Pharmacometrics

Application of Modeling & Simulation to Pediatric Drug Studies & Individualized Dosing

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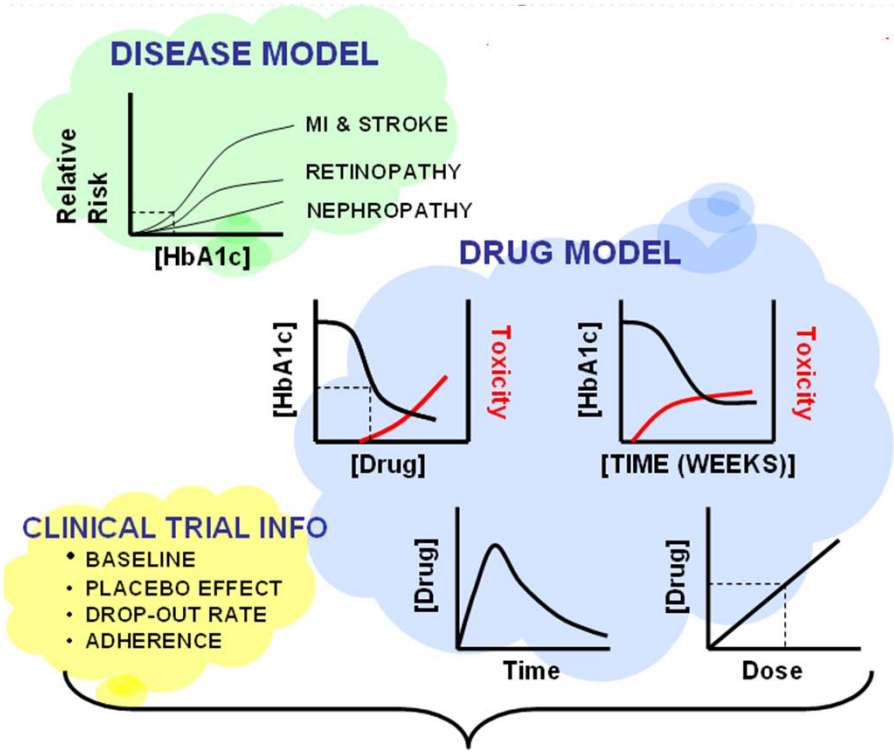
Pharmacometrics

the Science of Quantitative Pharmacology

- Use of models based on pharmacology, physiology and disease for quantitative analysis of interactions between drugs and patients
- This involves PK, PD and disease progression with a focus on populations and variability
- To better predict and control exposure and response in individual patients
- Achieve paradigm shift in way we do pediatric clinical drug studies



M&S to Support Key Decisions

http://en.wikipedia.org/wiki/Pharmacometrics

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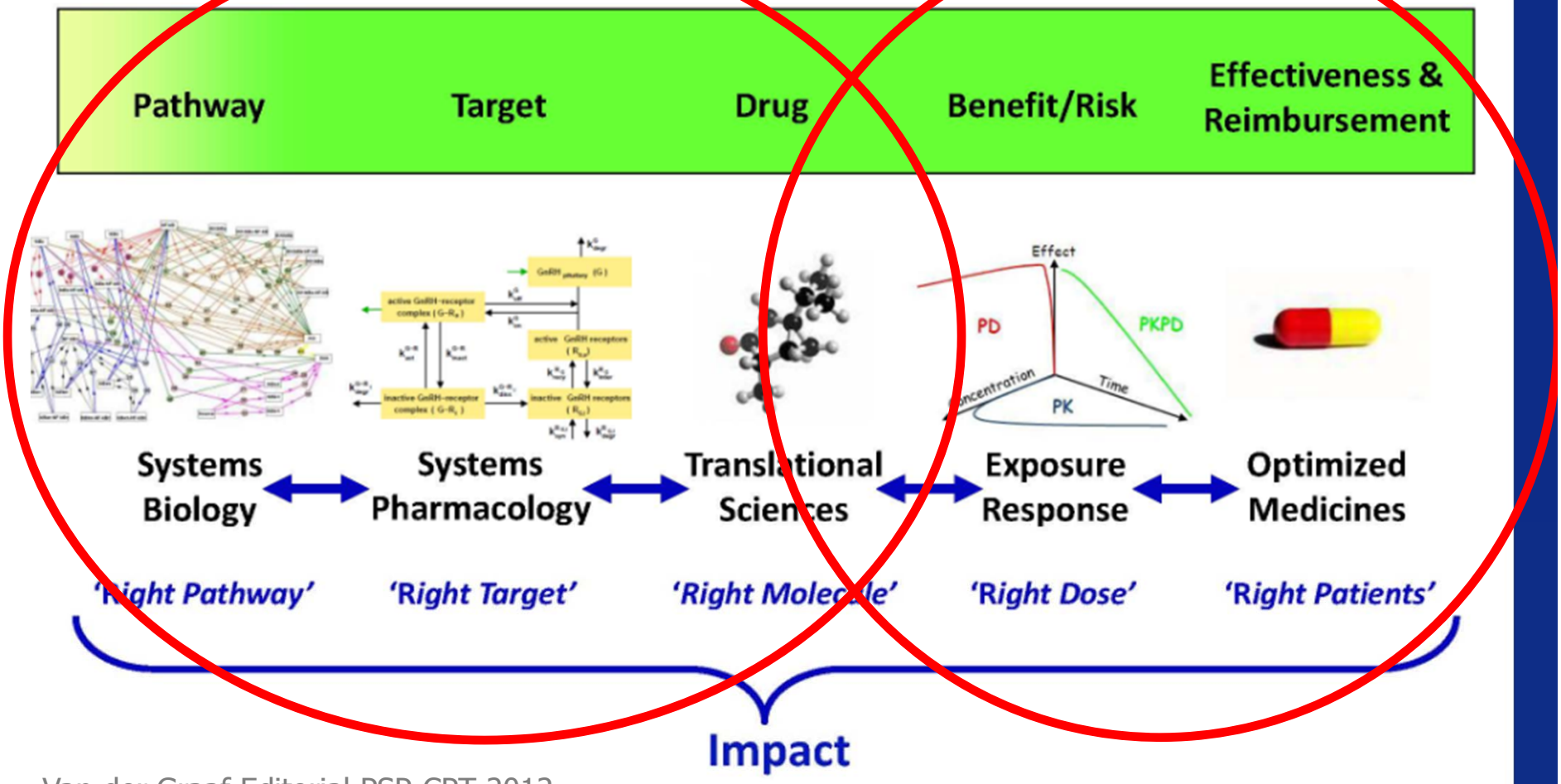
Pharmacometrics & Systems Pharmacology

Integration of model-based drug discovery and development



Van der Graaf Editorial PSP-CPT 2012

Why Pediatric Pharmacometrics

- Off-label use of 50-60% in children and up to 90% in (premature) neonates
- Missing information on Pharmacokinetics, Efficacy and Safety
- Lack of informative pediatric drug labels
- Missing age-appropriate dosage forms for the pediatric population

Informative PK/PD Study Design

- Getting the Dose right
- How many patients?
- How many samples
- Modeling & Simulation

How to Double Success Rate of Pediatric Trials?

