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TUTORIAL

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

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Mathematical models of drug action and disease progression can inform pediatric pharmacotherapy. In this tutorial, we explore the key issues that differentiate pediatric from adult pharmacokinetic (PK) / pharmacodynamic (PD) studies, describe methods to calculate the number of participants to be enrolled and the optimal times at which blood samples should be collected, and therapeutic drug monitoring methods for individualizing pharmacotherapy. The development of pediatric-specific drug dosing dashboards is also highlighted, with an emphasis on clinical-relevance and ease of use.
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KEY ISSUES IN PEDIATRICS

Pediatrics remains a largely untapped area of opportunity for pharmacometric analyses. Consequently, pediatric pharmacokinetic (PK) and pharmacodynamic (PD) studies are needed to inform dosing selection for efficacy trials and for establishing dosing recommendations for pediatric subpopulations. The two biggest obstacles are the lack of compelling, pediatric-specific biomarkers and ill-defined or absent pediatric disease progression measures. Additionally, there is wide variation in how basic study design constructs (e.g., sample sizes, sampling strategies, and dosing regimens) are implemented in pediatric clinical trials and the degree to which modeling and simulation are used to support these critical study design elements. Dosing objectives are intimately tied to the assumptions of disease similarity between pediatric and adult indications, which is rarely demonstrated. The question of similarity between adult and pediatric disease is at the top of the US Food and Drug Administration's (FDA) decision tree and the answer to this question dictates the regulatory path that is taken, which may involve an exposure-equivalence analysis, PK/PD, and/or efficacy/safety trials.[1,2]

Similarly, modeling and simulation objectives are focused on recommending doses that are adequately demonstrated to be similar to those established in adults (an equivalence approach) or those which allow mapping of the exposure–response relationship to suspected target activity thresholds. In either case, considerations of size, maturation, organ function, and disease state must be incorporated within the testing scenario to support dosing targets across regulatory-defined age strata. This hinges on an appropriate sample size (in total and within each age strata) and a PK/PD sampling strategy that is optimized through simulation and incorporates alternative constructs, which are appropriate for each pediatric subpopulation. The basic tenet for the approach we will outline herein is to illustrate how modeling and simulation methods can be used to design a pediatric-specific clinical trial that meets the performance objectives of the trial. More specifically, we will also demonstrate how to design a pediatric clinical trial with an appropriate number of subjects to ensure adequate statistical power with a sufficient number of optimally timed samples to yield PK/PD parameters that are unbiased and precise, which can then be used to facilitate the creation/revision of drug dosing recommendations. Additionally, for drugs with narrow therapeutic windows, modeling and simulation methods are presented to allow clinicians to develop individualized dosing regimens.

POWER AND SAMPLE SIZE CALCULATIONS

Power and sample size calculations are vitally important for pediatric trials, as most drug development programs only conduct a single pediatric trial, the results of which are then used to justify dosing recommendations for future studies and regulatory approval.[3] Several methods for defining an appropriate sample size for pediatric population PK studies have been proposed, each of which is associated with relative strengths and weaknesses.[4–7] The most well-known approach was put forth by the FDA in 2012.[3] This approach aims to precisely estimate PK parameters (e.g., clearance and volume of distribution). The regulatory requirement that evolved from this approach states that a pediatric trial "must be prospectively powered to target a 95% confidence interval within 60-140% of the geometric mean estimates of clearance and volume of distribution [...] in each pediatric subgroup with $\geq$80% power."[3] Pediatric subgroups are most commonly derived from stratifications based on age; however, other physiologic (e.g., weight) or pathophysiologic (e.g., rate of disease progression) factors that influence the exposure–response profile should also be considered to ensure that the sample size is appropriate given the trial's objectives. In three examples put forth by the FDA, including two antibiotics and one sympatholytic drug, the following age groups have been used: 3 to $<$6 months, 6 to $<$12 months, 1 to $<$2 years, 2 to $<$6 years, 6 to $<$12 years, and 12 to 18 years.[3]

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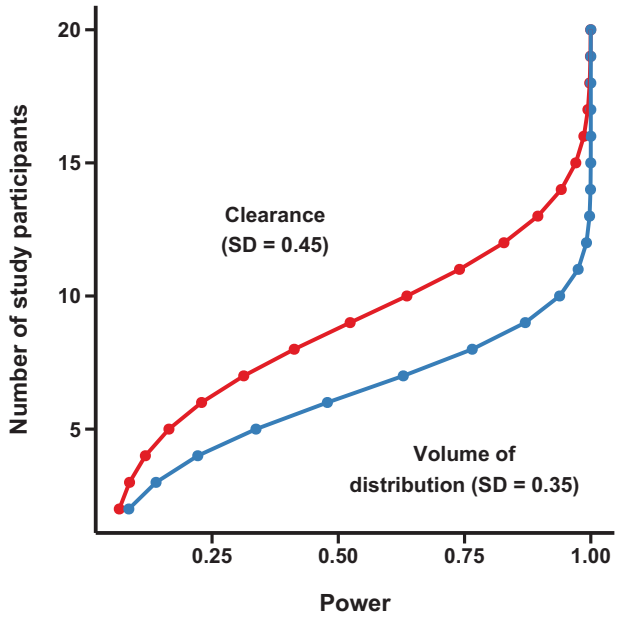

Figure 1 A graphical comparison of sample size vs. power (the probability of deriving a PK parameter estimate with a 95% confidence interval within 60–140% of the geometric mean estimate) for a hypothetical drug with a standard deviation of 0.45 and 0.35 for clearance (depicted in red) and volume of distribution (depicted in blue), respectively, using a noncompartmental approach.

