THE RIGHT DOSE

Application of PK/PD modeling in pediatric antibiotic development

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PLAN FOR TODAY

PRE-STUDY DOSE OPTIMIZATION

DATA ANALYSIS

LEVERAGING EHR

FUTURE DIRECTIONS

MOST COMMON ELIMINATION

LIVER

KIDNEYS

OTHERS

FECES, BILE, LUNG, SKIN

FACTORS AFFECTING DOSING

SIZE

MATURATION
- LIVER, RENAL

ORGAN FUNCTION

OTHERS
- CON MEDS, BODY COMPOSITION

PK/PD: WHAT IS IT?

PHARMACOKINETICS

WHAT THE BODY DOES TO THE DRUG

PHARMACODYNAMICS

WHAT THE DRUG DOES TO THE BODY

PK/PD: WHY IS IT USED?

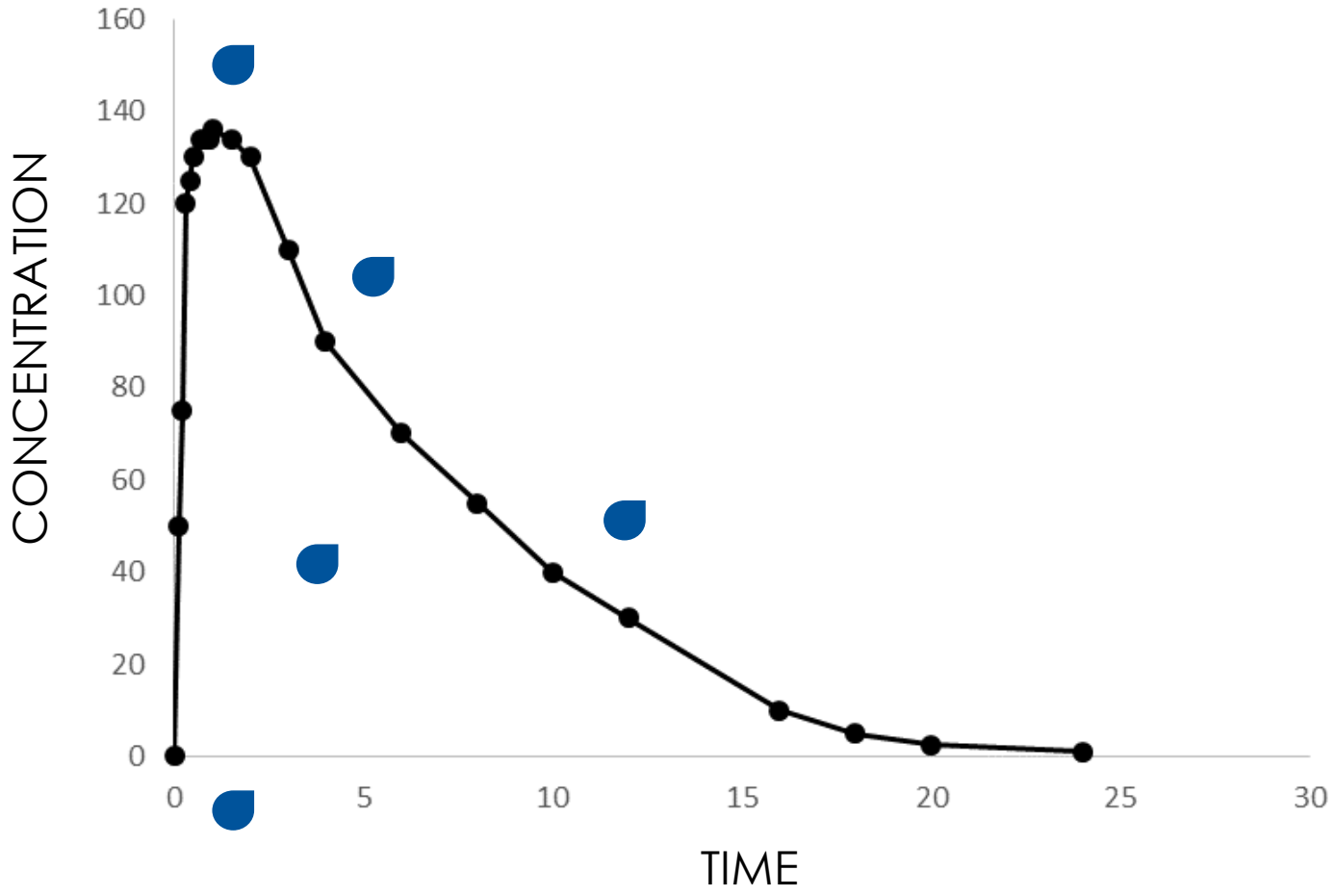
UNDERSTAND ADME

ABSORPTION **D**ISTRIBUTION **M**ETABOLISM **E**LIMINATION

UNDERSTAND EXPOSURE-RESPONSE

GET THE DOSE RIGHT

THE PK CURVE: GET IT RIGHT



CHALLENGES

SAMPLE SIZE

PK SAMPLING

ANALYSIS EXPERTISE

CONSENTING

EXAMPLE #1

SOLITHROMYCIN

FLUOROKETOLIDE

INDICATION

CABP

PEDIATRIC REQUIREMENT

PK AND SAFETY

SOLITHROMYCIN

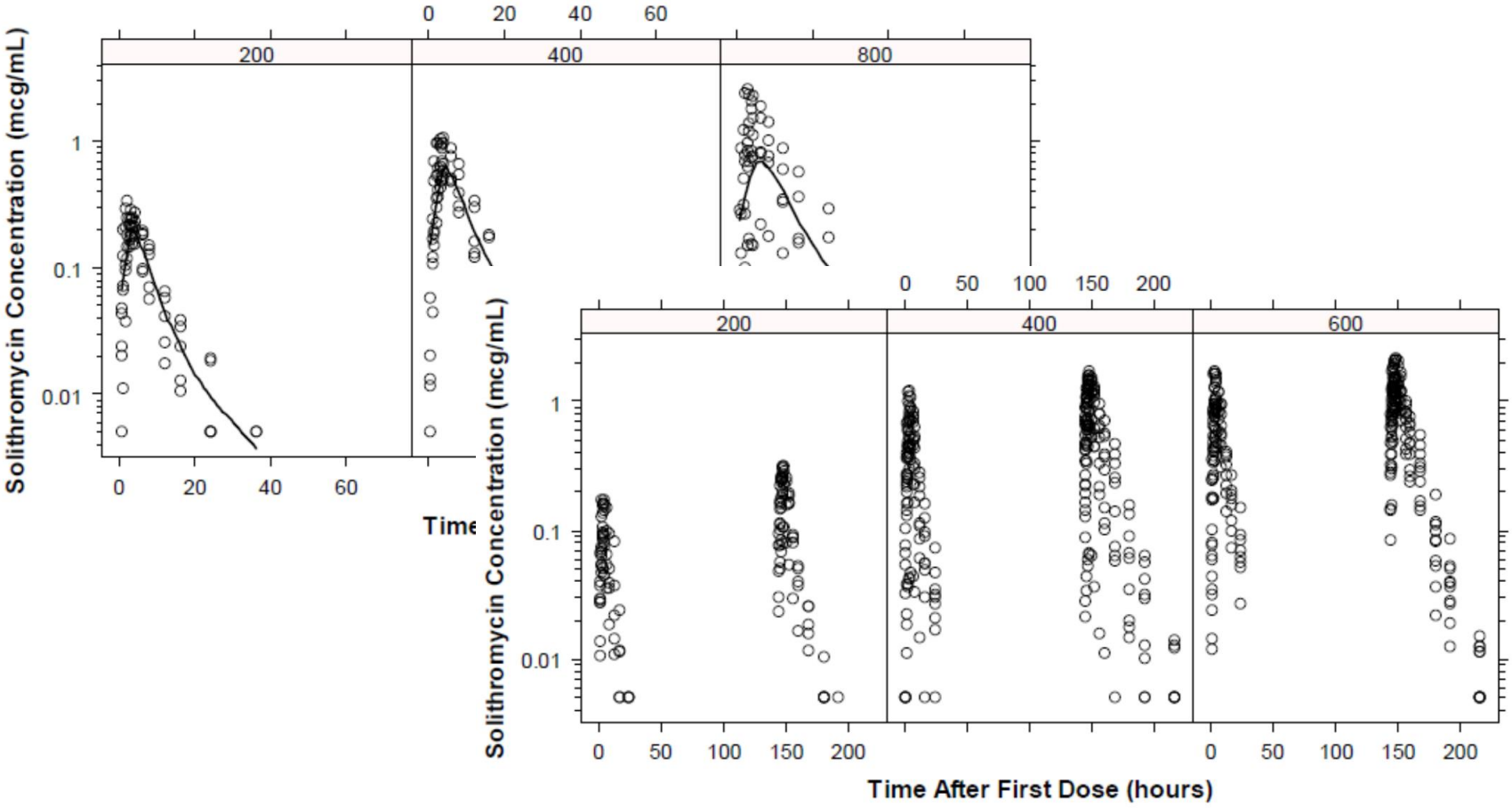
PRE-STUDY DOSE OPTIMIZATION