Simulate2Design

Model4Approval

Joga Gobburu

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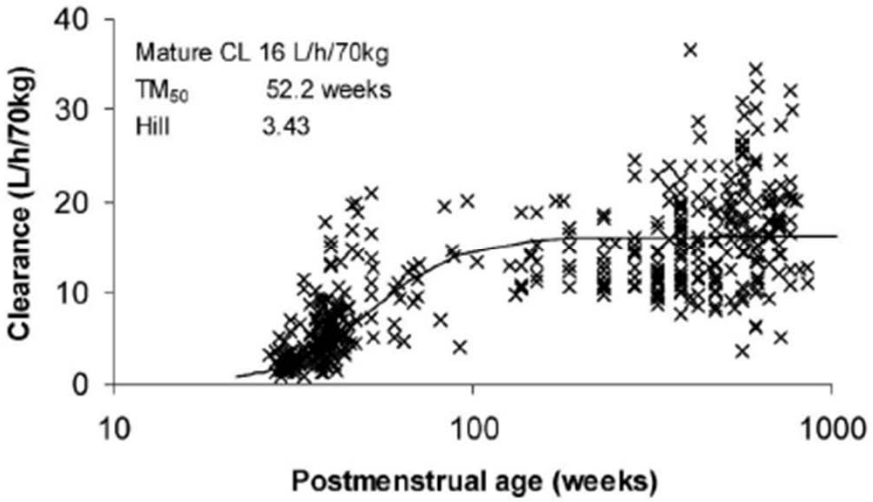
www. List site

Developmental Pharmacology Concepts

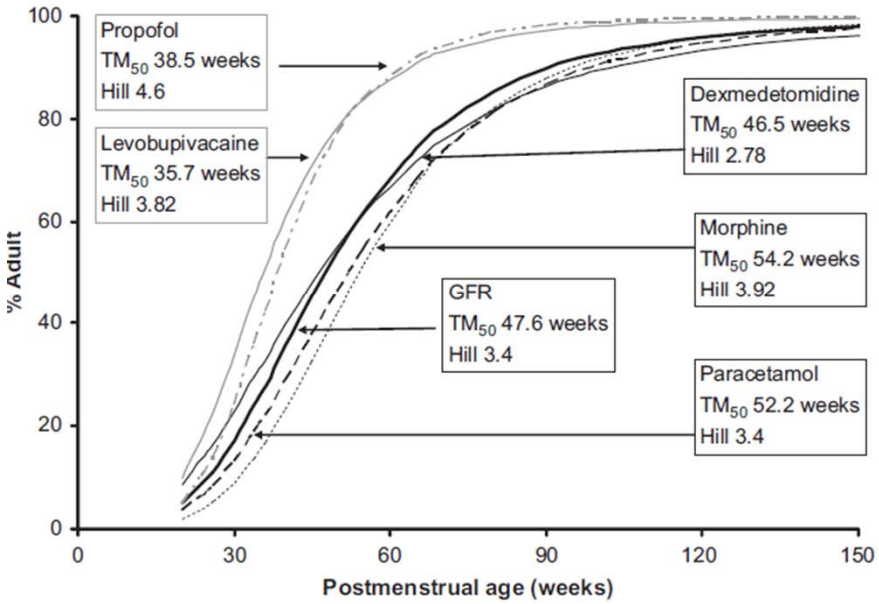
- Growth and development are two linked co-linear processes in children
- Size standardization is achieved by allometric scaling
- Age is used to describe maturation of clearance

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).

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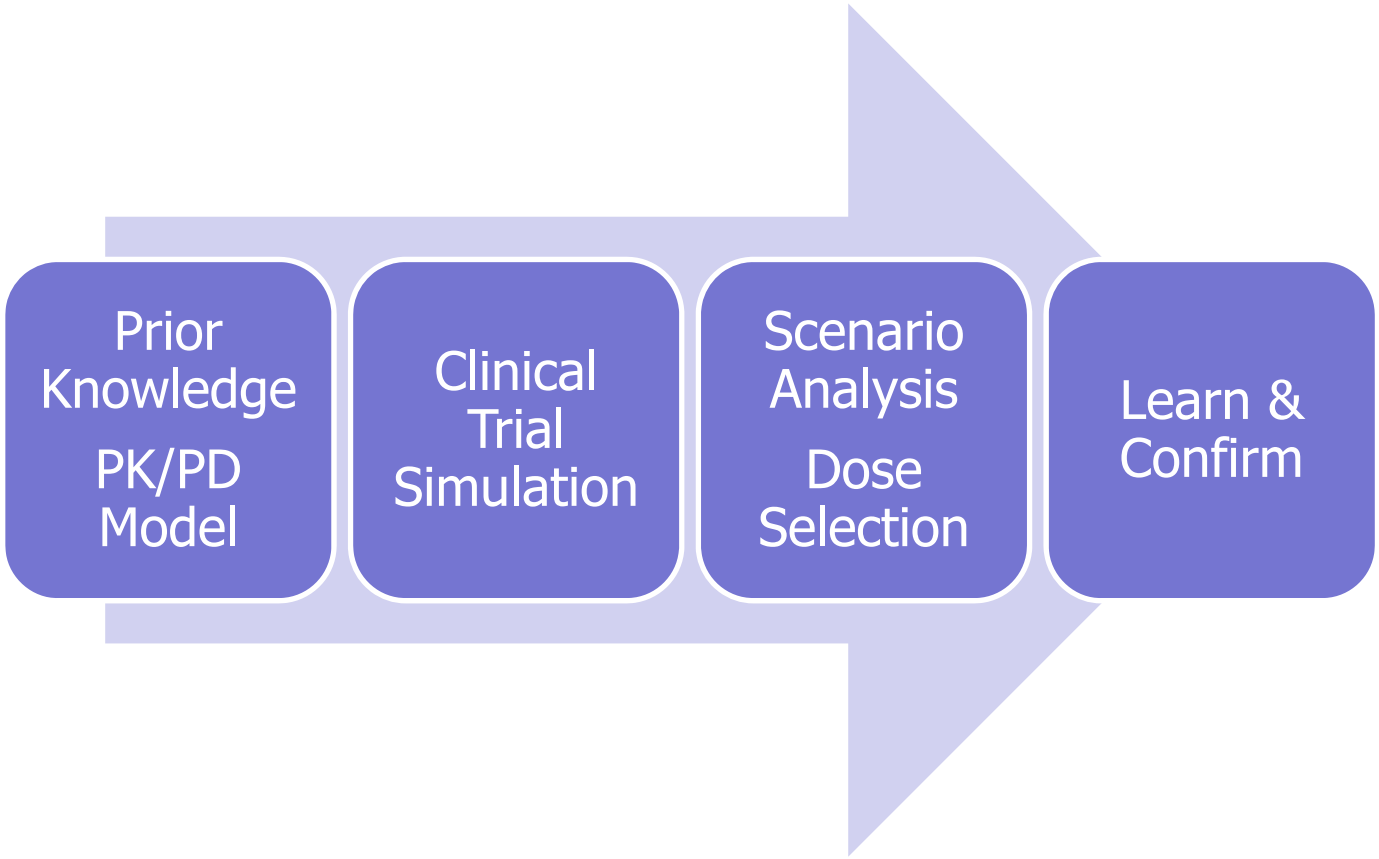
Model-based Trial Design



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

↓

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

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Development of Population Model based on prior knowledge

- 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 data

From literature & available data

From available data

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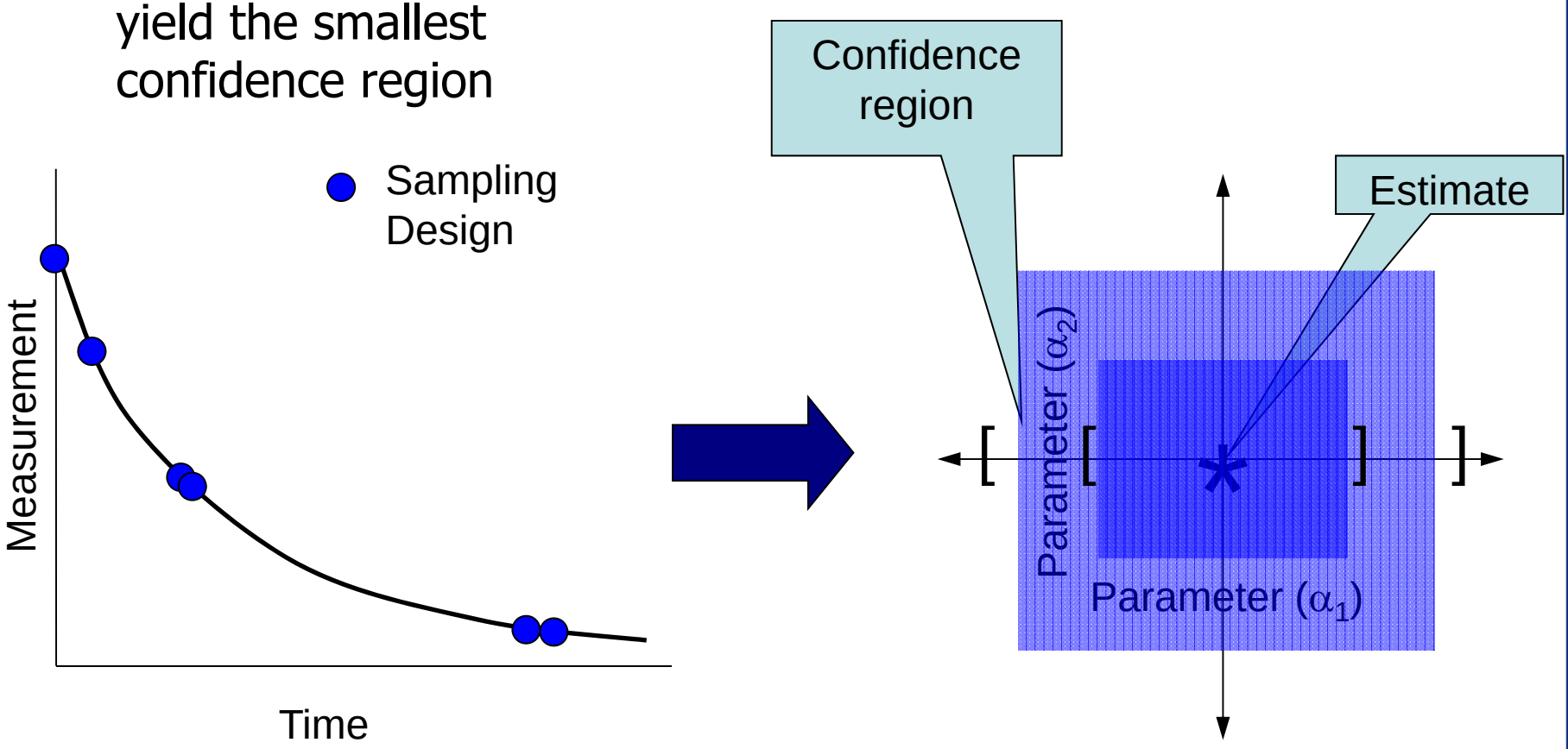
Determining Sample Size

