Clinical trial design optimization in paediatrics using prior knowledge combined with modelling and simulations

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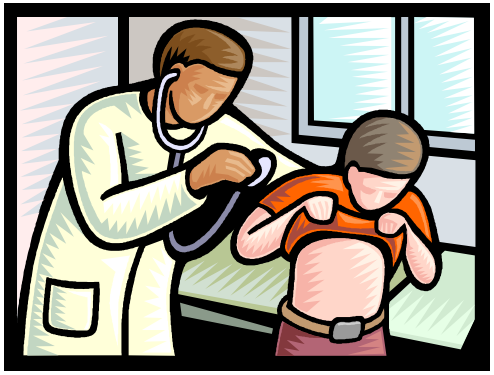


Overview

- Introduction
  - PK and PK/PD in children *versus* adults
  - How M&S can help in the design of paediatric studies
  - Use of prior knowledge for developing paediatric PK/PD simulation models
  - Data analysis methods of paediatric studies
- Three of our M&S examples in paediatrics
  - Proposing a dose adaptation rule for iv levetiracetam in children
  - Paediatric study with a renally cleared antiviral drug aiming to characterize the PK and safety
  - Ongoing M&S of a pharmacodynamic endpoint to optimize the design of a paediatric study

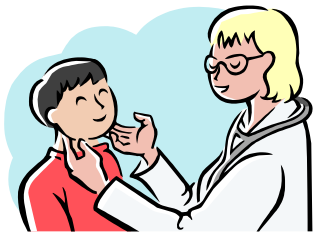
Infants and children are no little adults !!

- Absorption: Increased gastric pH, different motility
- Distribution: Decreased protein binding, Increased total body water, variable fat content
- Elimination: Immature and changing hepatic clearance mechanisms, glomerular filtration and tubular excretion

- Target tissues/organs/systems are in development
- Immune system in young children is different from adults
- Dose-response can be different
- Diseases specific to children or different from adults
- Also adverse events may differ

These differences necessitate specific paediatric studies, but there are some constraints:

- Practical constraints:
  - Invasive sampling (pain, anxiety)
  - Number of blood samples
  - Sampling volume
  - Recruitment (age categories)



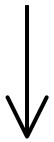
- Ethical constraints:
  - Direct benefit often absent in PK studies
  - Consent from parents sometimes difficult to obtain

➢ We need to be most efficient with the information/subjects we do have in paediatric studies

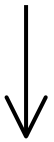
➢ Optimization of clinical trial design using M&S

How M&S can help in the design of paediatric studies?

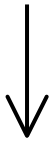
Development of a population PK-PD-disease model using prior knowledge



Simulation of 'realistic virtual patients'

