Using Pharmacometrics to Optimize Sparse Sampling Study Designs in Paediatric and Special Population Studies.

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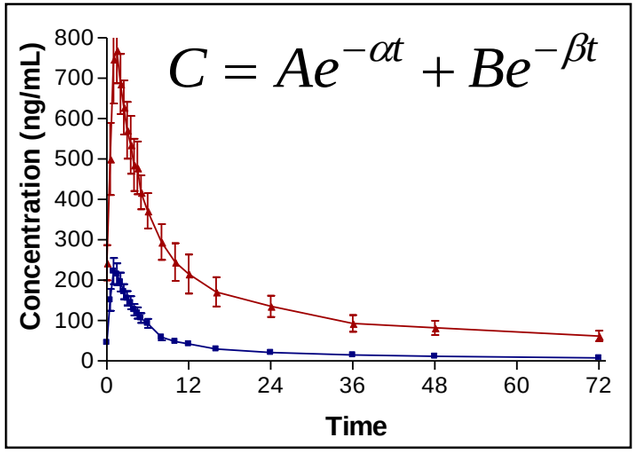
I’ve heard of pharmacokinetics and pharmacodynamics maybe even pharmacogenomics, but what is pharmacometrics?

Pharmacometrics: The Science of Quantitative Pharmacology

- The science that quantifies drug, disease and trial information to aid efficient drug development, regulatory decisions and clinical decisions.
- Drug models describe the relationship between exposure (or pharmacokinetics), response (or pharmacodynamics) for both desired and undesired effects, and individual patient characteristics.
- Disease models describe the relationship between biomarkers and clinical outcomes, time course of disease and placebo effects.
- The trial models describe the inclusion/exclusion criteria, patient discontinuation and adherence.

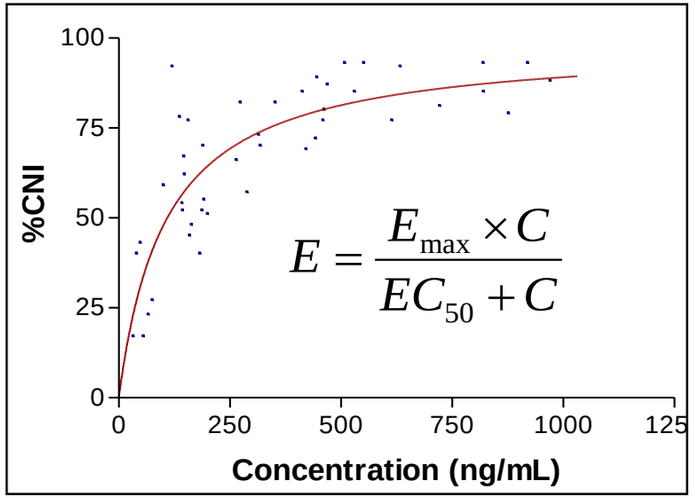
-Adapted from FDA
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm167032.htm#Overview

Pharmacokinetics (A.D.M.E.T)



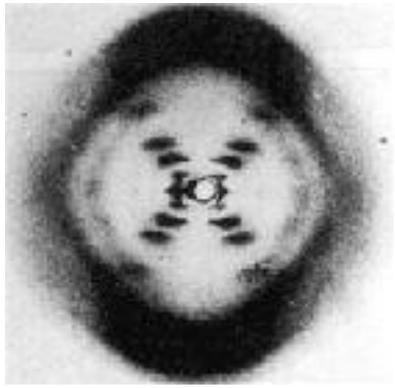
Concentration vs Time

Pharmacodynamics (PD): Direct



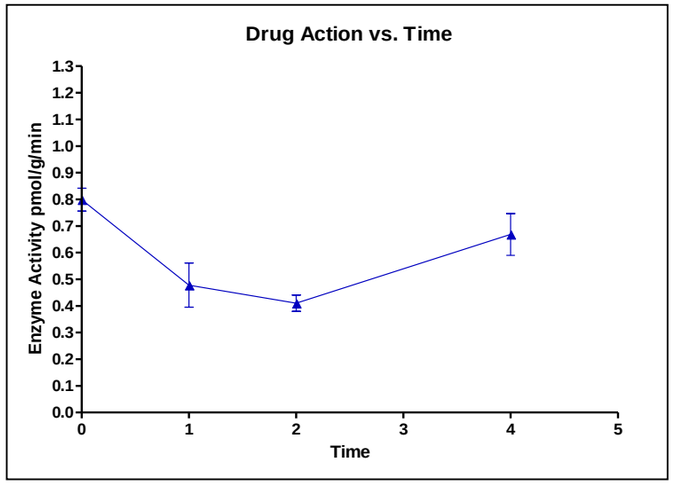
Concentration - Effect

Pharmacogenomics (PGx)



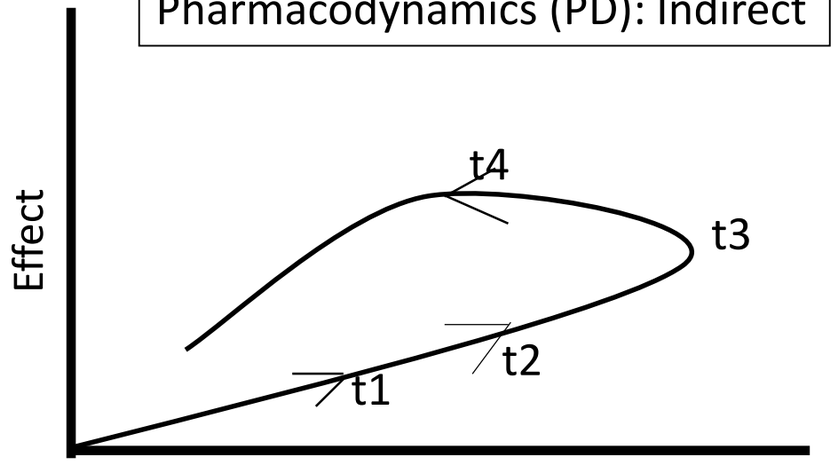
Pharmacogenetics (PGt)

PK-PD

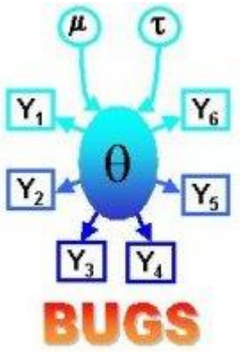


Effect vs Time

Pharmacodynamics (PD): Indirect



$$Ce = \frac{keoKaFD}{Vc}\left[\frac{e^{-Kat}}{(K-Ka)(keo-Ka)} + \frac{e^{-Kt}}{(Ka-K)(keo-K)} + \frac{e^{-keot}}{(Ka-keo)(K-keo)}\right]$$



Disease Progression Model: Bayesian Network

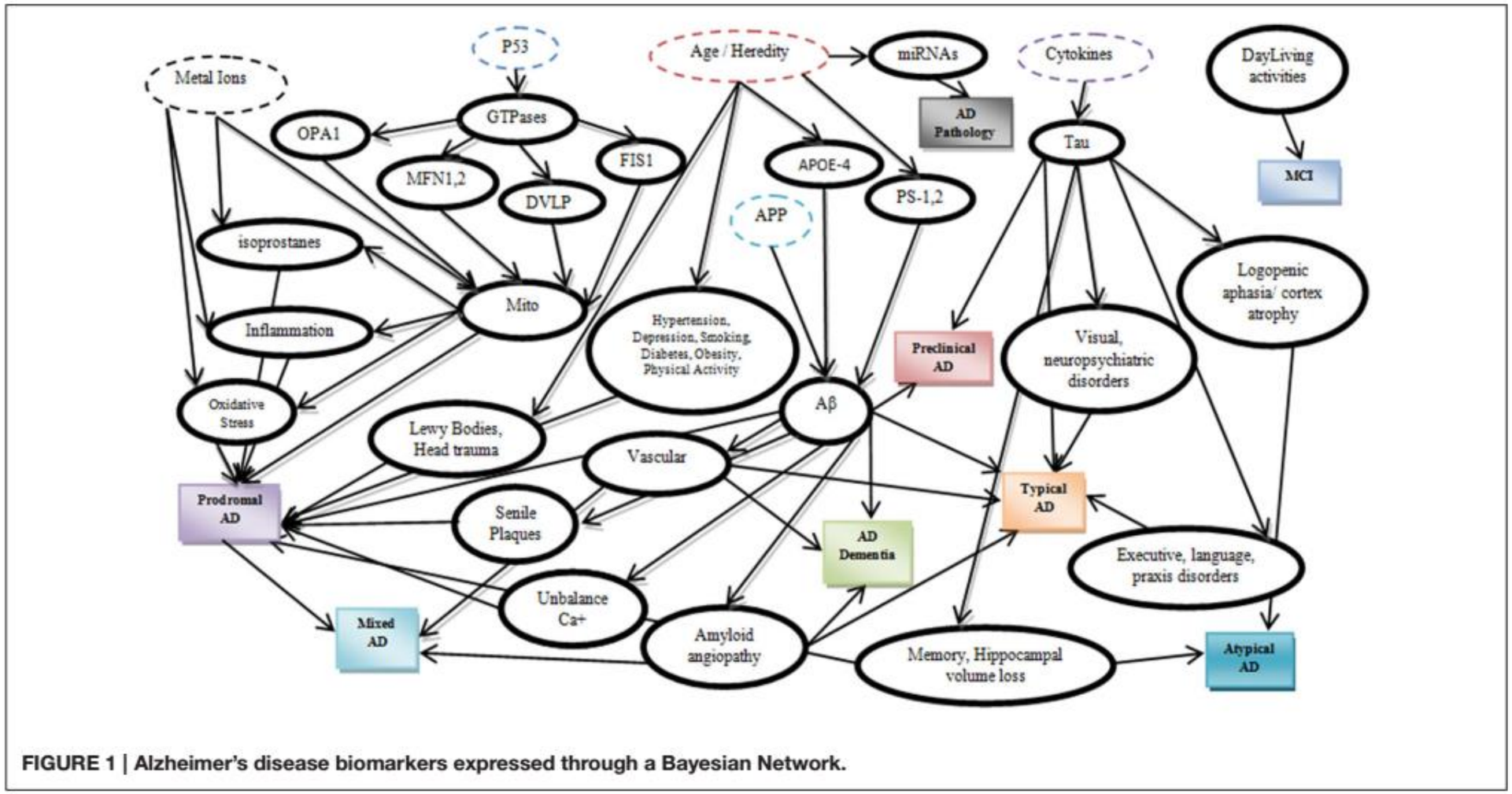
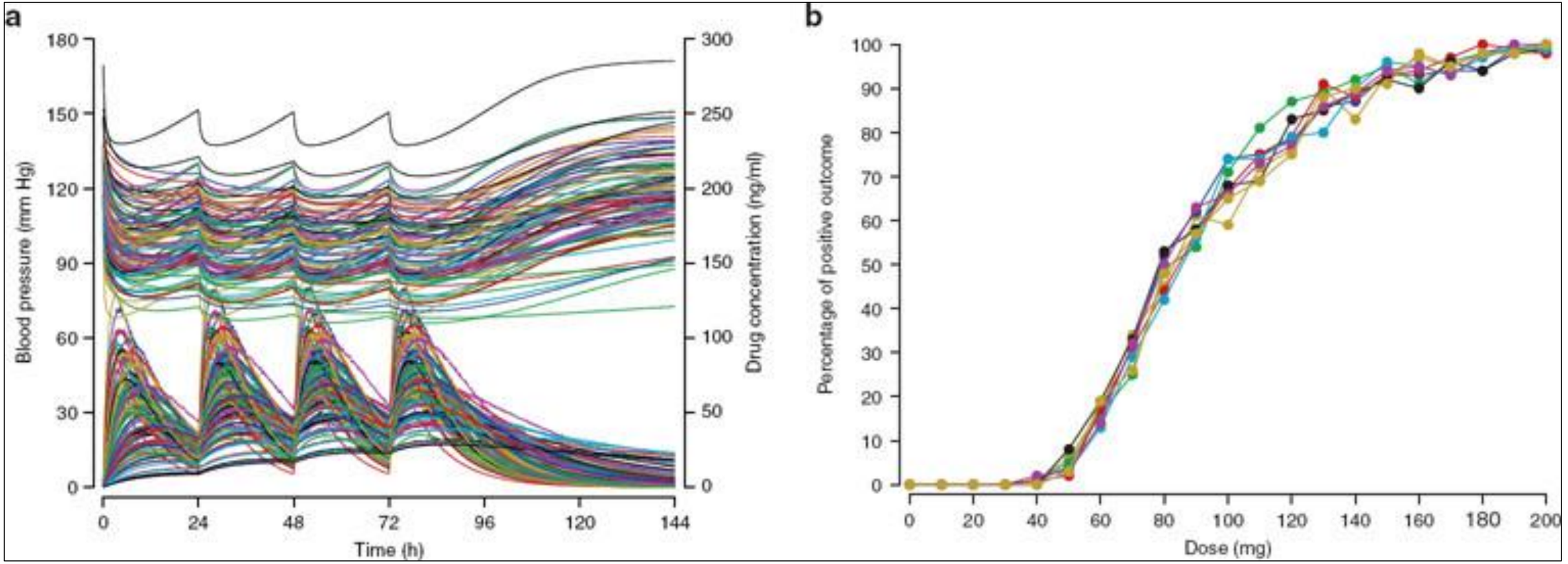


FIGURE 1 | Alzheimer's disease biomarkers expressed through a Bayesian Network.

