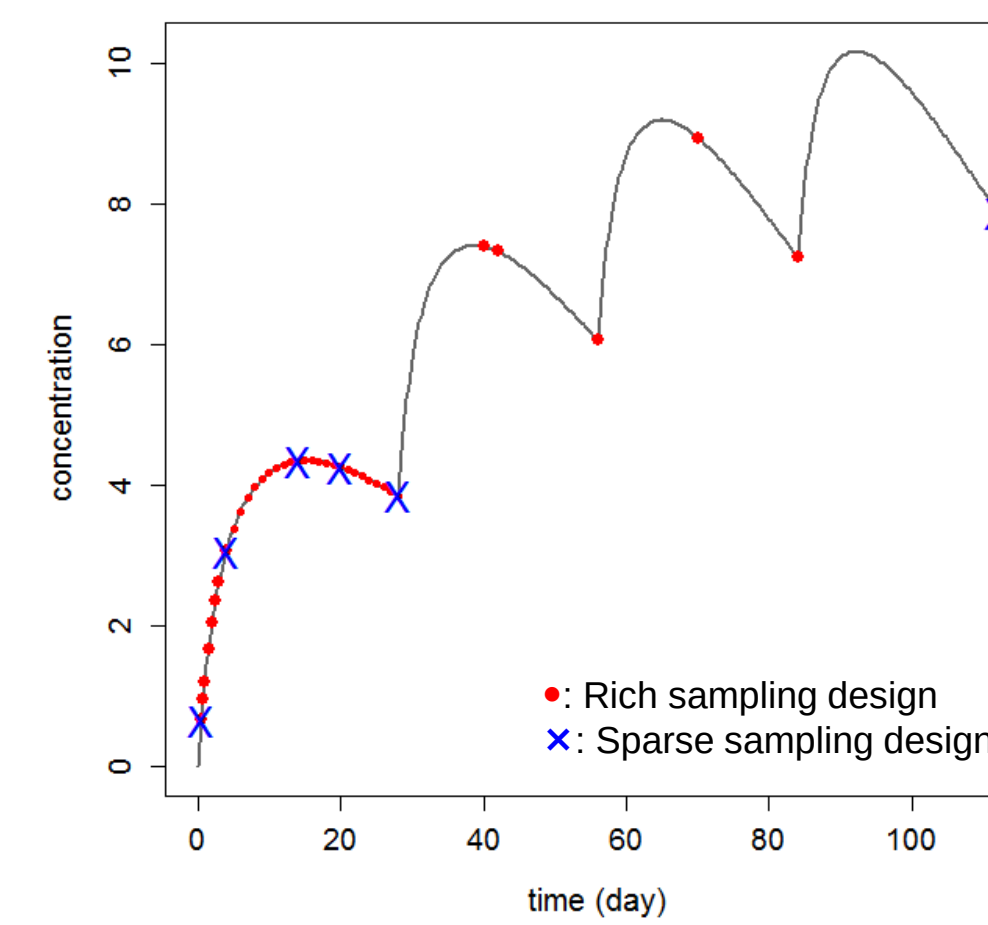
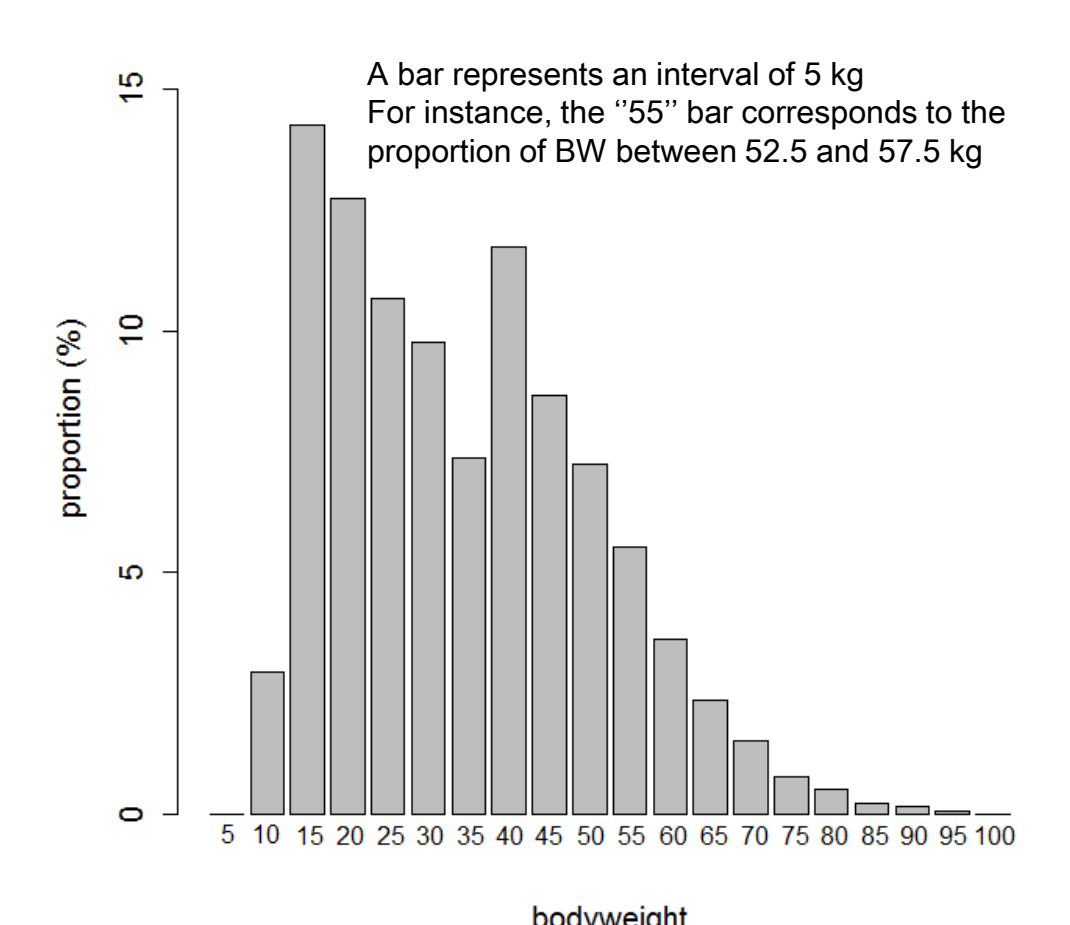