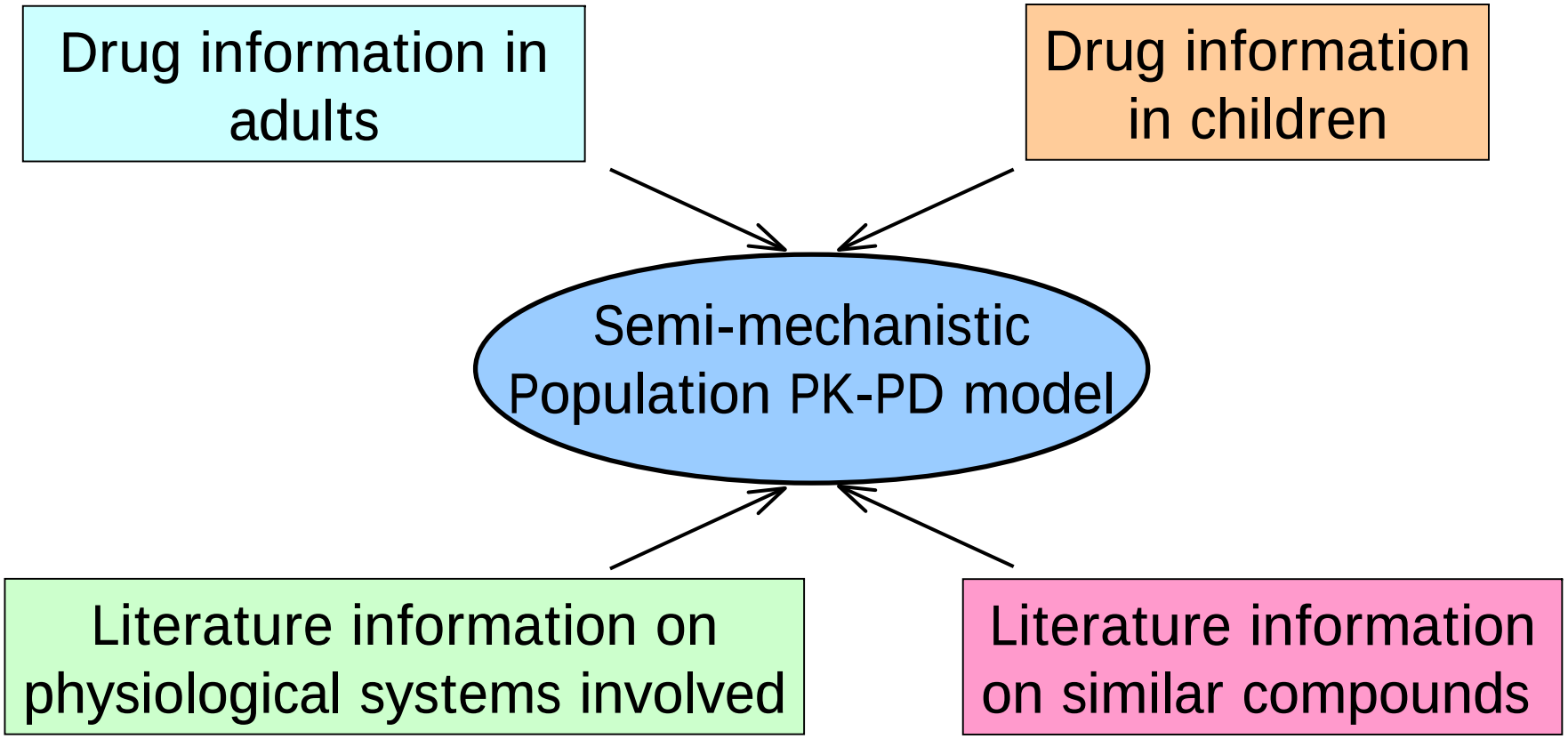


Simulation of virtual clinical trials

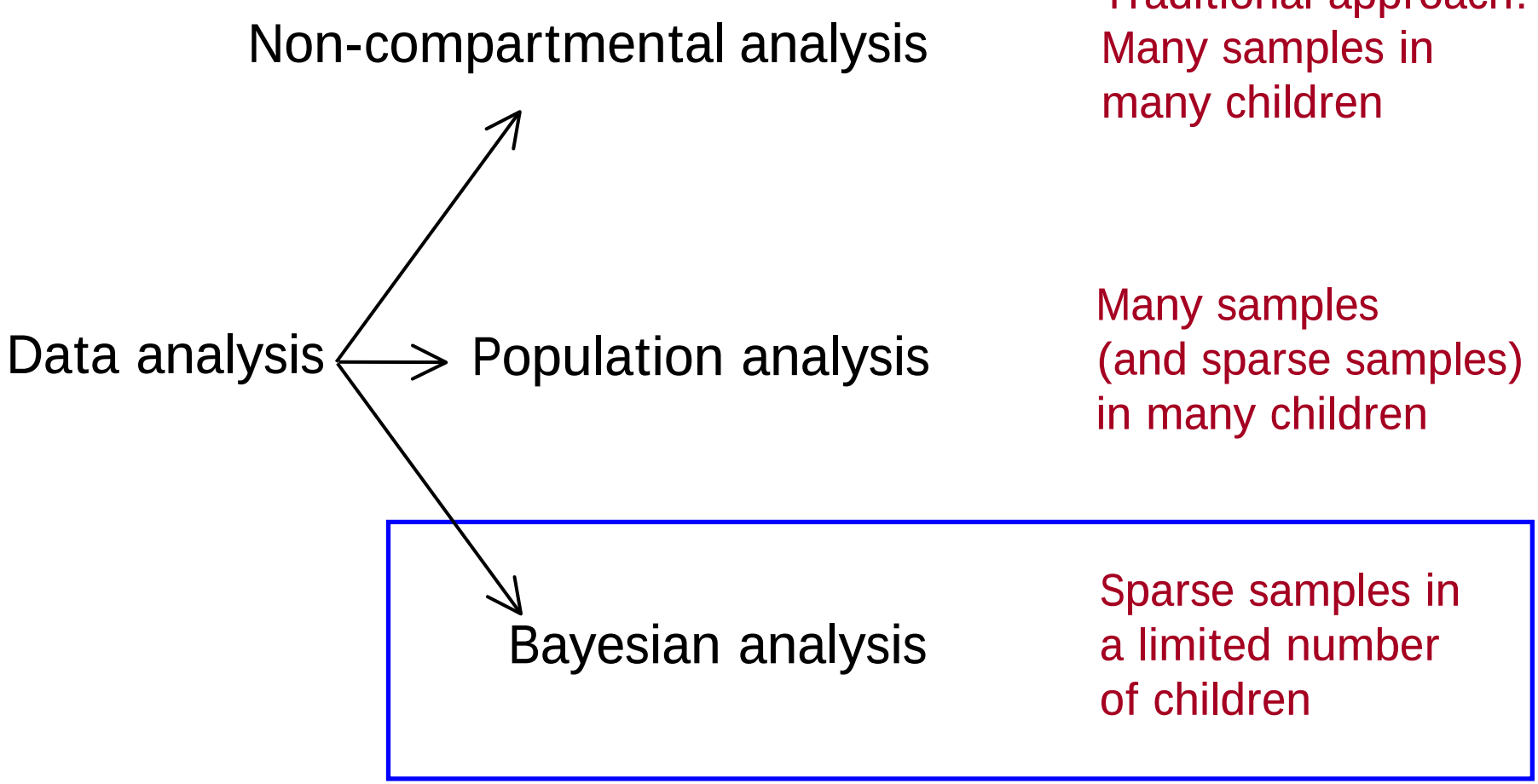


Optimization of study design and data analysis method prior to the study

Use of prior knowledge for developing paediatric PK/PD simulation models:



The design of a paediatric trial highly depends on the data analysis method:



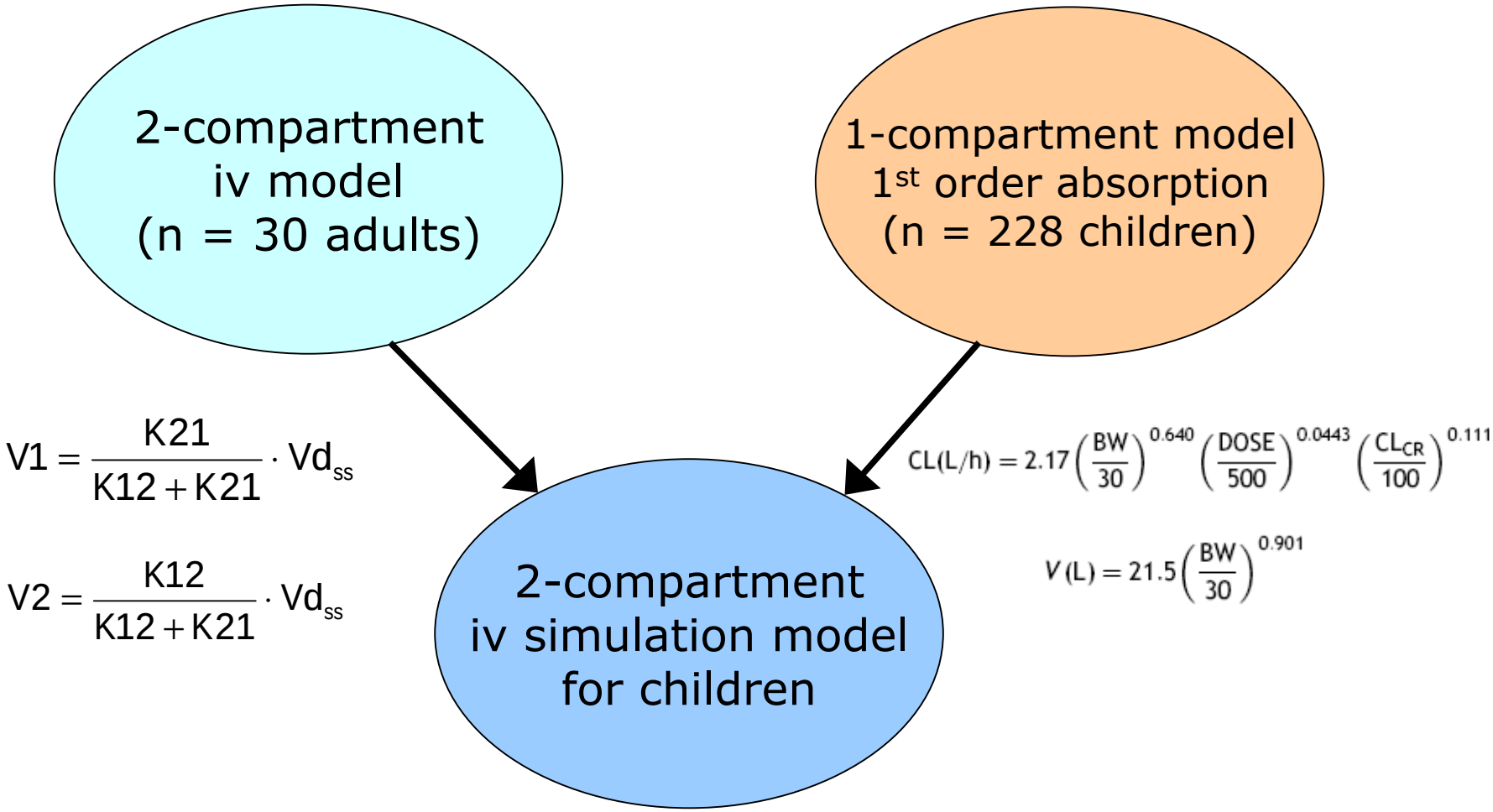
Example I

Proposing a dose adaptation rule for
iv levetiracetam in children

Goals and available data:

- To advise about a dose adaptation rule for iv levetiracetam in children
  - iv dose and duration of infusion
  - AUCτ and Cmax in children and adults after iv levetiracetam should be in the same range
- Available data and prior knowledge:
  - Population pharmacokinetics after oral levetiracetam in children
  - Population pharmacokinetics after iv levetiracetam in adults
  - Covariate influences on CL and V

Two population PK models were combined to obtain a simulation model for iv levetiracetam in children:



Simulations based on covariate values for typical children...

Subject	Twice daily dose	Age (years)	Weight (kg)	Height (cm)	CL_{CR} (mL/min)
Child					
1	30 mg/kg	4	15	98	43
2	30 mg/kg	8	25	127	63
3	30 mg/kg	12	40	148	85
4	30 mg/kg	14	50	162	100
Adult					
1	1500 mg	20	50	157	98
2	1500 mg	20	75	179	129
3	1500 mg	20	100	190	153

Based on stature-for-age and weight-for-age percentile graphs (National Center for Health Statistics)

- The iv paediatric model was successfully qualified for simulations
- Existing covariate influences on CL and V in children were retained
- Inter-individual variability on CL, Vd_{ss} and K12
- Residual error of 30% CV
- Simulation model was implemented in TS2
- Simulation of 2000 steady-state plasma concentration-time profiles
- Calculation of C_{trough}, C_{max} and AUC_{τ}

... showed that Cmax,ss and AUCτ after a 15-min iv infusion of 30 mg/kg in children were within the range of those after iv 1500 mg in adults:

Table 3 Median, 5th and 95th percentiles of simulated steady-state C_{trough}, C_{max} and AUCτ following twice daily 15-min intravenous infusion or oral administration of 30 mg/kg levetiracetam in epileptic children and 1500 mg in adults

Subject	Levetiracetam 15-min intravenous infusion			Oral levetiracetam		
	C_{trough} (μg/mL)	C_{max} (μg/mL)	AUCτ (μg h/mL)	C_{trough} (μg/mL)	C_{max} (μg/mL)	AUCτ (μg h/mL)
Child						
1	14 (6–30)	72 (39–140)	373 (261–536)	17 (7–35)	51 (29–88)	371 (238–560)
2	17 (8–35)	76 (42–143)	419 (294–597)	20 (9–40)	57 (33–97)	419 (270–630)
3	20 (9–41)	81 (46–150)	470 (331–679)	23 (10–46)	63 (37–107)	469 (304–700)
4	22 (10–44)	85 (47–158)	495 (345–716)	24 (11–48)	66 (39–111)	495 (321–735)
Adult						
1	22 (10–45)	86 (46–160)	499 (348–727)	24 (11–48)	66 (39–111)	495 (322–737)
2	17 (8–34)	62 (34–114)	371 (259–530)	19 (9–37)	49 (29–81)	371 (242–551)
3	14 (7–29)	50 (27–91)	303 (207–434)	16 (7–31)	39 (24–65)	302 (197–449)

C_{trough}, plasma concentration at time zero; C_{max}, maximum plasma concentration; AUCτ, area under the plasma concentration-time curve over a dosing interval.

Added value of M&S for iv levetiracetam in children:

With no iv data of levetiracetam in children, but with separate population PK models developed based on iv data in adults and oral data in children, it was possible to evaluate dose adaptation rules of iv levetiracetam in children in terms of:

- iv dose and infusion duration:
  - to avoid high plasma concentrations and thus minimizing the risk of adverse events
  - to have an AUCτ similar to adults and thus to obtain a similar efficacy
- Predicted PK of iv levetiracetam in children
- Similar inter-compartmental distribution rates between adults and children should be confirmed in paediatric studies

Example II

Paediatric study with a renally cleared antiviral drug aiming to characterize the PK and safety

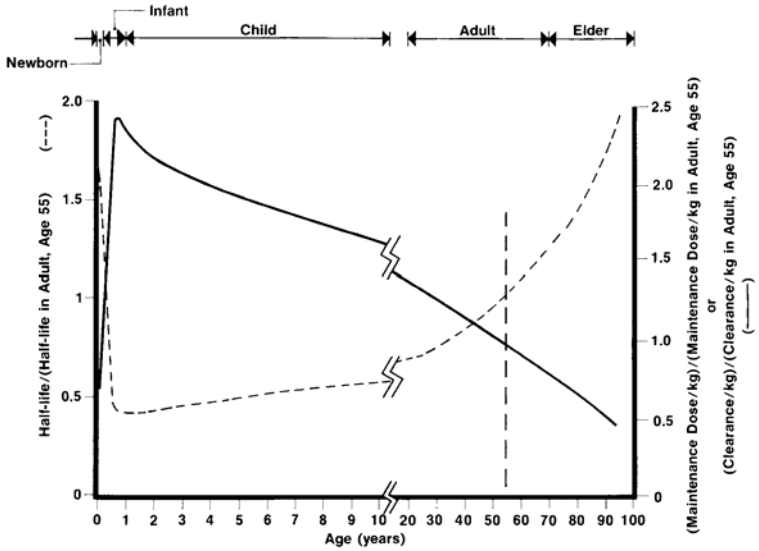
Goals and available data:

- To advise about a dose adaptation rule
- Study design optimization
  - Dose(s)?
  - How many samples and at what time points?
  - How many children?
- What might happen in neonates and infants?
- Available data and prior knowledge:
  - General PK characteristics of the drug
  - Literature information on CL related to AGE and BW and kidney maturation
  - Limited data on PK in adults and children

What is the expected behaviour of the drug that we are studying in children, knowing that it is renally cleared?