Alexiou, Athanasios, et al. "A Bayesian model for the prediction and early diagnosis of Alzheimer's disease." *Frontiers in aging neuroscience* 9 (2017): 77.

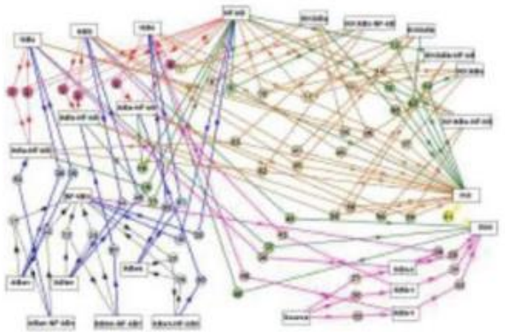
Clinical Trial Simulation: Blood Pressure Drug

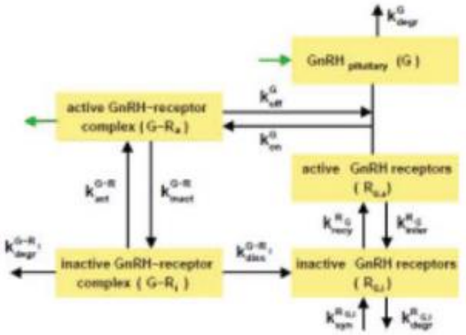


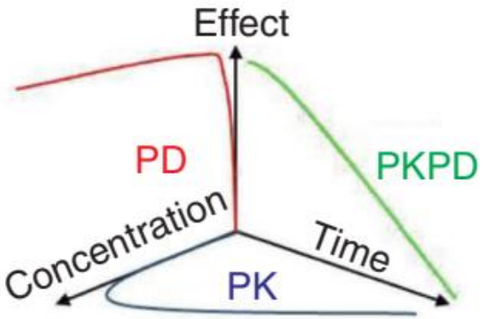
-Andrea Krause & PJ Lowe: Visualization and Communication of Pharmacometric Models with Berkeley Madonna

Pharmacometrics & Systems Pharmacology:
Integration of model-based drug discovery and development

Pathway	Target	Drug	Benefit/risk	Effectiveness and reimbursement





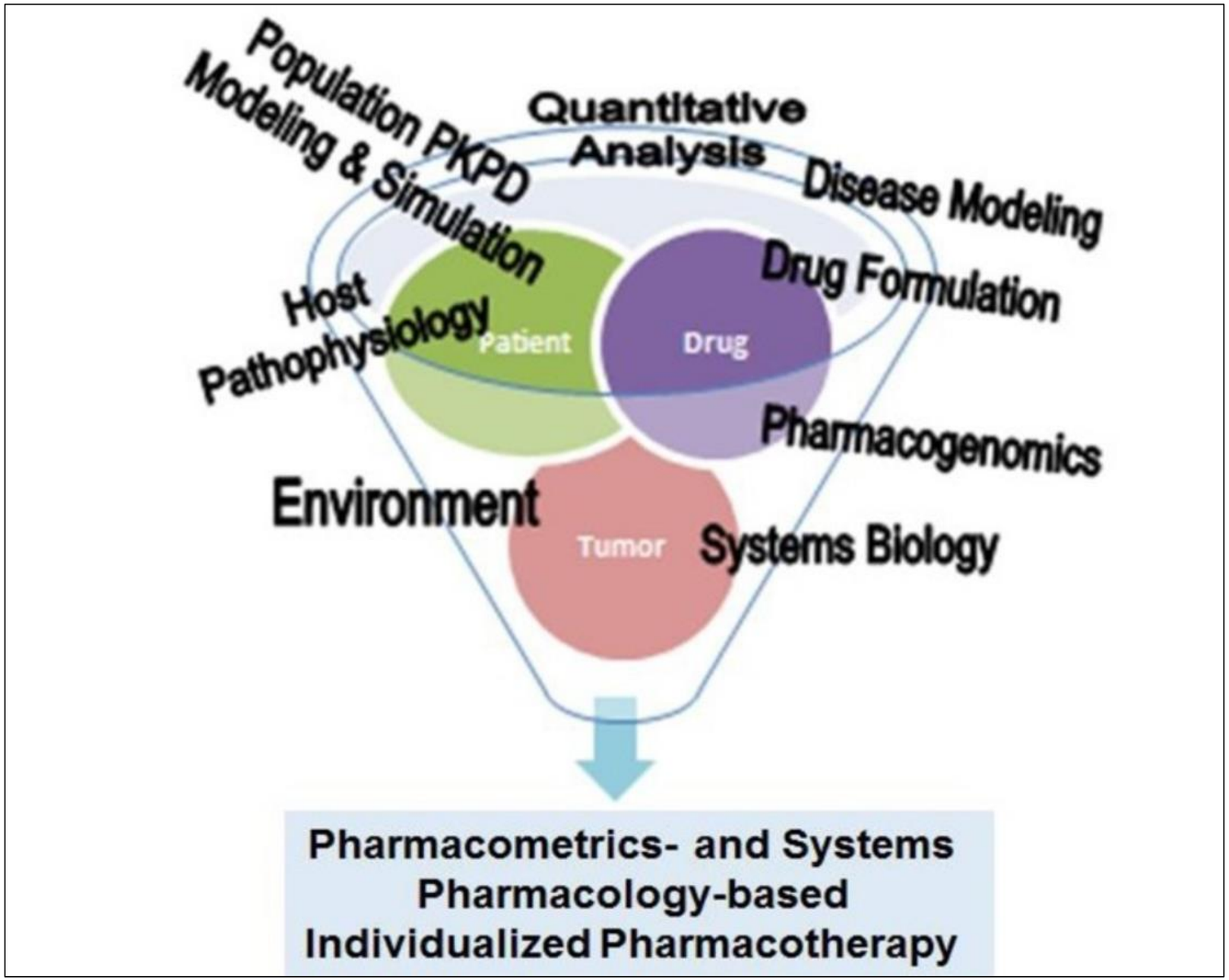


Systems Biology ⟷ Systems Pharmacology ⟷ Translational Sciences ⟷ Exposure Response ⟷ Optimized Medicines

'Right pathway' *'Right target'* *'Right molecule'* *'Right dose'* *'Right patients'*

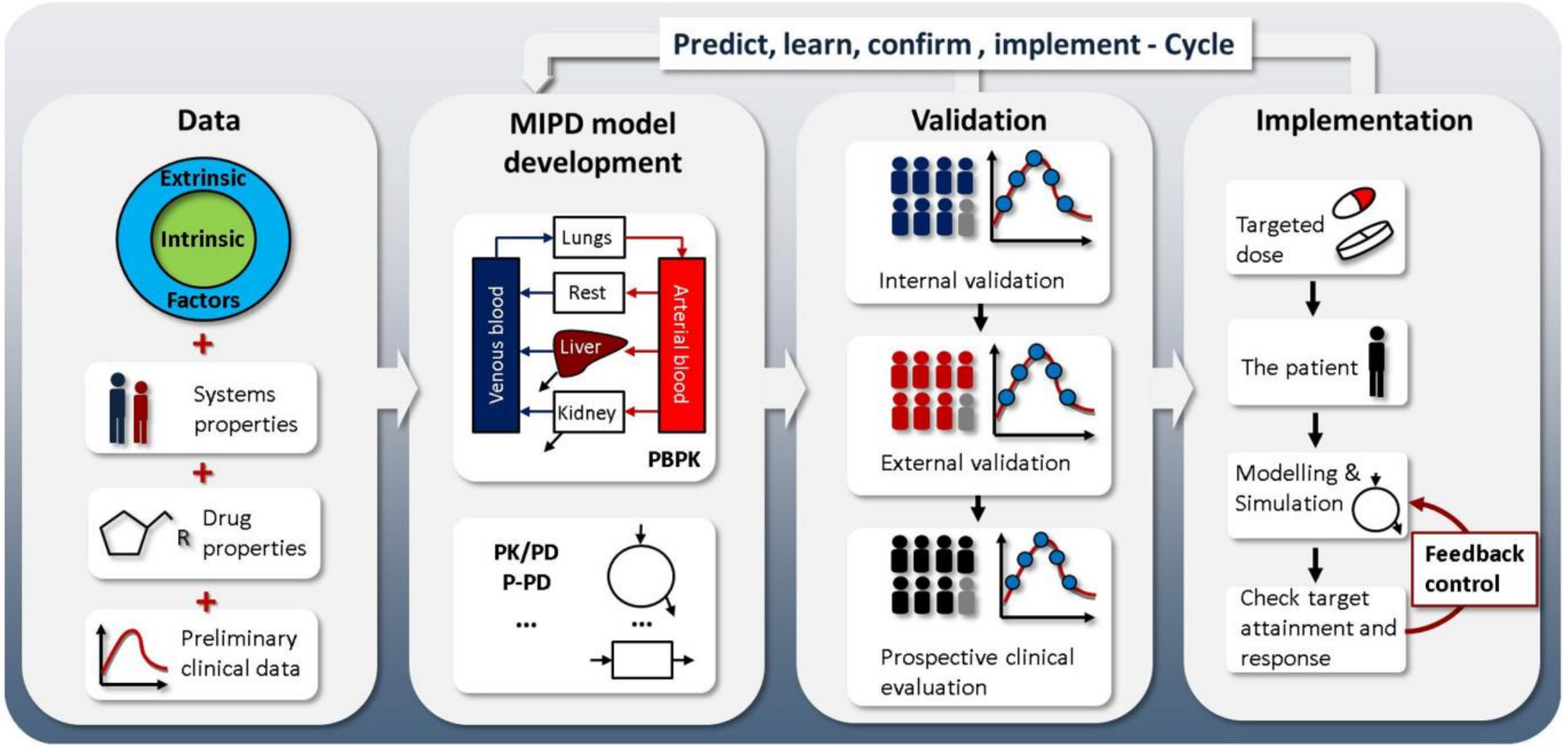
Impact

van der Graaf, Piet H. "CPT: pharmacometrics and systems pharmacology." *CPT: pharmacometrics & systems pharmacology* 1.9 (2012): 1-4.

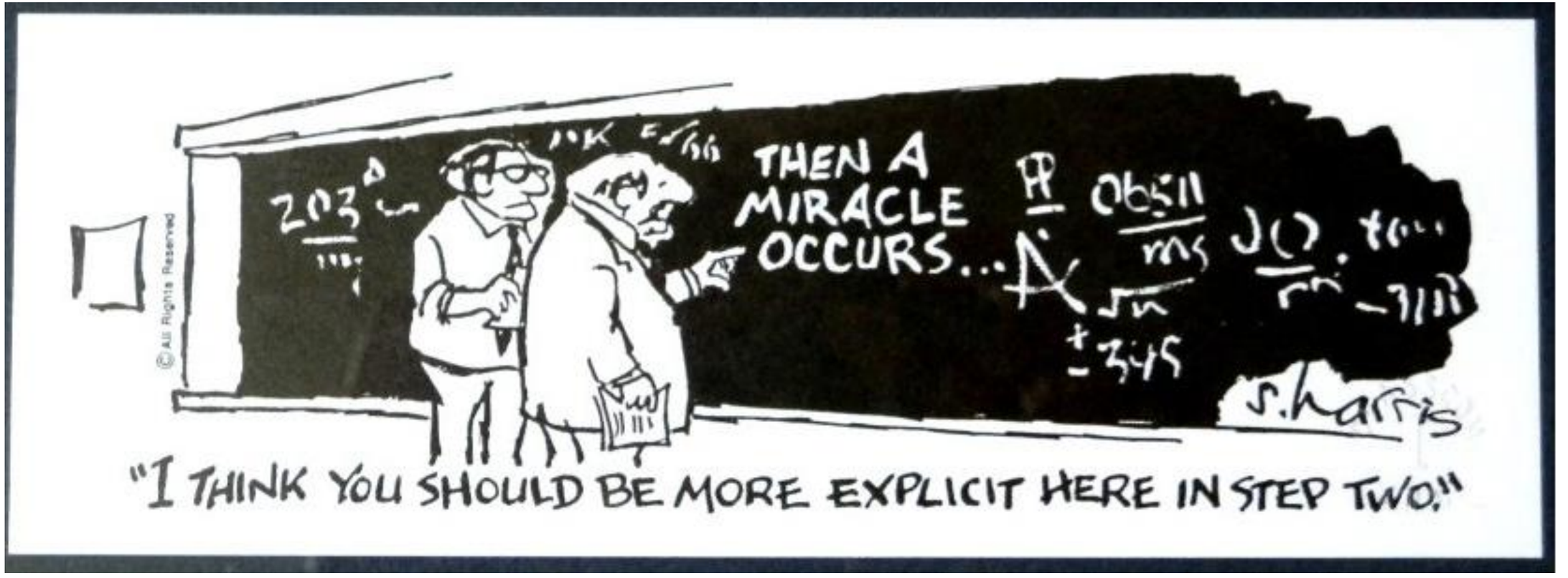


Danhof, Meindert. "Systems pharmacology–towards the modeling of network interactions." European Journal of Pharmaceutical Sciences 94 (2016): 4-14.