INCREASE CHANCES OF GETTING DOSE RIGHT

DATA ANALYSIS

INFORMS MODELS AND ASSUMPTIONS

DOSE OPTIMIZATION: STEPS



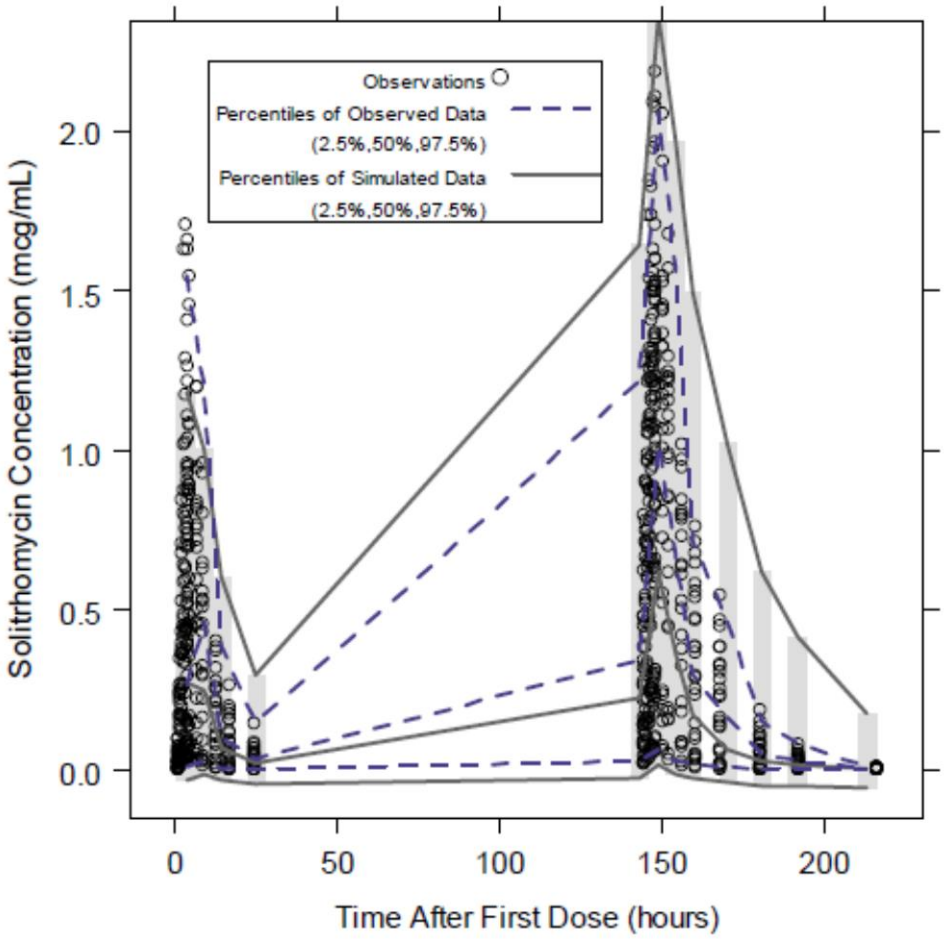
DOSE OPTIMIZATION: STEPS

Capacity Limited First Pass Metabolism

$$F1 = \frac{F_{MAX} * Dose^{HILL}}{FDose_{50}{}^{HILL} + Dose^{HILL}}$$

Dose → KA

ALAG

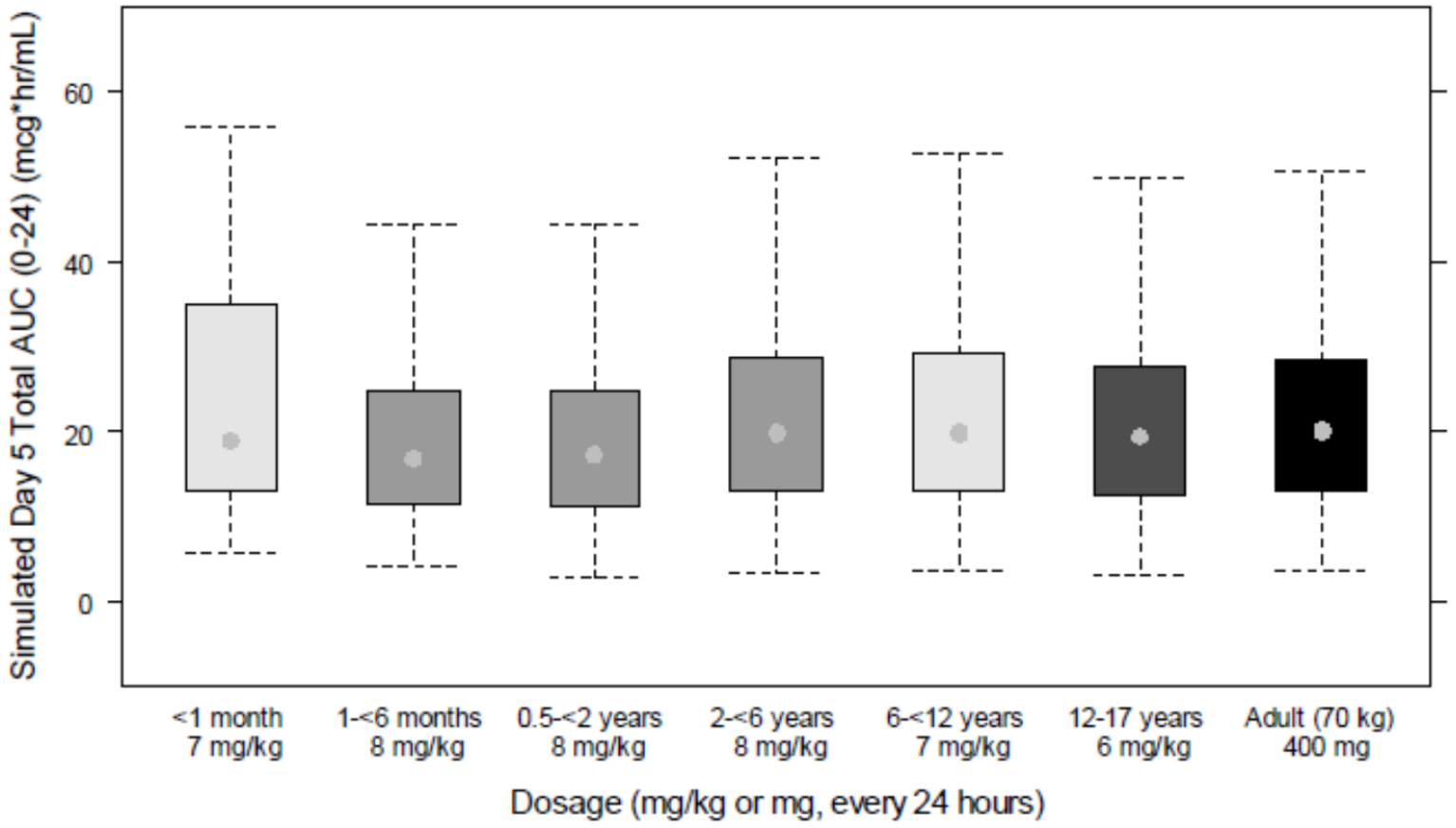


DOSE OPTIMIZATION: STEPS

$$CL = CL_{std} * \left(\frac{WT_i}{70\ kg}\right)^{0.75} * \frac{PMA^{HILL}}{TM_{50}{}^{HILL} + PMA^{HILL}}$$