The first step in performing a power and sample size calculation for a pediatric population PK or PD study is to define the objective(s) of the trial (e.g., assess individual PK parameters, including: an evaluation of absorption processes, assessments of drug distribution, quantification of the rate/extent of metabolism and excretion, and determination of whether different dosing regimens are needed to account for developmental or maturational changes). After the primary objective has been established it is then incumbent on the study design and modeling and simulation teams to define the subgroups that will be evaluated. For particularly vulnerable patient populations it may be necessary to consider reducing the number of samples collected from each participant or use alternative sampling methods (e.g., a heel stick on a newborn as opposed to placing an indwelling line). When defining these subgroups, the investigators should also explore logistical considerations that may preclude certain study designs. For example, a PK study involving serial sampling every few hours over a 5-day period may prove to be unduly burdensome for children attending school. Additionally, opportunistic or observational sampling schemes should be considered when possible to minimize participant discomfort and improve retention. As an example, we recently enrolled children who were undergoing an outpatient surgical procedure and obtained blood samples after the child had been anesthetized, which allowed us to minimize the discomfort to the patient and also allowed easy access to the systemic circulation due to the placement of a peripheral catheter for routine anesthesia.

When the research objectives and the subgroups have been defined, the investigators should next consider whether a noncompartmental analysis (NCA) or a population PK analysis is more appropriate. Although this tutorial is focused on population PK modeling, we have provided R code in **Appendix 1** that can be used to generate sample size vs. power comparisons such as that depicted in **Figure 1** using an NCA approach. As described above, power reflects the probability of achieving a 95% confidence interval within 60–140% of the geometric mean estimate for each pharmacokinetic parameter.

For population PK analyses, sample size vs. power can be compared in a similar manner. Allometric scaling is frequently used to scale adult PK parameters to young children and vice versa, so we shall consider an example in which the objective is to precisely define clearance for drug x using a power model of the form:

$$CL = CL_{std} * \left(\frac{WT_{ind}}{70\ kg}\right)^{Coef_{allo}} \quad (1)$$

where WT_{ind} refers to the weight of the individual patient, which has been standardized to a typical adult value of 70 kg. The allometric coefficient ($Coef_{allo}$) can be fixed to a certain value (e.g., 0.75) or it can be estimated.[8,9] By taking the logarithm of CL (LCL) we then derive the linear function:

$$LCL = CL_{std} + Coef_{allo}\left(\frac{WT_{ind}}{70\ kg}\right) \quad (2)$$

Using this covariate model structure we can now use estimates from the literature or past experiments as inputs within our sample size code to calculate the power of the trial with varying numbers of subjects as shown in **Appendix 2**.

OPTIMAL SAMPLING TIMES

The selection of optimal sampling times is critical when conducting pediatric population PK/PD studies. Attention to the design of the sampling strategy can reduce the cost of the trial and the burden imposed on the study's participants. One example of a design metric used to evaluate sampling strategies is the D-optimality criterion.[10] D-optimality assumes that the structural PK model is known and that reliable data exist regarding the size and distribution of the parameters.[7] This means the optimal design can only be as accurate as the parameters used to determine the optimal sampling times. However, in situations where limited data exist for the population of interest, initial PK parameter estimates may be derived from adult studies or, in some cases, animal models, which may be the best place to start. From these initial studies, the variance of the estimated parameters should also be identified, as these will be necessary when determining the optimal sampling time points.

Several open source software programs are freely available for use in developing optimal sampling times for population PK studies, some of which include: PFIM/PFIMOPT (developed at INSERM, Universitè Paris 7, France)[11,12]; PopDes (developed at the University of Manchester, United Kingdom)[13]; PopED (developed at Uppsala University, Sweden)[14]; POPT/WinPOPT (developed at the University of Otago, New Zealand)[15]; and ADAPT (developed at the University of Southern California, United States).[16] A more

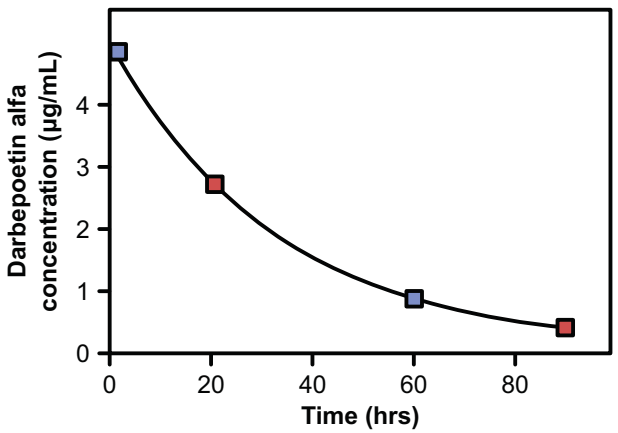

Figure 2 Predicted darbepoetin alfa concentration (μg/mL) vs. time (hours) profile for neonates undergoing hypothermia for the treatment of hypoxic-ischemic encephalopathy. Two D-optimal sampling times were identified at 1 and 60 hours (represented by blue boxes) when designing a neonatal trial that seeks to describe darbepoetin alfa PK with a one-compartment model. However, if a two-compartment model is used four D-optimal sampling times were identified at 1, 21, 60, and 90 hours (represented by blue and red boxes).

detailed discussion of optimal design, including the advantages and disadvantages associated with different methods and software programs, can be found in detailed reviews by Roberts *et al*. and Nyberg *et al*.[17,18]

To explore the power of optimal design theory we will use data from a recently completed phase I PK and safety trial of darbepoetin alfa, which is used in the treatment of hypoxic-ischemic encephalopathy.[19] This study involved 30 neonates and employed sparse sampling techniques to generate a total of 95 serum concentrations.[20] A population PK analysis indicated that a one-compartment model provided the best fit to the data; however, it was unclear if the sampling times employed in this small pilot study were optimal and should be recommended for use in an upcoming phase II/III trial. Additionally, it was unclear if the one-compartment model was the best descriptor of darbepoetin alfa PK in neonates or whether the data were too sparse and precluded fitting a more appropriate two-compartment model. Optimal design techniques can be used to answer these questions.