Why Has Model-Informed Precision Dosing Not Yet Become **Common Clinical Reality**? Lessons From the Past and a Roadmap for the Future



Clinical Pharmacology & Therapeutics, Volume: 101, Issue: 5, Pages: 646-656, First published: 09 February 2017, DOI: (10.1002/cpt.659)


THEN A MIRACLE OCCURS...
S. Harris
"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

If you can use Pharmacometrics to determine the right dose for the right patient, could you just take that information from adults and apply it to children or other special populations?

Why Pediatric & Special Population Pharmacometrics

- Off-label drug accounts for 50-60% of drugs used in children and up to 90% in (premature) neonates.
- We lack information on pharmacokinetics, pharmacodynamics, efficacy and safety.
- Lack informative pediatric drug labels.
- Missing age-appropriate dosage forms for the pediatric population.

What about other special populations?

- Frail elderly
- Rare diseases in very sick patients
- Renal failure: Small sample sizes:
  - Decreasing GFR and Dialysis required for NDA
  - Especially important for drugs with high renal clearance
- Hepatic Failure: Small sample sizes Pugh-Child A,B,C
  - Especially important for drugs with high hepatic clearance
  - Required for NDA

Typical Phase 1 Study Designs

- Phase 1: Single Ascending Dose
  - Healthy volunteers
  - PK Sampling: Pre-Dose, 0.5, 1.0, 1.5, 2, 4, 6, 8, 12, 16, 18, 24, 36, 48, 72 h
  - 15 Blood Samples:
- Phase 1: Multiple Ascending Dose

Healthy volunteers

  - PK Sampling: Pre-Dose, 0.5, 1.0, 1.5, 2, 4, 6, 8, 12, 16, 18, 24, 36, 48, 72 h
  - 15 Blood Samples: on Day 1 and then accumulation to steady state Day 10 or longer
  - Trough samples during accumulation phase
- Phase 2: Pivotal First Dose in Disease State: Rich or Sparse Sample
- Phase 3: Pivotal Trial for Approval: Rich or Sparse Sample

} PopPK model required for NDA

PopPK: Spaghetti Plot of Raw Data

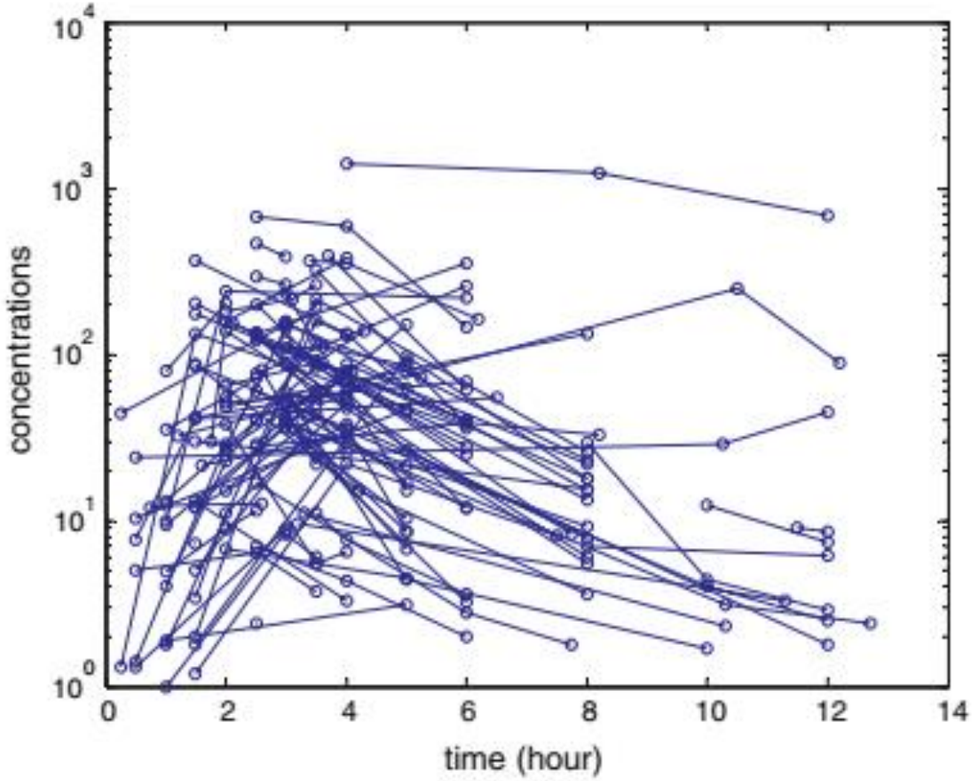


Fig. 1. Observed individual concentrations (in ng/ml) of saquinavir.

Model Building: The Quest for the Ultimate Covariate Model!

Table I. For the Basic Model and Several Models with One, Two or Three Covariates on log(CL/F): Log-likelihood (LL), BIC and Estimated Fixed Effects (β) of the Covariates with the Corresponding P-value of the Wald test

Model	Cov 1	Cov 2	Cov 3	LL	BIC	β_1	p_{val1}	β_2	p_{val2}	β_3	p_{val3}
1				−1241.48	2482.96						
2	Sex			−1240.85	2487.18	0.416	0.2651				
3	Age			−1240.82	2487.12	−0.013	0.4475				
4*	BMI			−1236.83	2479.14	0.107	0.0024				
5	CL_{CR}			−1239.61	2484.70	0.013	0.0211				
6*	Diarrhea			−1237.00	2479.48	−0.982	0.0027				
7	CD4			−1238.40	2482.28	0.002	0.0144				
8	Xylose			−1239.95	2485.38	0.599	0.0367				
9	L/M			−1240.05	2485.58	−4.677	0.0326				
10	St. weight			−1240.61	2486.70	−0.001	0.2333				
11	APL			−1239.98	2485.44	−0.001	0.1606				
12	Albumine			−1240.13	2485.74	0.029	0.1590				
13	CL_{CR}	BMI		−1236.13	2483.22	0.007	0.2124	0.093	0.0097		
14	Diarrhea	BMI		−1235.14	2481.24	−0.677	0.0590	0.078	0.0368		
15	CD4	BMI		−1236.28	2483.52	0.001	0.0875	0.093	0.0090		
16	Xylose	BMI		−1236.28	2483.52	0.360	0.2178	0.095	0.0131		
17	L/M	BMI		−1236.30	2483.56	−2.263	0.2940	0.099	0.0076		
18	CL_{CR}	Diarrhea		−1235.39	2481.74	0.010	0.0873	0.897	0.0076		
19	CD4	Diarrhea		−1235.53	2482.02	0.001	0.0986	−0.820	0.0155		
20	Xylose	Diarrhea		−1236.74	2484.44	0.274	0.3482	−0.845	0.0180		
21	L/M	Diarrhea		−1237.16	2485.28	−2.524	0.2961	−0.830	0.0295		
22	CL_{CR}	BMI	Diarrhea	−1234.28	2485.00	0.006	0.2692	0.062	0.1129	−0.625	0.0773
23	CD4	BMI	Diarrhea	−1233.82	2484.08	0.001	0.1694	0.069	0.0603	−0.537	0.1321
24	CL_{CR}	CD4	Diarrhea	−1234.80	2486.04	0.009	0.1220	−0.001	0.1280	−0.716	0.0382
25	CL_{CR}	BMI	CD4	−1235.42	2487.28	0.007	0.2440	0.077	0.0394	0.001	0.0845

*The two models with the smallest BIC.

Final PopPK Covariate Model

PopPK Covariate Model

Drug used in the disease state

BMI: Alters Clearance
Diarrhea: Alters Clearance

Hand the drug over to the
Clinician with the knowledge
Drug should be dosed based
On BMI and dose adjusted
For diarrhea!

We do not require all the samples
Used in Phase 1 studies!

Table II. Estimated Population Pharmacokinetic Parameters of Saquinavir with the Two Final Models

	Model 4		Model 6	
	Estimate	SE (CV %)	Estimate	SE (CV %)
$\text{Exp}(\mu_{CL/F})$ in L/h	1.26	0.19 (15%)	1.25	0.18 (15%)
$\beta_{BMI\_CL/F}$*	0.11	0.04 (33%) (p-value = 0.0024)		
$\beta_{DIARRHEA\_CL/F}$*			−0.98	0.33 (33%) (p-value = 0.0027)
$\exp(\mu_{V/F})$ in L	0.86	0.22 (26%)	0,96	0.24 (25%)
$\exp(\mu_{ka})$ in h^{-1}	0.58	0.05 (9%)	0.61	0,05 (8%)
$\exp(\mu_{Tlag})$ in h	1.13	0.12 (11%)	1.12	0.12 (12%)
$\omega^2_{CL/F}$	1.41	0.30 (22%)	1.38	0.29 (21%)
$\omega^2_{V/F}$	2.43	0.65 (27%)	2.45	0.60 (24%)
ω^2_{ka}	0.22	0.07 (29%)	0.17	0.05 (28%)
ω^2_{Tlag}	0.51	0.13 (25%)	0.53	0.12 (23%)
σ^2 in $(ng/ml)^2$	85.3	12.5 (15%)	85.7	12.8 (15%)

*Effect on log(CL/F).

Example: Phase 1 Study Estimate Blood Loss

Table 9.1 Approximate Blood Volumes

Assessment	Sample Volume [a] (mL)	No. of Samples	Total Volume [a] (mL)
Safety			
Serum chemistry	3.5	13	45.5
Coagulation	1.8	3	5.4
Hematology	2.0	9	18.0
Viral serology	3.5	1	3.5
Serum pregnancy test [b]	3.5	2	7.0
Follicle stimulating hormone (FSH) [b]	3.5	1	3.5
Plasma tryptase and C3a [c]	2.0	3	6.0
Cytokines	3.0	4	12.0
Complement (Bb)	2.0	4	8.0
Pharmacokinetic			
DLin-MC3-DMA, PEG_{2000}C-DMG, free total PCS siRNA	3.0	21	63.0
Free and encapsulated PCS siRNA[d]	3.0	4	12.0
Pharmacodynamic			
PCSK9	2.0	18	36.0
Serum LDL-C [e]	12.0	19	228
PCSK9 mRNA	12.0	2	24.0
Other			
Exploratory biomarkers (hepatocyte derived proteins):			
Plasma	1.0	15	15.0
Serum	1.0	15	15.0
Total			
Males:			491.4
Females:			501.9

[a] Sample volumes are based on direct venipuncture; where a canula is used an extra 1 mL will be drawn and discarded.
[b] Female subjects only
[c] These samples are only to be collected in the event of an infusion reaction
[d] These samples are only collected from cohort 4 onwards (including any optional cohorts)
[e] HDL-C and total cholesterol beta-quantification safety tests will also be analysed from this sample.

Used to establish

1. SAFETY
2. Drug PK
3. Drug Dose for Phase 2

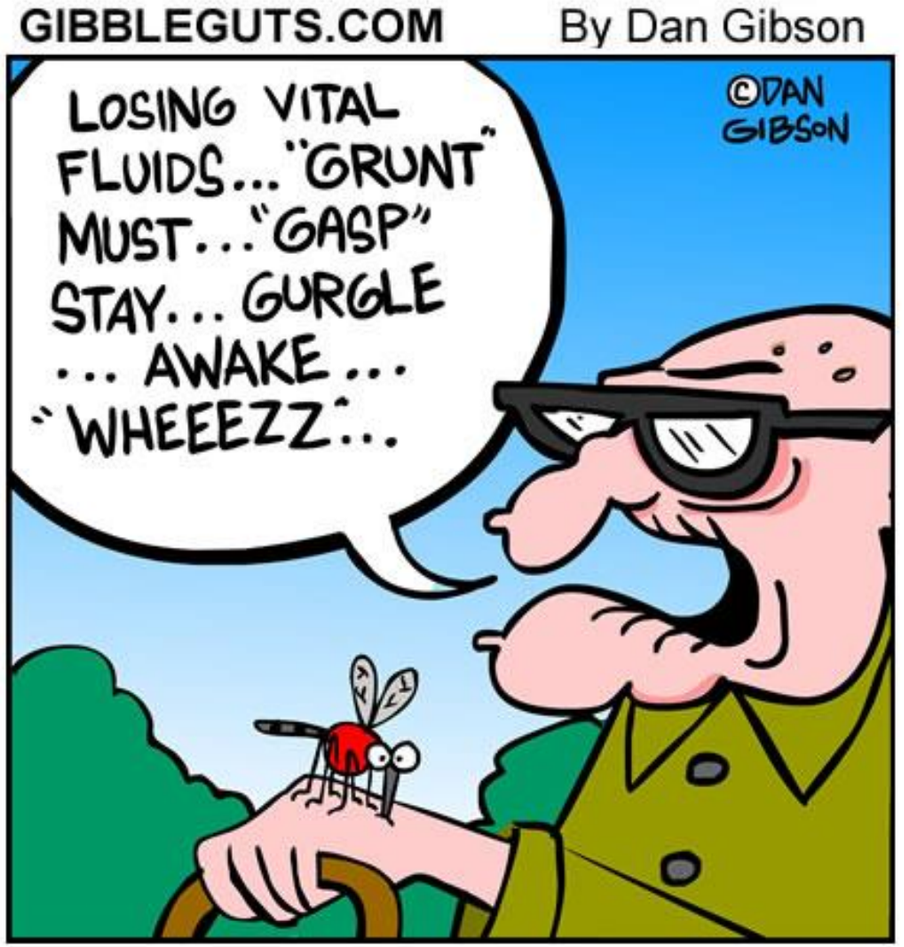
Requires a lot of blood, not a problem
For healthy participants.