Figure 2: non-uniform BW distribution (N_A)



Results

Figure 3: RSE of the typical value parameters (μ) for each BW distribution assumption and $N=20, 30, 40$ children

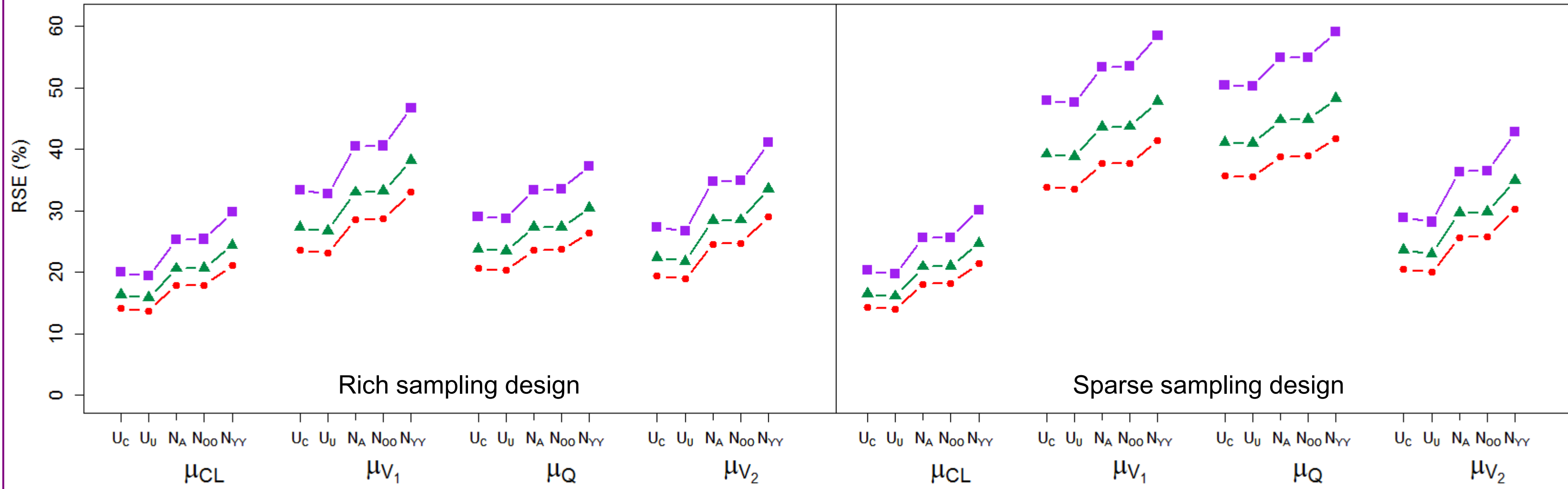
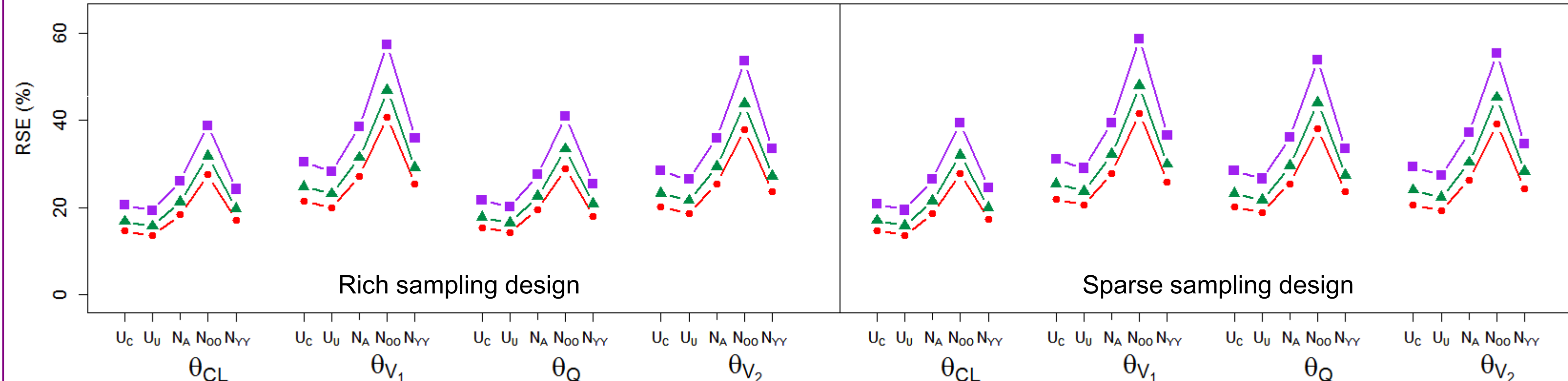