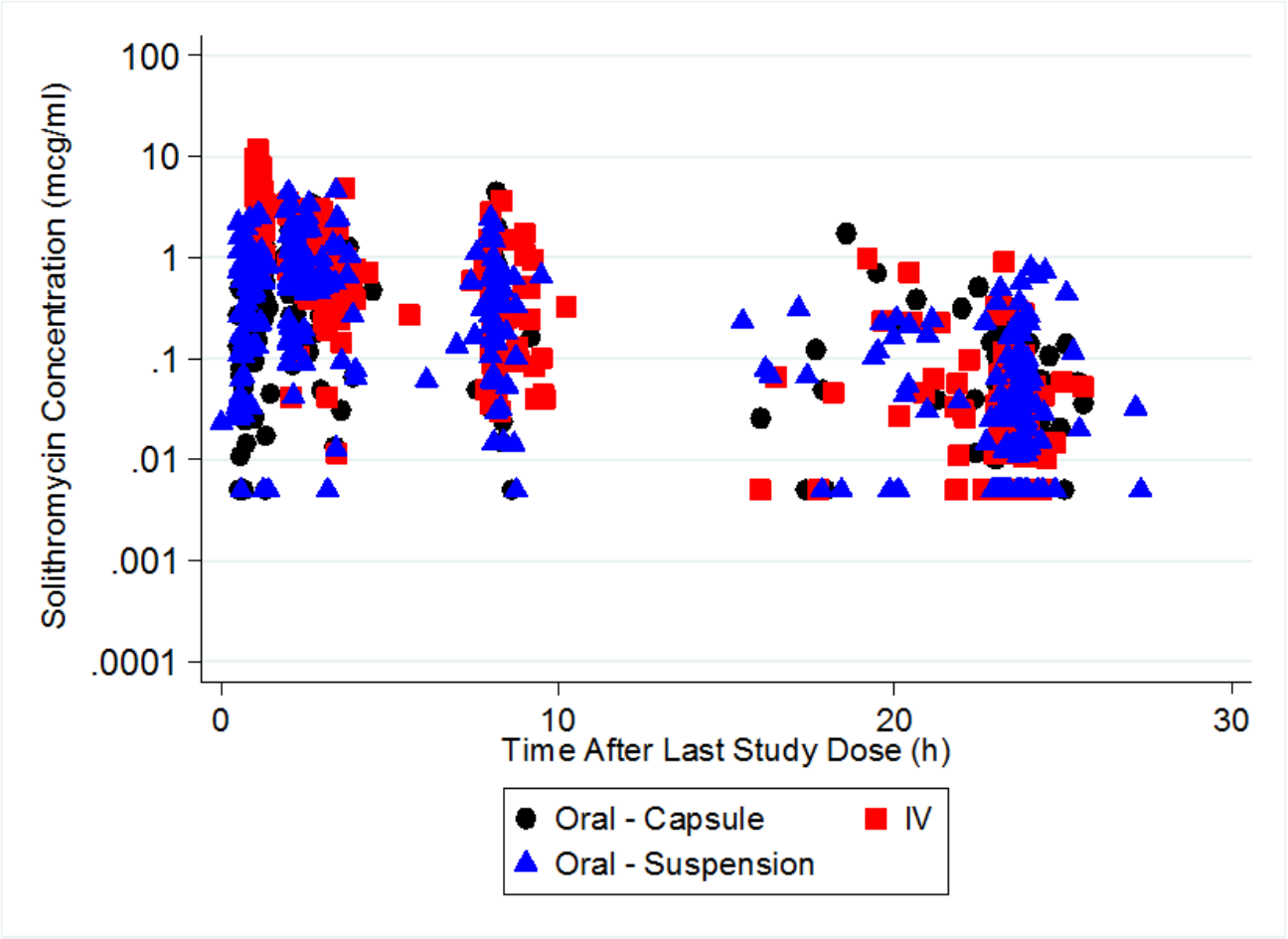
$$\mathrm{V} = V_{std} * \left(\frac{WT_i}{70\ kg}\right)^{1}$$

DOSE OPTIMIZATION: STEPS



TRIAL RESULTS

N=96



TRIAL RESULTS

N=34

Age (years)	Route	Sim Dose	Final Dose
12 to 17	IV	6 mg/kg	8 mg/kg or 400 mg
6 to <12	IV	7 mg/kg	8 mg/kg or 400 mg
2 to <6	IV	8 mg/kg	8 mg/kg
0 to <2	IV	8 mg/kg	8 mg/kg

