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Innovative Study Designs Optimizing Clinical Pharmacology Research in Infants and Children

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Abstract

Almost half of recent pediatric trials failed to achieve labeling indications, due in large part to inadequate study design. Therefore, innovative study methods are crucial to optimize trial design while also reducing the potential harms inherent with drug investigation. Several methods exist to optimize the amount of pharmacokinetic (PK) data collected from the smallest possible volume and with the fewest number of procedures, including the use of opportunistic and sparse sampling, alternative and non-invasive matrices, and micro-volume assays. In addition, large research networks using master protocols promote collaboration, reduce regulatory burden, and increase trial efficiency for both early- and late-phase trials. Large pragmatic trials that leverage electronic health records can capitalize on central management strategies to reduce costs, enroll patients with rare diseases on a large scale, and augment study generalizability. Further, trial efficiency and safety can be optimized through Bayesian adaptive techniques that permit planned protocol changes based on analyses of prior and accumulated data. In addition to these trial design features, advances in modeling and simulation have paved the way for systems-based and physiologically-based models that individualize pediatric dosing recommendations and support drug approval. Lastly, given the low prevalence of many pediatric diseases, collecting de-identified genetic and clinical data on a large scale is a potentially transformative way to augment clinical pharmacology research in children.

Keywords

Clinical pharmacology; Pediatrics; Clinical trials; Pharmacokinetics/pharmacodynamics

INTRODUCTION

Advances in trial design over the past decade have increased available therapies for many childhood diseases. In addition to these advances, pediatric clinical trials are incentivized through legislative requirements enacted by the US Food and Drug Administration (FDA),

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European Medicines Agency (EMA), and regulatory bodies in Asia.^{1–3} In the United States, for example, the Pediatric Research Equity Act permits the FDA to require that pediatric studies be conducted for drugs that are likely to be used in children or from which children are likely to receive significant benefit, whereas the Best Pharmaceuticals for Children Act offers extended patent protection, exclusivity, and governmental authority to request studies of off-patent drugs.⁴ Despite advances, 42% of recent pediatric trials failed in achieving labeling indications, highlighting the unique difficulty of establishing drug efficacy and safety in children.^{5,6} Because up to 15 years of basic research, clinical trials, and regulatory approvals are necessary to market a potential drug, a failed trial is enormously costly and negatively impacts pediatric care.⁷ Common reasons for trial failure in children include poor dose selection, different disease mechanisms in children compared with adults, high placebo response, and inadequate study design.⁵ In addition, it is challenging to identify useful biomarkers of drug response in a small and heterogeneous pediatric population with low disease prevalence.⁸ Further, pediatric trial design must account for ontogeny in drug disposition resulting from changes in body composition and physiologic maturation in drug biotransformation processes.⁹ Collectively, these challenges have resulted in a significant lack of pharmacokinetic/pharmacodynamic (PK/PD) data, which further contributes to failure in pediatric drug trials.¹⁰ Thus, despite progress made in pediatric research, new and innovative study designs are imperative to address current clinical pharmacology gaps and to ensure future therapeutics are safe and effective for children. Table 1 summarizes current approaches for optimizing early and late phase studies.

CLINICAL TRIAL OPTIMIZATION

Because clinical trials are a significant investment in time and resources, both for participants and for the medical community, trials must be adequately designed and powered to generate data that will improve clinical care. New trial innovations aim to optimize trial efficiency and time to drug approval while also reducing the costs and potential harms inherent with drug investigation. However, because early-phase and late-phase studies differ in their scope and challenges, different strategies are needed at each stage of trial execution.

Early-Phase Trials

Early-phase clinical trials are imperative to understanding drug disposition and guiding safe dosing in children. However, it is difficult to execute pediatric early-phase trials due to low enrollment, lack of biomarkers and suitable PD endpoints, and ethical limitations.¹¹ For example, phase I studies often involve more than minimal risk, making it difficult to study many pediatric therapeutics.¹¹ As a result, innovative trial designs need to optimize data collection and reduce risk to participants while also achieving sufficient enrollment. Several methods exist to overcome these limitations, including the use of sparse sampling, dried matrix spot sampling, and micro-volume assays, which are supported by the FDA as methods to reduce the frequency and volume of blood sampling.¹² In addition, large research networks that capitalize on master protocols have revolutionized the ability to enroll and execute pediatric clinical pharmacology studies on a large scale. Collectively, these and other advances optimize early-phase trials in children by capturing PK data with minimal or negligible risks to participants.

Opportunistic designs and sparse/scavenged sampling

Opportunistic designs capitalize on having only one study procedure—the collection of a biologic specimen during the time of standard-of-care drug administration, thereby eliminating investigational drug exposure.¹³ By also timing specimen collection during routine procedures (e.g., lab draws), the opportunistic approach reduces extra or unnecessary procedures, resulting in high patient acceptance and enrollment.¹³ Although the resulting sparse data collection minimizes the total amount of blood collected, disadvantages include the need for a larger overall sample size and population PK/PD modeling for analysis.¹³ Broadly, this approach has been used successfully in the observational, multi-center, multi-national POPS (Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care) trial.¹⁴ Started in 2011, the ongoing POPS trial is enrolling a total of 3000 children to evaluate the PK of >30 understudied drugs, including trimethoprim sulfamethoxazole,¹⁵ clindamycin,¹⁶ and ampicillin,¹⁷ among others. Similar European initiatives are also capitalizing on opportunistic study designs to characterize the PK of understudied drugs (e.g., ciprofloxacin).¹⁸

Additional opportunistic approaches include the use of scavenged sampling where samples are collected from unused or excess specimens that were obtained for clinical purposes.¹³ As with sparse sampling, scavenged samples may increase study enrollment and minimize participant harm by reducing the number of procedures and blood volume required.^{13,19} Limitations of this approach include the potential for poor sample and data quality depending on specimen age, storage condition, and recording of collection time; however, these limitations can usually be overcome with careful planning or by enriching the data with traditional PK collection.^{13,19} Further, enriching PK models with scavenged sampling may actually augment precision by capturing samples during the drug distribution phase.²⁰ For example, an opportunistic population PK study of teicoplanin in children with malignancy supplemented 123 samples collected from therapeutic drug monitoring (TDM) with 20 scavenged samples.²⁰ A 2-compartment model was developed with allometrically scaled weight and creatinine clearance as significant covariates. Individualized dosing derived from this model significantly improved target concentration attainment from 58–68%.²⁰ Other recent studies also highlight the role of opportunistic methods to obtain PK data in infants. For example, opportunistic PK studies were promptly employed during an H1N1 outbreak and were instrumental for studying oseltamivir in term and pre-term infants.^{21,22} Scavenged samples have also been used to characterize the PK of several antimicrobials in term and preterm infants, including piperacillin,²³ metronidazole,²⁴ and fluconazole.²⁵ More broadly, sparse sampling with population PK/PD modeling has been used to characterize the PK of several other antimicrobials.^{26–32} An opportunistic design was also used to guide real-time PK and dosing optimization for zidovudine in preterm infants exposed to HIV; this trial resulted in direct benefit to patients and families where dosing had not been established, underscoring how opportunistic studies can change clinical practice.^{19,33}