World Health Organization

Six Month Baby Girl 7.3 kg

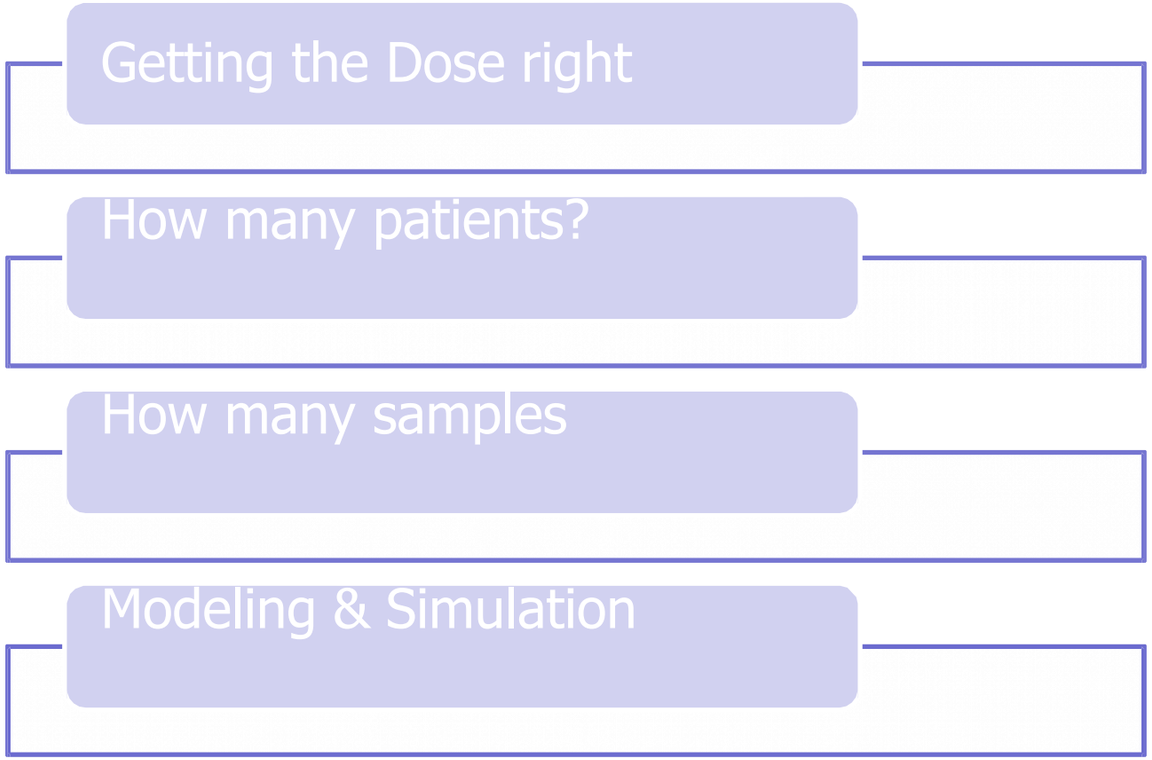
Institution/Body	Maximum volume allowed for a single draw: % of TBV	Maximum volume allowed for a single draw: ml/kg	Maximum cumulative draw volume allowed
Toronto Hospital for Sick Children Research Ethics Board[29]	5	*3.75–4.0*[a]	5% of TBV within 3 months
USC/LA Children's Hospital[22]	*2.5–2.7 (within 24 hour)*[a]	2	4 ml/kg within 30 days 29.2 mL
Wayne State University[23]	1	0.8	10% of TBV or 8 ml/kg within 8 weeks
Partners Human Research Committee[24]	*3.6–3.9*[a]	<>	< 3 ml g="" within="">
University of California Davis[25]	*2.5* *Note: Minimum blood Hb required at time of blood draw, 7 g/dl (9–10 g/dl if cardiorespiratory compromise present)*	*2*[a]	5% of TBV within 30 days
Duke University[26]	For expedited IRB approval		3 ml/kg or 50 ml total (whichever is less) over 8 weeks
	2.5[a] (for review by convened IRB; *note: special precautions and justification required for more than this limit*)	2, up to 200 ml total	7 ml/kg over 8 weeks (up to 5 draws of 7 ml/kg per year) 51.1 mL
KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya[b]	*1.9–2.3*[a] (2005 guideline for *total*volume drawn)	1.7–2.4	Not stated
	1.3[a] (2008 guideline for volume drawn for *research*purposes in addition to volume needed for routine care)	1	5 ml/kg within 8 weeks
US Dept of Health and Human Services, Office for Human Research Protections[17]	*3.8*[a]	3, up to 50 ml total	3 ml/kg, up to 50 ml total within 8 weeks
Kauffman 2000[28]	3.0	*2.4*[a]	Not stated
Gambia Government–MRC Joint Ethics Committee[27]	*Range: 2.4 (e.g.1-kg infant) to 0.3 (e.g. 20-kg 4-year-old or 30-kg 9-year-old)*[a]	2, up to max 5 ml (age 0–4 yr); 10 ml (age 5–9 yr); 15 ml (age 10–14 yr); 30 ml (age ≥ 15 yr)	Within 3 months same as for one draw, "usually"

Blood sample volumes in child health research: review of safe limits Stephen RC Howie Volume 89, Number 1, January 2011, 46-53



500 mL blood loss will be a problem in neonates, pediatrics and some special populations
Even if assay sensitivity allows a < 3 mL sample, blood volume is a problem.

Informative PK/PD Study Design



What if some time points are more informative than others?
What if we can minimize blood draws and spread sampling over the entire study population?
How can we know this? Modeling& Simulation, Informative priors

-Adapted from **Alexander (Sander) A. Vinks, PharmD, PhD, FCP**

Developmental Pharmacology Concepts

- Growth and development are linked co-linear processes in children
- Size standardization is achieved by allometric scaling.
- Age is used to describe maturation of clearance.

Allometry

- Technique used to describe the non-isometric variation by regressing a variable of interest against body mass.

$$\log y = \log a + b\text{Log Mb}$$

$$y = aM_b{}^{b}$$

Where: y is the variable of interest, such as Drug Clearance
a is the allometric coefficient,
Mb is body mass and
b is the allometric exponent.

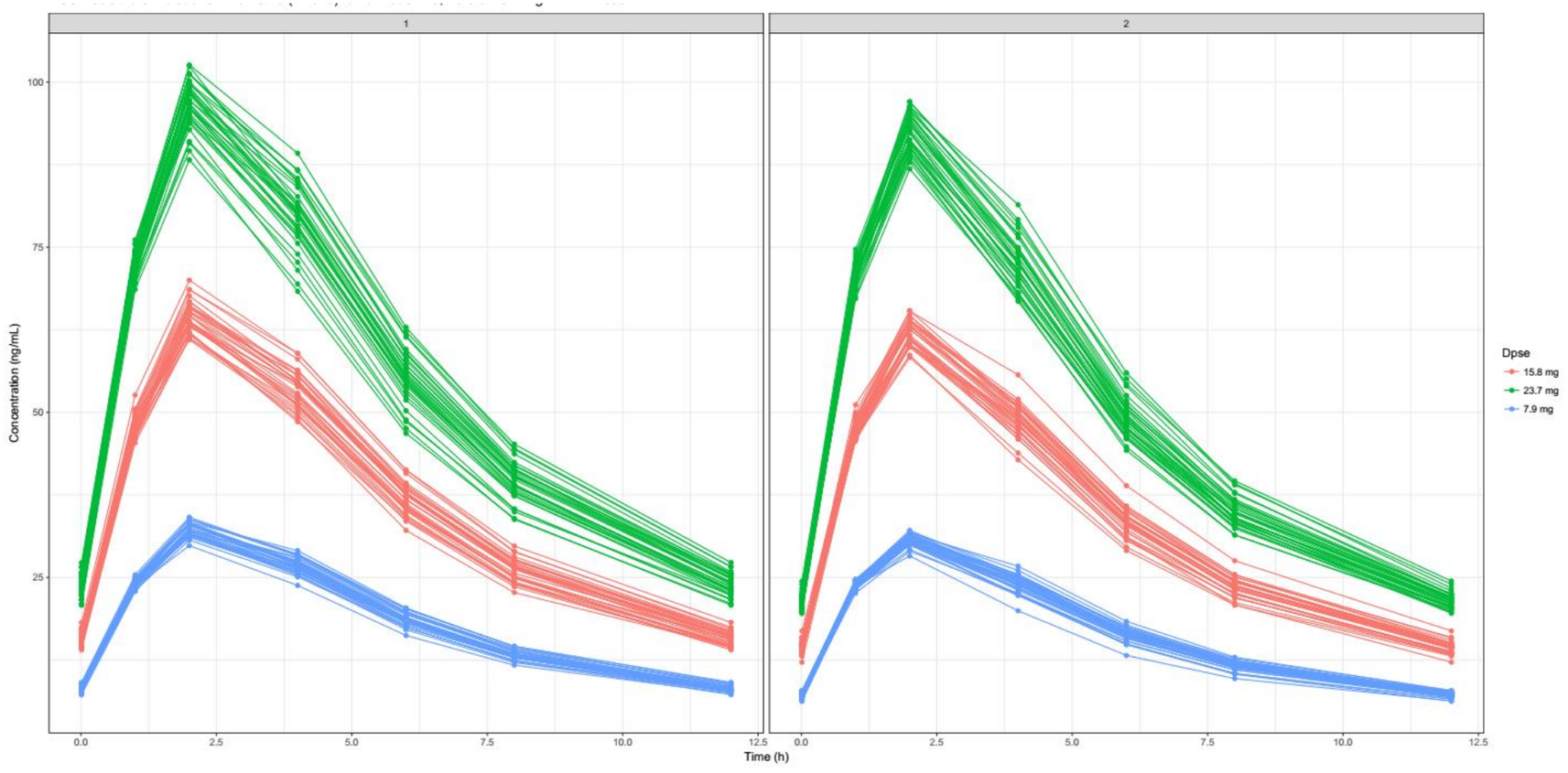
Allometric Scaling from Human Adults to Children

FDA/EMA Recommendations

$$CL/F = \theta_1 * \left(\frac{WT}{70}\right)^{0.75}$$

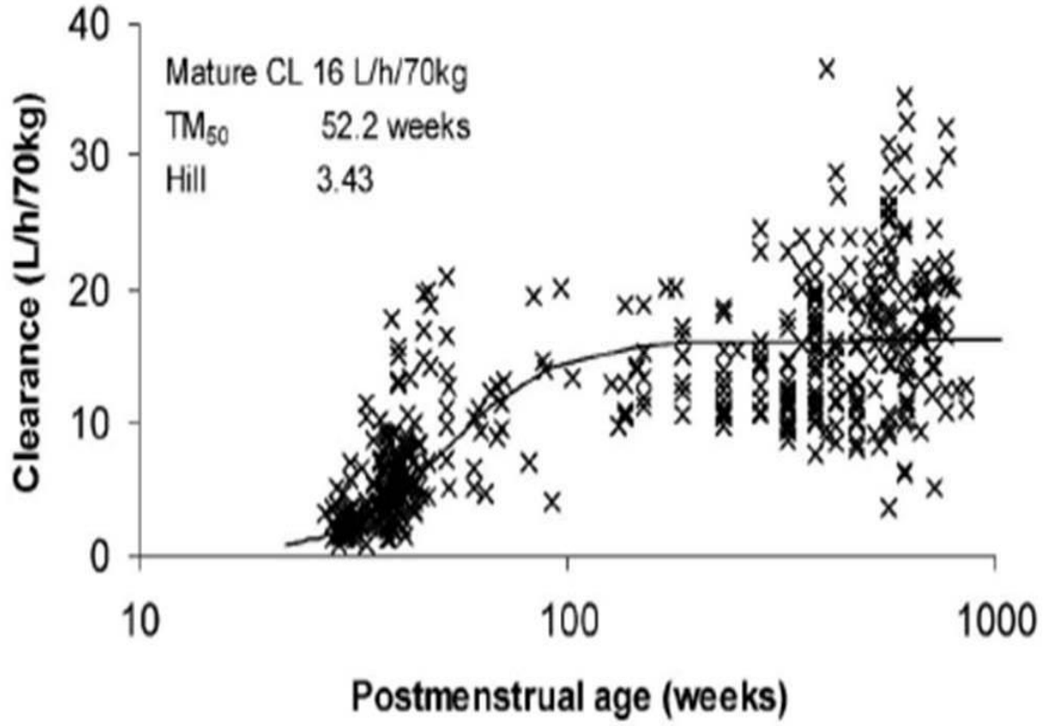
$$V2 = \theta_2 * \left(\frac{WT}{70}\right)^{1.0}$$