EXAMPLE #2

AMPICILLIN

BETA-LACTAM

INDICATION

MULTIPLE

PEDIATRIC REQUIREMENT OFF-PATENT

PK AND SAFETY IN PREMATURE INFANTS

AMPICILLIN

DATA ANALYSIS

LEVERAGING EHR

- INCREASES SAMPLE SIZE
- RARE EVENTS
- ‘REAL WORLD’ DATA

AMPICILLIN

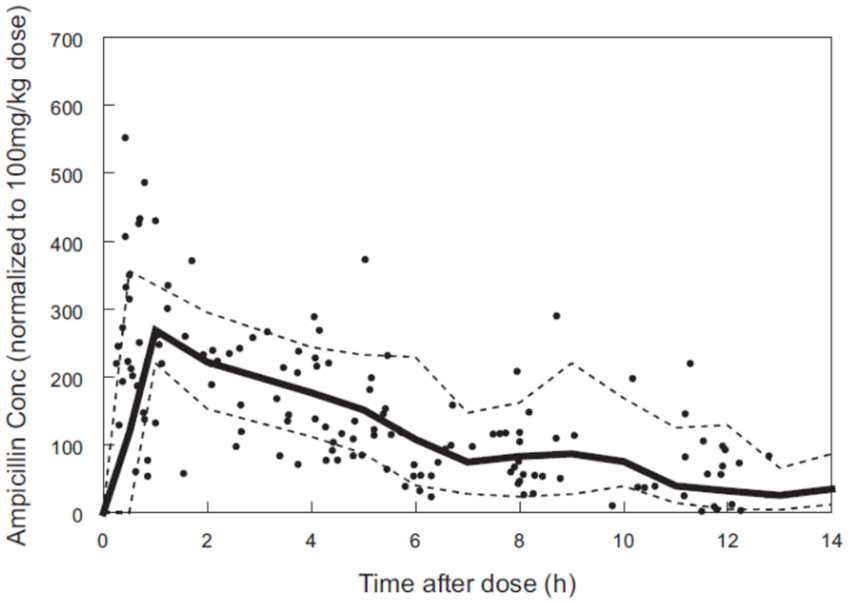
PK DATA

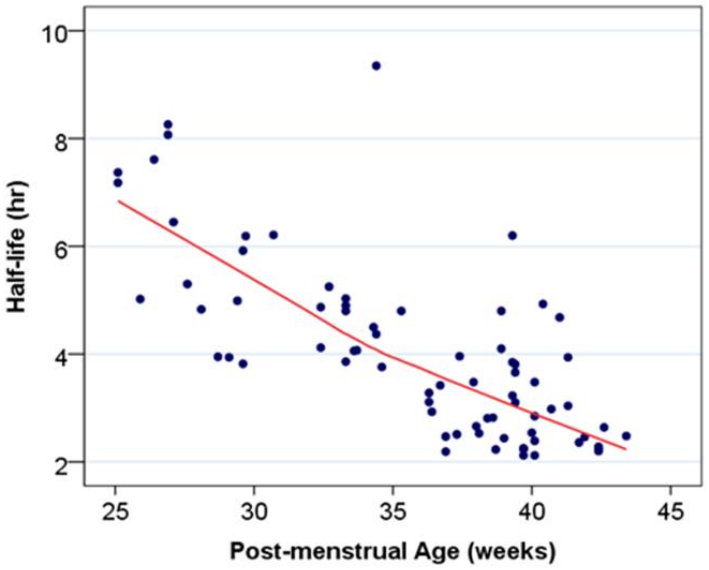
- POPS(PEDIATRIC OPPORTUNISTIC PK STUDY)
- US, 9 SITES, 73 INFANTS

EHR SAFETY DATA

- PEDIATRIX
- SIMILAR DEMOGRAPHICS AS PK POPULATION
- AE OF SPECIAL INTEREST
  - SEIZURES

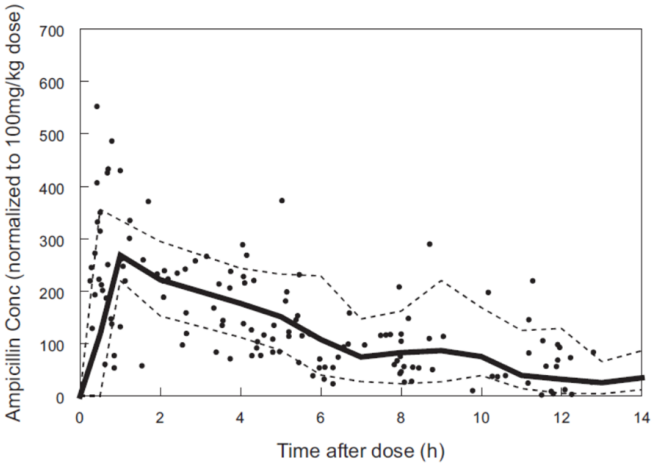
DEVELOP PK MODEL





$$CL = \theta CL \cdot WTKG \cdot (0.6/SCR)^{\theta(2),SCR} \cdot (PMA/37)^{\theta(2),PMA}$$

SIMULATE EXPOSURE INTO EHR



Sub ID	Dose (mg/kg/day)	WT (kg)	Age (days)	SrCr (mg/dL)	Cmax sim (mg/L)	Seizures (Y/N)
1	300	2.5	7	1.8	178	Y
2	150	2.0	10	0.4	65	N
…						

EXPOSURE-OUTCOME ANALYSIS

N = 131,723

Table III. Adjusted odds of seizure

	OR* (95% CI)
C_{maxss} (μg/mL)	1.01 (1.01, 1.02)
C_{maxss} (SD)†	1.10 (1.03, 1.17)
$C_{maxss} > 140$ μg/mL	1.76 (1.35, 2.30)
AUC_{24} (μg*h/mL)	1.01 (1.01, 1.02)
AUC_{24} (SD) †	1.11 (1.05, 1.18)

*Adjusted for GA and PNA, bacteremia, meningitis, mechanical ventilation, and inotropic support;
†OR represents change in 1 SD of C_{maxss} and AUC_{24} respectively.

EXAMPLE #3

CLINDAMYCIN

LINCOMYCIN

INDICATION

cIAI, STAPH (OFF-LABEL)