Microdosing

Microdosing studies capitalize on administering a single subtherapeutic dose, defined as 1/100th of the dose necessary for pharmacologic effect (maximum 100 mcg for synthetic

drugs and 30 nmol for proteins), for the purpose of evaluating exploratory PK.³⁴ Key advantages of microdoses include a very high margin of safety and an ability to leverage animal safety data to initiate the study, no FDA regulatory requirements for a dedicated pharmacologic safety study, and low sample volume requirements (20–250 μ L).^{13,34} Potential limitations, however, include difficulty correlating PK between microdoses and therapeutic doses because of saturable drug transporters and drug metabolizing enzymes, and (if radiolabeled drugs are chosen) limited pediatric safety data.¹³ Despite concerns with radiation, however, the estimated radioactive exposure from a theoretical microdose of a ¹⁴C drug with a half-life of 40 days is 0.33–0.8 microSV, which is significantly less than a chest x-ray (12 microSV).³⁵ Two European initiatives studied the use of ¹⁴C-paracetamol and ¹⁴C-midazolam microdose probes in neonates/children, and the preliminary data show good study feasibility and acceptable PK linearity between microdoses and therapeutic doses.³⁵ A ¹⁴C-paracetamol microdose in children was also used to show age-related developmental changes in paracetamol metabolism (i.e., a decrease in sulfation and increase in glucuronidation in the first 6 years of life).³⁶ While microdose studies in children are still rare, the high margin of safety and limited studies to date suggest that it is a promising and underutilized method to evaluate drug PK and ontogeny.

Bioanalytical optimization

Classical PK sampling volumes require 1–2 mL per sample, which can be challenging to obtain in premature infants or critically ill children who already have limited blood volumes.¹³ Ultra-low-volume assays are capable of determining drug concentration in substantially smaller volumes (~100 μ L per sample), with some assays capable of quantifying drug concentration in as little as 20 μ L.¹³ Multiplex assays that evaluate the concentration of multiple drugs from the same sample are often used in combination with ultra-low-volume technologies to further optimize the amount of PK data that can be collected from the smallest possible volume.¹³ In addition, the efficiency of trials where multiple drugs are administered is greatly increased because multiple assay validations are not necessary.¹⁹ Multiplex assays with ultra-low volumes have been used to characterize the PK of multiple drugs, including acetaminophen, caffeine, phenytoin, and several antimicrobials, among others.^{37–40}

Dried matrices, including dried blood spots (DBS), dried plasma spots (DPS), or dried urine spots (DUS), are biological samples collected on filter paper using low volumes (5–30 μ L).¹³ While DBS have been used for years as part of routine newborn screening, dried matrices have more recently been used to measure drug concentration due to their advantages of low required volumes and possibly simplified storage (room temperature) and shipping methods.^{13,41} As with other bioanalytical optimization approaches, dried matrices are an attractive option for reducing blood volume requirements, particularly for neonates. While dried matrices have significant potential, there are several important limitations, including the need to account for partitioning into red blood cells with DBS (often correcting with hematocrit), concerns with sample degradation and extraction after long-term storage, and heterogeneity in sample collection and extraction from the paper.¹³ Because of these limitations, an FDA draft guidance document suggests that correlative studies with traditional sampling be conducted.⁴² One such correlative study was recently used to

develop an accurate and precise method for measuring trimethoprim (TMP) and sulfamethoxazole (SMX) in DPS and DUS samples.¹⁵ Opportunistic whole blood and dried matrices were collected from participants in the POPS trial, resulting in 47 paired liquid plasma spot (LPS) and DPS samples from 34 subjects, and 21 paired liquid urine spot (LUS) and DUS samples from 16 subjects. The results from the study showed good correlation between DPS/DUS and LUS/DUS for TMP; however, correlation was not as strong for SMX due to variability between the matrices at higher concentrations.¹⁵ The study also highlights the challenge of sample extraction, as analysis of the punches from the centers and edges of the filter papers confirmed that TMP-SMX concentrations were not homogeneously distributed.¹⁵ To overcome this limitation, larger (6 mm instead of 3 mm) punches were used to sample the majority of the spot.

Microneedle sampling is another novel approach to collect PK samples while reducing sample volume requirements and procedural discomfort. Microneedles (typically 50–900 µm), superficially penetrate the skin to sample interstitial fluid (IF) or blood while avoiding deeper (painful) structures such as nerves.^{43,44} For example, a microneedle system was used to sample IF glucose in adult participants; this study showed a strong correlation between IF glucose area under the curve (AUC) and plasma glucose AUC and could potentially be used to monitor postprandial glucose in diabetes.⁴⁵ In addition, the vast majority of respondents in the study did not report pain during microneedle sampling.⁴⁵ While microneedle sampling may be preferred by children⁴⁶ and parents,⁴⁴ there is a paucity of published studies using this technique for PK or TDM in children. Thus, additional studies in children are needed to directly measure drug concentrations using microneedle assays and correlate these measurements to traditional PK sampling methods.

Research networks

By combining efforts and expertise from multiple disciplines, research networks have facilitated significant advances in pediatric trial design and therapeutics.¹⁹ Between 1994 and 2010, the National Institute of Child Health and Human Development (NICHD) developed the Pediatric Pharmacology Research Units (PPRU) to promote clinical trials and drug labeling in children, and to advance pediatric and developmental clinical pharmacology.⁴⁷ By combining efforts from 13 sites, the network achieved label changes for 20 drugs and contributed to >250 publications in areas such as pharmacometrics, ontogeny, and pharmacogenetics.⁴⁸ In addition, the PPRU created a clinical data repository using a common data form and dictionary that allowed data sharing.⁴⁷ Similarly, the Pediatric Trials Network (PTN) began in 2010 to fill knowledge gaps in pediatric therapeutics by conducting 30 high-quality, phase I–IV studies involving >5000 children.^{19,49} PTN is capitalizing on several innovative strategies, including opportunistic studies, to examine the PK of drugs prioritized by the Best Pharmaceuticals for Children Act administered to children per standard of care.¹⁹ Other major national and international research networks include Global Research in Paediatrics (GRiP), the International Neonatal Consortium (INC), the Pediatric Trials Consortium (PTC), the Pediatric Trials Network Australia (PTNA), and the Medicines for Children Research Network (MCRN). In addition, several new trial networks are being implemented to further advance pediatric studies, including the Canadian KidsCAN trial network, and through the Innovative Medicines Initiative, a pan-European pediatric trials

network.⁵⁰ Similarly, the FDA has recently accepted applications for a cooperative agreement (U18) to develop a global pediatric trials network.⁵¹

Other initiatives to improve trial methodology and increase operational efficiency include the Clinical and Translational Science Award (CTSA) Trial Innovation Network. Through trial and recruitment innovation centers, this network will harmonize central institutional review boards (IRBs), protocol systems, master contracts, and recruitment strategies.^{52,53} Collectively, the advances made by these large research networks underscore the need to continue building and supporting collaborative efforts as a means to advance drug studies in children.