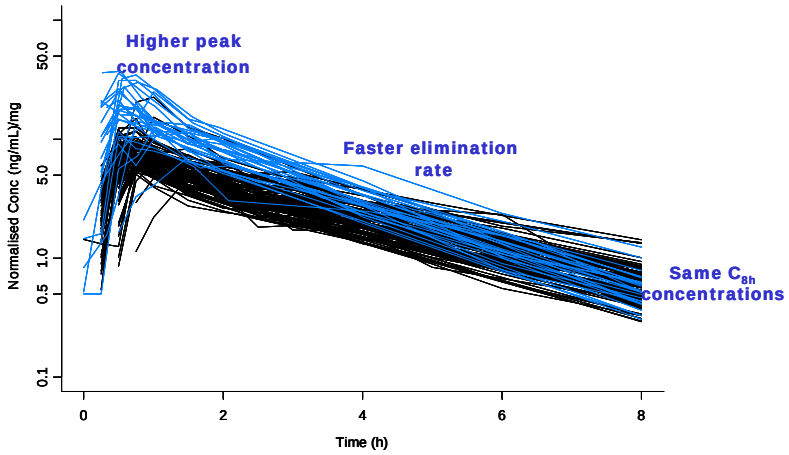
- The drug
  - distributes in body water
  - has a low protein binding
  - is mainly renally excreted unchanged

$$CL\{mL/min\} = \frac{CL_{ref}\{mL/min\}^{a} \cdot [140 - AGE\{y\}] \cdot BW\{kg\}^{0.7}}{1660}$$



Rowland and Tozer: Clinical Pharmacokinetics Concepts & Applications

Dose normalised plasma concentration in children and adults



Tod M, Lokiec F, Bidault R, De Bony F, Petitjean O, Aujard Y. Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. Antimicrob Agents Chemother 2001 45:150-7

$$MF = \frac{PCA^{6.17}}{13.4^{6.17} + PCA^{6.17}}$$

MF = Maturation Factor
PCA = Post Conceptional Age in months

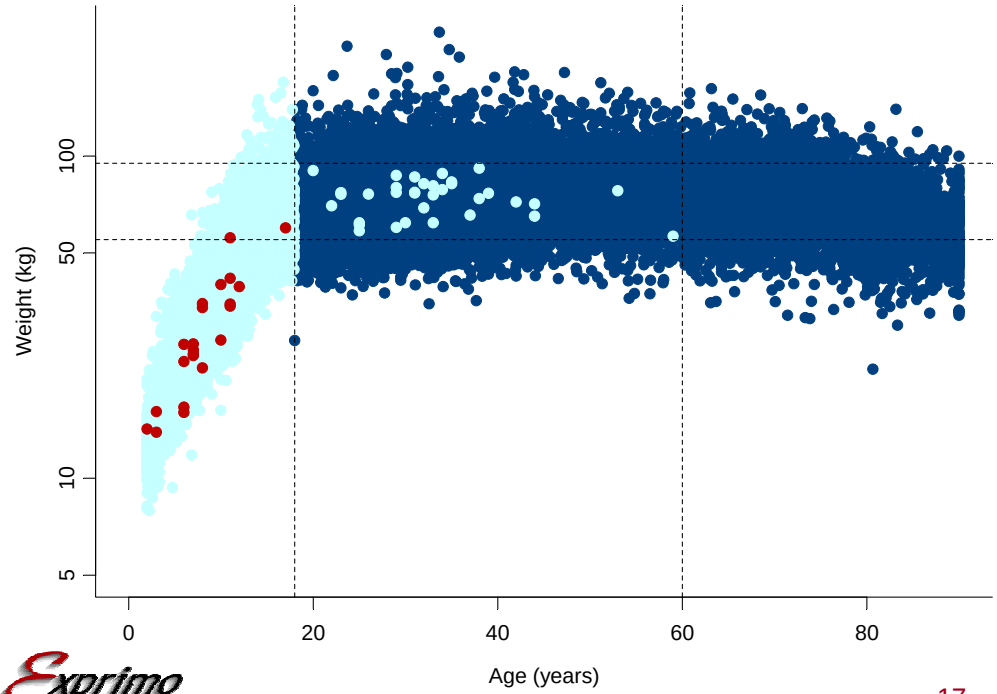
For simulations using virtual realistic patients the relationship between age and weight need to be known

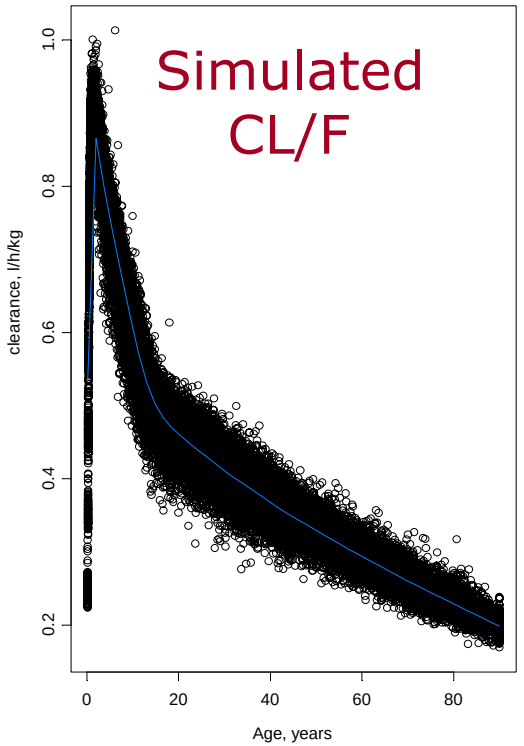
Model:

$$CL = \theta_1 \cdot \frac{(140 - AGE)}{105} \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot MF \cdot \exp(\eta)$$