GOAL

DECREASE SAMPLE SIZE

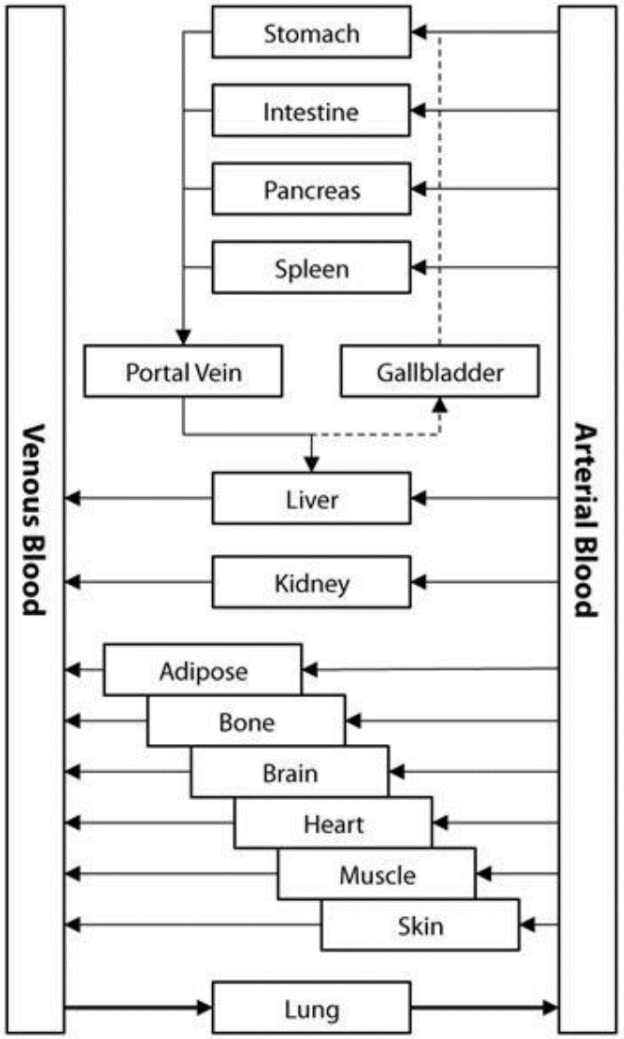
CLINDAMYCIN

NEW METHOD DEVELOPMENT

PHYSIOLOGICALLY-BASED PK MODELS

- MECHANISTIC MODELS – MODELS ARE 'SET'
- OPPORTUNISTIC PK DATA TO DEVELOP
- REDUCE SAMPLE SIZE
- INTENSE DATA TO CONFIRM

CLINDAMYCIN



CLINDAMYCIN

PK DATA

- ADULT
  - LITERATURE
- CHILDREN
  - DEVELOPMENT: POPS, N=48
  - EVALUATION: PBPK TRIAL, N=23

PBPK MODEL

- DRUG PHYSICOCHEMICAL PROPERTIES
- GUIDANCE DOC FOR DEVELOPMENT

TRIAL RESULTS

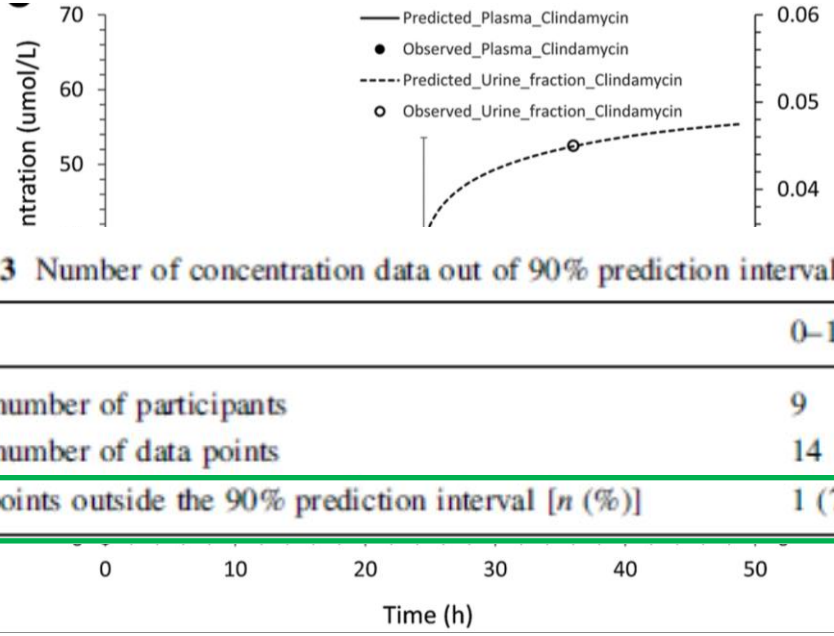
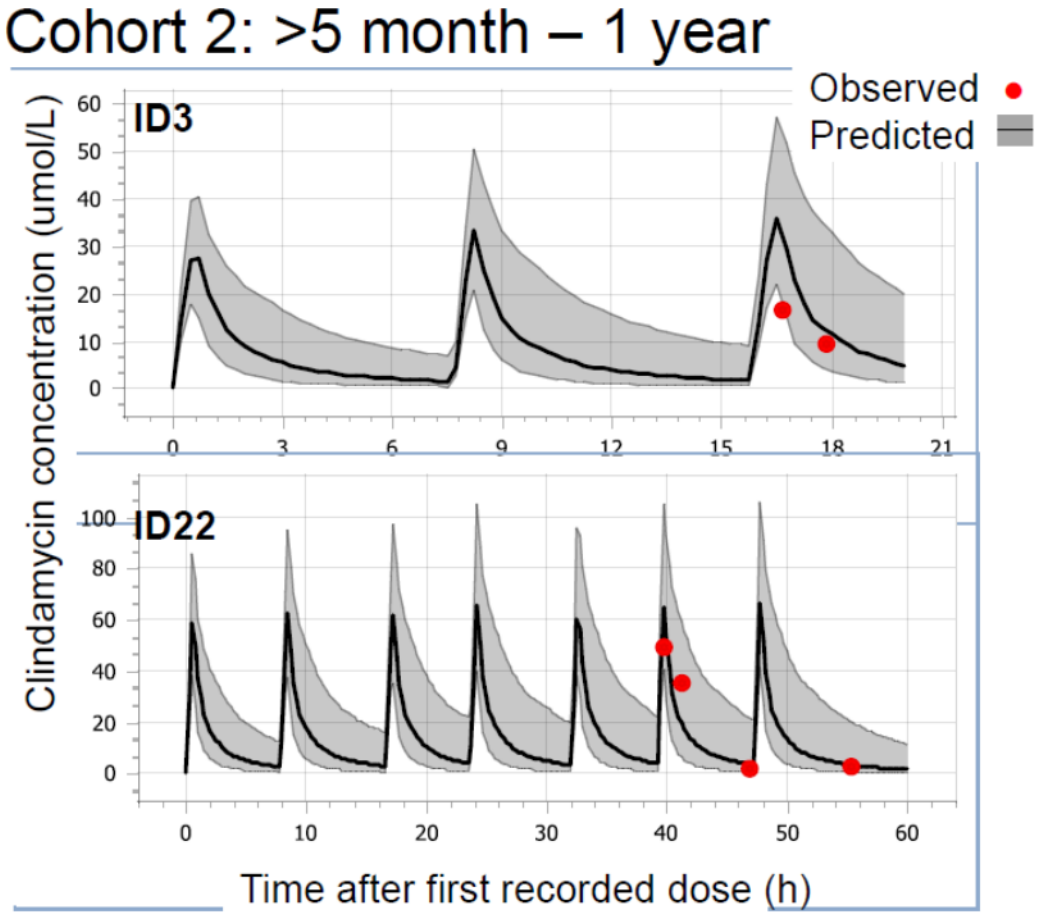


