A workflow for evaluating and optimizing the designs of paediatric studies

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Objective

To develop a standardized in-silico workflow for efficiently designing paediatric PK studies, aligning with the FDA precision criteria for sample size justification [1].

Workflow template

The template workflow was developed for RStudio and Quarto, using an example inspired by multiple real-life examples [2]. In this example, the drug was first studied in adults. The adult PK model was a two-compartment linear model with a first order absorption.

We proceeded with the following workflow structure:

1. Paediatric PK model
Assumed to be the same as the adult PK model with the inclusion of the respective allometric scaling and maturation functions:

$$CL = \theta_1 \cdot (WT/WT_{median})^{\beta_1} \cdot PMA^{\gamma}/(PMA50^{\gamma} + PMA^{\gamma}) \cdot e^{\eta_1}$$
$$V_c = \theta_2 \cdot (WT/WT_{median})^{\beta_2} \cdot e^{\eta_2}$$

The values of the parameters governing these functions were obtained from literature, and to be latter estimated based on data from the future paediatric study.

2. Model implementation in mrgsolve
The model implementation was validated by comparing mrgsolve [3] population predictions with the population predictions from NONMEM, see supplementary material.

3. Proposed study design
In absence of good starting dosing regimens for the proposed design, doses can be optimized based on a known PK target, see supplementary material.
In this example, the proposed design for the paediatric study included age and weight-based dosing regimens, and five age-based cohorts of 25 patients, see supplementary materials.

4. Design evaluation:
The proposed design was evaluated in PopED [4,5] as follow:

a) All patients in each cohort were assumed to have the same covariates, using the expected median age and weight from NHANES database, per cohort.

b) Each patient was assigned an individual age and weight, sampled once from NHANES database [6] to achieve a realistic covariate distribution.

c) The sampling from NHANES database was repeated 100 times to generate 100 realizations of this design and their corresponding mean RSE (%).

Results from these different evaluations are presented in Table 1.

5. FDA precision criteria:

"The study must be prospectively powered to target a 95% CI within 60% and 140% of the geometric mean estimates of CL and V_c for the drug in each paediatric sub - group with at least 80% power". [1,7]

Computations

PopED evaluation results (Figure 1) were used to compute 95% CIs for apparent CL and V_c across all age groups.

To compute the power, we performed N simulations to construct N confidence intervals. The power was then calculated as the percentage of the 95% CIs that fell within 60 and 140% of the geometric mean estimates.

6. Optimization
When unsatisfactory results are obtained, different design aspects (sampling schedule, doses, N of subjects per cohort etc.) can be optimized to arrive at an optimized design, see supplementary material.

The optimized design is then evaluated in PopED to compute the power per FDA precision criteria, as presented in Figure 2.

7. Stochastic simulation and estimation (SSE):
To confirm PopED results for the optimized design, we sampled 100 different data sets from the NHANES data and performed SSE using NONMEM. The results of the SSE were in good agreement with PopED results, as shown in Figure 3.

Conclusions

We successfully developed and show-cased a workflow for optimizing and evaluating paediatric studies based on available PK models in adults, before access to paediatrics data.

Table 1. Expected parameter RSE (%) for the proposed and optimized design evaluations.

		Parameter								
Design	Evaluation	CL	V_c	Q	V_p	k_a	β_1	β_2	γ	PMA50
Proposed	a	13	16	28	16	23	27	13	651	444
	b	10	13	22	13	23	14	10	59	12
	c	9	11	20	9	23	11	8	35	8
Optimized	c	8	10	17	10	17	9	7	26	4