Master protocols

The goal of a master protocol is to accelerate drug discovery by evaluating several different agents (platform approach) or diseases (basket approach) in parallel “substudies” using a common design to increase operational efficiency and reduce both regulatory time (e.g., using one investigational new drug [IND] application) and costs.^{54,55} Master protocols can be used for early-phase discovery studies, where patients are screened for multiple biomarkers with a standardized assay at study entry to guide placement into a substudy, or late-phase confirmatory studies.⁵⁴ By using a common screening platform, a participant can be screened once to determine eligibility for multiple studies, thereby reducing redundant data collection and shortening enrollment time.⁵⁶ Further, participants have more opportunities to be eligible to participate in a trial, increasing access to therapies that may offer direct participant benefit.⁵⁶ Enrollment in early-phase discovery studies can also be maximized by permitting a “non-matched” subgroup for participants who do not have any biomarkers of interest.⁵⁴ By using a centralized infrastructure to streamline logistics (e.g., central IRB, data monitoring committee, and electronic data capturing system), start-up time can be significantly reduced.⁵⁶ An example of an early-phase discovery study in adults is NCI-MATCH (National Cancer Institute-Molecular Analysis for Therapy Choice), in which patients with solid tumors, lymphomas, or myelomas are enrolled into 1 of 19 treatment arms based on genomic testing of their tumors (e.g., epidermal growth factor receptor mutation).⁵⁷ NCI-MATCH is an example of the basket approach that enrolls several malignancies that may respond to a common treatment approach.⁵⁵ While master protocols are more common in adult trials, several examples of pediatric master protocols exist, including the previously mentioned POPS trial. In addition, the proposed iMATRIX master protocol proposes a platform for phase I/II studies for oncology drugs in pediatrics whereby the trial is gated (e.g., early evaluation of PK and potential biomarkers) to identify which agents warrant further development.^{58,59} While limited pediatric experience suggests that master protocols are a significant advancement in trial design, some concerns remain. In addition to a complex study design that may require standardizing endpoints across substudies, it may be difficult to convince industry sponsors to collaborate if there is perceived competition between sponsors or drug therapies.⁵⁴

Several landmark trials using master protocols in adult oncology have also capitalized on combining a master protocol in the context of other innovative designs. For example, the I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging

and Molecular Analysis) trial included an adaptive randomization to assign patients to the best treatment group while also using Bayesian methodologies to determine if inferior treatments should be discontinued.⁵⁶ These innovations, discussed in more detail in later sections, may optimize enrollment by offering a more favorable benefit-risk ratio for participants.

Other design strategies

Many children and their families do not enroll in early-phase clinical trials due to fear of discontinuing background therapy and subsequent disease progression. One method to alleviate this concern is to add an early-phase study drug while continuing existing or background therapy. To further minimize burden on participants, it is important that a multiple-dose vs single-dose study be chosen judiciously (depending on half-life) to minimize overall study time. Lastly, limiting inclusion and exclusion criteria is an important measure in early-phase studies to ensure 1) optimal enrollment and 2) the necessary heterogeneity to discover important covariates that may influence drug dosing.

Late-Phase Studies

Adult efficacy extrapolation—Most drugs are first studied and approved in adults; therefore, appropriately using data derived from adult studies may help guide the design of a pediatric trial.^{12,60} Extrapolation applies available information from a source population (e.g., adults) to the target population (e.g., children) with the goal of reducing the overall amount of clinical trial data needed in the target population.⁶¹ Extrapolation can significantly reduce the time and cost for a pediatric drug-development program, especially if a dedicated pediatric efficacy trial is unnecessary. In recognition of this, extrapolation is becoming more common in drug development; for example, a review of pediatric studies submitted to the FDA between 1998–2008 found that partial extrapolation of adult data was used to support pediatric drug development in 113 (68%) of 166 products, while 24 (14%) had full extrapolation.⁶² The FDA has proposed an algorithm to guide the extrapolation of adult data to the design of pediatric trials, highlighting 3 general approaches: a PK-only approach (full extrapolation), a PK/PD approach (partial extrapolation), and a PK-efficacy approach (no extrapolation).¹² However, to appropriately apply this algorithm, it is critical to understand pediatric disease progression, expected response to intervention, and the exposure-response relationship.¹² Therefore, pediatric research efforts to develop disease-progression and exposure-response models may allow for optimal extrapolation.⁶⁰ The EMA has published similar guidance, emphasizing that the extent of pediatric extrapolation exists on a spectrum, with varying degrees of data requirements depending on the predicted similarity (and residual uncertainty) between the source and target population.⁶³

Pragmatic trials and leveraging electronic health records (EHRs)—Whereas traditional clinical trials enroll a narrow group of participants and operate under ideal conditions, large pragmatic trials aim to demonstrate the real-world effectiveness of an intervention in the broader population.⁶⁴ To optimize trial generalizability and enrollment, inclusion and exclusion criteria are minimized, and the number of study visits and procedures are reduced.⁶⁴ Further, pragmatic trials can reduce or possibly eliminate the need for individual sites by using a management strategy where enrollment, randomization, and

data collection all occur centrally.^{60,65,66} Central management is especially advantageous for smaller pediatric research sites where limited funding combined with fewer investigators and coordinators often preclude trial participation. Pediatric pragmatic trials have several other potential advantages, including the ability to enroll large sample sizes (including rare diseases), resulting in better representation of multiple age groups. In addition, the reduced emphasis on study visits may reduce time, cost, and travel burden to families.⁶⁰ Lastly, many pragmatic trials have successfully collected outcome data entirely from available medical records, eliminating the need for dedicated data-collection visits and further reducing encumbrances on investigators and families.⁶⁴ Ideally, the use of EHRs for outcome data should focus on meaningful outcomes that are well defined, unambiguous, and easily verified (e.g., mortality, hospitalization).⁶⁴ While pragmatic trials offer several enrollment advantages, the ‘real-world’ settings of most pragmatic designs (e.g., high non-adherence, heterogeneous population, often open-label) can result in reduced internal validity when compared with traditional clinical trials.⁶⁴

While pragmatic drug trials in children are generally lacking, recent interventional pragmatic trials provide some insight into trial execution. The Breathe Well study was a pragmatic interventional study designed to evaluate adherence in pediatric asthma by comparing usual care to speech recognition calls using personalized EHR information (e.g., child’s name and sex, physician name, medication name) when inhaled corticosteroid refills were due.^{67,68} The intervention resulted in a 25% increase in adherence (9% absolute difference); however, there was no observed difference in sick visits or beta-agonist use.⁶⁷ The study capitalized on Kaiser Permanente databases to identify participants (enrolling >1100 children) and collect outcome measures, highlighting that EHR databases can facilitate the execution of large-scale pragmatic trials. However, participants were required to have Kaiser Permanente insurance, a working telephone, and have filled at least one prescription in the 6 months prior to enrollment, potentially excluding those with very low adherence, low income, and at risk for poor outcomes.^{67,68} Broad inclusion criteria are therefore essential to optimize generalizability when designing pediatric pragmatic trials.