Figure 4: RSE of the BW effect parameters (θ) for each BW distribution assumption and $N=20, 30, 40$ children



- Similar predicted RSE for μ_{k_a} and all variance parameters for each BW distribution (unshown results)
- Predicted RSE on fixed effects parameters (μ and θ) for CL, V_1 , Q and V_2
 - Slight increase between rich and sparse design for the same BW distribution
 - Similar RSE between U_C and U_U distributions $\Rightarrow$ good approximation of BW distribution by categorization
 - Similar RSE between N_U and N_{YY} , RSE increase between N_U and N_{OO} $\Rightarrow$ influence of BW distribution assumption

Table 2: $\det(M_F)$ for 40 children and each BW distribution assumption

Design	U_C	U_U	N_A	N_{OO}	N_{YY}
Rich	$3.7 \cdot 10^{33}$	$6.6 \cdot 10^{33}$	$5.6 \cdot 10^{32}$	$2.3 \cdot 10^{31}$	$1 \cdot 10^{33}$
Sparse	$2.5 \cdot 10^{30}$	$4.4 \cdot 10^{30}$	$3.8 \cdot 10^{29}$	$1.6 \cdot 10^{28}$	$6.9 \cdot 10^{29}$

Table 3: $NSN_{RSE, f}$ and $NSN_{RSE, v}$ for each BW distribution assumption

Design	$NSN_{RSE, f}$					$NSN_{RSE, v}$				
	U_C	U_U	N_A	N_{OO}	N_{YY}	U_C	U_U	N_A	N_{OO}	N_{YY}
Rich	25	24	37	74	49	20	20	20	20	20
Sparse	57	57	67	77	78	48	48	48	48	48

Table 4: NSN_{power} for each BW distribution assumption and each H_1

BW effect (Y)	Design	U_C	U_U	N_A	N_{OO}	N_{YY}
(1, 1, 1, 1)	Rich	8	7	12	26	10
	Sparse	8	7	13	28	11
(0.75, 1, 0.75, 1)	Rich	10	9	15	34	13
	Sparse	11	9	17	36	14

- $NSN_{RSE} = \max(NSN_{RSE, f}, NSN_{RSE, v})$
 - Rich design: higher than 40 for N_{OO} and N_{YY} distributions
 - Sparse design: higher than 40 for all BW distributions
 - $NSN_{RSE}=40$ for all BW distributions and both designs if $RSE_f < 42\%$ and $RSE_v < 55\%$
- NSN_{power}
 - Below NSN_{RSE} for both designs, all BW distributions, and both H_1
 - Higher for $Y=(0.75,1,0.75,1)$ than $Y=(1,1,1,1)$
 - Similar between rich and sparse designs for each H_1
 - Highest NSN_{power} for N_{OO} distribution

Conclusion

Optimal design through M_F approach is a powerful tool to help planning paediatric PK studies. The assumption on the expected BW distribution is important to choose a number of children sufficient to demonstrate a significant BW effect on the PK parameters but the precision of the parameter estimates should not be neglected.

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[1] Mentré F, Mallet A and Baccar D. *Biometrika*. 1997

[2] Ogungbenro K, Gueorgueiva I and Aarons L. PopDes, www.pharmacy.manchester.ac.uk/capkr/popdes