- 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

How to get Best Estimates?

- Create a design that will yield the smallest confidence region



http://wiki.the-magister.com/uploaded/Defense_Presentation.ppt

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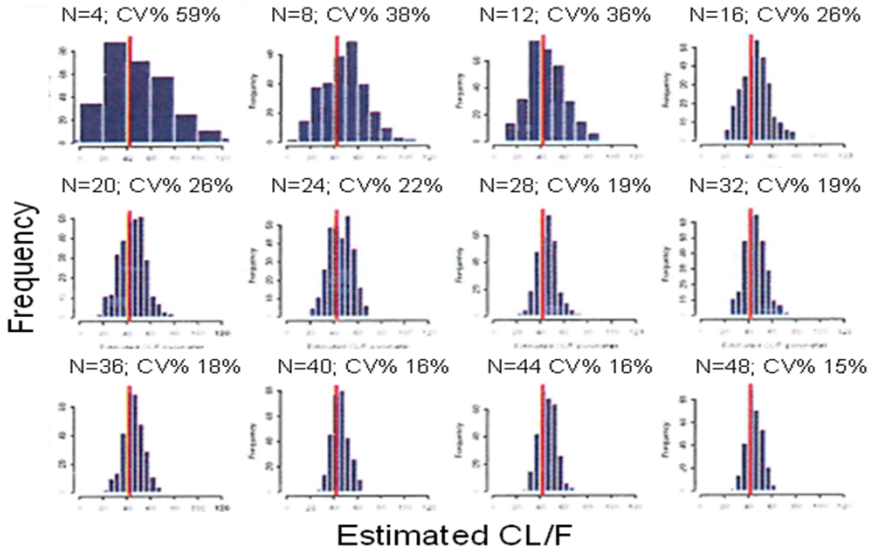
Powering Population PK studies



- 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

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BRIEF REPORT

Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies

Yaning Wang, PhD, Pravin R. Jadhav, PhD, Mallika Lala, PhD, and Jogarao V Gobburu, PhD

Keywords: *pediatric drug development; pharmacokinetics; regulatory requirement; precision*

Journal of Clinical Pharmacology, XXXX;XX:xxx-xxx

The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power.

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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

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

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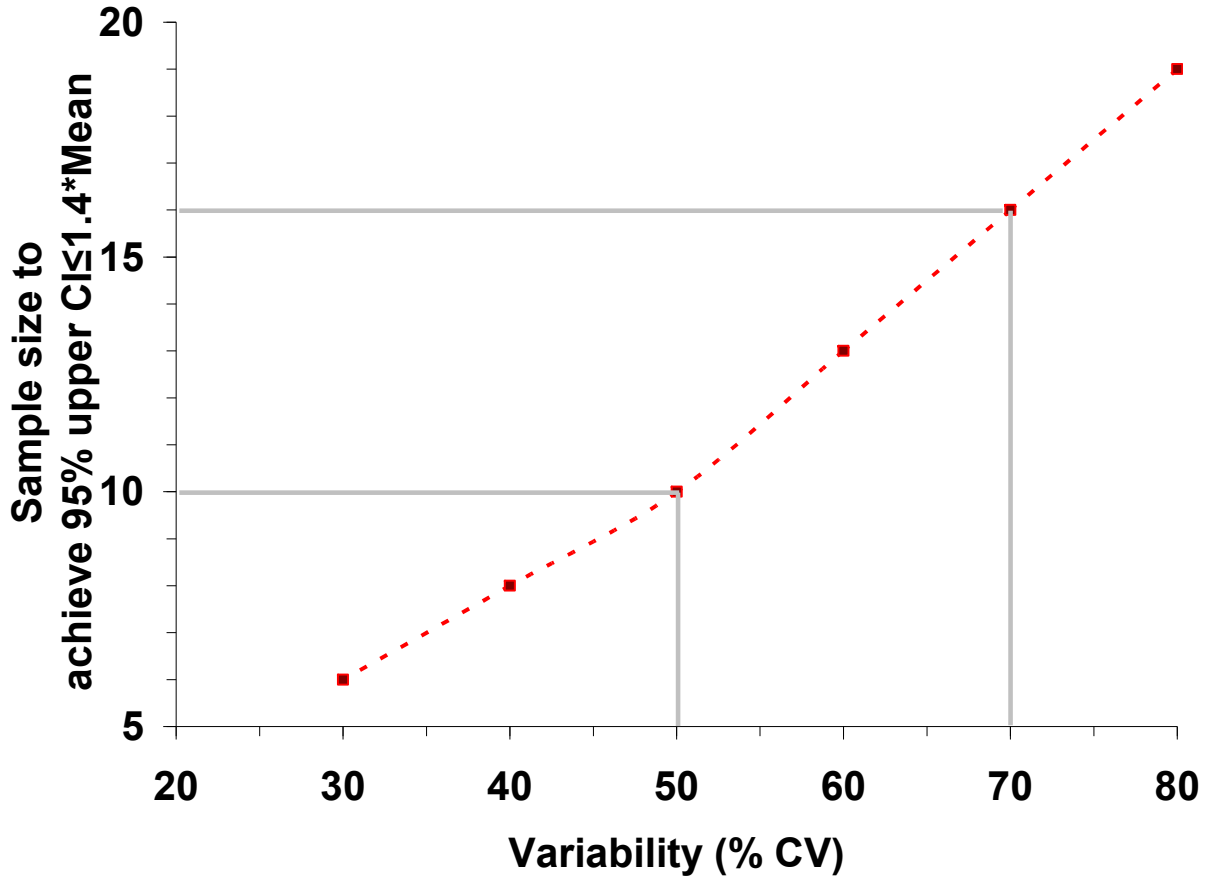
Sample Size Requirements based on FDA criterion



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Feasibility of Regulatory Requirements

Drug	Age Group	N	%CV	Pass CL?	%CV	Pass V?
Piperacillin	3-<6 mo	11	42%	Yes	26%	Yes
	6-<12 mo	5	44%	No (1.73)	44%	No (1.75)
	1-<2 yr	8	29%	Yes	17%	Yes
	2-<6 yr	12	35%		37%	
	6-<12 yr	20	50%		35%	
	12-18 yr	3	27%	No (1.93)	40%	No (2.68)
Guanfacin	6-<12 yr	13	53%	Yes		
	12-<18 yr	26	51%			
Ertepenem	3-<6 mo	6	49%	No (1.65)	33%	No (1.44)
	6-<12 mo	12	23%	Yes	15%	Yes
	1-<2 yr	15	25%		26%	
	2-<6 yr	9	23%		32%	
	6-<12 yr	16	45%		39%	
	12-18 yr	13	44%		41%	

Table 2: Sample sizes per age group for three drugs submitted as a part of a BPCA pediatric exclusivity program. The failure to meet the proposed quality standard is indicated by "Pass CL?" and "Pass V?".
For the failed groups, the ratio of 95% upper CI and the mean are presented.