Master protocols—As with early-phase studies, master protocols are an attractive method to optimize late-phase studies by reducing regulatory burden, reducing cost, and increasing trial efficiency. For example, the Lung-MAP (Lung Cancer Master Protocol) phase II–III trial uses a common genomic marker screening platform to compare 3 experimental agents and a non-matched immunotherapy group against standard-of-care treatment for squamous cell lung cancer.⁶⁹ Screening failure is reduced by 1) using next-generation sequencing to identify multiple eligible biomarkers, and 2) including the non-matched group.⁶⁹ The master protocol infrastructure (e.g., single IND application) facilitates the addition of new investigational substudies over time⁶⁹ and may allow accelerated drug approval by streamlining progression from phase II to phase III. Master protocols can also use a shared control group to reduce overall costs and required sample sizes.^{55,56} As discussed earlier, the increased efficiency provided by master protocols may offer a new paradigm for executing pediatric studies.

Endpoints and PK/PD confirmation—Choosing the appropriate endpoint for a pediatric drug trial is challenging due to differences between adults and children in disease pathophysiology that limit the use of common endpoints.^{5,10} In addition, developmental changes may impact PD response through alterations in drug receptor affinity, density, and other changes.⁷⁰ Further, many biomarkers and surrogate endpoints lack validation in children. As a result, several pediatric trials have failed as a result of poor endpoint selection. For example, an analysis of pediatric antihypertensive drug trials showed that a reduction in diastolic blood pressure correlated better with dose compared with systolic blood pressure; further, all pediatric trials that used systolic blood pressure as the primary endpoint failed.¹⁰ This was likely due to diastolic blood pressure having less patient variability.¹⁰ Thus, it is important for future drug trials in children to ensure endpoints are based on direct and clinically relevant outcome measures that are specific for pediatric disease pathophysiology.

For drugs that have multiple therapeutic effects, using a composite endpoint is one method to increase the likelihood of trial success and augment clinical applicability. As an example, drugs used to treat juvenile arthritis may concomitantly reduce joint pain, joint swelling, improve range of motion, and improve functional status. Designing a drug trial targeting only one of these measures would miss several important responses, potentially leading to trial failure. Further, using a composite endpoint increases the overall event rate and reduces the required sample size.⁷¹ Capitalizing on this approach, many successful trials in pediatric rheumatology used a composite measure that incorporated patient and physician global assessments of disease activity, functional status, joint exams, and biomarkers of inflammation (e.g., the erythrocyte sedimentation rate).⁶⁰ However, results from trials using a composite endpoint can be difficult to interpret if the treatment affects one measure more so than others.⁷¹

In addition to endpoint selection, another common reason for pediatric trial failure is poor dose selection. Out of 44 pediatric trials between 2007–2014, 10 trials failed as a result of 1) not testing a range of pediatric doses, and/or 2) inappropriately extrapolating adult drug exposure.⁵ Therefore, in addition to having sufficient early-phase PK/PD modeling data to guide initial dose selection, late-phase trials should also routinely analyze PK/PD. In doing so, the exposure-response relationships can be confirmed in the target population; and in the case of adaptive trial designs (discussed later), dosing during the trial can be changed. Confirming exposure response is particularly important for drugs approved in adults for indications other than those being tested in children; in this case, different disease mechanisms may significantly alter the necessary pediatric dose.⁵

Research networks—As with early-phase studies, research networks are essential to overcoming the enrollment barriers that often hinder late-phase studies. Particularly for rare diseases, research networks have successfully executed multinational trials that would otherwise not be feasible on a smaller scale. For example, the 3 major pediatric rheumatology research networks have collectively coordinated dozens of trials in >60 countries,⁶⁰ contributing to the approval of most available therapeutics for juvenile idiopathic arthritis. The success of these research networks is not just limited to a single specialty; within oncology, for example, 90–95% of children under age 15 with malignancy are seen at a Children's Oncology Group-associated institution, and enrollment rates are as

high as 50–90%, depending on age.⁷² In addition to overcoming enrollment barriers, research networks can optimize the design of late-phase studies to become more patient-centric. For example, the Patient-Centered Outcomes Research Institute (PCORI) invested \$250 million into a network (PCORnet) designed to engage patients and families to help execute practical, patient-relevant trials.⁷³ PCORnet leverages 13 clinical data research networks and 20 patient-powered research networks to promote several study designs, including pragmatic interventional, observational, and health system studies.^{73,74} These studies capitalize on several innovations through PCORnet, including centralized IRBs, electronic consent, and standardized data capture through the Common Data Model.⁷⁴ PCORI has successfully engaged several pediatric partner networks and highlights the importance of including children and their families as stakeholders to optimize pediatric clinical pharmacology studies.

SIMULATION AND MODELING

Clinical trial simulations

Clinical trial simulations (CTS) combine disease modeling with PK/PD modeling to simulate trial design features such as the effects of disease progression, placebo response, and dropout; in doing so, CTS increases trial success, operational efficiency, and precision.⁷ In addition, CTS can optimize early-phase studies by confirming optimal sparse sampling strategies, estimating dose-response relationships, and guiding dose selection for late-phase trials.⁷ In recognition of this, regulatory authorities use CTS as part of the end of phase IIa discussions.⁷⁵ In some cases, CTS can leverage existing datasets to make dosing recommendations without the need for an additional trial. For example, a CTS of etanercept in juvenile idiopathic arthritis was used to support FDA approval for a once-weekly dose.^{7,76} To develop the population PK model, 353 PK samples were obtained using a sparse sampling strategy from 69 patients who participated in a multicenter clinical trial of etanercept 0.4 mg subcutaneously twice per week for juvenile idiopathic arthritis.⁷⁶ Using the final one-compartment model, Monte Carlo trial simulations of 200 virtual patients were then conducted to compare the PK profile of the trial dose vs the proposed once-weekly dosing using a parallel, double-blind, 12-week design. The study showed overlapping steady-state concentrations between the 2 doses.⁷⁶ The results from the etanercept trial simulation were later confirmed in a prospective clinical trial.⁷⁷ CTS has also been used to leverage dosing recommendations in children for sotalol⁷⁸ and gatifloxacin,⁷⁹ among others.