Table 3 Number of concentration data out of 90% prediction interval of the pediatric population PBPK model

	0–1 year	2–5 years	6–11 years	12–18 years
Total number of participants	9	11	10	18
Total number of data points	14	16	11	27
Data points outside the 90% prediction interval [*n* (%)]	1 (7)	6 (37.5)	2 (18)	4 (22)

TRIAL RESULTS

Age Group	N Enrolled
1-12 months	7
2-6 years	10
7-12 years	5
13-16	5



SUMMARY: PK/PD MODELING

STREAMLINE TRIALS

INCREASE CHANCES OF 'RIGHT DOSE'

CAN BE COMBINED WITH EHR DATA
- INCREASE POWER

CAN BE USED TO DEVELOP NEW METHODS
- LOWER SAMPLE SIZE

IMPACT ON CHILD HEALTH

MICAFUNGIN
ANIDULAFUNGIN
FLUCONAZOLE
PIPERACILLIN
METRONIDAZOLE
AMPICILLIN
MEROPENEM
DAPTOMYCIN
DOXYCYCLINE
VANCOMYCIN
CEPHALEXIN
MOXIFLOXACIN
VORICONAZOLE
GENTAMICIN
CLINDAMYCIN
ACYCLOVIR
SOLITHROMYCIN
TRIMETHOPRIM
SULFAMETHOXAZOLE

FUTURE DIRECTIONS

NON-INVASIVE MEASUREMENTS

MASTER PROTOCOLS

EXPOSURE-RESPONSE RELATIONSHIPS

- BIOMARKERS

INDIVIDUALIZED DOSING

NON-INVASIVE MEASUREMENTS

ANIMAL MODEL

LABELED COMPOUND IN RATS

- INDOCYANINE GREEN

USE OPTICAL IMAGING OF RETINA

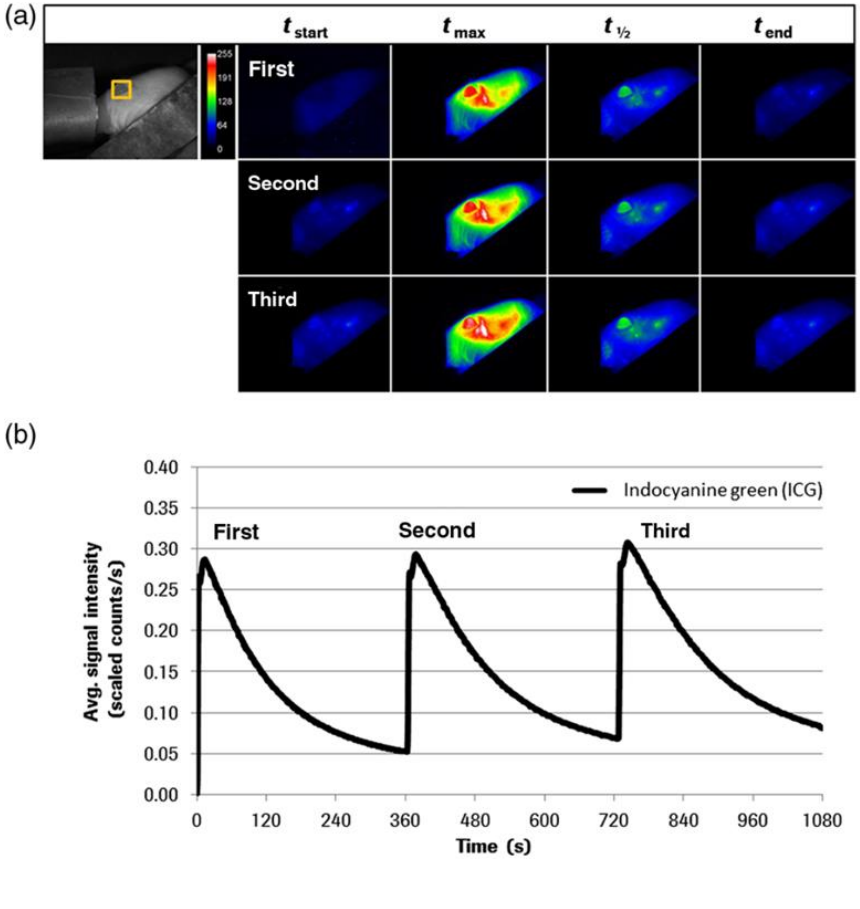
- NON-INVASIVE NEAR-INFRARED (NIR)