The software programs ADAPT 5 and PFIM were used to design an optimal sampling strategy for a future phase II/III darbepoetin alfa neonatal trial in **Appendices 3 and 4**, respectively.[16,21] For this study, the design originally had four sampling times, which have been used as initial inputs in this example to optimize the sampling times for both darbepoetin alfa clearance and volume of distribution. As the drug is administered intravenously we did not seek to optimize the absorption rate constant K_a.

For this example, two optimal sampling times were identified, which is in agreement with D-optimal design theory, which states that a single optimal time will exist for each parameter to be optimized.[22] We sought to estimate darbepoetin alfa clearance and volume of distribution and the D-optimal design suggested obtaining two samples at nearly time 0 and at 57 hours postdose. However, since it is difficult to obtain a concentration immediately after a drug has been administered (particularly if the same venous line must be used for both dosing and sample collection), it may be appropriate to fix the first sample collection at 1 hour. Additionally, it may be easier to obtain a sample at 60 hours postdose as opposed to 57 hours. In this case, we would also fix the last sampling time at 60 hours postdose.

As mentioned previously, it is unclear if darbepoetin alfa PK in this neonatal population are best described using a one- or a two-compartment model. Using previously published data from adults, it is possible to design a two-compartment optimal design (**Figure 2**).[23] In this scenario, the 1- and 60-hour sampling times were fixed based on the results of the one-compartment model (blue boxes) and the other two timepoints were optimized to precisely estimate the intercompartmental clearance and the volume of distribution in the peripheral compartment (red boxes).

As there is uncertainty in the PK model that best describes the kinetic profile of this drug in neonates, it may be appropriate to consider employing an adaptive design in the phase II/III clinical trial, whereby four sampling times are initially used for the first half of the patients who are enrolled. Then an interim PK analysis may be performed to determine if a one- or a two-compartment model best describes darbepoetin alfa PK in this population. At this point, if it is determined that a one-compartment model performs well then the remaining 50% of the patients who will be enrolled could have only two samples obtained for the purpose of estimating darbepoetin alfa PK parameters. Alternatively, if a two-compartment model fits the data better the trial may proceed, with the remaining 50% of patients having four samples collected at the optimal sampling times defined above as determined by D-optimality. For additional information regarding adaptive designs in population PK studies see Foo and Duffull and Dumont *et al*.[24,25]

DATA ANALYSIS

Pharmacokinetics

The development of a population PK model can be broadly divided into two stages. The first stage concentrates on the selection of an appropriate structural model (e.g., one-compartment with first-order absorption and elimination) and the second stage focuses on characterizing relationships between covariates and the PK parameters of interest. The selection of an appropriate structural model for pediatric PK studies is similar to the approach used in adult PK studies, albeit with the caveat that simpler, compartmental models are often favored for pediatric studies due to the limited number of blood samples that can be obtained from small children. The majority of the differences in pediatric PK modeling arise when developing the covariate model structure.

Covariate models are used to define the sources of PK variability within a population.[26] For children, normal developmental processes and pathophysiologic changes can complicate efforts to develop uniform dosing recommendations.[27] In particular, aspects of growth and development associated with differences in body size and age can be investigated when building a covariate model and may be useful in explaining the predictable components of between-subject variability.[27] As mentioned previously, allometric scaling is often used to standardize

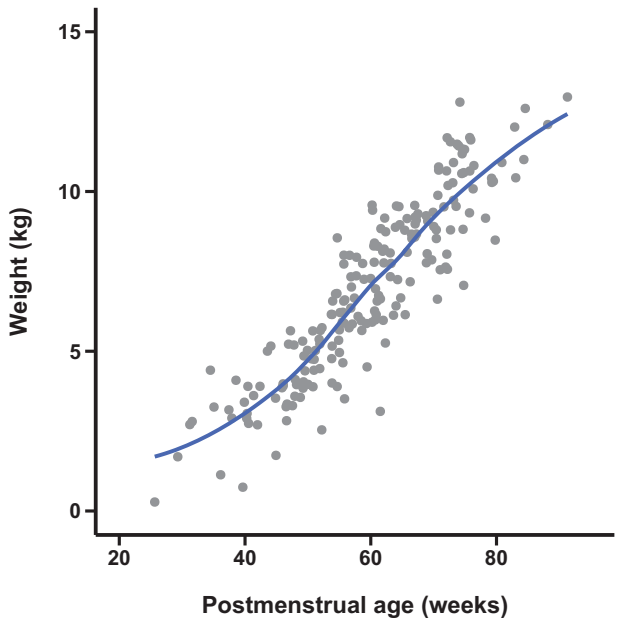

Figure 3 Correlated postmenstrual age (weeks) vs. weight (kg) values for a population of 200 simulated children.

differences in size.[8,28] Allometric scaling is frequently used when developing population PK models to extend data from animal models to derive extrapolated human PK parameter estimates and to scale adult PK parameters to children.[29] The decision to fix the allometric coefficient (e.g., 0.75 for clearance) or have the model estimate the allometric coefficient should be guided by an evaluation of the predictive performance of the model, as described by Krekels *et al.*[30] Age is also commonly used to describe the maturation of drug clearance mechanisms (e.g., maturation of renal function).[8] Several quantitative approaches have been used to model the maturation of drug clearance processes, including: linear, exponential, first-order, and sigmoidal models.[31] To demonstrate the application of these methods in the development of a pediatric population PK model, we developed a simulated dataset with a range of weights and ages (**Figure 3**). The R code used to develop this dataset is featured in **Appendix 5**.