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Case study

Teduglutide PK/PD in Pediatric Patients with Short Bowel Syndrome

- Teduglutide - a synthetic glucagon-like peptide-2 analog
  - evaluated for treatment of short-bowel syndrome (SBS)
- Design Pediatric multiple-dose Phase-I clinical study
  - determine safety, efficacy and PK of teduglutide in pediatric patients with SBS aged 0-12 months
- Application of clinical trial simulations
  - novel generalized additive modeling approach for location scale and shape (GAMLSS)
  - facilitates simulating population specific demographic covariates
- Goal was to optimize likelihood of achieving target exposure and therapeutic effect
  - based on observations in adult patients

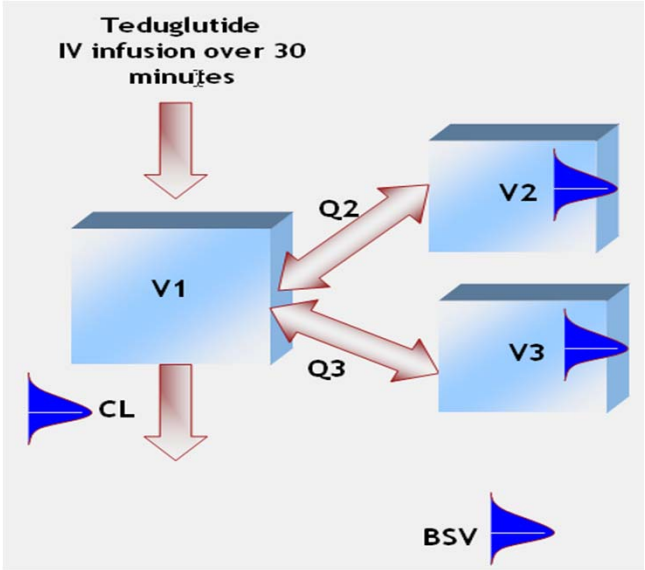
Mouksassi et al. Clinical pharmacology and therapeutics. 2009;86:667-71.

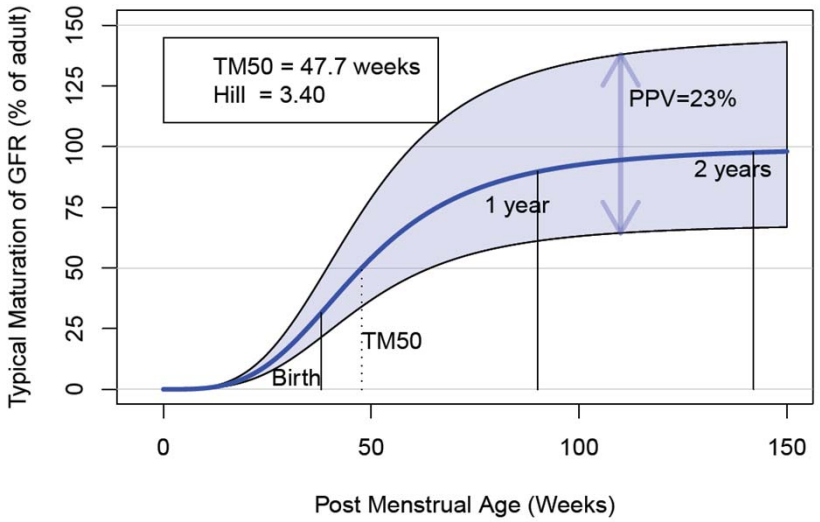
Development of Pediatric Population Model

- Structural 3-compt PK model with oral absorption (NONMEM)
  - Healthy volunteers (IV data)
- Allometric scaling component on clearance (CL) and volume of distribution (V)
- Model modified to include glomerular filtration rate (GFR) maturation as part of TDG clearance change over time
  - MF= PMA^{Hill} / (TM50 + PMA^{Hill})
  - TM50 is the maturation half-time

$$CLi = CLadult \bullet \left(\frac{WTi}{WTadult} \right)^{0.75}$$

Where CLi is Clearance of the individual, e.g. child or neonate. Expressed as L/h/70Kg





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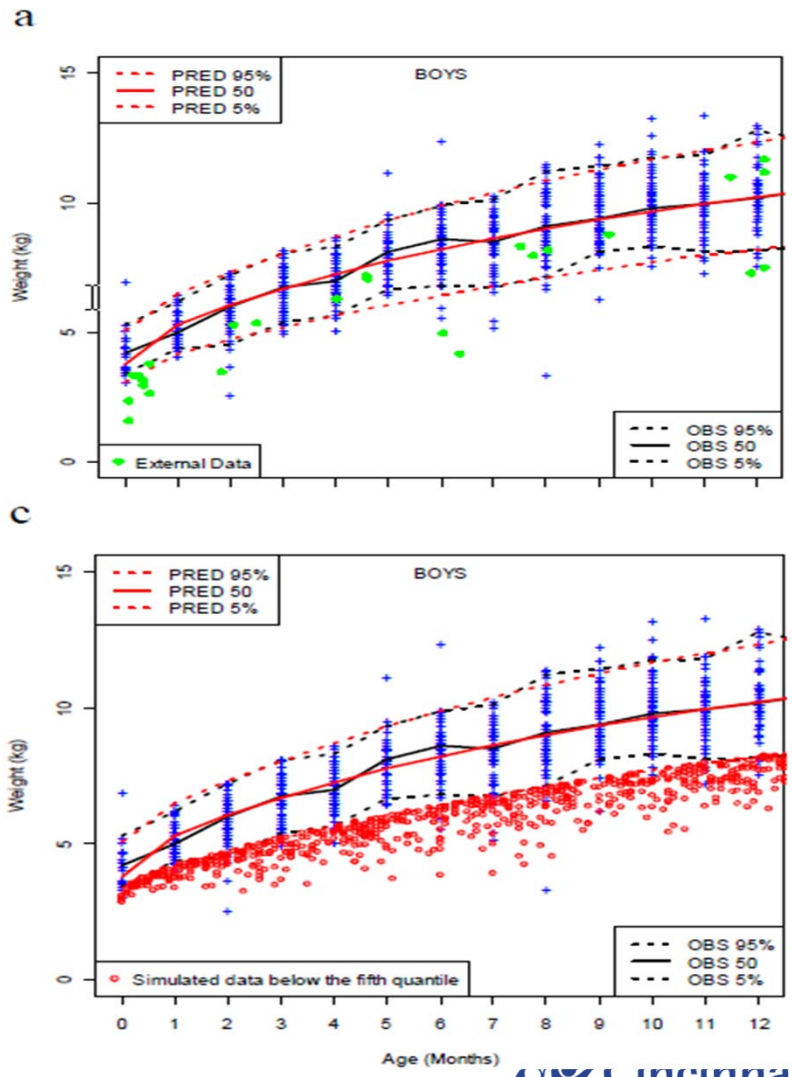
Generating Realistic Covariates

- SBS patients have body weights below the 5th quantile of their respective age groups
- GAMLSS modeling was used to simulate age-matched body weights values below the 5th quantile (R code)