$$V = \theta_3 \cdot \left(\frac{WT}{70}\right)^{\theta_4} \cdot \exp(\eta)$$

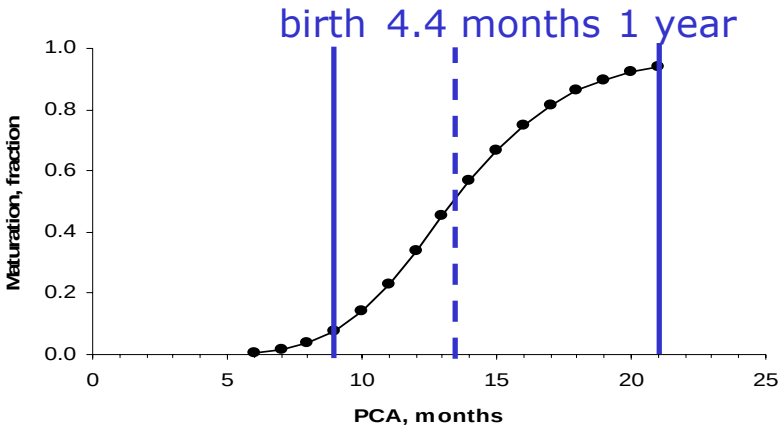
Population:





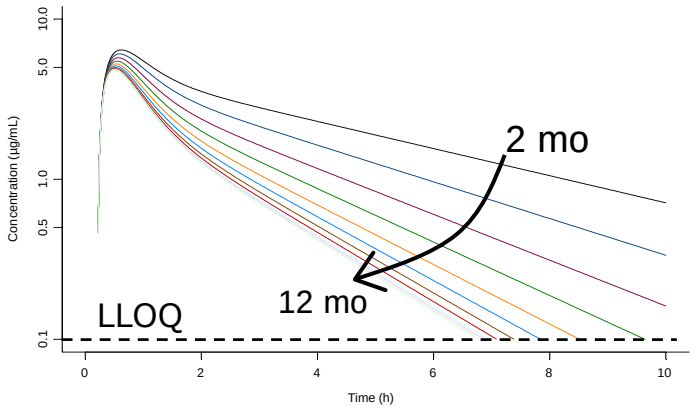
Exploration of the model shows that maturation of the renal function has a large influence on the PK profile

$$MF = \frac{PCA^{6.17}}{13.4^{6.17} + PCA^{6.17}}$$

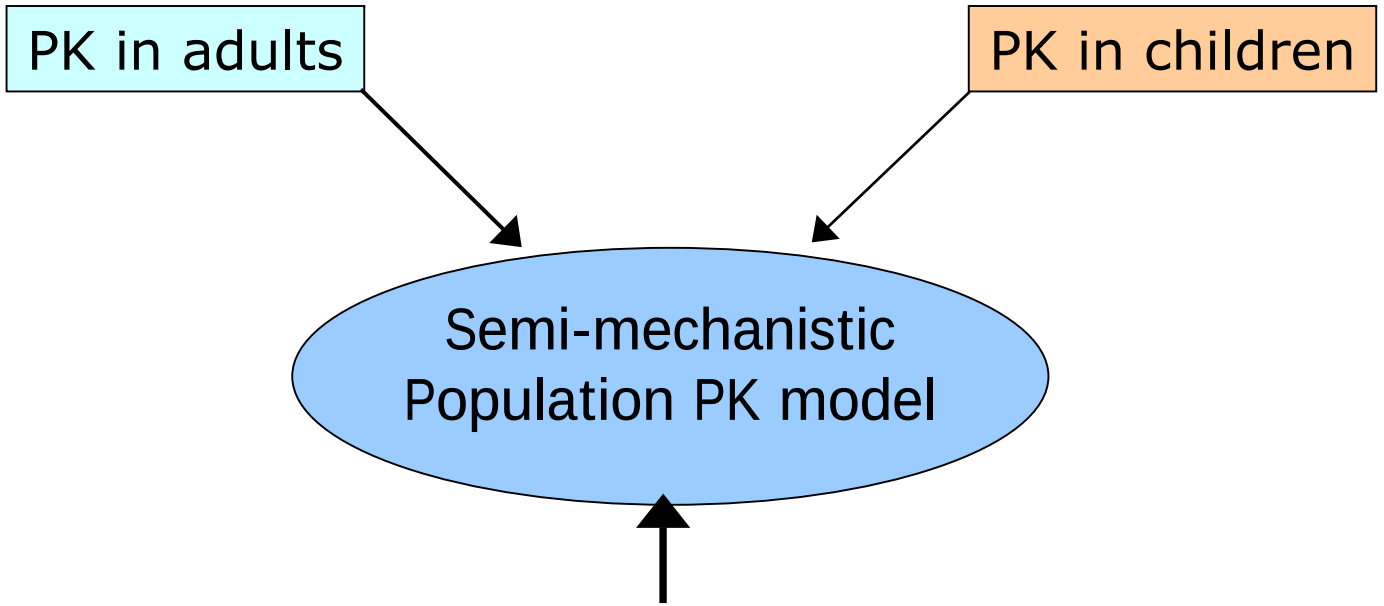


$$CL_{infant} = \theta_1 \cdot \frac{(140 - AGE)}{105} \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot MF \cdot \exp(\eta)$$

$$V_{infant} = \theta_3 \cdot \left(\frac{WT}{70}\right)^{\theta_4} \cdot \exp(\eta)$$



Population PK simulation model of renally cleared antiviral drug in children and adults:



$$CL_{infant} = \theta_1 \cdot \frac{(140 - AGE)}{105} \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot MF \cdot \exp(\eta)$$