Pediatric Simulations Allometric Scale: CL-$(WT/70)^{0.75}$, V-$(WT/70)^{1.0}$

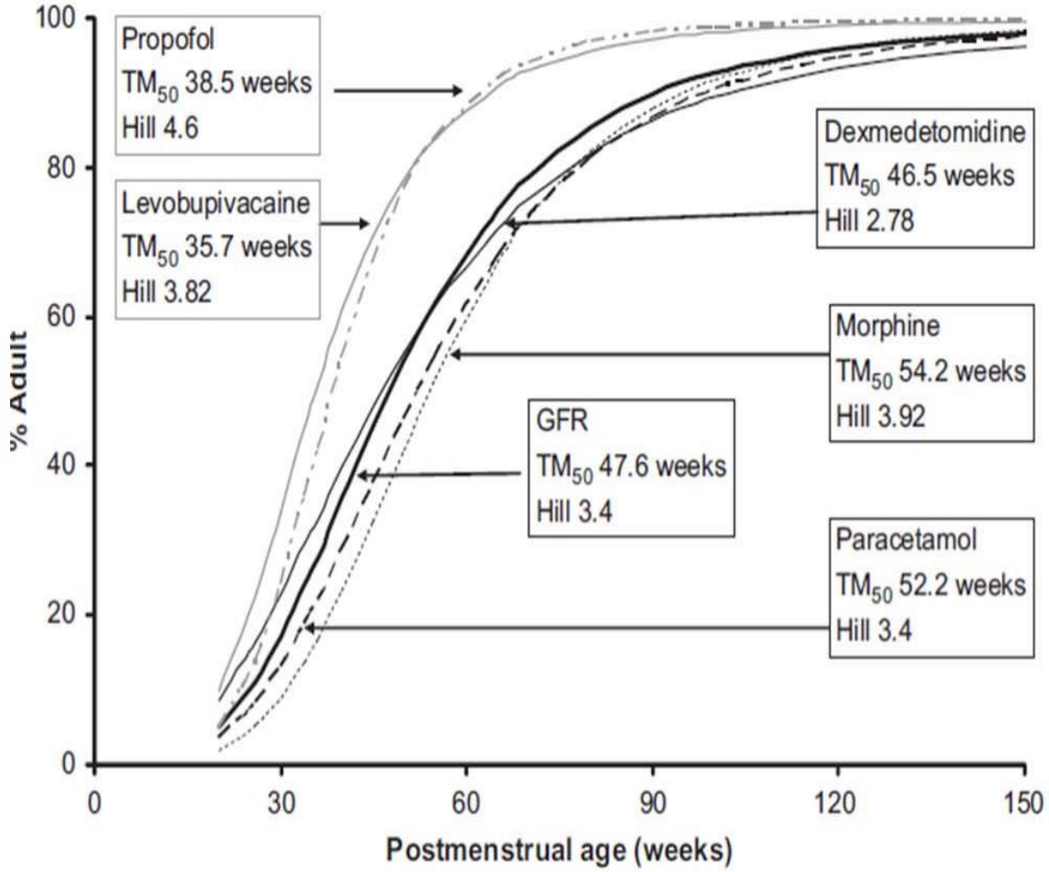


Mechanistic Basis of Using Body Size and Maturation to Predict Clearance

Acetaminophen Clearance



Maturation of GFR and other drugs



Anderson B, Holford N. Drug Metab. Pharmacokinet. 24 (1): 25–36 (2009).

How modeling and simulation can help in the design of pediatric studies

Development of a population PK/PD/PG model using newly generated or prior knowledge from adult data

↓

Simulation of 'realistic' virtual patients

↓

Simulation of the virtual clinical study

- *How many patients & how many samples*
- *what are the best times for sampling*

↓

Optimizing of trial design and data analysis method prior to the study

-Adapted from **Alexander (Sander) A. Vinks, PharmD, PhD, FCP**

Development of Population Model Based on PRIOR Adult Data

- Population analyses
  - Non-compartmental (WinNonlin)
  - One-compartmental model (NONMEM)
    - Absorption model with/without lag time
- Covariates e.g. WT, AGE, PGx
    - Allometrically scaled: $CL = CL_{std} \bullet (WT/70)^{0.75}$
- Variability components
    - IIV on all parameters except F and lag time
    - IOV on bioavailability, Ka and lag time
- Simulations
  - Across age range
  - Sample from realistic age-weight distribution

From available adult data

From literature & available data

From available data

Decision Tree for Pediatric Studies

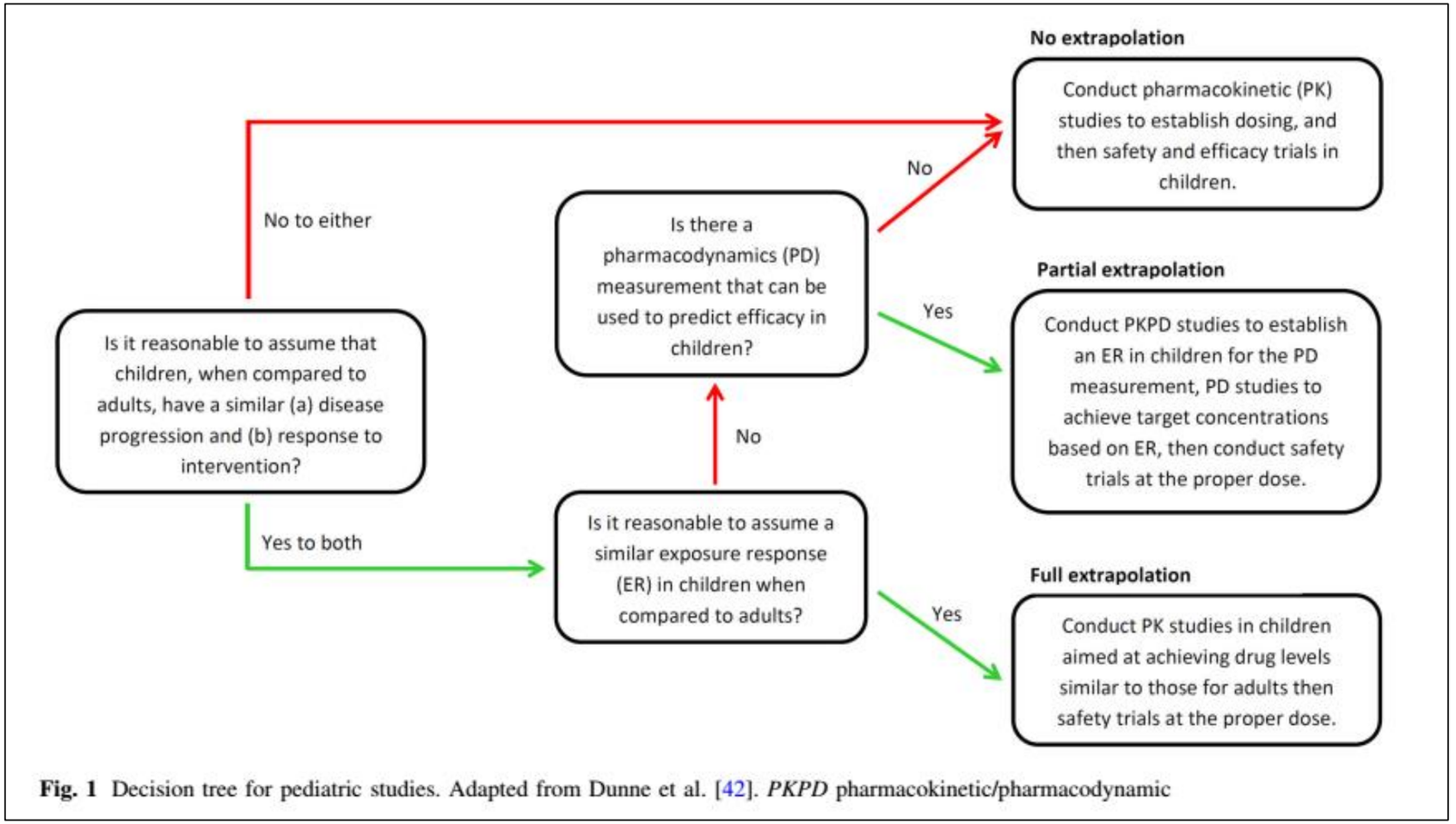


Fig. 1 Decision tree for pediatric studies. Adapted from Dunne et al. [42]. *PKPD* pharmacokinetic/pharmacodynamic

Germovsek, Eva, et al. "Pharmacokinetic–pharmacodynamic modeling in pediatric drug development, and the importance of standardized scaling of clearance." *Clinical pharmacokinetics*(2019): 1-14.

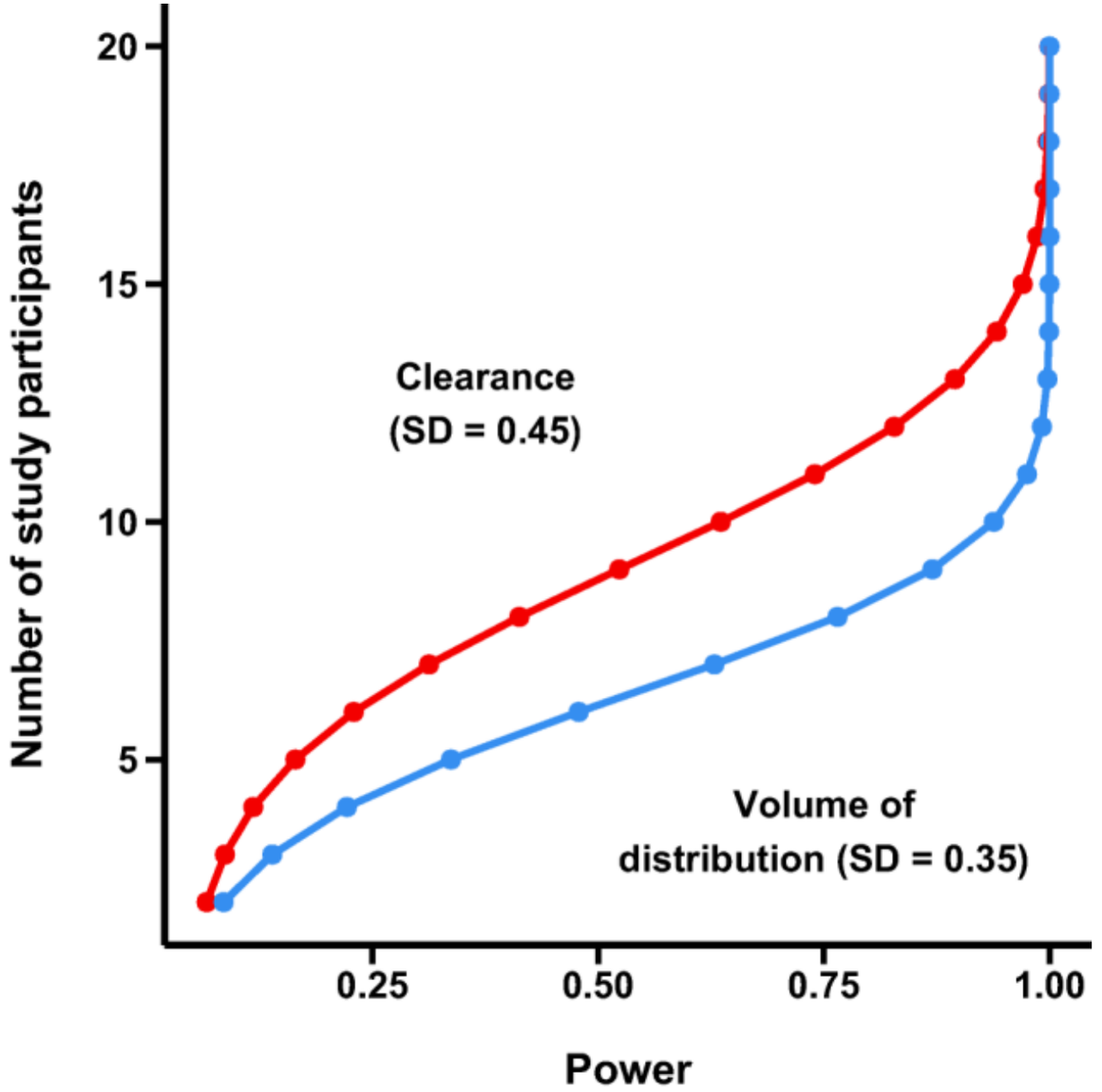
Sample Size Calculations

- How many patients?
  - Required number of patients for statistically robust estimation of PK/PD relationship(s)
- How many samples per patients?
- What best times to sample
  - Optimal sampling strategies

Use of Modeling and Simulation in the Design and Conduct of Pediatric Clinical Trials and the Optimization of Individualized Dosing Regimens

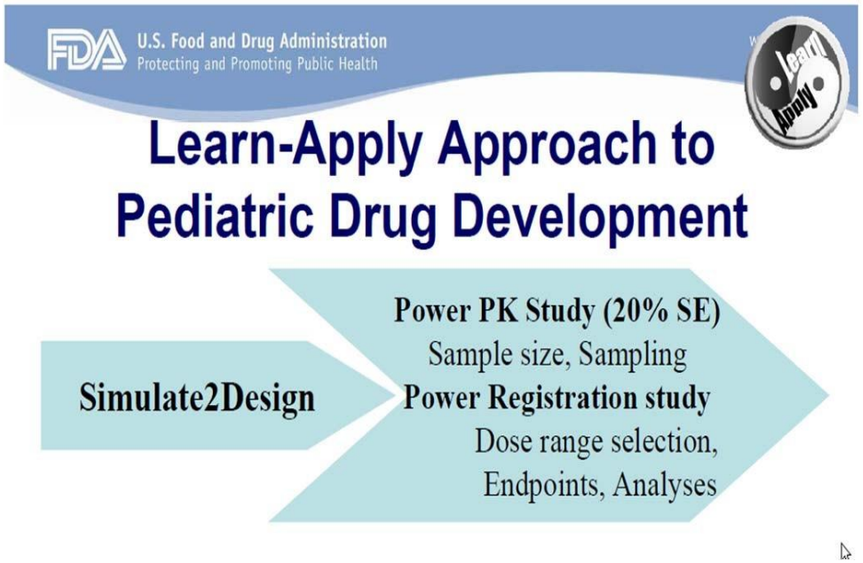
Sample Size from Non-Compartmental Analysis (NCA) data based on error Associated with Clearance And Volume of Distribution.