GAMLSS: Generalized Additive Models for Location, Scale and Shape

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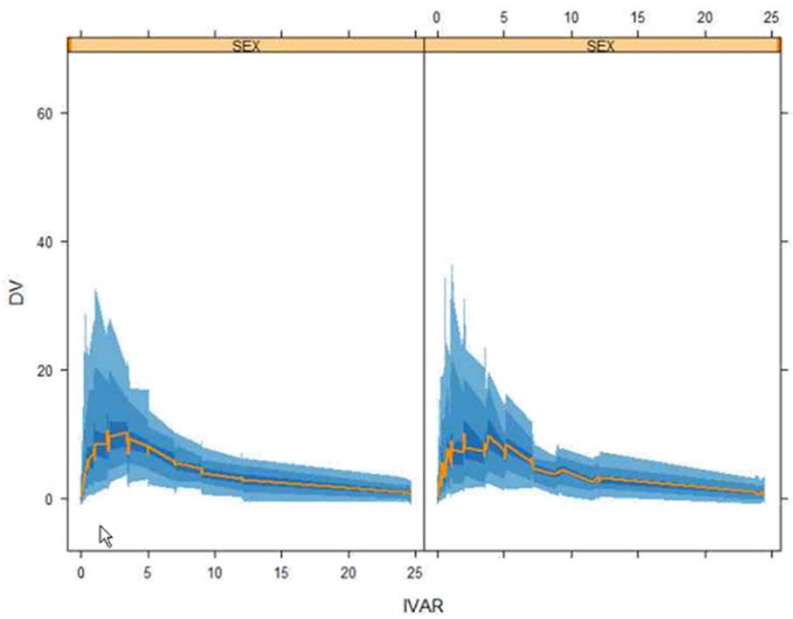
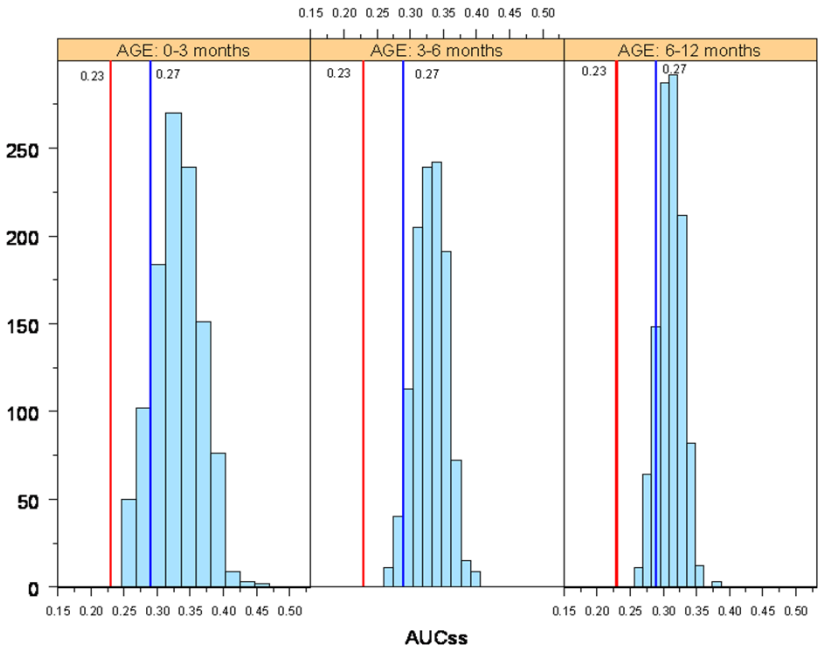
Predicted Teduglutide Exposure based on Clinical Trial Simulations





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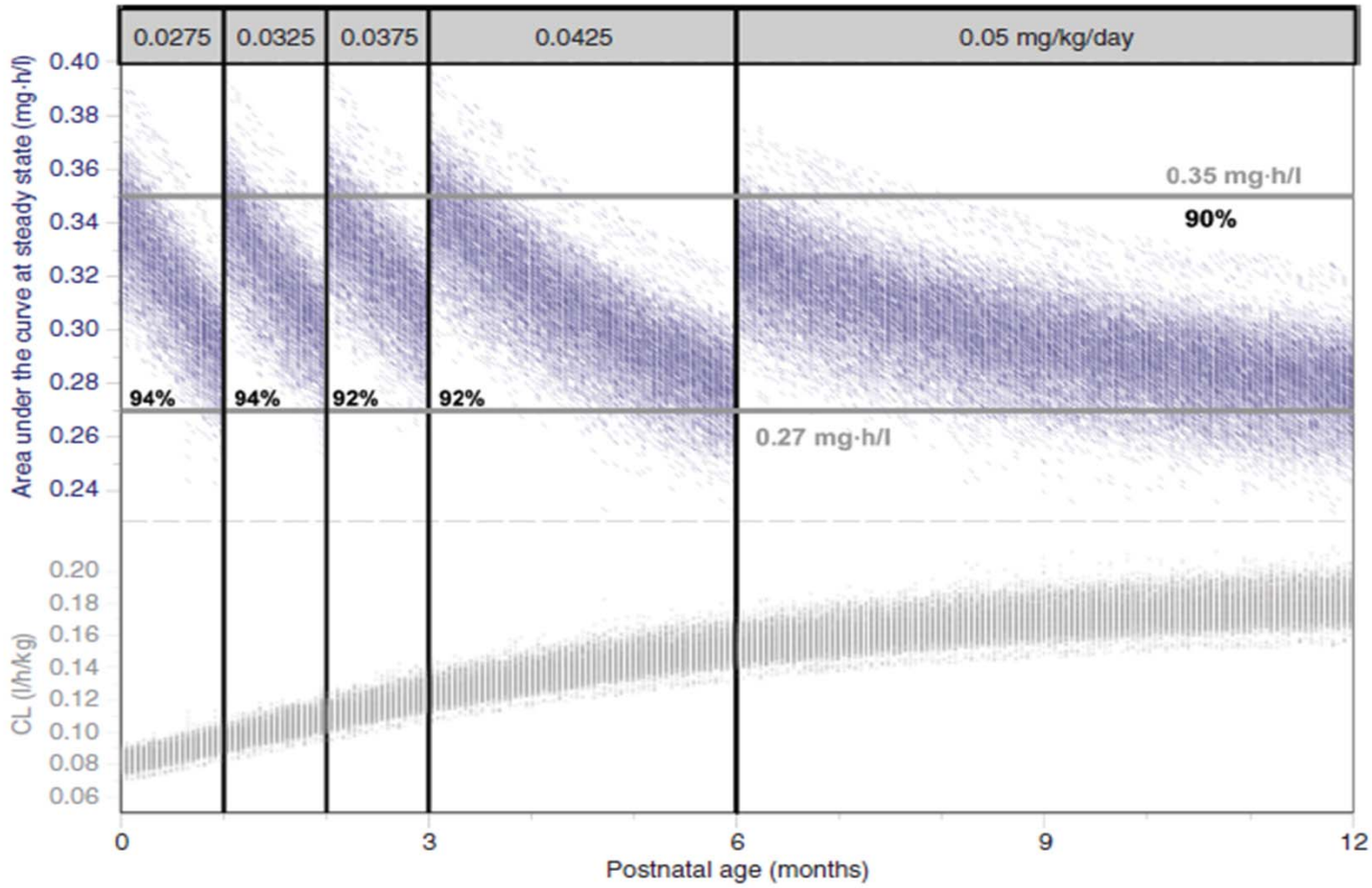
Clinical Trial Simulation results

Teduglutide dosing strategy to achieve optimal target attainment



- Dose reductions of 55, 65, 75, and 85% in the 0–1-, 1–2-, 2–3-, and 3–6-month age groups, compared with the optimal dosing regimen in the 6–12-month age group.
- Percentages of patients with steady-state teduglutide exposure within the targeted window of efficacy