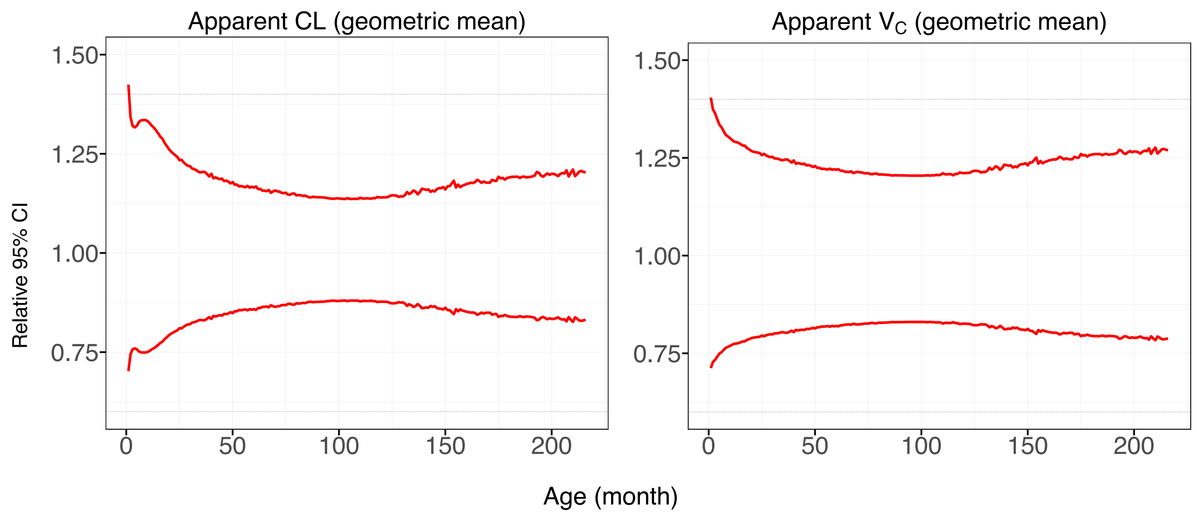

Figure 1. FDA criteria for the geometric mean of the apparent CL and V_c from evaluation (c) with the proposed design in PopED. The relative 95% CI for the geometric mean estimate (red lines) should be between 0.6 and 1.4 (black dotted lines) for both parameters to pass the criteria.

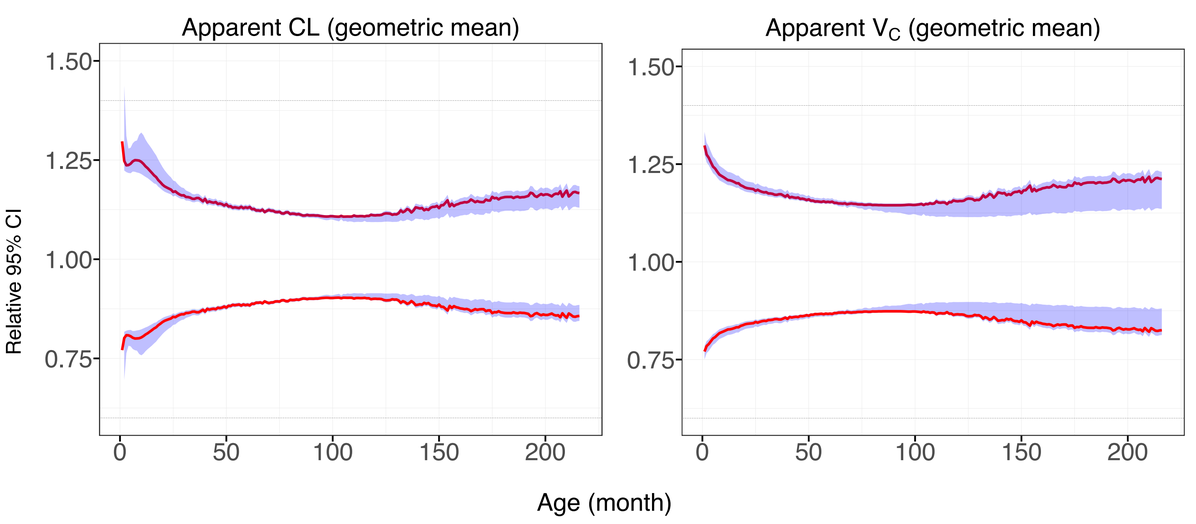

Figure 2. FDA criteria for the geometric mean of the apparent CL and V_c of the optimised design in PopED. The relative 95% CI for the geometric mean estimate are the red lines. The shaded blue areas are the confidence intervals around the 2.5th and 97.5th percentiles of the 95% CI. The power can be calculated as the percentage of the 95% confidence intervals that are within 0.6 and 1.4. The power for the apparent CL was 89% and for the apparent V_c was 100%.