This dataset features sigmoidally correlated postmenstrual age (defined as the period ranging from the first day of the last menstrual period through the date of assessment) and weight values that were adapted from the US Centers for Disease Control and Prevention's (CDC) infant growth curves.[32,33] If our drug of interest is known to be primarily eliminated through renal mechanisms, then we may consider employing a variable slope sigmoidal model, such as that described by Anderson *et al.*,[31] which incorporates a postmenstrual age function (F_{PMA}) of the form:

$$F_{PMA} = \frac{PMA^{Hill}}{\left(PMA^{Hill} + TM_{50}^{Hill}\right)} \quad (3)$$

In this model, the maturation of renal clearance is described as a function of postmenstrual age (*PMA*), the PMA at which 50% of adult clearance is reached (TM_{50}), and a Hill coefficient (*Hill*) that governs the shape of the sigmoidal curve. This sigmoidal maturation model can be implemented in the nonlinear mixed effects modeling program NONMEM as:

```
$PROBLEM    Sigmoidal maturation example
$INPUT C ID TIME AMT DV MDV RATE WT PMA
 ;   ID     =     Subject identifier
 ;   TIME   =     Time (measured in hours)
 ;   AMT    =     Dose amount (mg)
 ;   DV     =     Drug concentration (mg/L)
 ;   MDV    =     Missing dependent variable
 ;   RATE   =     Infusion rate (mg/hr)
 ;   WT     =     Weight (kg)
 ;   PMA    =     Postmenstrual age (weeks)

$DATA CPT_PSP_TUTORIAL_DATA_4.CSV  IGNORE=C
$SUB ADVAN1 TRANS2

$PK
 TVCL    =    THETA(1)*(WT/70)**0.75 * (1/
(1+(PMA/THETA(3))** (-(THETA(4)))))
 CL      =    TVCL * EXP(ETA(1))
 TVV     =    THETA(2) * (WT/70)**1.0
 V       =    TVV * EXP(ETA(2))
 TM50    =    THETA(3)
 HILL    =    THETA(4)

$ERROR
 A1      =    A(1)
 Y       =    F + F * ERR(1) + ERR(2)
 IPRED   =    F
 SIM     =    IREP

$THETA
 0.5     ;    THETA1 (Clearance coefficient)
 2.5     ;    THETA2 (Volume coefficient)
 40      ;    THETA3 (Maturation midpoint)
 4       ;    THETA4 (Hill coefficient)

$OMEGA
0.1      ;    ETA1 (Clearance)
0.1      ;    ETA2 (Volume)

$SIGMA
 0.05    ;    SIGMA1 (Proportional error)
 1.0     ;    SIGMA2 (Additive error)

$SIM (123456) NSUB=24
$TABLE ID TIME AMT MDV TVCL CL TVV V TM50 HILL
SIM IPRED CWRES NOPRINT ONEHEADER FILE=sim.fit
```

This sigmoidal clearance maturation model has been used to describe vancomycin clearance in preterm and full-term neonates.[34,35] For vancomycin, it was determined that 49% of the variability in clearance was explained by body weight, 18% by PMA, and 14% by renal function (as measured by serum creatinine concentration).[34] The use of this sigmoidal maturation model to describe the relationship

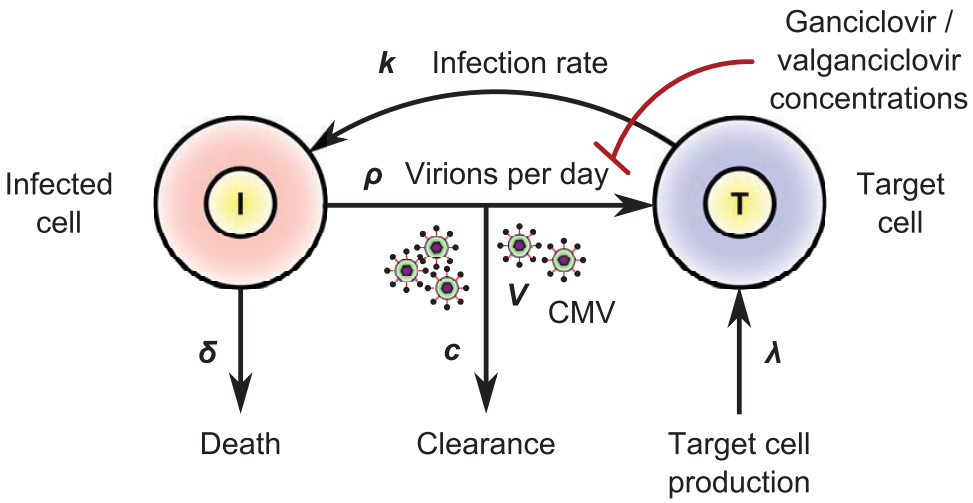

Figure 4 A visual schematic of the inhibitory effects of ganciclovir (and its oral prodrug valganciclovir) on human cytomegalovirus (CMV) replication. In this model, target cells (*T*) are produced at a constant rate (λ), and die at a constant rate (*d* [not shown]). Target cells are infected by CMV virions (*V*) at rate *k* (the infection rate). Infected cells (*I*) die at a constant rate (δ) and produce ρ virions per cell, which are then cleared from the body at rate *c*.

between PMA and vancomycin clearance also allowed the investigators to scale data from their population of preterm neonates to adults, which would not be possible in reverse without accounting for the maturation of renal clearance mechanisms.[34] It is worth noting that the sigmoidal function featured above in Eq. 3 is an example that may be applied to other maturational and developmental processes.

Decreasing variability in PK parameters improves our ability to develop dosing regimens that reliably achieve therapeutic targets. For vancomycin, explaining 81% of the variability in clearance among neonates using a combination of body weight, PMA, and serum creatinine concentrations allows for more accurate estimation of the probability of achieving a ratio of the 24-hour area under the concentration vs. time curve to the minimum inhibitory concentration (AUC_{24}/MIC) $\geq$400, which has been associated with improved clinical and microbiological outcomes in adults with lower respiratory tract infections caused by the methicillin-resistant bacterium *Staphylococcus aureus*.[36] Additionally, more accurate estimation of vancomycin clearance allows us to develop dosing regimens that are less likely to result in potentially toxic trough concentrations.[35,37] Recently, using an externally validated neonatal vancomycin population PK model that incorporates body weight, PMA, and serum creatinine concentrations, we found that the percentage of neonates predicted to achieve a therapeutic AUC_{24} was 100% using the population PK model, as compared with 39–51% for dosing regimens recommended in nomograms published by the British National Formulary (based on NeoFax dosing recommendations) and the American Academy of Pediatrics' Red Book.[38–40] Moreover, the proportion of neonates predicted to have a potentially toxic trough concentration was 0% using the population PK model, as compared with 0–5% using the NeoFax and Red Book dosing nomograms.[38,39] In aggregate, these findings reveal that externally validated pediatric-specific population PK models can be used to reliably inform treatment decisions at the level of an individual patient, thereby improving patient care.