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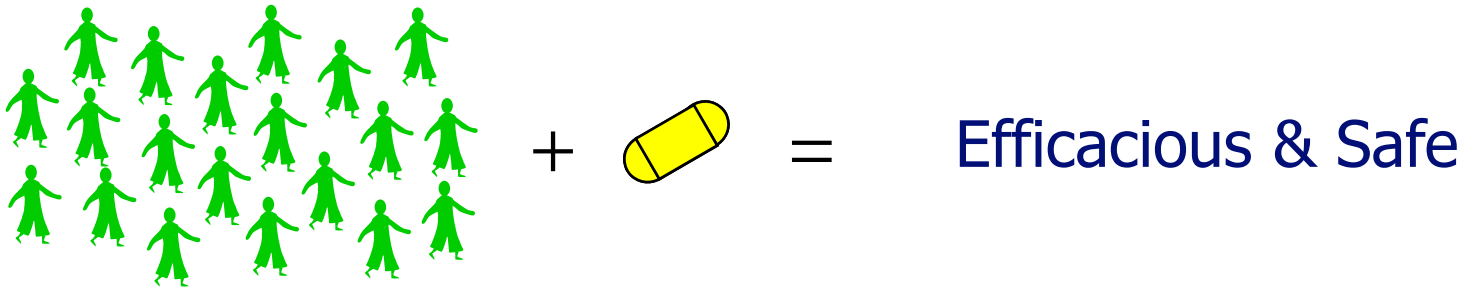
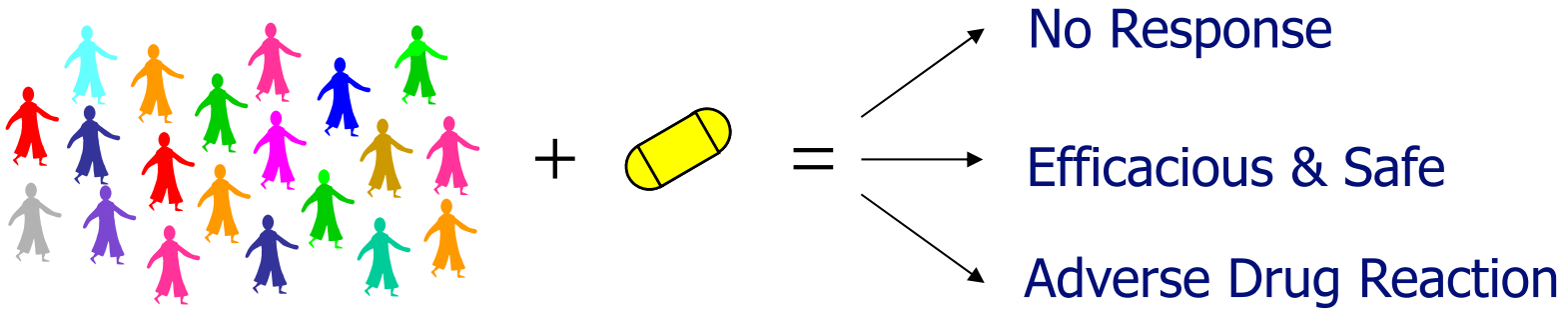
Continuing Paradox of Drug Development

1. Clinical trials provide evidence of efficacy and safety at usual doses in *populations*



2. Physicians treat *individual* patients who can vary widely in their response to drug therapy



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DASHBOARDS

Web-based decision support for individualized immunosuppression

What if we had ***pharmacokinetic and pharmacogenetic data,***
*…**adherence data** and……**protocol recommended drug exposure targets** and…**patient reported outcomes** (side effects)*
*and……**passive patient reported outcomes…***
***all in the same place**?*

David K. Hooper, MD, MS - Nephrology & Hypertension
Keith Marsolo, PhD - Biomedical Informatics
Ahna Pai, PhD - Center for Treatment Adherence
Alexander A. Vinks, PharmD, PhD - Clinical Pharmacology

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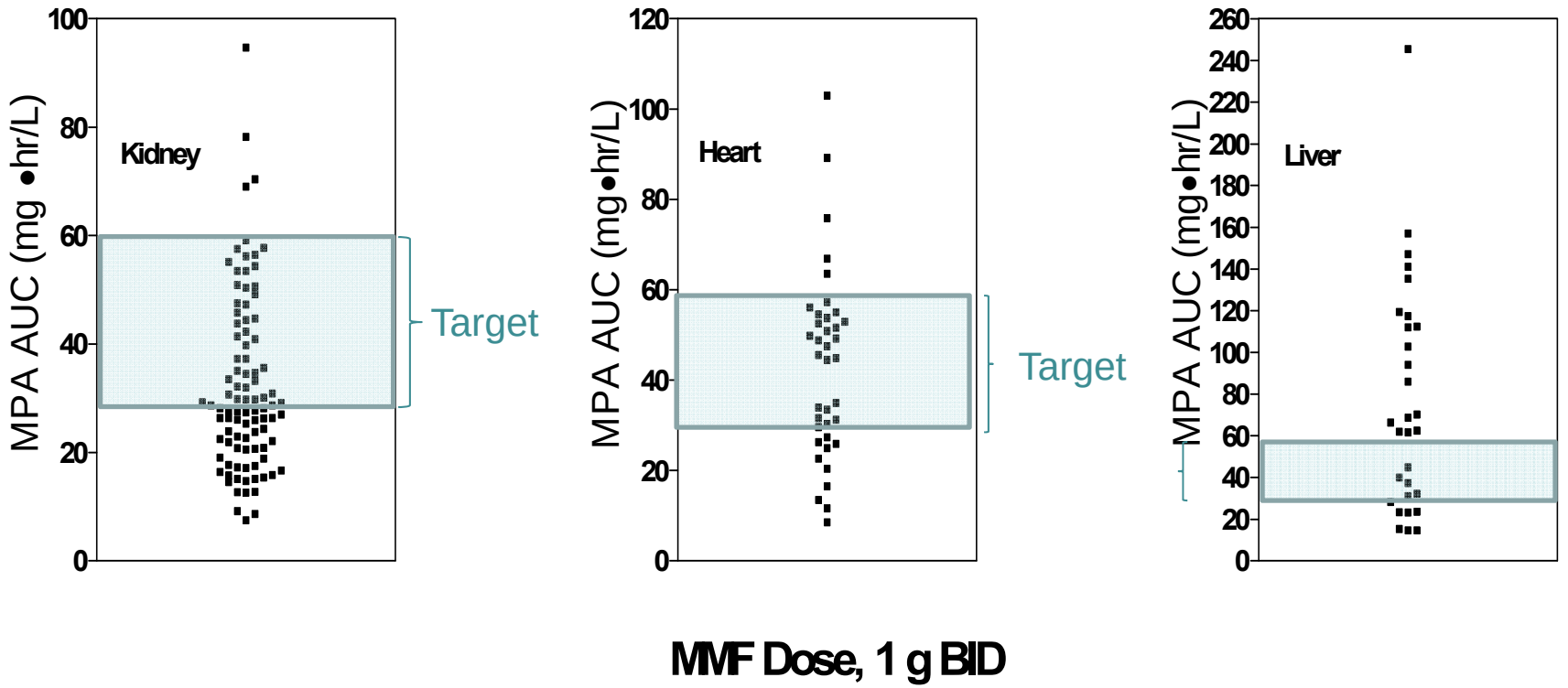
Supported by a Place Outcomes Award

One Dose Does Not Fit All

Large variability at standard doses



Shaw LM, et al, Am J Transplantation, 2003

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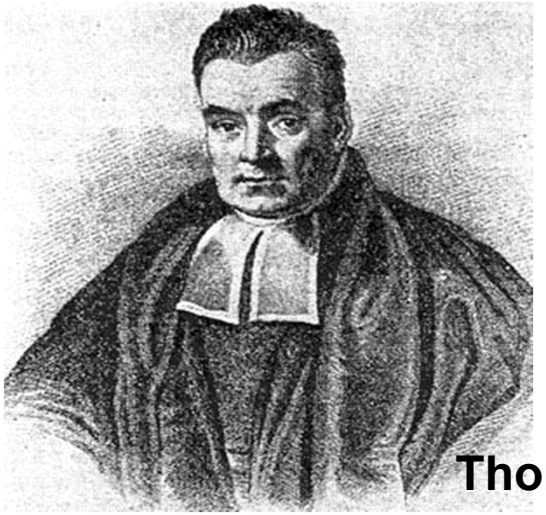
Bayesian



Estimation

Thomas Bayes 1702 - 1761

Prior Probability	New Info	Objective Function	Posterior Probability	Goals	Control
Population Model	Concentration Biomarker	Consider Prior + New	Individual Model	Look at Patient Think	Select drug Calculate Dose

$$\Phi_2 = \sum_{i=1}^{n}\left(\frac{C_i - E_i}{S_i}\right)^2 + \sum_{k=1}^{m}\left(\frac{\theta_k - \mu_k}{\sigma_k}\right)^2$$