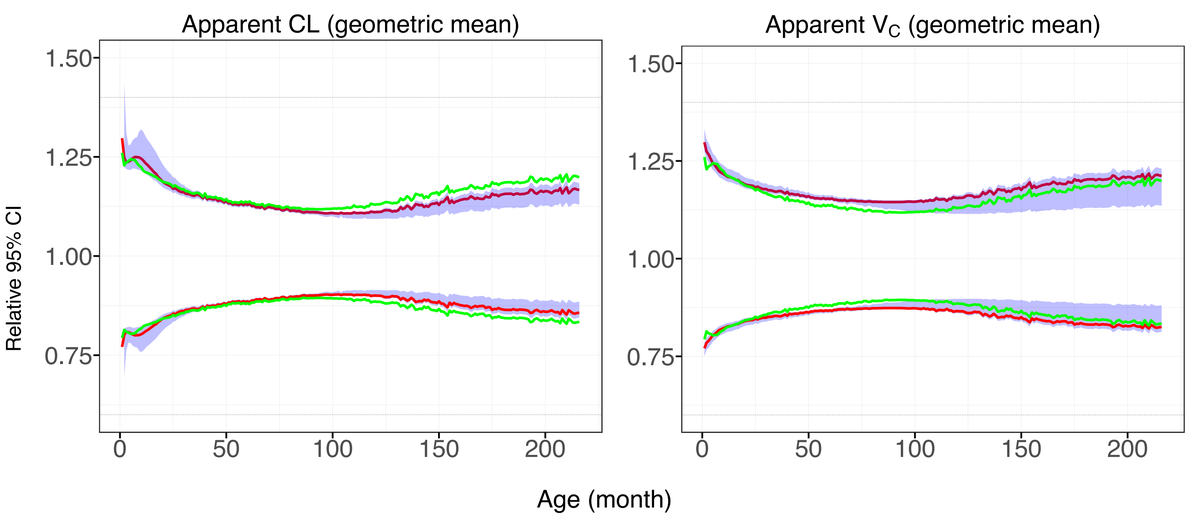

Figure 3. FDA criteria for the geometric mean of the apparent CL and V_c of the optimized design from the stochastic simulations and estimations. The relative 95% CI for the geometric mean estimate (green lines) overlaps with results from PopED (red lines and blue shaded areas).

References

1. Y. Wang, et al, J Clin Pharmacol 2012, 52, 1601.
2. G. Montepiedra, et al, CPT: PSP 2023, 13, 270.
3. K. Baron, "Mrgsolve: Simulate from ODE-Based Models." 2022.
4. M. Foracchia et al, Comput Methods and Programs Biomed 2004, 74, 29.
5. J. Nybergey, et al, Comput Methods and Programs Biomed 2012, 108, 789.
6. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. 2017-2020.
7. Draft Guidance - General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products Guidance for Industry, FDA-2013-D-1275, 2022

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Supplementary material

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Proposed study design

The proposed design for the paediatric study included age and weight-based dosing regimen, as presented in Table S1.

The proposed study design contained 5 age-based cohorts with N=5 per cohort:

< 3 years (with 3 subjects < 6 month) | 3 - <6 years | 6 - <9 years | 9 - <12 years | 12 - <18 years

Table S1. Proposed drug dosing nomogram, subjects younger than 12 month receive the oral solution formulation, otherwise, they receive the tablet formulation