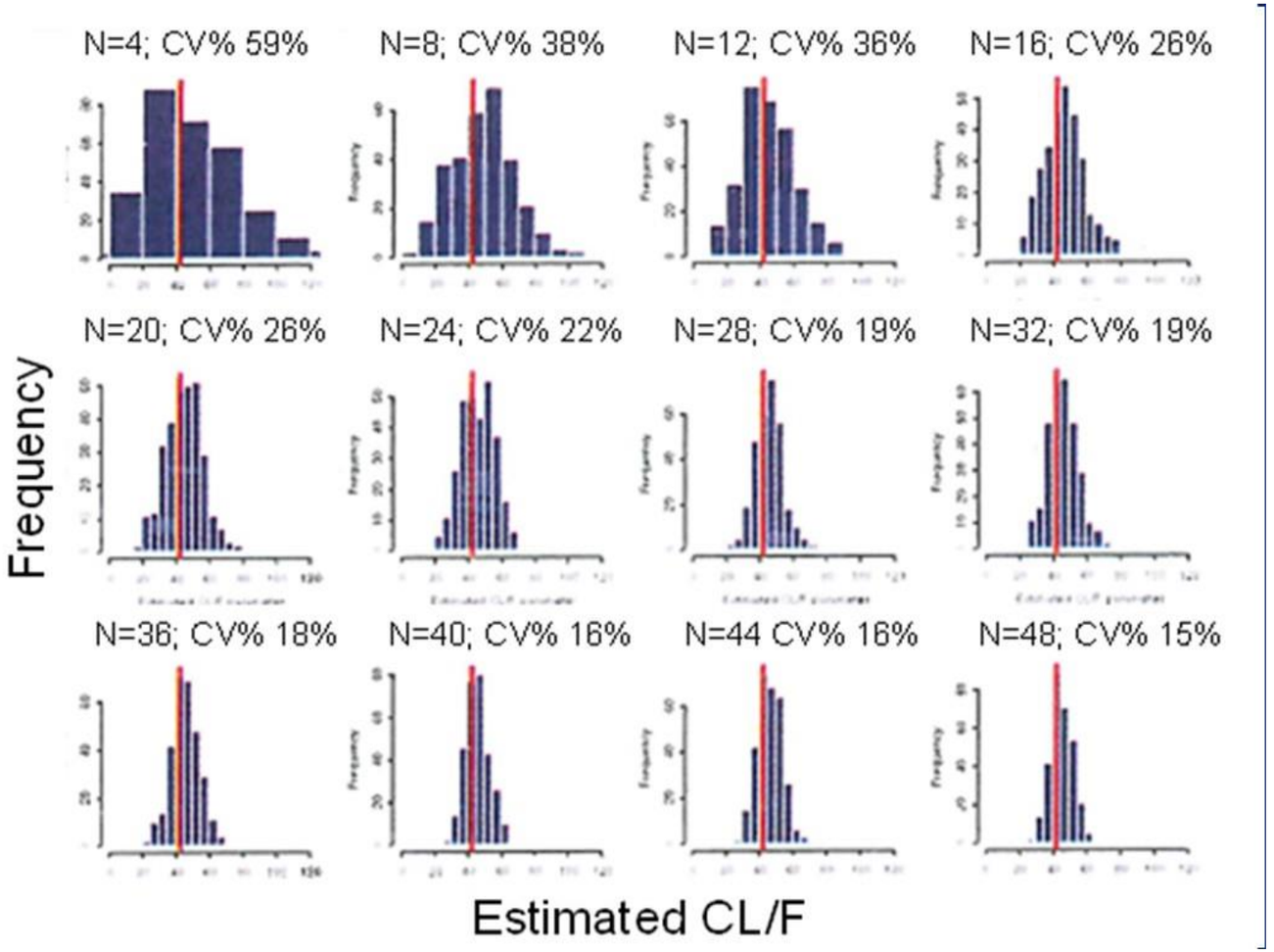
Available from standard Phase1 Studies.



CPT: Pharmacometrics & Systems Pharmacology, Volume: 4, Issue: 11, Pages: 630-640, First published: 15 September 2015, DOI: (10.1002/psp4.12038)

Powering Population PK studies





- Power equation to determine sample size or sampling, a 20% SE has been proposed as the quality standard

Gobburu, Pediatric advisory committee meeting, 2009 Jacqmin, J&J Pediatriuc Symposium, 2005

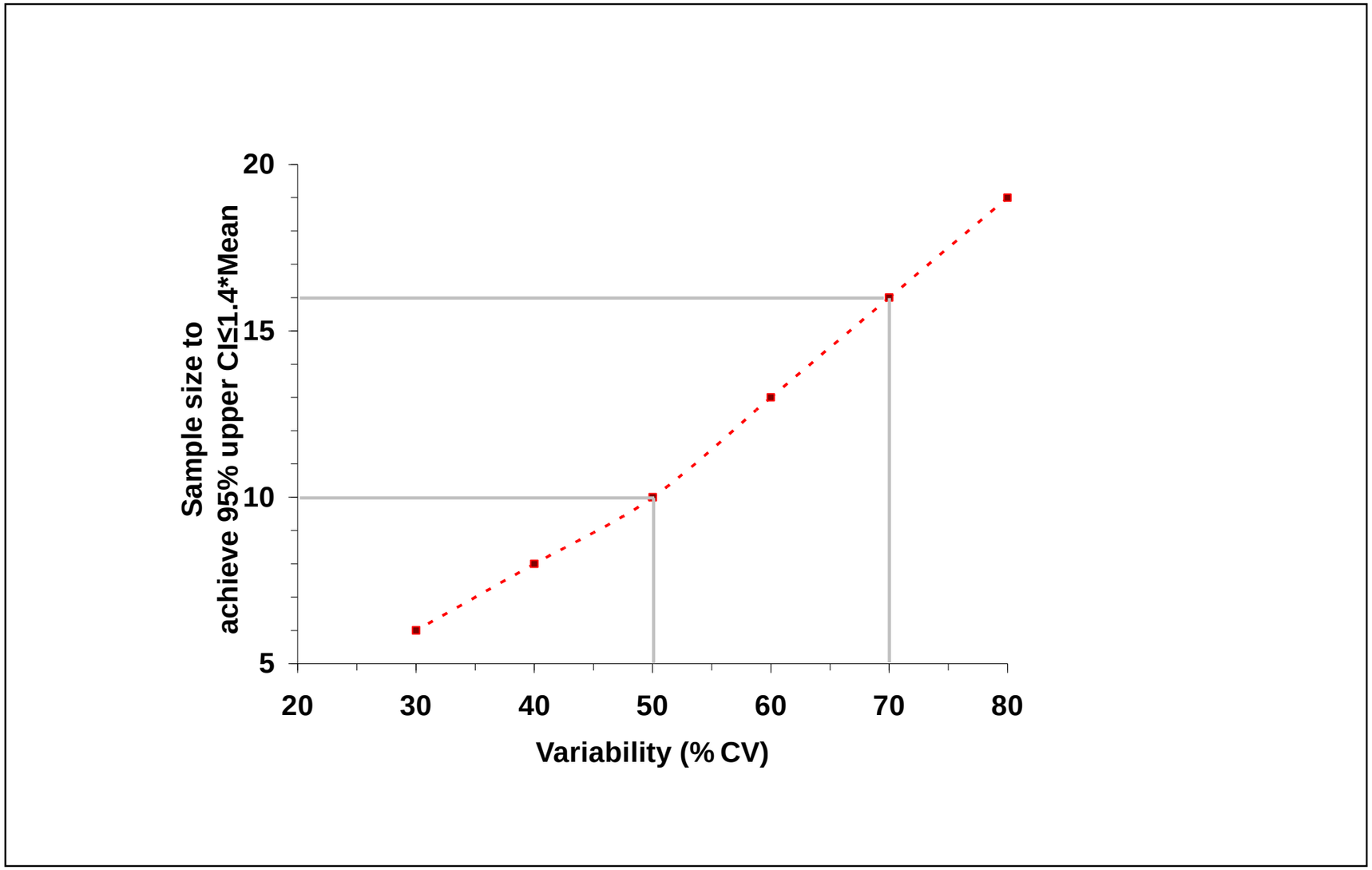
Sample Size Calculation for for PopPK Analysis

- Sparse/Rich PK sampling design
- Nonlinear mixed-effect modeling & clinical trial simulation is generally needed to derive the appropriate sampling schedule and the sample size.
- FDA quality standard:
  - Calculate the 95% CI for a derived parameter such as CL when a covariate model is applied for this parameter

$$CL_i = CL_{pop} \cdot \left[\frac{WT_i}{70kg}\right]^{0.75} + \eta_{CL,i}$$

FDA: Standard allometric scale-up
WT ^0.75

Sample Size Requirements based on FDA criterion



Adult PopPK Model from Rich Sampling Phase 1 and from Sparse Sampling in Disease State

Adult Model
Derived from Phase 1
Phase2 and Phase 3

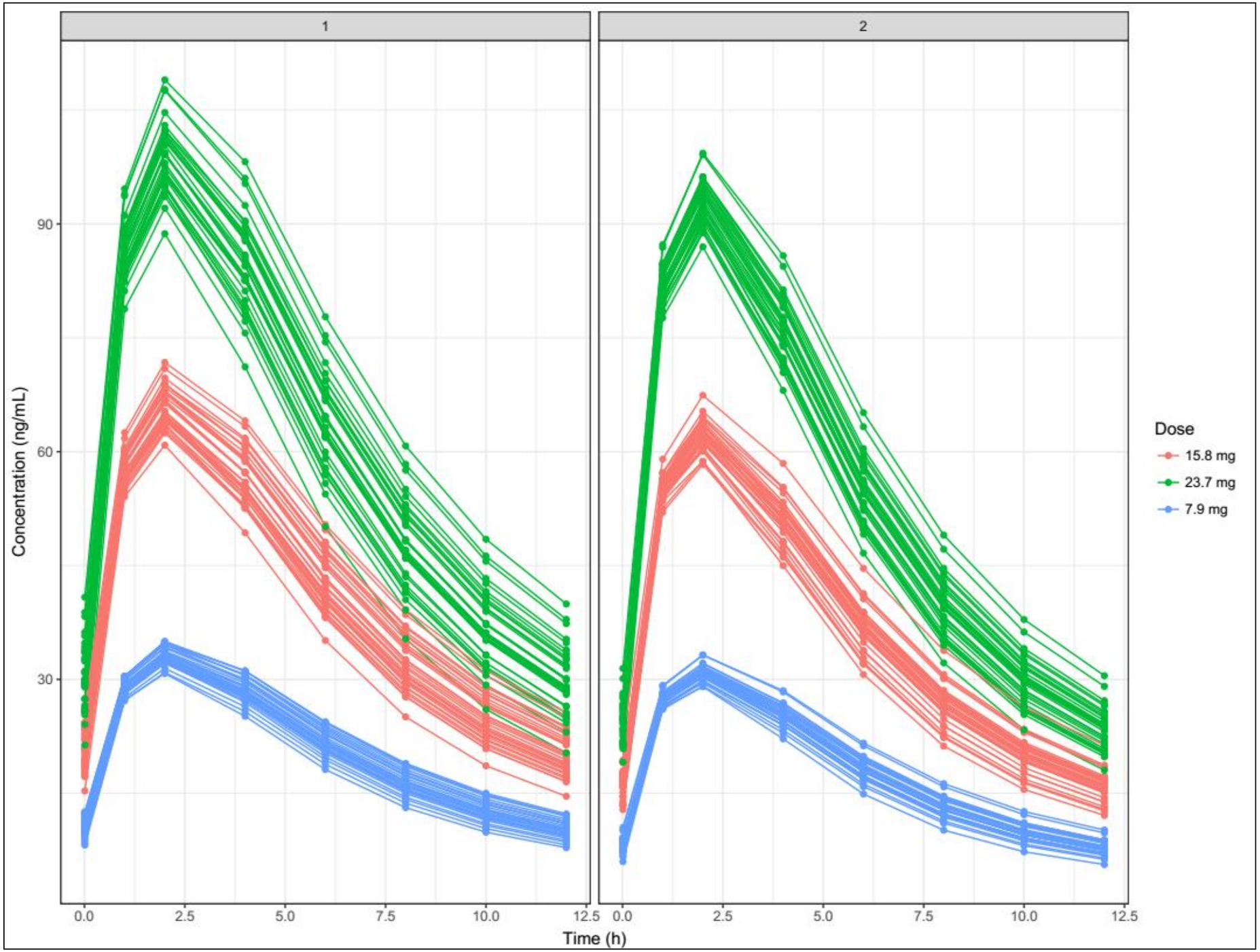
$$CL/F = \theta_1 * \left(\frac{WT}{70}\right)^{0.853} * \left(\frac{ALT}{20}\right)^{0.104} * \left(\frac{AGE}{37}\right)^{0.104}$$