Courtesy: Roger Jelliffe, MD, USC, Los Angeles

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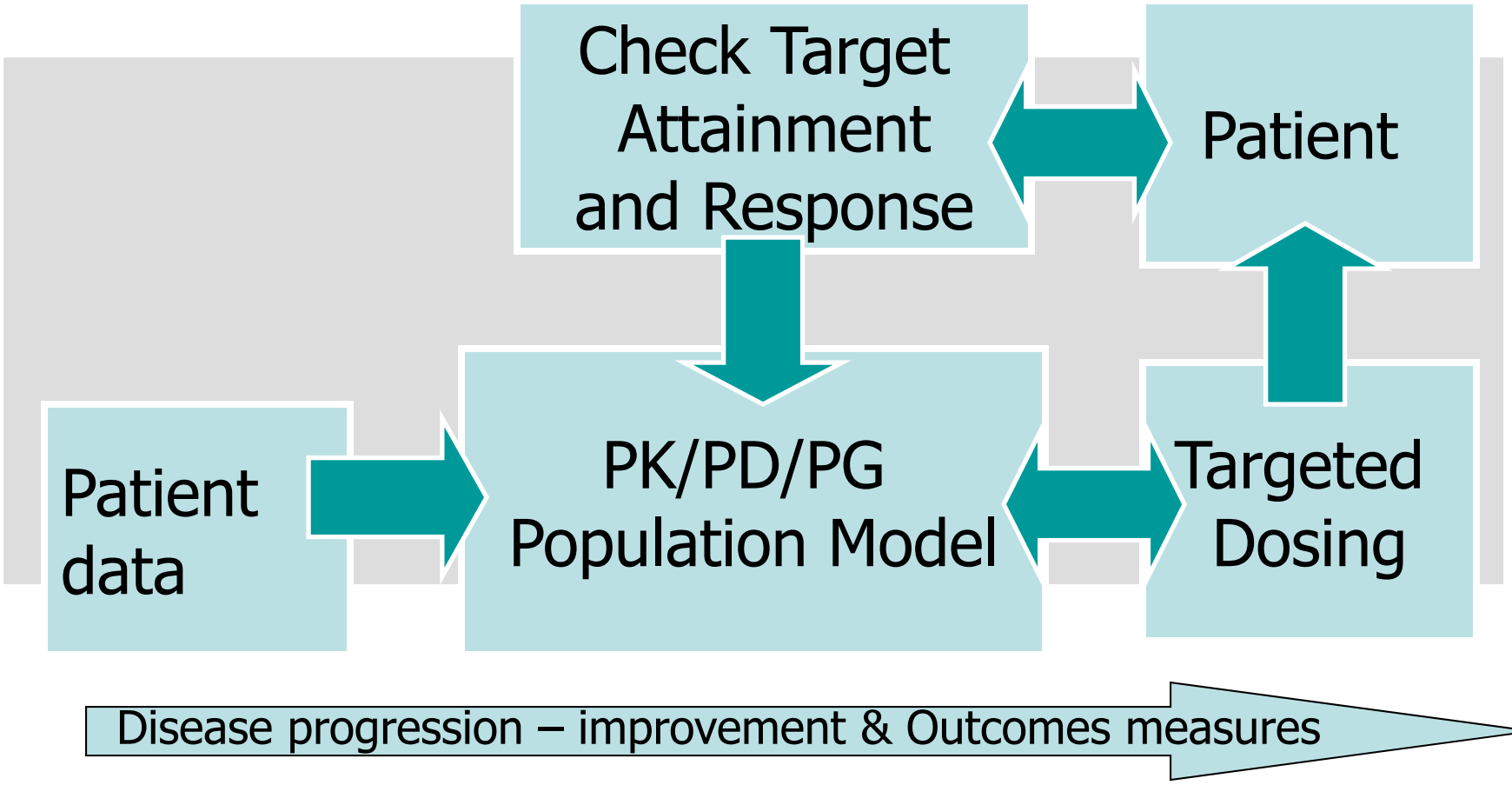
Target-Controlled Model-Based Individualized Dosing



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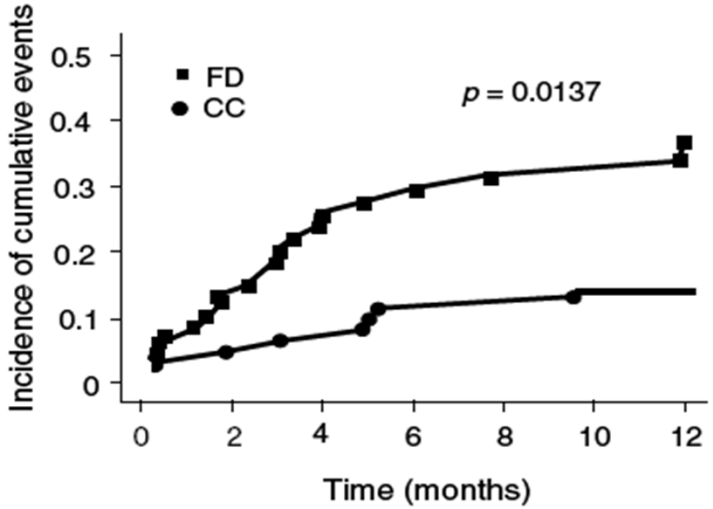
American Journal of Transplantation 2007; 7: 2496–2503
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.01983.x

Individualized Mycophenolate Mofetil Dosing Based on Drug Exposure Significantly Improves Patient Outcomes After Renal Transplantation

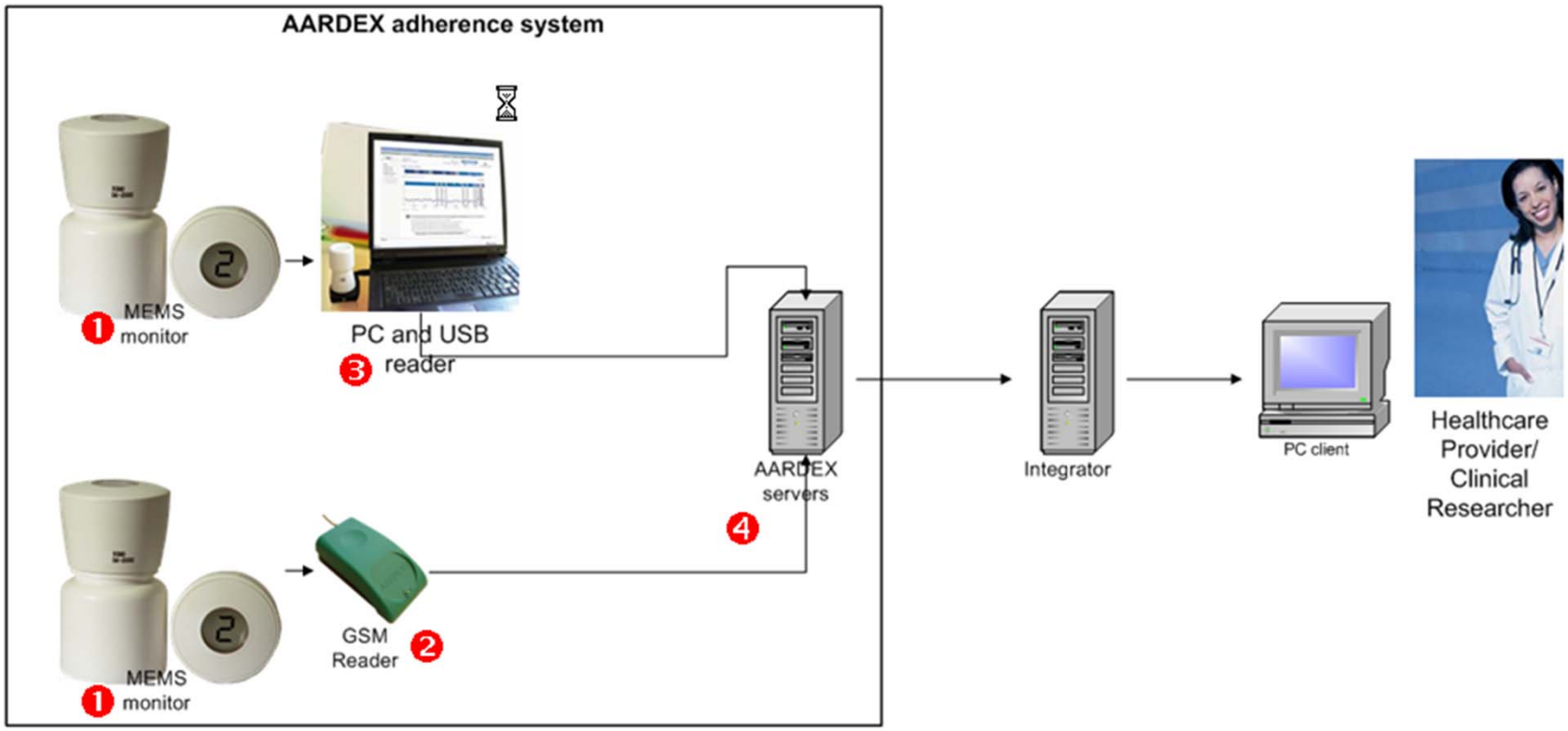
Y. Le Meur[a,*], M. Büchler[b], A. Thierry[c], S. Caillard[d], F. Villemain[e], S. Lavaud[f], I. Etienne[g], P.-F. Westeel[h], B. H. de Ligny[i], L. Rostaing[j], E. Thervet[k], J. C. Szelag[a], J.-P. Rérolle[a], A. Rousseau[l], G. Touchard[c] and P. Marquet[m]