Single Dose [mg]	Weight [kg]										
Age	2.5–<3	3–<4	4–<5	5–<7	7–<9	9–<11	11–<13	13–<21	21–41	41–<81	>81
0– <1 m	11	11	11	17	––	––	––	––	––	––	––
1– <2 m	11	11	17	17	––	––	––	––	––	––	––
2– <3 m	11	17	17	25	––	––	––	––	––	––	––
3– <4 m	11	17	25	25	30	––	––	––	––	––	––
4– <5 m	17	17	25	30	35	––	––	––	––	––	––
5– <6 m	––	17	25	30	35	40	––	––	––	––	––
6– <7 m	––	––	25	30	40	40	––	––	––	––	––
7– <8 m	––	––	25	30	40	50	––	––	––	––	––
8– <9 m	––	––	30	35	40	50	––	––	––	––	––
9– <10 m	––	––	30	35	40	55	––	––	––	––	––
10– <11 m	––	––	––	35	50	55	70	––	––	––	––
11– <12 m	––	––	––	40	50	55	70	––	––	––	––
1– <1.5 y	––	––	––	50	55	60	75	80	––	––	––
1.5– <2 y	––	––	––	50	55	70	75	80	120	––	––
2– <2.5 y	––	––	––	––	60	70	80	100	140	––	––
2.5– <3 y	––	––	––	––	60	70	100	100	140	220	300
3– <6 y	––	––	––	––	60	70	100	100	140	220	300
6– <9 y	––	––	––	––	––	80	100	100	140	220	300
9– <12 y	––	––	––	––	––	80	100	100	140	220	300
12– <18 y	––	––	––	––	––	80	100	100	140	220	300

Table S2. Study design variables

Dosing interval	Study duration	Drug formulation	Therapeutic window	Cohorts
12 hours	Five days	Oral solutions< 12 month Tablets ≥ 12 month	20-300 μg/L	5 cohorts x 5 subjects

Dose optimization

In absence of good starting dosing nomogram for the proposed design, doses can be optimized based on a known PK target, e.g. $C_{ss,min}$ of 100 μg/L, by defining a cost function in PopED, to optimize a design with the median age and weight for each possible dosing category.

```
crit_fcn <- function(poped.db,...){
    pred_df <- model_prediction(poped.db)
    sum((pred_df[pred_df["Time"]==120,"PRED"] - rep(100,n_groups))^2)
}
```

Table S2. The optimized doses for the possible nomogram categories based on the cost function.

Single Dose [mg]	Weight [kg]										
Age_category	2.5–<3	3–<4	4–<5	5–<7	7–<9	9–<11	11–<13	13–<21	21–41	41–<81	>81
0– <1 m	13	15	18	22	––	––	––	––	––	––	––
1– <2 m	16	18	22	26	––	––	––	––	––	––	––
2– <3 m	19	22	26	31	––	––	––	––	––	––	––
3– <4 m	22	26	30	36	43	––	––	––	––	––	––
4– <5 m	25	29	34	41	49	––	––	––	––	––	––
5– <6 m	––	32	38	45	54	63	––	––	––	––	––
6– <7 m	––	––	42	50	59	68	––	––	––	––	––
7– <8 m	––	––	45	54	64	74	––	––	––	––	––
8– <9 m	––	––	48	58	69	79	––	––	––	––	––
9– <10 m	––	––	51	61	73	83	––	––	––	––	––
10– <11 m	––	––	––	64	77	88	98	––	––	––	––
11– <12 m	––	––	––	67	80	91	102	––	––	––	––
1– <1.5 y	––	––	––	50	59	68	76	94	––	––	––
1.5– <2 y	––	––	––	56	66	76	84	104	151	––	––
2– <2.5 y	––	––	––	––	70	80	89	110	159	––	––
2.5– <3 y	––	––	––	––	73	83	92	114	164	251	323
3– <6 y	––	––	––	––	76	87	97	119	171	261	336
6– <9 y	––	––	––	––	––	88	98	121	174	266	341
9– <12 y	––	––	––	––	––	89	99	122	175	267	343
12– <18 y	––	––	––	––	––	89	99	122	175	267	344

As the drug is only available in limited packages, the optimal doses in Table S2 must be rounded to the closest possible dosage package, which will result in a proposed dosing nomogram very similar to Table S1.