Physiologically based pharmacokinetic (PBPK) modeling

PBPK modeling is a technique that mathematically incorporates organ-specific physiologic compartments to describe drug PK, response to therapy, and safety.⁶¹ It is well accepted by regulatory authorities for pediatric drug development, and it has been used to optimize study design and dosing, evaluate the effects of organ dysfunction, and predict enzyme and transporter ontogeny.^{12,61} Over the past decade, pediatric PBPK models have been published for >30 drugs⁶¹ and are also complementary to other drug-modeling techniques. For example, a population PK model supplemented with a PBPK model was used to support the regulatory approval of valganciclovir in infants <4 months of age.⁸⁰ Using this complementary approach, an existing PBPK model was extended to neonates and used to

confirm physiologic similarity between young infants and older children with parameters important for valganciclovir (e.g., esterase activity, renal clearance, active transporters); population PK modeling was then used to simulate drug exposure with the proposed dosing algorithm.⁸⁰ Because the original population PK dataset had insufficient representation of neonates, PBPK modeling successfully bridged this knowledge gap using known physiologic differences.⁸⁰ Other recent examples of PBPK models include methotrexate and 6-mercaptopurine, which in combination with disease models, is being used to support clinical trial simulation for childhood leukemia.^{81,82} In addition, opportunistic PK data were recently used to develop a pediatric PBPK model of clindamycin by first creating an adult model from existing data and then scaling it to children.⁸³ This model was able to predict concentrations of clindamycin in target tissues (e.g., bone, skin) and confirm appropriate dosing. Collectively, these innovations underscore that PBPK modeling is a powerful tool that can play a significant role in optimizing pediatric dosing, supporting drug approval, and ensuring clinically relevant drug concentrations are achieved at the appropriate site of action. Despite significant potential, however, PBPK modeling in pediatric submissions to the FDA are uncommon, comprising only 17% of records between 2008–2015.⁸⁴ This is likely due to uncertainty regarding the ontogeny of many pediatric PK processes, including drug metabolizing enzymes and drug transporters.⁸⁴ Further, it is difficult to validate PBPK models in children due to the lack of available data and expertise. Nevertheless, as our understanding of developmental changes and drug disposition in children expand, PBPK modeling will likely play an increasingly prominent role in regulatory review.

Individualized/precision dosing and population PK

Pediatric dosing regimens that are simply extrapolated from adult dosing often assume a linear relationship between dose and size, which fails to account for differences in the exposure-response relationship, as well as maturational differences in absorption, distribution, metabolism, and excretion processes and biotransformation pathways.⁸⁵ Because age is a poor indicator of biologic maturation, surrogates such as body surface area (BSA) or allometric scaling are sometimes used to extend dosing from adults to children.^{61,85} BSA, while being convenient, does not correlate well with many physiologic processes and may overestimate dosing in infants and neonates.^{61,86} Conversely, allometric scaling is attractive as it more precisely relates body size with parameters of interest (e.g. clearance).⁸⁷ For example, a study of 14 drugs found that variable allometric scaling of adult clearance values produced good estimates of clearance in children >5 years of age.⁸⁸ However, allometric scaling was unreliable for younger children (<5 years of age) and required coefficient adjustments (Boxenbaum coefficient method), highlighting the need for additional considerations when applying allometric scaling to young children and neonates. As a result of the limitations using body size extrapolations to predict dosing, there is a significant need to individualize dosing, particularly for special populations where PK is expected to change most (e.g., prematurity, critically ill, obesity) and for those drugs with high PK variability and narrow therapeutic index.⁶¹ Several approaches to individualizing dosing for children exist, including concentration-guided trials, population PK modeling, and Bayesian forecasting.

Traditional clinical trials operate under the paradigm of evaluating a therapy in a population at a restricted dose(s); this approach is especially limited in children where there is variability in drug exposure due to physiologic changes. PK-guided trials, where real-time PK modeling is used to individualize a dose, is a promising new trial methodology that accounts for variability in dose response.⁶¹ Real-time PK sampling may be feasibly executed using sparse sampling combined with the previously discussed technological advancements, such as dried matrices and multiplex assays with ultra-low-volume collection.⁶¹ As an example of a concentration-guided trial, adjunctive everolimus was first evaluated in a phase I/II trial of refractory seizures related to tuberous sclerosis in 20 patients 2–21 years of age.⁸⁹ The trial was divided into a 4-week baseline observational period where everolimus was started at 5 mg/m²/day, followed by a 4-week titration period where dose was adjusted based on trough concentration (goal 5–15 ng/mL), and then a maintenance phase. The study showed an improvement in seizure control and subsequently led to a phase III trial designed to evaluate 2 everolimus trough concentration ranges. In the phase III trial, the efficacy of everolimus was confirmed in 366 participants with a response rate of 15% for placebo, 28% with the low-exposure group (3–7 ng/mL), and 40% for the high exposure group (9–15 ng/mL) ($P < 0.0001$).⁹⁰ The phase III trial included patients aged 2–65 years, highlighting that concentration-guided trials can inform dosing across multiple age spectrums. Assuming a shared and validated outcome measure exists, it may be possible to design simpler trials that enroll both adults and children using concentration targets instead of a fixed-dose design. In addition, concentration-guided trials may be more efficient for a given sample size.⁹¹

Population modeling can describe PK/PD at the population level and measure inter-individual variability in exposure or response, as well as the reasons (covariates) for this variability.⁹² Provided the PK/PD model has been sufficiently validated by internal and external data, covariates can be used to individualize or adjust therapy.⁹² However, traditional modeling approaches are both disease- and drug-specific, with limited ability to extrapolate to drugs of different classes.⁹² As a result, there is growing interest in developing systems-based pharmacology reference models that may permit extrapolation of a covariate from one drug to another that uses similar biologic pathways.⁹² For example, a model of amikacin clearance in preterm and term neonates using birthweight and postnatal age as covariates of renal maturation successfully predicted clearance in models of other renally cleared medications (netilmicin, tobramycin, vancomycin, and gentamicin).⁹³ Using this approach, system-specific information is derived from the pediatric covariate model, while drug-specific information is derived from the population model.⁹³ Using a systems-based pharmacology approach, it is possible to significantly reduce the time for model development,⁹³ thereby accelerating the capacity for PK/PD modeling and simulation to be used to develop dosing algorithms in children. There are several important considerations and potential limitations with extrapolating a reference covariate model to other drugs. For example, the covariate model should be based on large cohorts with sufficient patient heterogeneity and enough sampling, have extensive internal and external validation, and be extrapolated to models from similar clinical populations.⁹³ Lastly, population PK/PD modeling can also be used as a basis for Bayesian forecasting, whereby prior population PK/PD data can be updated with individual patient data to optimize dosing, particularly for