Pharmacodynamics

Determining the appropriate metric for assessing the adequacy of a patient's response to therapy is one of—if not the most—challenging aspects of pharmacometrics. The challenge is often compounded in pediatrics, in which direct extrapolations of adult efficacy measures may not be possible or appropriate.[41,42] Nevertheless, this is a vital component of pediatric clinical pharmacology for which modeling and simulation are that much more important due to the need to assess a range of physiologic markers of drug activity, often with limited data.

A motivating example may be found in the monitoring of human cytomegalovirus (CMV) viral loads among children who have undergone solid organ transplantation and received an organ from a donor who was CMV seropositive.[43] It is standard clinical practice to monitor the effectiveness of prophylactic therapy with valganciclovir by monitoring a patient's CMV load using quantitative polymerase chain reaction (qPCR).[44] The effectiveness of valganciclovir prophylaxis can then be varied using simulation to determine thresholds below which therapy will be ineffective and CMV is disseminated throughout the bloodstream (viremia) as compared with thresholds above which therapy is effective and CMV replication is effectively suppressed, thereby preventing breakthrough viremia.

When developing mechanistic (indirect) PD models it is helpful to consider a drug's mechanism of action. In this example, our drug of interest (valganciclovir) is an orally administered L-valine ester prodrug of ganciclovir.[45] Valganciclovir is rapidly converted to ganciclovir by intestinal and liver esterases, after which it undergoes phosphorylation to ganciclovir triphosphate, which inhibits viral DNA polymerase and slows DNA elongation.[46] This inhibitory effect on viral replication can be incorporated within a basic model of viral infection such as that featured in **Figure 4**.

Using a viral dynamics model adapted from Perelson,[47] target cells (*T*) are produced at a constant rate (λ) and are susceptible to infection by CMV virions (*V*). This infection

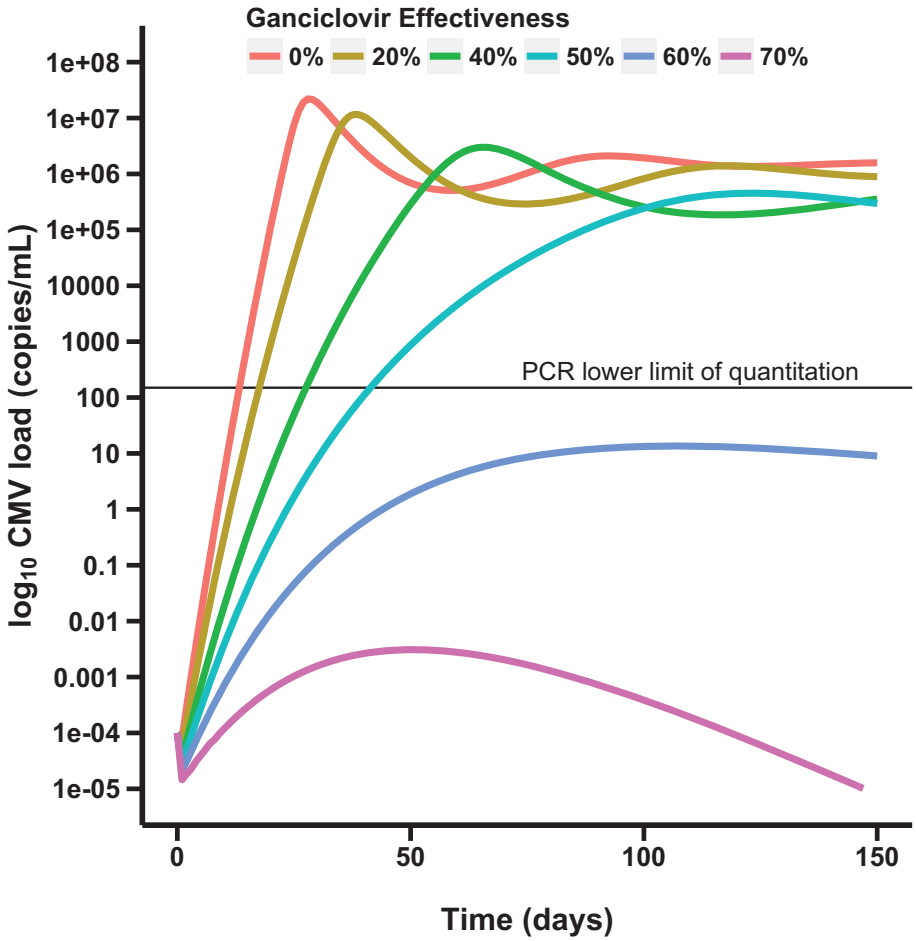

Figure 5 Simulations of human cytomegalovirus (CMV) loads over 150 days with a starting inoculum of 1×10^{-4} virions. Varying thresholds of valganciclovir's effectiveness are presented with colored lines. With the initial conditions specified in **Appendix 6,** this simulation reveals that if a valganciclovir prophylaxis regimen achieves $\geq$60% suppression of CMV replication, breakthrough viremia is unlikely to occur.

process is governed by the infection rate *k*. Following infection, infected cells (*I*) produce new CMV virions at rate ρ and die at rate δ per cell. Virions are cleared from the body at rate *c* per virion. Although not shown in the figure, target cells also die at a rate *d* per cell. The inhibitory effect of valganciclovir (and its active metabolite ganciclovir triphosphate) on viral replication is illustrated in red.