Weight and Age
Allow scaling to pediatric population

	Model 7				
OFV	Objective function value	26313.59	%RSE		
TH 1	CL	42.4	5.40%		
TH 2	[CL~WT]	0.853	12.90%		
TH 3	[CL ~ ALT]	0.104			
TH 4	[CL ~ AGE]	0.104			
TH 5	V2	10.3			
TH 6	Q	66	23.30%		
TH 7	V3	98	16.30%		
TH 8	KA	0.439	0.70%		
TH 9	Prop.RE sd	0.446	2.90%		
TH 10	Add.RE sd	11.5	20.50%		
OM 1	IIV CL	0.359	10.70%		
OM 2	IIV V	0	0.428	10.70%	
OM 3	IIV Q	0	0	0.135	97%

Create Theoretical Pediatric Trial Data Set

- Pediatric simulations were based on an age and sex-specific database constructed using normative data for children
  - Group 1: Aged 5 to < 12 years
  - Group 2: Aged 12 – 18 years
- Clinical chemistries were constructed from the data previously published in pediatric Disease State studies.
  - Done to generate realistic covariates
- A data set of 200 patients was constructed divided into the two age groups.



1. Three doses simulated
2. Younger age group higher exposures

Design a Study with Sampling Strategy to Confirm the scaled PopPK Model

What are the most informative time points?

Time1	Time2	Time3	Time4	Time5	Time6
0.5	2	4	6	8	11.5 or 12

How to determine this?

1. Modeling and Simulation
2. Minimize Fisher-Information Matrix Methods
3. D-optimization Methods

Example: Joint PK/PD modeling of Warfarin

(Bazzoli, Retout, Mentré, *American Conference on Pharmacometrics (ACOP)*, Mars 2008)

- **PK: time course of total racemic warfarin plasma concentration**
- **PD: effect on prothrombin complex activity (PCA)**
- **A priori PK knowledge**
  - single oral dose of 100 mg
  - 1 compartment model, 1st order absorption and elimination
  - CL=0.133; V=7.95; Ka=1.6; ω_{CL}=0.0634; ω_{V}=0.0206; ω_{KA}=0.701
  - exponential modelling of the random effects
  - Var(ε)=(0.2 f)²
- **A priori PD knowledge**
  - turnover model with inhibition of the input
  - Imax=1(FIX); Rin=5.41; C_{50}=1.2; Kout=0.056; ω_{Rin}=0.19; ω_{Kout}=0.0167; ω_{C50}=0.0129
  - exponential modelling of the random effects
  - var(ε)=3.88
- **Evaluation of an empirical design**
  - one group of 32 subjects
  - 13 sampling times for PK and 7 sampling times for PD
- **Design optimisation with the Federov-Wynn algorithm under constraints**
  - only 4 sampling times per subject common to both responses performed into 32 subjects

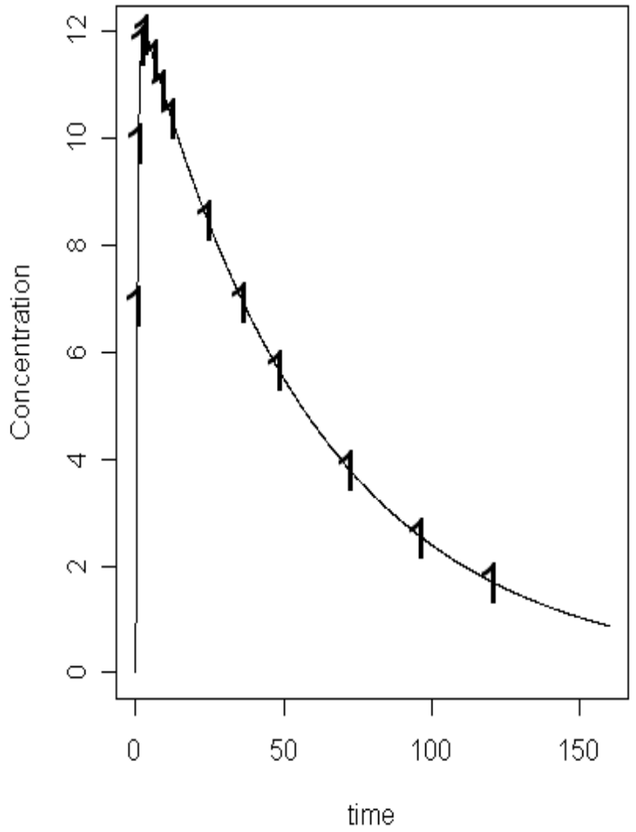
Evaluation of the pop PK design with PFIM

```
PFIM 3.0

Project:  PKPDWarfarine_indirect_model

Date:  Tue Nov 27 11:01:40 2007

**************************** INPUT SUMMARY *********************************

Differential Equations form of the model:

function(t,y,p)
{
ka<-p[1]
cl<-p[2]
V<-p[3]
Rin<-p[4]
C50<-p[5]
kout<-p[6]

      yd1<--ka*y[1]
      yd2<-ka*y[1]-(cl/V)*y[2]
      yd3<-Rin*(1-((1*y[2]/V)/((y[2]/V)+C50)))-kout*y[3]

list(c(yd1,yd2,yd3),c(y[2]/V,y[3]))
}


Population design:
Sample times for response: A
                                                    subjects
c(0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96, 120)       32
Sample times for response: B
                                  subjects
c(0, 24, 36, 48, 72, 96, 120, 144)       32

 Variance error model response A : ( 0 + 0.2 *f)^2

 Variance error model response B : ( 3.88 + 0 *f)^2

 Initial Conditions at time 0 :

 100 0 Rin/Kout

 Between-subject variance model: Trand =  2

 Error tolerance for solving differential equations system: RtolEQ = 1e-08 , AtolEQ = 1e-08 , Hmax =  Inf
```

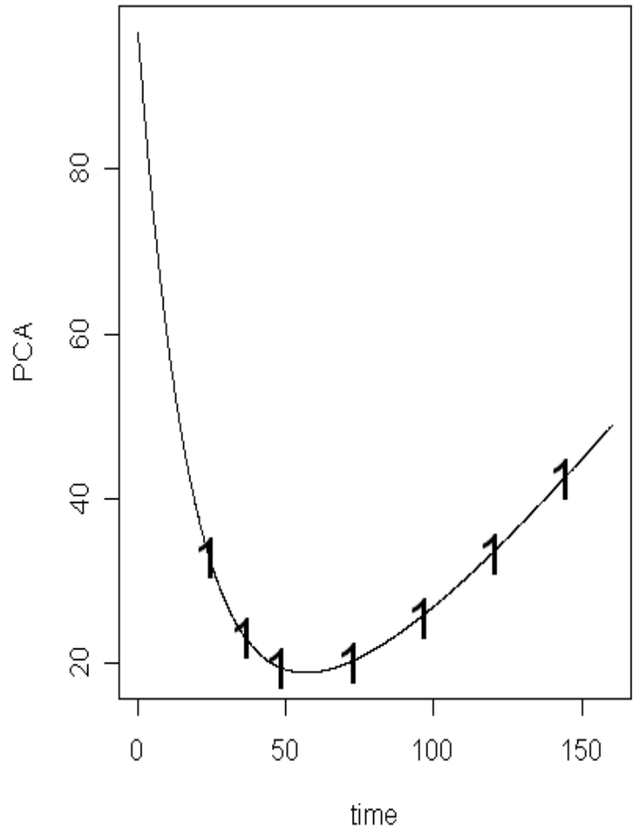
```
*************************** EXPECTED STANDARD ERRORS **********

------------------------ Fixed Effects Parameters -----------

      Beta    StdError        CV .
Ka    1.600 0.252176029 15.761002 %
CL    0.133 0.006135812  4.613393 %
V     7.950 0.235561806  2.963042 %
Rin   5.410 0.628097943 11.609943 %
C50   1.200 0.108824055  9.068671 %
Kout 0.056 0.002358841  4.212215 %


------------------------ Variance of Random Effects --------

      Omega    StdError        CV .
Ka    0.7010 0.196597447  28.04528 %
CL    0.0634 0.016879177  26.62331 %
V     0.0206 0.006811926  33.06760 %
Rin   0.1900 0.055624579  29.27609 %
C50   0.0129 0.032727257 253.69967 %
Kout 0.0167 0.007849129  47.00077 %


------------------------ Variance of residual error ---------

           SIG    StdError       CV .
sig.slopeA 0.20 0.007865186 3.932593 %
sig.interB 3.88 0.226415910 5.835462 %


******************************** DETERMINANT *****************

3.505562e+39
```

Evaluation of the pop PK design with PFIM

PK



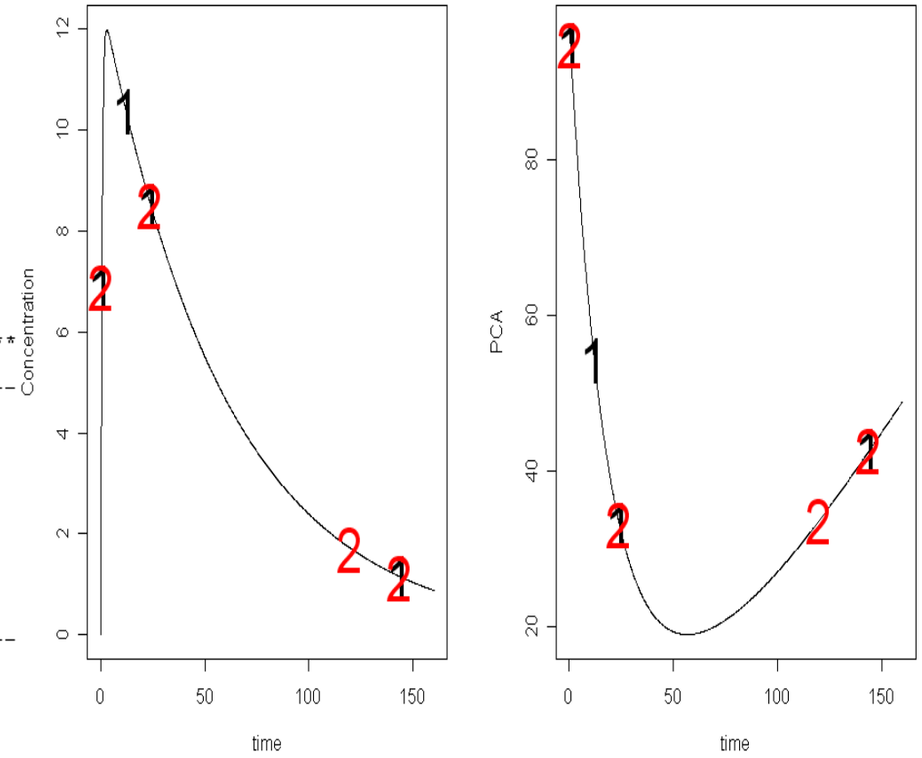
PD



- ✓ **One group of 32 subjects**
- ✓ **Total of 640 sampling times**

Optimisation of a pop PK design with PFIM

```
*************************** OPTIMISED DESIGN ************:
Optimised population design:
Sample times for response: A
              prot.opti subjects.opti Subjects
1  c(0.5, 12, 24, 144)      0.6768466 21.65909
2 c(0.5, 24, 120, 144)      0.3231534 10.34091


Sample times for response: B
              prot.opti subjects.opti Subjects
1  c(0.5, 12, 24, 144)      0.6768466 21.65909
2 c(0.5, 24, 120, 144)      0.3231534 10.34091

Associated optimised criterion: 580.1989

************************ EXPECTED STANDARD ERRORS *********

------------------------ Fixed Effects Parameters -----------

       Beta     StdError        CV .
Ka    1.600 0.263353095 16.459568 %
CL    0.133 0.006533504  4.912409 %
V     7.950 0.322403263  4.055387 %
Rin   5.410 0.437881955  8.093936 %
C50   1.200 0.052867047  4.405587 %
Kout 0.056 0.001737771  3.103163 %


-------------------------- Variance of Random Effects --------

       Omega     StdError        CV .
Ka    0.7010 0.206505767  29.45874 %
CL    0.0634 0.017561742  27.69991 %
V     0.0206 0.012226360  59.35126 %
Rin   0.1900 0.050298864  26.47309 %
C50   0.0129 0.016460059 127.59736 %
Kout 0.0167 0.007665362  45.90037 %


------------------------ Variance of residual error ---------

             SIG  StdError       CV .
sig.slopeA 0.20 0.0216894 10.84470 %
sig.interB 3.88 0.4677695 12.05591 %
```