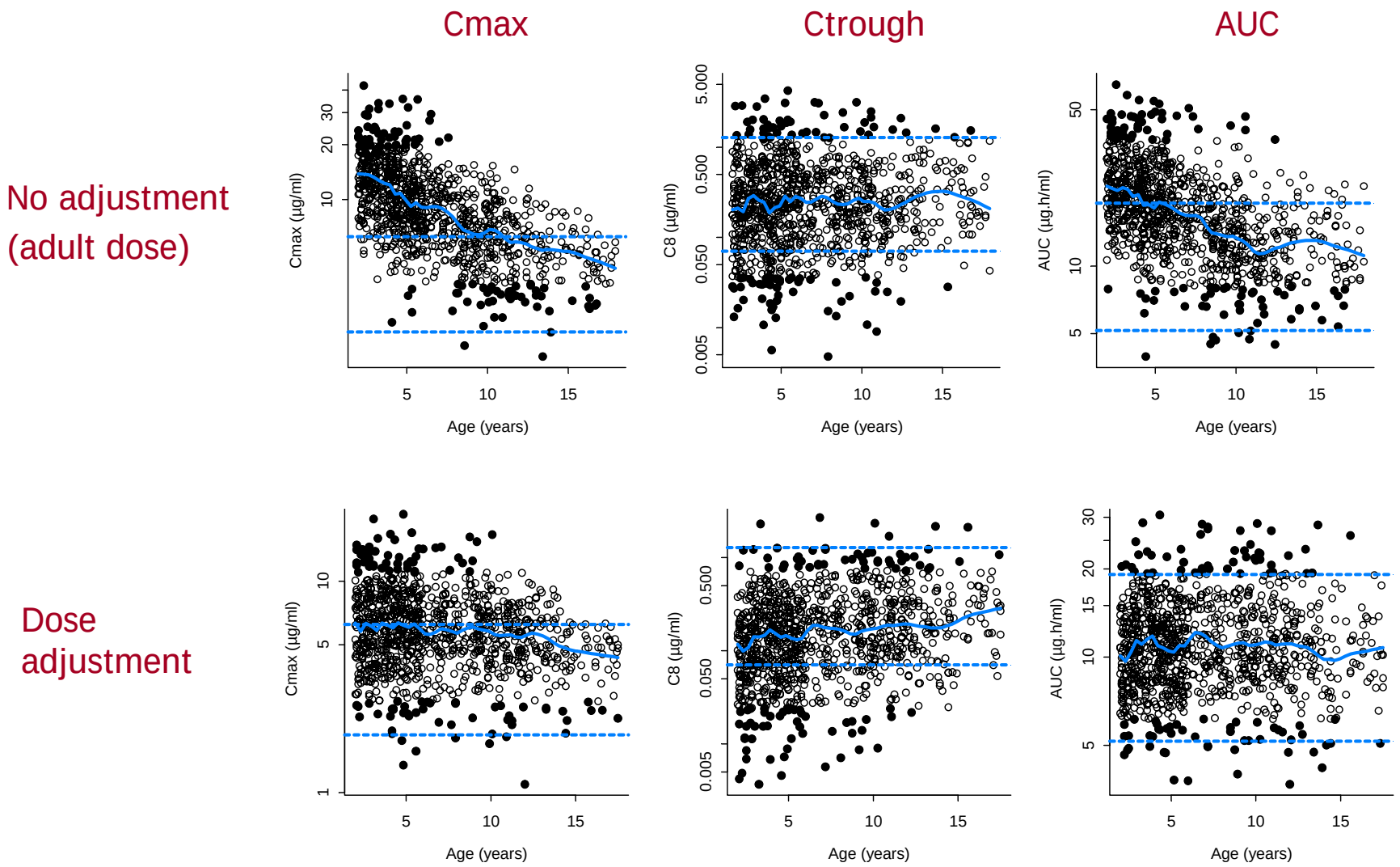
$$MF = \frac{PCA^{6.17}}{13.4^{6.17} + PCA^{6.17}}$$

$$V_{infant} = \theta_3 \cdot \left(\frac{WT}{70}\right)^{\theta_4} \cdot \exp(\eta)$$

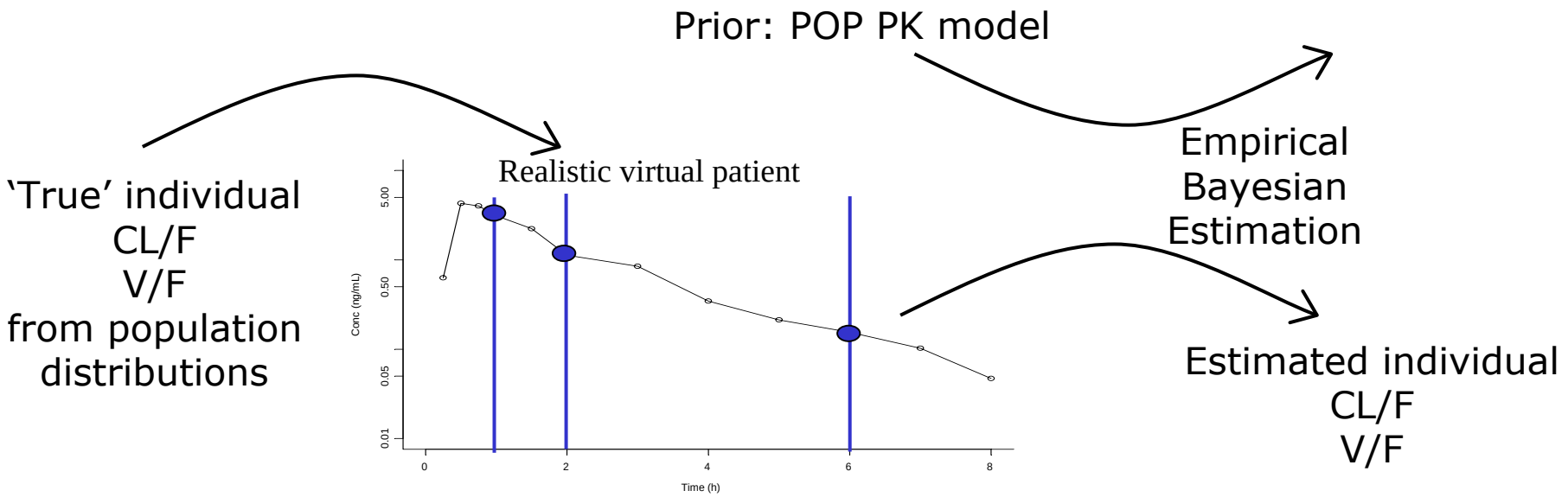
Literature information physiological systems involved

Literature information similar compounds

Adjustment of the dose to 12.5 mg/kg below 40 kg gives comparable AUC with acceptable Cmax and Ctrough:

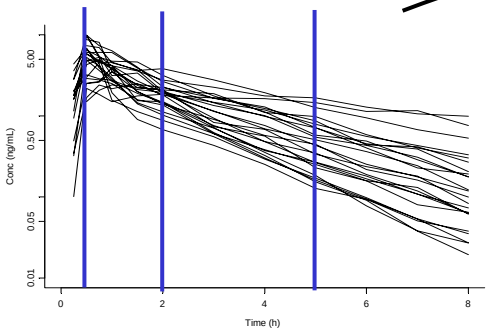


Simulations to determine the optimal number of samples and sampling times

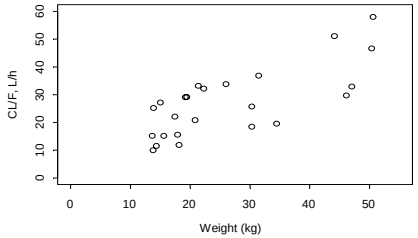


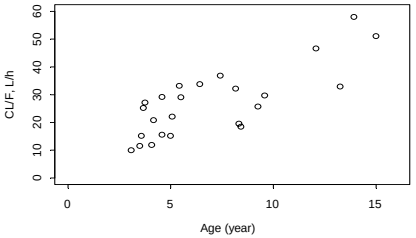
- Simulation of concentration-time profiles in virtual patients (using the dose adaptation rule)
- Drawing of virtual samples at various time points
- Estimations of parameters (CL/F and V/F)
- Comparison with 'true' values used in the simulation

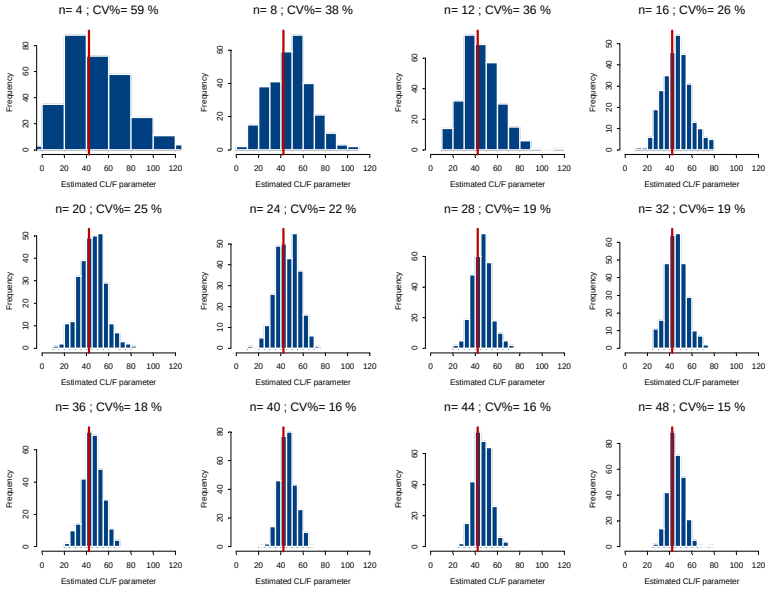
The number of children required to confirm the PK in children is indicated by the decrease in the uncertainty of determining CL/F in simulated studies

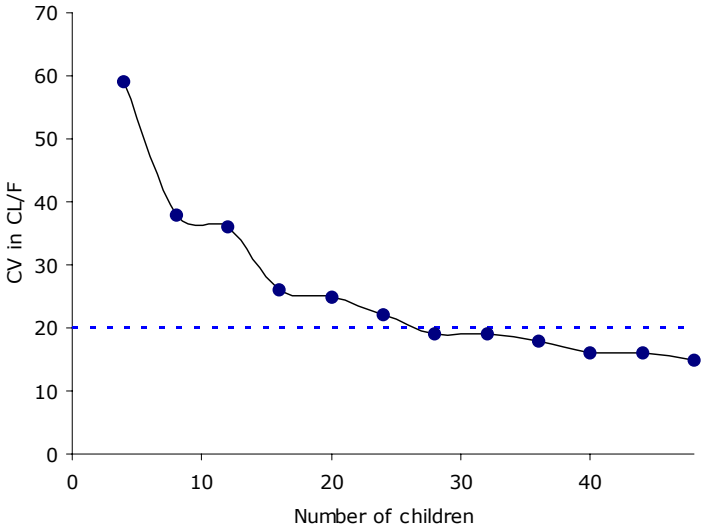


Individual Empirical Bayesian Estimates









Added value of M&S in this paediatric case study with a renally cleared antiviral drug

With relatively little data, and application of literature information, it was possible to make a well-founded informed decision for the design of a paediatric study in terms of:

- Dose adaptation rule: 12.5 mg/kg below 40 kg
- Number of samples: 3
- Optimal sampling times: 0.75, 1.5 and 5 h
- Number of children: 28 - 32
- Analysis method: Bayesian Empirical Estimation
- Predicted PK in neonates and infants