drugs with complex disposition.^{61,94} For example, a population PK model was developed to characterize the PK of mycophenolic acid in children with systemic lupus, accounting for enterohepatic recirculation.⁹⁵ Because weight-based dosing of mycophenolate in systemic lupus does not accurately predict exposure to the active metabolite, future efforts may use the population PK model in conjunction with a Bayesian estimator to individualize mycophenolate dosing.⁹⁵ Further, commercially available software (e.g., InsightRX) has capitalized on using Bayesian estimation to support precision dosing. The platform leverages validated population PK models as population priors, which can then be updated using an individual patient's concentration (e.g., TDM measurements) in real-time.⁹⁶ Currently, the platform offers modules for 7 drugs, including vancomycin, busulfan, and tacrolimus. Broadly, Bayesian feedback “dashboard” systems that use data captured from electronic medical records to provide real-time feedback and dosing decisions to clinicians are reviewed elsewhere.⁹⁷

FUTURE DIRECTIONS

Pharmacogenomics

Genetic tests that directly influence the choice or dose of a medication are far more common than previously believed; for example, one study found that 91% of adult patients who underwent preemptive pharmacogenomics testing had a clinically actionable variant to at least one of 5 well-established drug-gene interactions (clopidogrel, simvastatin, warfarin, thiopurines, and tacrolimus).⁹⁸ Approximately 42% of individuals in the study had actual exposure to one of these medications,⁹⁸ underscoring that pharmacogenomics have a common and important role in promoting drug safety. Within pediatrics, a comprehensive program developed by St. Jude Children's Research Hospital (PG4KDS) combines preemptive pharmacogenetic testing with EHRs to guide prescribing, and it has been very well received by patients and families, with >95% enrollment.⁹⁹ Consistent with adult data, 78% of pediatric patients in the St. Jude's cohort had at least one actionable genotype in their EHR.⁹⁹ The early success of large-scale, preemptive testing underscores that, as our knowledge base expands with respect to drug-gene interactions, future pharmacogenomic testing might be routinely performed on all individuals.¹⁰⁰ Nevertheless, important pharmacogenetic differences may exist between adults and children. For example, variants for a drug transporter (SLCO1B1) were associated with decreased pravastatin concentrations in children, whereas these variants in adults are associated with increased pravastatin concentrations.^{101,102} These differences underscore that potential changes in gene expression, physiology, and disease processes may alter pharmacogenetic relationships in children compared with adults.¹⁰¹ Therefore, ontological studies in children are needed to characterize genetic changes throughout childhood and allow optimal use of existing adult data.¹⁰¹

To facilitate the identification of gene-drug interactions in children and translation of these interactions to clinical practice, it will be necessary to collect genomic information from children on a large scale.¹⁰¹ In addition to ethical considerations, the wide-scale collection of biospecimens presents several logistic challenges. Vanderbilt has developed a de-identified “DNA biobank” where any unused blood samples are retained for genetic research

unless a patient “opts out” on the standard consent-to-treat form.¹⁰³ De-identified genetic results are then linked with electronic records, resulting in a robust clinical research database. The highly successful program obtains 700–900 specimens per week, and although children were initially automated exclusions,¹⁰³ thousands of pediatric samples have since been obtained. Given the low prevalence of many pediatric diseases, collecting de-identified genetic and clinical data on an institution-wide scale is a potentially transformative way to augment clinical pharmacology research in children. However, important ethical concerns should first be resolved, including the handling of incidental variants, implications of genetic findings for family members, and misattributed paternity.¹⁰¹

Adaptive Designs/Bayesian Trials

Adaptive trials allow for change to trial execution (e.g., dropping an inferior treatment group, adjusting dose, changing endpoints) after enrollment for the purpose of identifying the best treatment using the most efficient means.^{60,104} While most adaptive designs are used for late-phase studies, early-phase adaptive dose-finding designs may be used to reassess the dose-response relationship as trial data accumulate, allowing for dose changes after each subject and potentially reducing enrollment requirements.^{104,105} Adaptive trials are particularly attractive for pediatric studies by maximizing benefits and reducing the potential for harm or trial failure. For example, an interim analysis could precisely estimate power and ensure proper sample size attainment, or reduce ethical concerns by altering randomization to favor a more effective treatment arm.^{60,104} Limitations to adaptive designs include difficulty estimating treatment effect if variability in response occurs at different time points, and propensity for type I and type II errors, particularly if interim analyses are unblinded.^{104,105} As a result, FDA guidance recommends that changes be prospectively planned and analyses must be adequately blinded.¹⁰⁵

Bayesian statistics are complementary to most adaptive designs. At the time of analysis, traditional clinical trials investigate data derived only during the trial, ignoring potentially meaningful prior data. In contrast, Bayesian methodologies capitalize on both prior data (the prior distribution) and evidence accumulated continuously throughout a trial, thereby being naturally adaptive, efficient, and informative.^{55,106} Bayesian methodologies can be employed both at trial design (e.g., to estimate power) or during the time of an interim analysis to augment decision making (e.g., whether to stop a trial).⁵⁵ For example, a phase II Bayesian trial evaluated the use of mycophenolate mofetil for steroid-dependent pediatric nephrotic syndrome.¹⁰⁷ After 23 children completed the study, Bayesian analyses were performed and the accumulated data were used to determine that enrolling additional patients would not alter study conclusion, thereby permitting the trial to be stopped without additional, unnecessary enrollment.¹⁰⁷ This study highlights how Bayesian analysis can be used to strengthen decision-making during a trial. When designing a trial that includes Bayesian analysis, FDA guidance highlights that prior information should be derived from empirical studies or other trials instead of expert opinion.¹⁰⁶

Bioanalysis/Non-Invasive Drug Concentration Measurements

The failure of eliminating HIV in reservoir tissues is one of many examples that underscore the critical need to approximate drug concentrations within tissues to ensure adequate drug

exposure.¹⁰⁸ However, obtaining tissue for direct drug quantification is challenging in pediatric patients, where it is important to minimize invasive procedures. To overcome this limitation, novel techniques aim to correlate non-invasive drug concentration measurements with tissue exposure. For example, cervicovaginal fluid (CVF) and rectal fluid (RF) were collected from healthy volunteers given 1 of 4 anti-retroviral drugs; the study authors found that CVF and RF were related to plasma and tissue biopsy concentrations.¹⁰⁹ Correlating these and other non-invasive fluid measurements as a surrogate for tissue concentration may allow investigators to qualitatively assess drug exposure during clinical trials, particularly for drugs where tissue penetration is paramount (e.g., HIV, inflammatory bowel disease).¹⁰⁹ This may be accomplished through evolving technologies that combine Raman spectroscopy with microscopy to permit the simultaneous quantification and localization of drugs in tissues without sample destruction.¹¹⁰ Raman technology has been successfully leveraged to study drug penetration in skin (e.g., ibuprofen¹¹¹) and even map the intracellular disposition for 6-mercaptopurine and methimazole.¹¹²