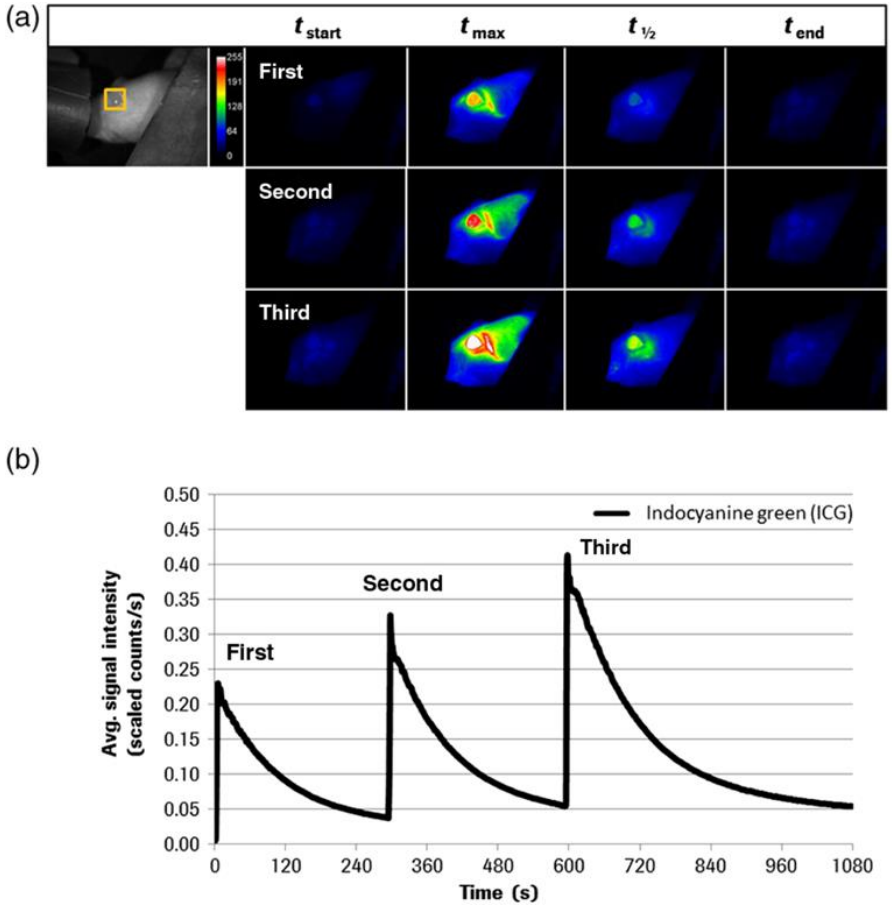
FLUORESCENCE SIGNAL INENSITIES

- CAPTURED SERIALLY

OBTAIN PK PROFILE

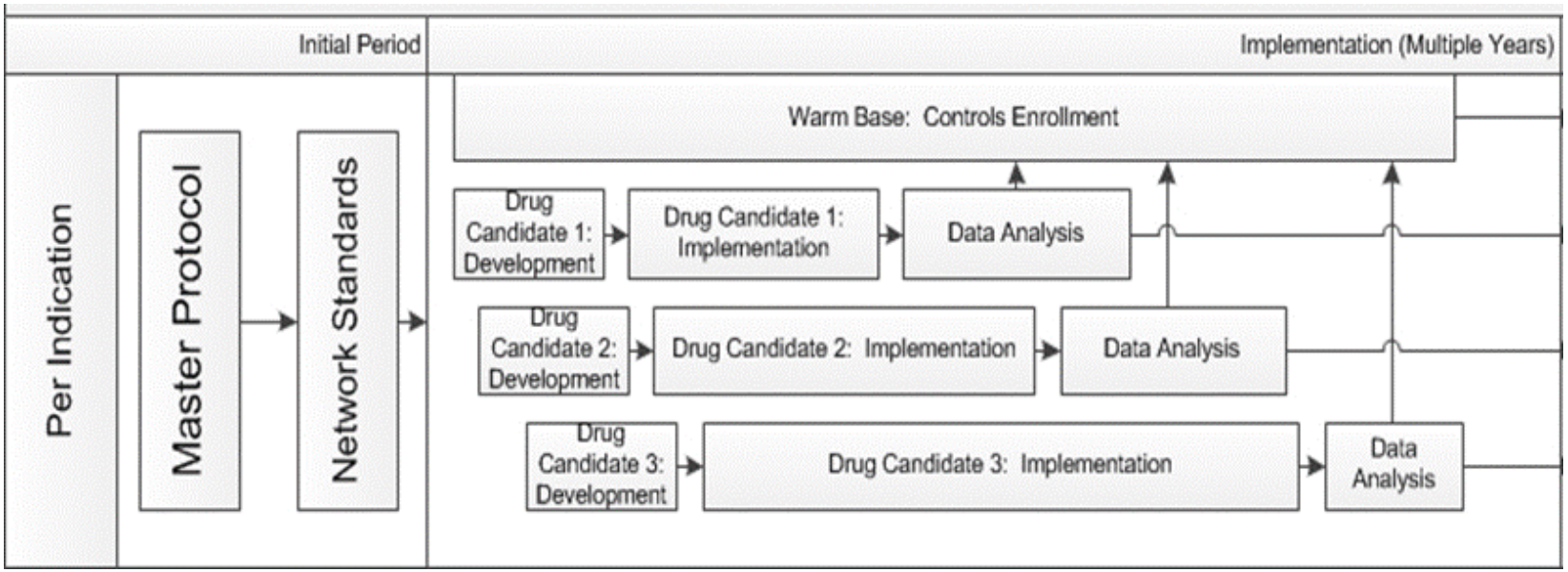
NON-INVASIVE MEASUREMENTS





Dobosz et al. J. of Biomedical Optics, 2014

MASTER PROTOCOLS



Courtesy: Vance Fowler

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PEDIATRIC TRIALS NETWORK

STUDY SITES

FAMILIES