Using this model, we can simulate the rate of viral growth over a 150-day period of prophylaxis at varying valganciclovir effectiveness thresholds. Longitudinal CMV loads can be modeled using the following differential equations:

$$\frac{dT}{dt} = \lambda - dT - kVT \quad (4)$$

$$\frac{dI}{dt} = kVT - \delta I \quad (5)$$

$$\frac{dV}{dt} = (1 - eGAN) * \rho I - cV \quad (6)$$

where valganciclovir prophylaxis (*eGAN*) is assumed to be 0%, 20%, 40%, 50%, 60%, and 70% effective in suppressing CMV replication. The data may then be visualized for each of these scenarios as shown in **Figure 5**. The lower limit of quantification for the CMV qPCR assay is 150 copies/mL, which is denoted by the gray horizontal line.

These simulations reveal that breakthrough CMV viremia among pediatric solid organ transplant recipients is unlikely to occur when valganciclovir prophylactic regimens achieve $\geq$60% suppression of viral replication. It is therefore reasonable to expect that dosing modifications may be based on physiological and pathophysiological factors that influence ganciclovir and valganciclovir PK, which have the potential to influence the concentration–effect relationship. Additionally, it should be noted that in this example age-dependent effects on the response to ganciclovir/valganciclovir were not modeled; however, such effects may exist for other drugs and should be explored in the model-building process. Alternative scenarios may be explored using the R code provided in **Appendix 6**.

INDIVIDUALIZED DOSING

After developing a population dosing regimen that incorporates patient characteristics (covariates) that significantly

influence a drug's pharmacokinetic parameters it is possible that additional unmeasured factors may contribute to significant variability in the observed effectiveness of the regimen. In situations such as these it may be necessary to measure drug concentrations from each patient receiving treatment to ensure that they achieve therapeutic and safe drug exposure levels.

Therapeutic Drug Monitoring

If the drug under investigation features a narrow therapeutic window and displays highly variable pharmacokinetics in the patient population being studied, it may be necessary to measure drug concentrations in real time and alter the dosing regimen accordingly to target a therapeutic and safe range of concentrations—a practice known as therapeutic drug monitoring.[48] Therapeutic drug monitoring is built on the strength of previously defined exposure–response relationships, which describe how changes in drug exposure affect selected measures of efficacy and/or tolerability.[49,50] When the best PK predictor of the response to therapy is unknown or insufficient validation of targets has been performed, therapeutic drug monitoring is of limited utility. Consequently, well-designed pediatric population PK studies are invaluable, as the results of these trials may be used to develop targets that can be applied clinically to individualize therapy for drugs with narrow therapeutic windows.[51,52]

A motivating example of pediatric therapeutic drug monitoring can be found in the drug busulfan, which is an alkylating agent that is commonly used in conditioning regimens for hematopoietic stem cell transplantation (HSCT).[53] In previous studies, an AUC of 3.6–5.4 mg*hr/L has been shown to improve engraftment rates and has been associated with a decreased risk for drug-related toxicity (e.g., mucositis and sinusoidal obstruction syndrome).[54–56] High between-subject variability in busulfan pharmacokinetics makes it challenging to reliably achieve this target with the FDA-approved dose of 1.1 mg/kg for children $\leq$12 kg and 0.8 mg/kg for children $>$12 kg.[57] To ensure that children who are treated with busulfan achieve therapeutic and safe levels of drug exposure, busulfan concentrations are often measured as part of routine clinical care. Abnormally low AUCs are then used as justification to increase the busulfan dose and abnormally high AUCs prompt dose reductions.

Long-Boyle *et al.* recently evaluated 90 pediatric and young adult patients who had undergone an HSCT and received busulfan.[53] Busulfan was administered at the FDA-approved dose as a 2-hour infusion, every 6 hours, for a total of 16 doses. Blood samples were drawn for population PK modeling at 2, 2.25, 2.5, 3, 4, 5, and 6 hours after the first dose was administered. If dosing modifications were made, a second and third set of drug concentrations were obtained around the 9th and 13th doses, respectively. Using these doses, sampling times, and the population PK parameters reported in their analysis, we have recreated a simulated version of their study in NONMEM using the following code:

```
  $PROBLEM Busulfan therapeutic drug monitoring
example

  $INPUT C ID TIME AMT DUR DV MDV WT AGE

   ;       ID   =     Subject identifier
   ;       TIME =     Time (measured in hrs)
   ;       AMT  =     Dose amount (mg)
   ;       DUR  =     Infusion duration (hrs)
   ;       DV   =     Drug concentration (mg/L)
   ;       MDV  =     Missing dependent
variable
   ;       WT   =     Weight (kg)
   ;       AGE  =     Age (yrs)

  $DATA CPT_PSP_TUTORIAL_DATA_5.CSV IGNORE=C
  $SUB     ADVAN6     TRANS1    TOL5

  $MODEL

   COMP    =    (CENTRAL)

  $PK
   V1      =    THETA(1) * EXP(ETA(1))
   S1      =    V1
   VM      =    THETA(2)
   KM      =    THETA(3) * EXP(ETA(2))
   CL      =    ((VM * 1000/KM) * (WT/22)**0.75
* (1 + 0.032 * AGE)
   AUC     =    AMT/CL

  $DES
   CONC    =    A(1)/V1
   DADT(1) =    -VM * CONC/(KM + CONC)

  $ERROR
   IPRED   =    F
   SD      =    THETA(4)
   CV2SD   =    THETA(5)
   Y       =    IPRED + SD * EPS(1) * (1 + IPRED
* CV2SD)

  $THETA
   15.7    ;    THETA1 (Volume coefficient)
   28.96   ;    THETA2 (Vmax coefficient)
   6704    ;    THETA3 (Km coefficient)
   0.148   ;    THETA4 (Proportional residual
error[SD])
   47      ;    THETA5 (Additive residual error
[CV])

  $OMEGA
   0.08    ;    ETA1 (Volume)
   0.09    ;    ETA2 (Km)

  $SIGMA
   1 FIX   ;    SIGMA1 (Eps1)

  $SIM (123456) NSUB=1
  $TABLE ID CL V1 VM KM AUC WT AGE FIRSTONLY
NOPRINT ONEHEADER FILE=sim.fit
```