While CVF and RF matrices are considered relatively non-invasive in adults, routine collection of these samples in children will likely be less acceptable. Therefore, it is important to consider other approaches to non-invasive drug measurements such as hair samples, exhaled breath, or saliva. For example, using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) mass spectrometry imaging to analyze hair samples, investigators successfully described long-term adherence with antiretroviral medications.¹¹³ For drugs that are able to diffuse across alveolar capillary walls and the epithelium (e.g., fentanyl, methadone, propofol, valproic acid), mass spectrometry has been used to measure drug concentration in exhaled breath.^{13,114} Exhaled breath measurements have traditionally been limited by the need for intubation,¹³ making it unsuitable in children outside of critical care settings. However, newer technologies use specialized collection bags or glass bottles to collect exhaled breath and may allow for routine, non-invasive measurements of drugs and metabolites in children.^{114,115} Despite these advances, there are very few published PK studies in infants and children using exhaled breath. Lastly, PK studies using saliva are an attractive option due to high consent rates.¹¹⁶ Stimulated saliva may be best-suited for measuring drugs that are lipophilic, non-ionized, and with low protein binding, where distribution into saliva may be optimized.¹³ Despite limitations in collection technique and contamination from oral administration, salivary PK studies in children showed overall good plasma correlation with several medications, including risperidone,¹¹⁷ methylphenidate,¹¹⁸ busulfan,¹¹⁹ artemisinin,¹²⁰ and artesunate-amodiaquine.¹²¹ Although non-invasive measurements of drug exposure are promising new methods to increase both the number of overall PK samples collected and study enrollment, it is important to first correlate these matrices with blood PK and standardize collection methods to avoid introducing variability (e.g., saliva flow rate, mode of ventilation) or contamination (e.g., compounds on collection bag or swab).^{13,114,115} Because most exposure-response relationships are established using systemic exposure, good correlation between non-invasive drug measurements and blood measurements is a requisite for appropriate extrapolation.

Orphan Drug Development

Regulatory advances such FDA's internal Rare Disease Review Committee, expedited review programs, and financial incentives for drug sponsors through the Orphan Drug Act have resulted in a record number of approved orphan drugs.^{122,123} Other countries also have incentives to promote orphan drug development.¹²⁴ Despite this progress, developing orphan drugs still pose unique challenges due to very low sample sizes (often precluding traditional randomized placebo-controlled trials), lack of biomarkers and appropriate clinical endpoints, and poorly understood prevalence and outcome statistics.^{123,125} The challenges during orphan drug development may therefore result in high drug costs and limited access to these medications.¹²⁴ Promoting biomarker research for orphan diseases may overcome several of these challenges by 1) identifying clinically meaningful responses to replace long-term outcomes as efficacy endpoints (e.g. hemoglobin and type I Gaucher disease), and 2) identifying surrogate endpoints to accelerate drug approval (e.g. clearance of GB3 and Fabry disease).¹²⁶ These approaches were leveraged for the approval of four drugs for type I Gaucher disease (e.g. purified human glucocerebrosidase) and agalsidase beta for Fabry disease.¹²⁶

NOVEL APPROACHES

Although significant progress has been made in pediatric clinical pharmacology research, complementary strategies are necessary to translate these advances to clinical practice. For example, future advances in modeling, EHR, and bioanalytical capabilities may allow for real-time, point-of-care TDM to guide precision dosing at the bedside. For example, there is a gap in current clinical care in the treatment of neonatal sepsis whereby delays in therapeutic antimicrobial exposure may worsen outcomes. Therefore, there is an urgent need for early, optimized dosing that can be implemented at the point of care. Using a micro-volume PK sample or non-invasive drug concentration measurement (to minimize loss of blood volume), advanced bioanalytical technology could permit bedside measurement of drug concentration within a short time frame. For example, current devices that capitalize on paper spray ionization for mass spectrometry permit analyses in around 1 minute using low-cost cartridges and paper, suitable for point-of-care use.¹²⁷ By then capitalizing on validated population PK models and the bedside TDM measurements, Bayesian estimating software such as InsightRX could then optimize antimicrobial dosing in real-time and potentially improve outcomes. Further, accumulating patient data for a particular neonate (e.g., renal function, weight, additional TDM measurements) could be incorporated in an EMR "dashboard" to continually update the Bayesian model to provide precise dosing throughout a changing hospital course.

Because many children and their families often travel great distances to see a pediatric specialist, frequent or lengthy study visits can impede recruitment.⁶⁰ Telemedicine offers a potential solution by more efficiently connecting families with practitioners and clinical researchers. For example, telemedicine consults in one health system resulted in an average reduction in distance traveled of 278 miles per consultation, and an average time saving of 245 minutes.¹²⁸ Therefore, telemedicine may optimize clinical research by increasing patient engagement and study enrollment. Further, new telemedicine technologies permit the

collection of clinical data (e.g., physical exam or biospecimens) remotely through specially fitted cameras (e.g., to the tip of a self-applied tongue depressor), digital stethoscopes, temperature probes, and other health care devices (e.g., TytoCare).¹²⁹ This technology allows patients to play a central role in clinical research by directly collecting and submitting clinical data while also minimizing the burdens of study visits. Additionally, it may be more feasible to collect samples or data on an intense schedule from the convenience of home.

Changes in the maturation of drug-metabolizing enzymes, transporters, and target receptors continue to complicate research in clinical pharmacology and the care of children.⁷⁰ Because body weight does not correlate linearly with these physiologic changes,⁹ surrogate measures of physiologic maturation are needed to optimize the study of drug disposition. This is particularly relevant for newer drug classes (e.g., monoclonal antibodies), where non-traditional covariates such as metabolic rate may impact immunoglobulin half-life.¹³⁰ For example, resting energy expenditure (REE) was shown to have a positive association with infliximab clearance, potentially explaining why younger children (who have higher REE) have higher drug clearance.¹³⁰ If confirmed in additional studies using other drugs, REE may be a transformative method to characterize physiologic maturation and drug ontogeny.