[a]Department of Nephrology, University Hospital, Limoges, France



- APOMYGRE (Multicenter study, France):
- Randomized study evaluating model-based Bayesian dose adjustments
- 11 centers, 137 patients - first year post-transplantation
- Primary outcomes parameter: treatment failure
- Acute rejection - Graft loss – Death - GI, infections and hematological AEs

Adherence system is based on the MEMS monitor



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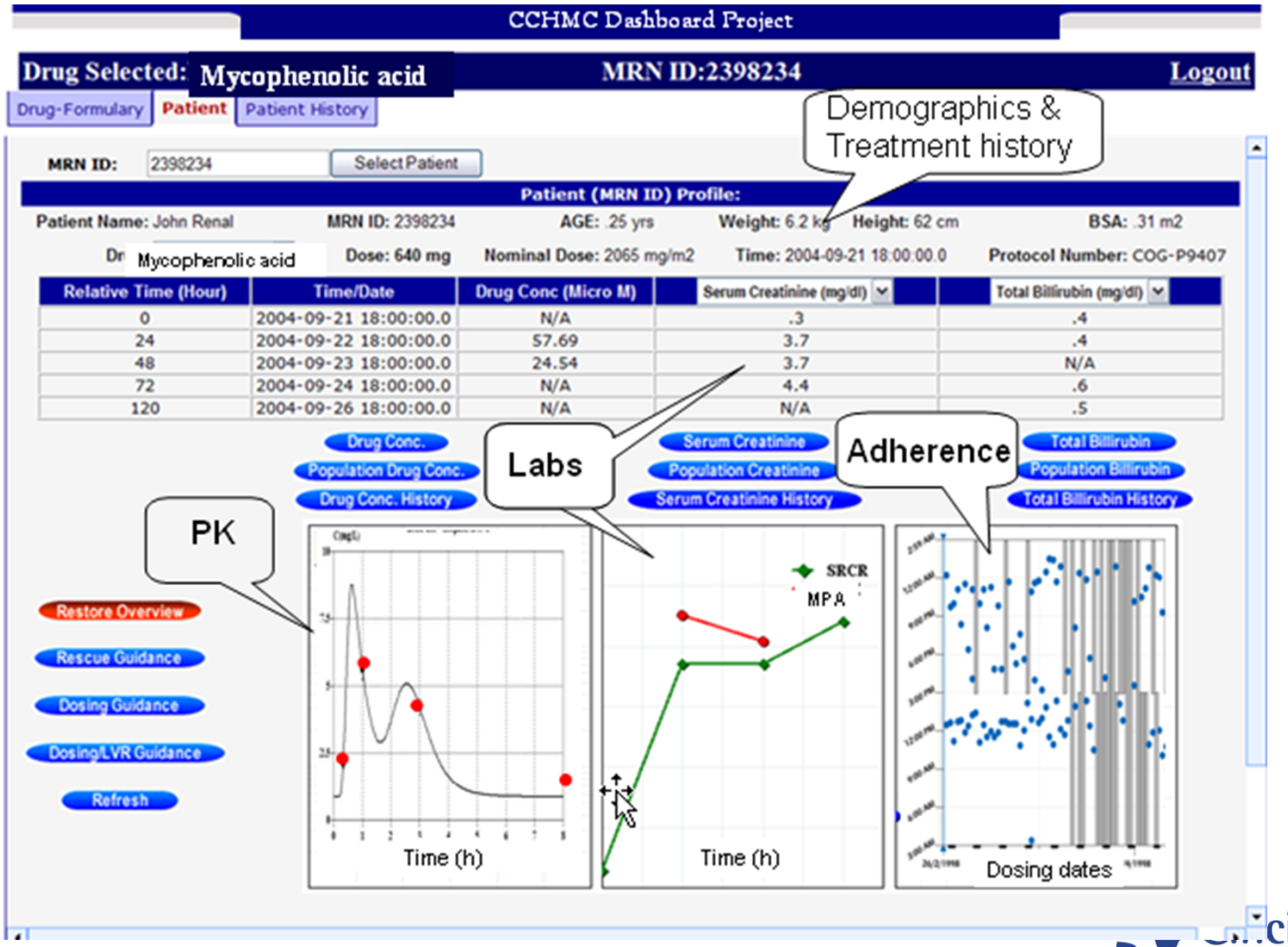
Prototype Dashboard MMF



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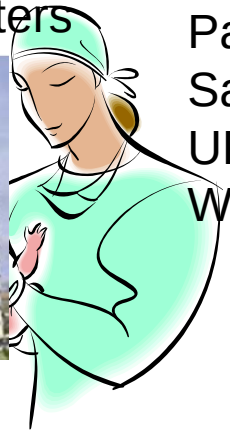
Real life application of M&S

Participating Centers



Patient visit
Sample collection
UPS shipment
Web/email notification

Centralized
LC-MS/MS
Analysis

Confirmation
Dose change

Bayesian estimation
Dosing recommendation
Uploaded to web
Email notification

Results reported
On Web
Email notification
Sent out

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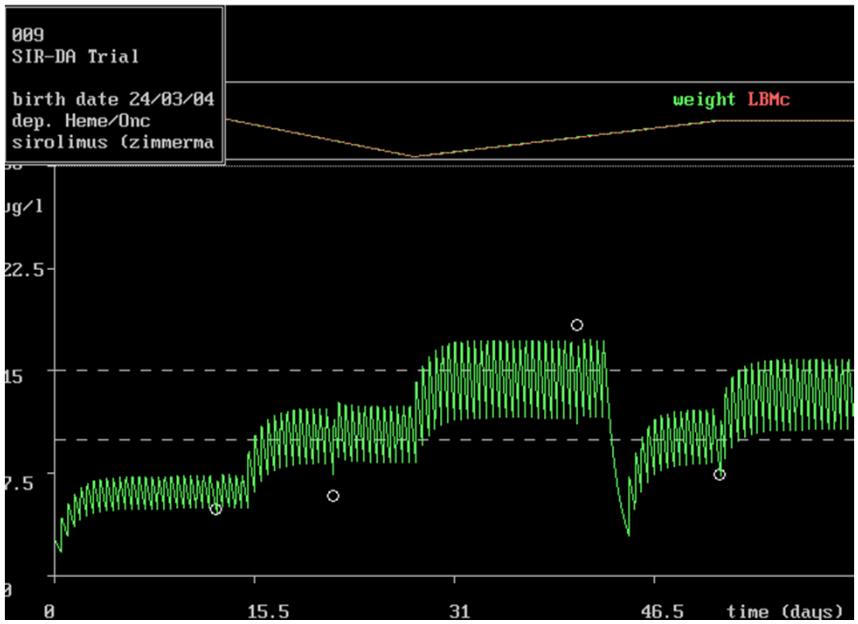
Model-based decision support



- Dose adjustment based on Bayesian feedback
- Capturing of maturation of clearance and changes over time
  - Disease progression/improvement
  - Other factor e.g. infections

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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 study design
- Implementation of D-optimal design will increase information content and improve the cost-effectiveness of studies
- Model-based dosing (Bayesian estimator) is the way forward in 'personalized' clinical trials

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change the outcome