Table 1 Dashboard selection categories used to derive objective and subjective rankings for potential drug candidates at a children's hospital

Rank	Criterion
Drug utilization	
1	Days of therapy per 1,000 hospital days
2	Total pharmacy costs (acquisition + administration)
Medical need	
1	Disease/condition with few pharmacotherapy options
2	Disease/condition with few pharmacotherapy options for children
3	Disease/condition with few pharmacotherapy options for a specific pediatric subpopulation (e.g., critically ill)
4	Target agent requires titration to effect without acceptable dosing guidance
5	Poor outcomes associated with subtherapeutic exposure
6	Toxic events associated with exposure
7	Toxicity associated with chronic administration (exposure or dose intensity)
Guidance outcome value	
1	Established relationship between activity (or efficacy) and exposure in children
2	Established relationship between safety (or adverse events) and exposure in children
3	Available PK or PK/PD model that is correlated with clinical outcomes in children
4	Established relationship between activity (or efficacy) and exposure in adults
5	Established relationship between safety (or adverse events) and exposure in adults
6	Available PK or PK/PD model that is correlated with clinical outcomes in adults
Dashboard viability	
1	Availability of a clinical champion (e.g., physician, pharmacist) to aid in designing the dashboard, optimizing its workflow, and encouraging its use
2	Availability of a pharmacometrician/clinical pharmacologist to design the model that will be used to inform pediatric dosing
3	Required data available in existing electronic medical records system(s) or data warehouse
4	A PK or PK/PD model that provides a forecasting routine and/or visualization tools that are adequately specified with respect to the dashboard's functional requirements for clinical use
5	Software that is capable of integrating multiple data sources and modeling software outputs, which ports the results into a user-friendly clinical interface
6	Adequate information technology (IT) support and programming resources available

In this example, the busulfan AUC is derived for each subject by dividing the administered dose by the individual-predicted clearance estimate. Of the 10 simulated subjects, 3 (30%) had an AUC within the target range of 3.6–5.4 mg*hr/L. The remaining seven (70%) subjects had busulfan AUCs that were below the lower end of the therapeutic window, which suggests that this dosing regimen may be insufficient. Based on these findings, Long-Boyle *et al.*[53] developed a user-friendly Excel tool that calculates the recommended dose based on an individual's clearance estimate and the desired AUC target:

$$Dose\,(mg) = AUC_{target}\,(mg{*}hr/L){*}CL_{individual}\,(L/hr) \qquad (7)$$

Using this equation, the authors found that the model recommended busulfan doses that were ~25% higher than those recommended on the package insert.[53] In a prospective evaluation, the authors observed that 81% of the 21 children who received the model recommended busulfan dose achieved the therapeutic target as compared with 52% of the 90 children who received the busulfan dose recommended in the package insert ($P = 0.02$).[53] Moreover, the proportion of children with subtherapeutic busulfan exposure decreased from 42% with conventional dosing to 10% with model-recommended dosing.[53]

Dashboard systems

Optimal pharmacotherapy is implicitly an endeavor in personalized medicine. While the caregiver inherits prescribing information from the drug label and the scientific literature, these are generally static sources of information constructed from somewhat idealized patients who consented to participate in earlier clinical trials. Likewise, the experience of the prescribing community is often empirically based and simply reflects the current practice as opposed to the best practice. The situation is obviously worse for children, given the heavy reliance on extrapolation from adult studies and the limited clinical evidence documenting the safety and effectiveness of drugs prescribed to children. The "management" of drug therapy falls well outside of simple dosing considerations based on size or maturation-based scaling. In clinical practice, the dosing regimen may need to accommodate drug–drug interactions or the potential for interactions with other concomitant medications.[58] Additionally, the intended regimen may need to be indexed and/or adjusted based on the monitoring of drug concentrations, biomarkers, or clinical signs and symptoms.[59] The concept of a dashboard, then, is an interface for relevant patient-centric readouts that is current and critical to the holistic view of the patient.

The goal of a drug dashboard is to provide a platform for displaying current, relevant indices of patient well-being in