Model implementation in mrgsolve

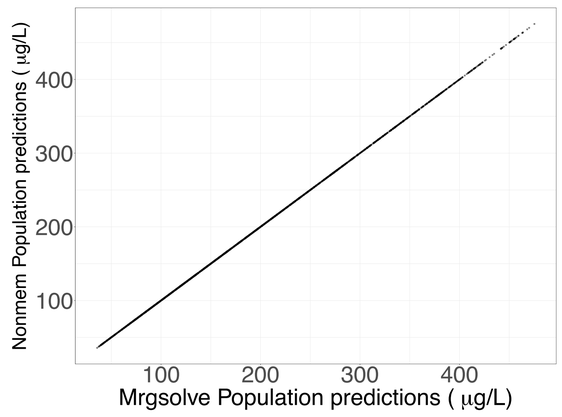

Figure S1. Nonmem population predictions vs Mrgsolve population predictions

Sampling schedule optimization

If it was possible to take only four samples per subject, we can optimize the sampling schedule to be different or to be the same between the treatment groups. In this example, we optimized the sampling schedule to be the same for all groups in PopED.

```
output_xt <- poped_optim( poped_db_xt,
                          opt_xt = TRUE,
                          parallel = T,
                          num_cores = num_cores_to_use,
                          method = c("ARS", "LS"))
```

Table S3. The optimized sampling schedule.

Obs_1	120
Obs_2	12
Obs_3	1
Obs_4	4

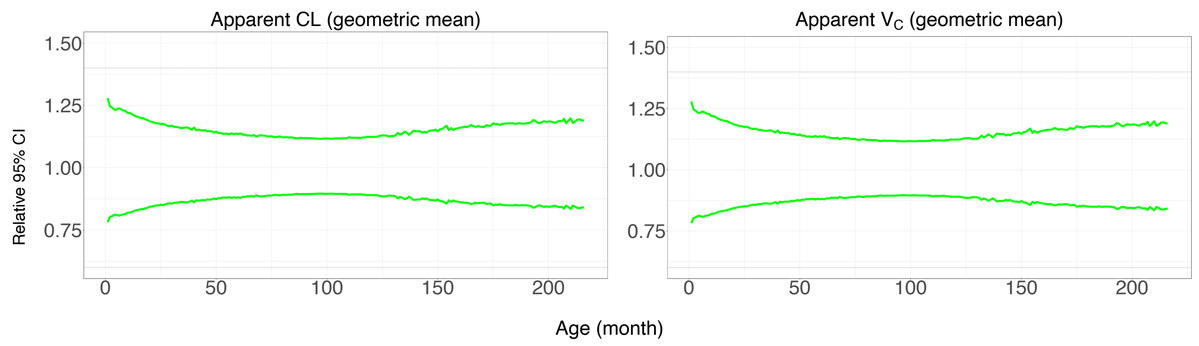

Figure S2. FDA criteria for the geometric mean of the apparent CL and V_c with the optimized sampling schedule from the stochastic simulations and estimations. The relative 95% CI for the geometric mean estimate (green lines) are within 0.6 and 1.4 for both parameters.

Optimizing N subjects per cohort

It is possible to obtain a good guess of the N of subjects needed to reduce the relative 95% CI of CL or V_c for a specific age.

For example, we can see that the upper relative 95% CI of V_c for patients with age of 1 month reaches 1.4 (0.4 above the reference) in Figure 1, and since:

$$SD = CI \cdot \sqrt{N}/Z$$

where SD is the standard deviation of V_c and Z is the Z-score, assuming symmetrical CI, then we can calculate SD:

$$SD = 0.4 \cdot \sqrt{5}/1.96 = 0.45$$

Now, we can calculate what will be the upper limit of the 95% CI of V_c when manipulating N, e.g., N=7

$$CI = 1.96 \cdot 0.45/\sqrt{7} = 0.33$$

Thus, when N=7, the upper limit of the 95% CI of V_c for patients with age of 1 month would be 0.33 instead of 0.4, and so on.

We aimed for an upper limit of the 95% CI of V_c of 0.3, N of subjects per cohort was iteratively evaluated, leading to the conclusion that N=9 was optimal, with at least N=6 subjects under the age of 6 months.