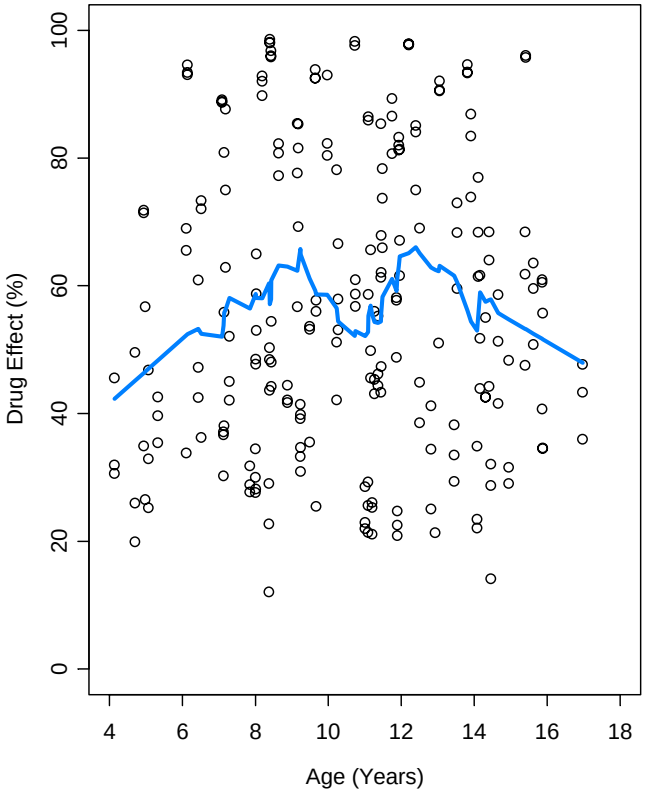
Example III

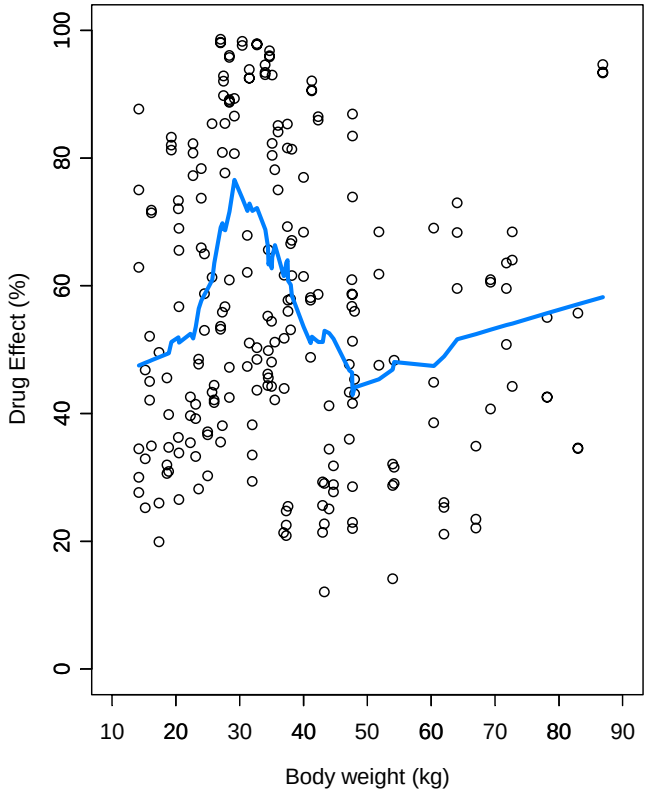
Ongoing M&S of a pharmacodynamic endpoint
to optimize the design of a paediatric study

Goals and available data:

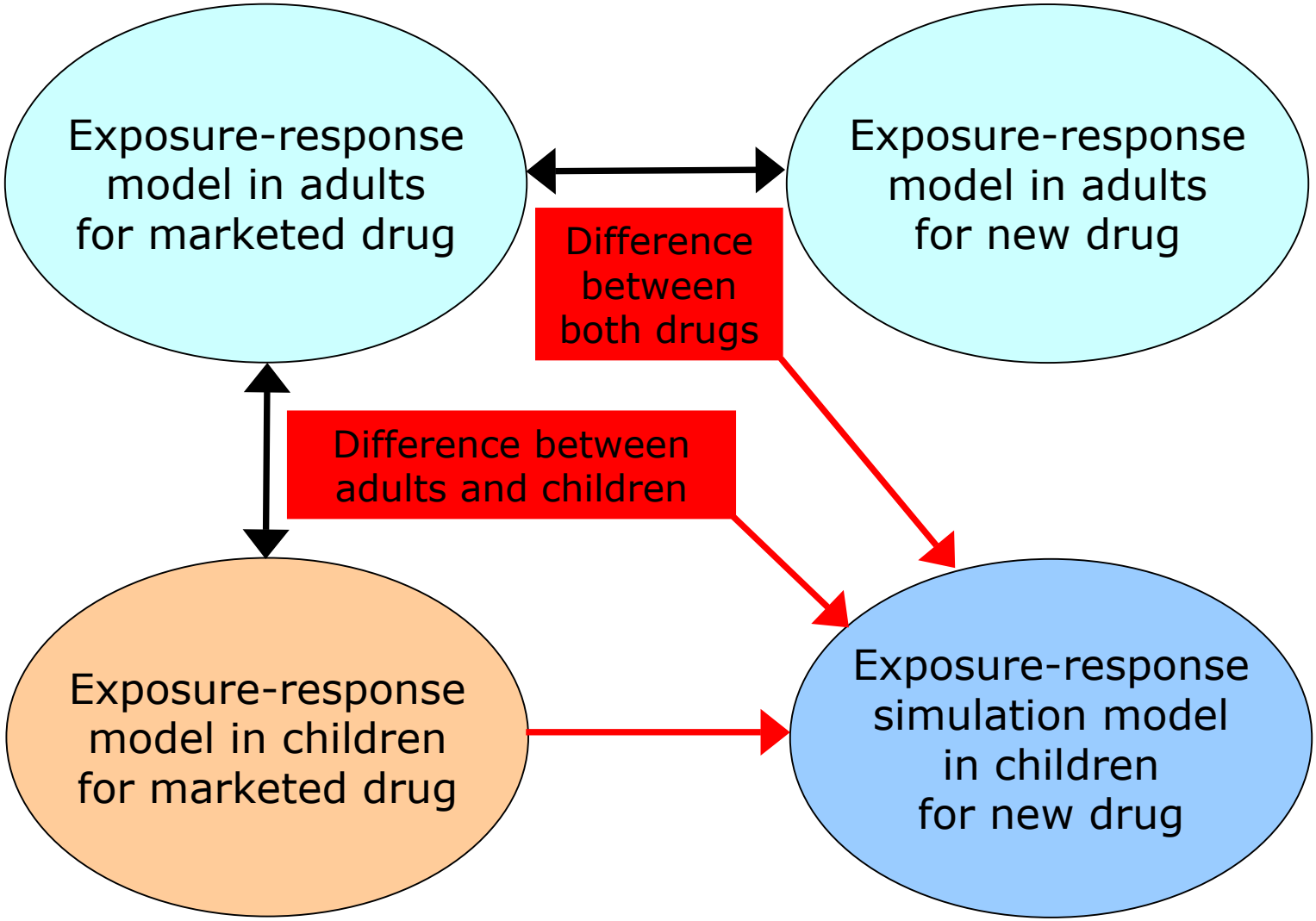
- To advise about a dose adaptation rule
- Study design optimization, e.g.:
  - Dose(s)?
  - Duration?
  - Baseline criteria?
  - How many children?
- Available data and prior knowledge:
  - Exposure-response model of PD endpoint in adults for drug on the market
  - Exposure-response model of PD endpoint in children for drug on the market
  - Exposure-response model of PD endpoint in adults for new drug

Covariate influences on PD endpoints in children may be less straightforward to describe:





Three models are currently combined to develop a simulation model for the PD endpoint of the new drug in children:



Conclusions:

- Prior knowledge can be used appropriately for developing paediatric PK/PD simulation models:
  - Literature information on physiological systems involved
  - Literature information on similar compounds
  - PK/PD data in adults
  - Available PK/PD data in children
- Bayesian Empirical estimation based on a population PK model in adults and children may allow sparse sampling in a limited number of children
- Modelling and simulations may help to make well-founded informed decisions about the design of planned paediatric studies

Acknowledgements:

- Novartis:
  - Mick Looby
  - Colin Pillai
  - Jean-Louis Steimer
- UCB:
  - Laura Sargentini-Maier
  - Armel Stockis
- Exprimo:
  - Philippe Jacqmin
  - Christian Laveille
  - Rik Schoemaker
  - Peter Vis