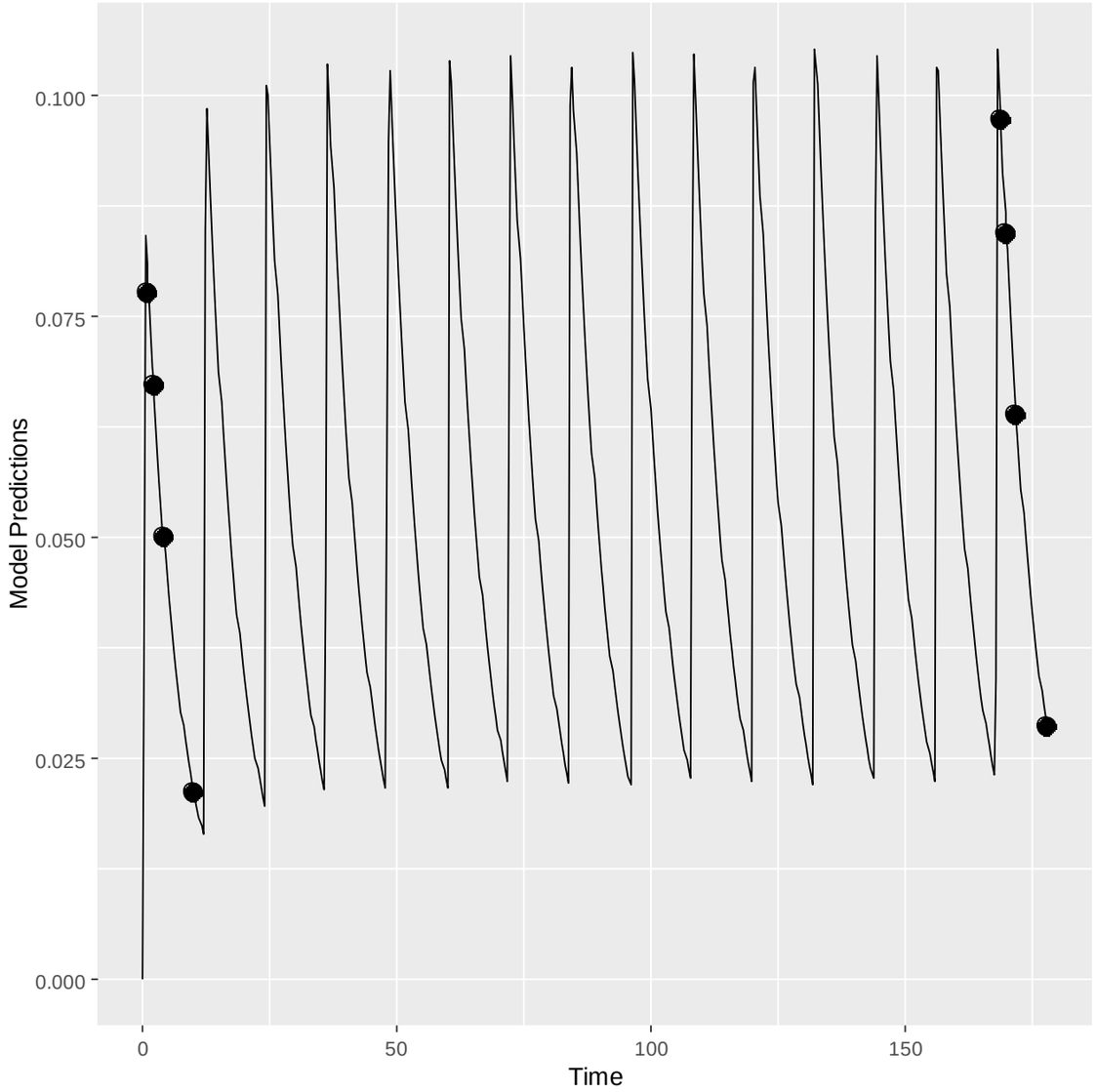


- **Two groups with 22 and 10 subjects**
- **Total of 256 sampling times**

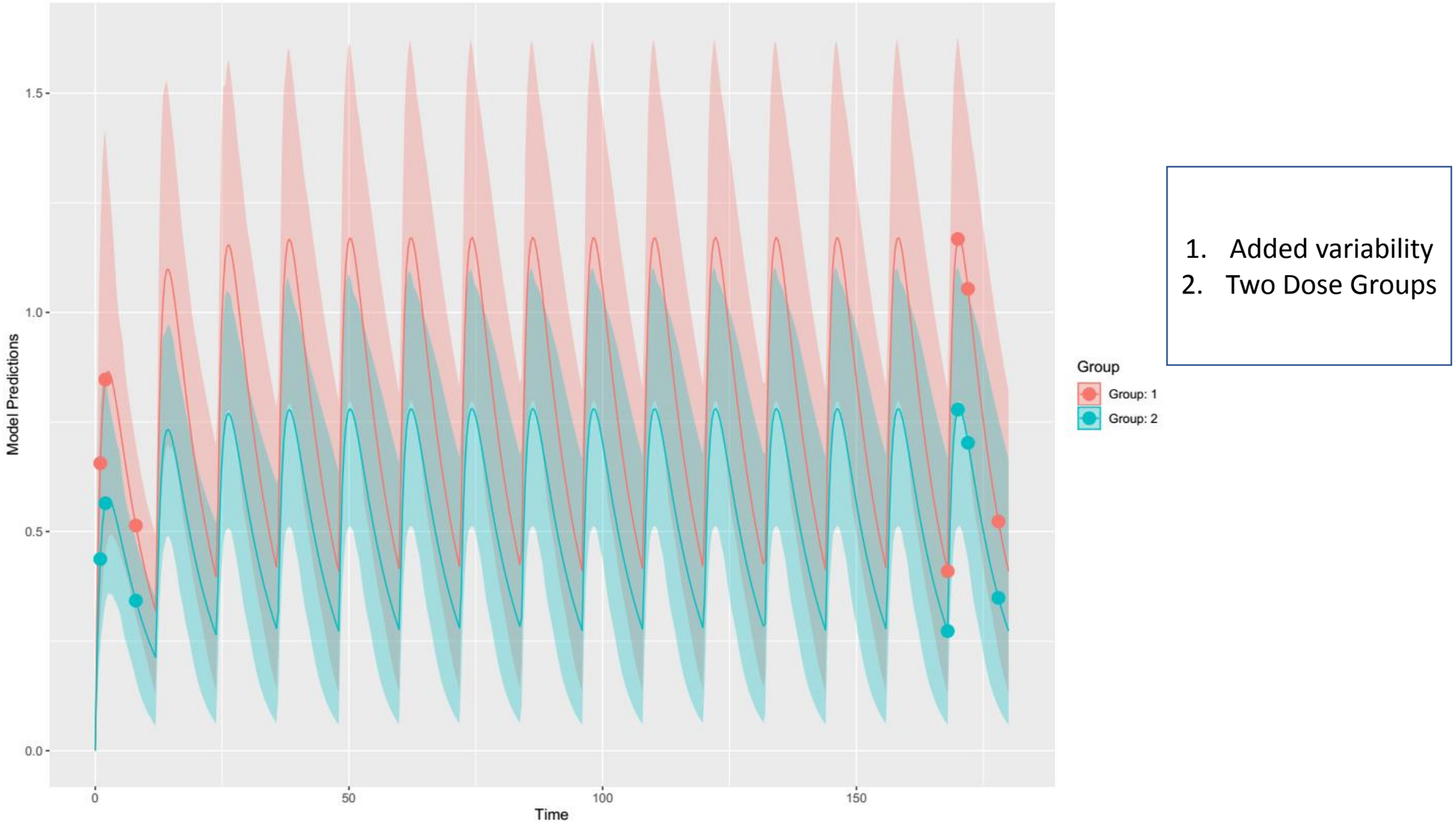
Did the same thing with Drug X: Simulated to steady state

Observations	1	2	3	4	5	6	7	8	9	10	11
Design0	0.5	2	4	6	8	12	84.5	86	90	96	
Design1	0.5	2	4	6	8	12	84.5	86	88	90	95.5
Design2	0.5	2	4	8	11.5	84.5	86	88	95.5		
Design3	0.5	2	4	6	11.5	84.5	88	90	95.5		
Design4	0.5	1	2	3	4	6	8	11.5	95.5		

Simulate Single Dose



Simulation with Variability to Confirm



1. Added variability
2. Two Dose Groups

Study Design and Sampling Protocol

Titration

Sampling

Week	Capsules	Dose	Sample Schema
Week 2	1 Cap BID	7.9 mg BID	25 Early Group: 0.5, 2.0, 4.0 25 Late Group: 6.0, 12.0
Week 3	2 Caps AM 1 cap PM	15.8 mg AM / 7.9 mg PM	-
Week 4	2 Caps PO BID	15.8 mg BID	25 Early Group: 0.5, 2.0, 4.0 25 Late Group: 6.0, 12.0
Week 5	3 Caps AM 2 Caps PM	23.7 mg AM and 15.8 mg PM	-
Week 6	3 caps PO BID	23.7 mg BID	25 Early Group: 0.5, 2.0, 4.0 25 Late Group: 6.0, 12.0

Maximum Blood Samples Intensive Group: 9 Blood Samples over 6 Weeks

*Blood Draw Volumes: 0.4 mL Minimum = 9 x 0.4 mL = 3.6 mL

2.0 mL Maximum = 9 x 2 mL = 18 mL

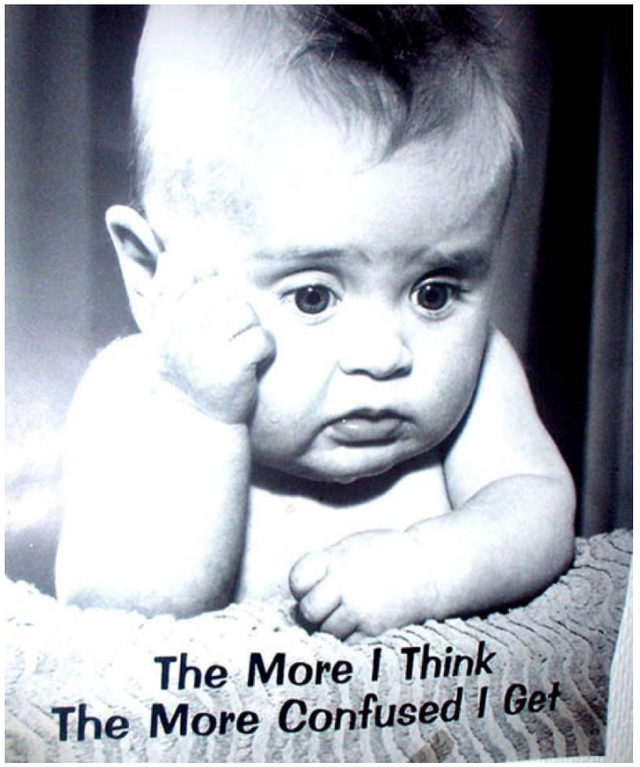
Predict Theoretical Pediatric Concentrations

Dose	Cmax (ng/mL) (Mean ± SD)	Cmax (ng/mL) Md(Max-Min)	C0 (ng/mL) (Mean ± SD)	C0 (ng/mL) Md(Max-Min)	AUCall (ng*h/ml) (Mean ± SD)	AUCall (ng*h/mL) Md(Max-Min)
7.9 mg	34.1± 2.1	34.1(38.8 -28.4)	9.9 ±1.8	9.6(14.3-6.5)	254.9 ±33.2	251.9 (329.8-182.1)
15.8 mg	68.2 ± 4.6	67.9(80.4-59.7)	19.5 ±3.7	18.7(29.4-13.8)	508.0 ± 68.5	501.8(680.1-392.0)
23.7 mg	102.4 ± 7.1	102.2(123.8-90.3)	29.3 ±5.9	28.2(49.1-21.8)	760.7 ±106.7	749.1(1079.6-606.7)

Run Phase 3 Pivotal Trial with sparse sampling to confirm

Conclusions

- Modeling and simulation are powerful tools for the design of informative PK/PD studies
- With relative little data, and application of literature information it is possible to make informed decisions on pediatric and other study designs
- Implementation of most informative samples design can increase information content and improve the cost-effectiveness of studies



Thank you!

Questions/Comments?