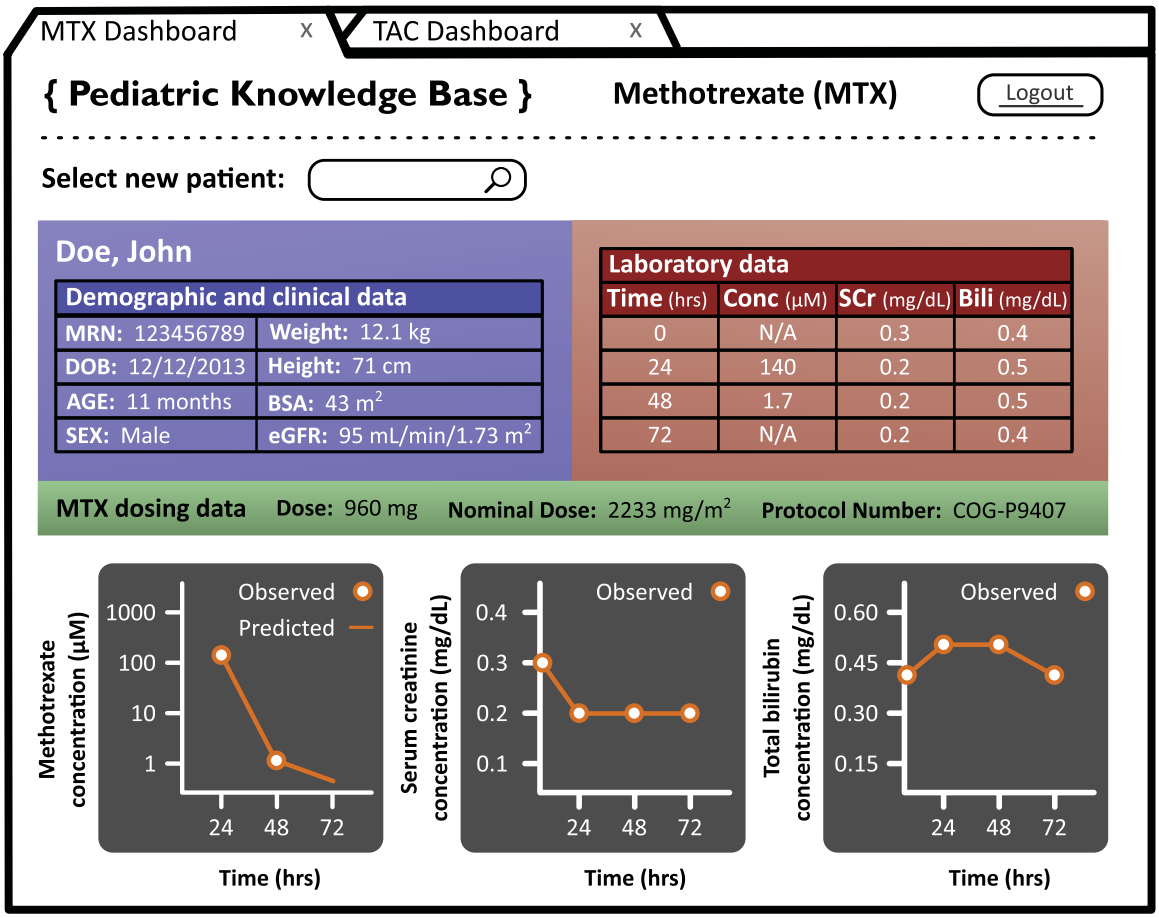

Figure 6 A dashboard for pediatric methotrexate dosing is envisioned that leverages demographic, clinical, and laboratory data to build a population PK model that rapidly generates individualized methotrexate dosing recommendations within an Internet browser.

response to longitudinal trends in pharmacotherapy. While there may be flexibility in the views that the caregiver selects or assesses, it is assumed that the dashboard is a centralized environment for key response elements. It is not principally a place to search for answers, document processes, or do research. While one element of the dashboard environment could indeed include scenario testing, particularly around the choice of pharmacotherapy options (e.g., drug selection, dosages), these answers must come quickly and without a steep user learning curve. Similarly, it is assumed that the source data populating the dashboard are of high quality and in a form to be quickly viewed, consumed, modeled, or simulated based on the desired functionality. Patient-centric views, decision support logic, and compliance with institutional protocols should be properly vetted, with clinical champions representing the end-user community. Moreover, any models and/or algorithms used to support treatment decisions must be properly validated with external data that are representative of the intended population of interest. These are essential elements of dashboard development and not merely "nice to haves" (**Table 1**).[58–60]

There are several examples of patient-specific dosing guidance/decision support systems that rely on therapeutic drug monitoring-based procedures. However, in actuality, very few dashboard systems are currently in production, although several are under evaluation. Dashboards are widely implemented in business intelligence software programs, which has the potential to hasten their development for clinical applications (e.g., Cognos, Tableau, etc.). The drugs targeted for dashboard systems are typically based on medical need, such that drugs with narrow therapeutic indices are often selected, particularly when the clinical benefit of therapeutic drug monitoring has been well established (e.g., mycophenolate, tacrolimus, methotrexate). For the pediatric population, we developed a high-dose methotrexate dashboard that is ultimately envisioned as a web-based environment that will provide global users with the ability to: (i) register their patient data; (ii) view dosing transactions based on institution/caregiver-specific criteria in real time; (iii) forecast future outcomes; and (iv) adhere to protocol-specific dosing guidances (**Figure 6**).[61]

CONCLUSION

In the past, the safety and effectiveness of many prescription medications were not evaluated in children.[62] Fortunately,

following the enactment of the FDA Modernization Act of 1997, the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act, and other regulatory initiatives, this paradigm has shifted, such that drugs that are not studied in children are now the exception rather than the norm.[63–66] However, there is a pressing need to ensure that the trials that are being conducted today are designed and analyzed appropriately, thereby generating high-quality data that can be used to meaningfully improve pediatric pharmacotherapy.

When designing pediatric PK/PD studies, it should be noted that the careful selection of an appropriate sample size and optimal sampling times depends heavily on the structure of the PK/PD model and the estimated variance of each of the parameters that will be estimated in the trial. If data to support these inputs for the target population (e.g., neonates or critically ill children) are lacking, then an adaptive design should be considered. Such an approach incorporates one or more interim PK analyses that are used to reconfigure the selection of sampling times and/or the number of participants to ensure that the trial's objectives are efficiently met for the target population.

At the level of an individual patient, population PK/PD studies are particularly valuable, as they can be used to establish targets that are reliably associated with improved clinical outcomes. Often such targets are extrapolated from the adult literature; however, where possible, pediatric studies should be encouraged to assess the similarity between pediatric and adult indications, as this is rarely proven.

Models of drug action and disease progression have been underutilized as ways of addressing dosing questions for pediatric patients. Mathematical drug/disease models paired with therapeutic drug monitoring are the most credible means available to inform clinical decision making. Such techniques force our clinical and pharmacometrics colleagues alike to make conscious decisions regarding which patient covariates influence the dose–exposure–response relationship. In this way, models help to make the complex biology of a disease and the physiological processes governing drug disposition more manageable and allow us to scrutinize and debate model-building and clinical decision-making processes with transparency. Although no single "ideal" method exists for developing pediatric PK/PD models, the methods described in this tutorial highlight several key features that are likely to be broadly generalizable and may be molded to fit other clinical scenarios as needed.

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