CONCLUSION

Research over the past several decades has resulted in a significant growth in our understanding of pediatric developmental pharmacology. In the next 20 years, advances in precision medicine may further transform clinical pharmacology research. These advances will likely include precision-guided trials and individualized dosing through Bayesian adaptive trial designs, PK/PD modeling, and integrated pharmacogenetic testing. To make the promise of precision medicine a reality, however, pediatric research will need to be viewed as a prioritized component of health care. Therefore, it is important to routinely engage children and their families as stakeholders and continue to advance bioanalytical, telemedicine, and electronic health technologies to optimize the amount of data collected with minimal to no risk for participants. Further, it will be necessary to develop better pediatric disease-progression and exposure-response models while accounting for developmental changes. Doing so will optimize efficacy extrapolation from adults and allow better use of CTS simulations to guide dosing and potentially reduce the need for dedicated pediatric efficacy trials. Through innovative study designs and the combined efforts of large research networks, patient and family stakeholders, clinicians, and pharmacologists, research can be optimized to leverage major advances in the care of children.

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References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006. Available at: http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf. Accessed 20 Aug 2017.
2. Zimmerman K, Gonzalez D, Swamy GK, Cohen-Wolkowicz M. Pharmacologic studies in vulnerable populations: Using the pediatric experience. *Semin Perinatol*. 2015;39(7):532–6. [PubMed: 26358805]
3. Japan Pharmaceutical Manufacturers Association. Pharmaceutical Administration and Regulations in Japan. Available at: <http://www.jpma.or.jp/english/parj/pdf/2017.pdf>. Accessed 20 Aug 2017.
4. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Addressing the Barriers to Pediatric Drug Development: Workshop Summary. Washington (DC): National Academies Press (US); 2008 Available from: <https://www.ncbi.nlm.nih.gov/books/NBK3994/>. Accessed 20 Aug 2017.
5. Momper JD, Mulugeta Y, Burckart GJ. Failed Pediatric Drug Development Trials. *Clin Pharmacol Ther*. 2015;98(3):245–51. [PubMed: 25963725]
6. Wharton GT, Murphy MD, Avant D, et al. Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. *Pediatrics*. 2014;134(2):e512–8. [PubMed: 25022732]
7. Holford N, Ma SC, Ploeger BA. Clinical trial simulation: a review. *Clin Pharmacol Ther*. 2010;88(2):166–82. [PubMed: 20613720]
8. Savage WJ, Everett AD. Biomarkers in pediatrics: children as biomarker orphans. *Proteomics Clin Appl*. 2010;4(12):915–21. [PubMed: 21137032]
9. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–67. [PubMed: 13679531]
10. Benjamin DK, Jr, Smith PB, Jadhav P, et al. Pediatric antihypertensive trial failures: analysis of end points and dose range. *Hypertension*. 2008;51(4):834–40. [PubMed: 18332283]
11. Rieder M, Hawcutt D. Design and conduct of early phase drug studies in children: challenges and opportunities. *Br J Clin Pharmacol*. 2016;82(5):1308–14. [PubMed: 27353241]
12. US Food and Drug Administration. General Clinical Pharmacology Considerations. Guidance for Industry. December 2014 Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf>. Accessed 5 July 2017.
13. Autmizguine J, Benjamin DK, Jr, Smith PB, et al. Pharmacokinetic studies in infants using minimal-risk study designs. *Curr Clin Pharmacol*. 2014;9(4):350–8. [PubMed: 24844642]
14. Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care (PTN_POPS). Available at: <https://clinicaltrials.gov/ct2/show/NCT01431326>. Accessed 5 July 2017.
15. Gonzalez D, Melloni C, Poindexter BB, et al. Simultaneous determination of trimethoprim and sulfamethoxazole in dried plasma and urine spots. *Bioanalysis*. 2015;7(9):1137–49. [PubMed: 26039810]
16. Gonzalez D, Melloni C, Yorgev R, et al. Use of opportunistic clinical data and a population pharmacokinetic model to support dosing of clindamycin for premature infants to adolescents. *Clin Pharmacol Ther*. 2014;96(4):429–37. [PubMed: 24949994]
17. Tremoulet A, Le J, Poindexter B, et al. Characterization of the population pharmacokinetics of ampicillin in neonates using an opportunistic study design. *Antimicrob Agents Chemother*. 2014;58(6):3013–20. [PubMed: 24614374]
18. Leroux S, Turner MA, Guellec CB, et al. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. *Clin Pharmacokinet*. 2015;54(12):1273–85. [PubMed: 26063050]
19. Laughon MM, Benjamin DK, Jr, Capparelli EV, et al. Innovative clinical trial design for pediatric therapeutics. *Expert Rev Clin Pharmacol*. 2011;4(5):643–52. [PubMed: 21980319]
20. Zhao W, Zhang D, Storme T, Baruchel A, Decleves X, Jacqz-Aigrain E. Population pharmacokinetics and dosing optimization of teicoplanin in children with malignant haematological disease. *Br J Clin Pharmacol*. 2015;80(5):1197–207. [PubMed: 26138279]

21. Acosta EP, Jester P, Gal P, et al. Oseltamivir dosing for influenza infection in premature neonates. *J Infect Dis.* 2010;202(4):563–6. [PubMed: 20594104]
22. Standing JF, Nika A, Tsagris V, et al. Oseltamivir pharmacokinetics and clinical experience in neonates and infants during an outbreak of H1N1 influenza A virus infection in a neonatal intensive care unit. *Antimicrob Agents Chemother.* 2012;56(7):3833–40. [PubMed: 22564835]
23. Cohen-Wolkowicz M, Benjamin DK, Jr, Ross A, et al. Population pharmacokinetics of piperacillin using scavenged samples from preterm infants. *Ther Drug Monit.* 2012;34(3):312–9. [PubMed: 22569355]
24. Cohen-Wolkowicz M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. *Antimicrob Agents Chemother.* 2012;56(4):1828–37. [PubMed: 22252819]
25. Wade KC, Wu D, Kaufman DA, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother.* 2008;52(11):4043–9. [PubMed: 18809946]
26. de Hoog M, Schoemaker RC, Mouton JW, van den Anker JN. Vancomycin population pharmacokinetics in neonates. *Clin Pharmacol Ther.* 2000;67(4):360–7. [PubMed: 10801244]
27. Garcia B, Barcia E, Perez F, Molina IT. Population pharmacokinetics of gentamicin in premature newborns. *J Antimicrob Chemother.* 2006;58(2):372–9. [PubMed: 16782742]
28. Capparelli E, Hochwald C, Rasmussen M, Parham A, Bradley J, Moya F. Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother.* 2005;49(7):2760–6. [PubMed: 15980347]
29. Pullen J, Stolk LM, Nieman FH, Degraeuwe PL, van Tiel FH, Zimmermann LJ. Population pharmacokinetics and dosing of amoxicillin in (pre)term neonates. *Ther Drug Monit.* 2006;28(2):226–31. [PubMed: 16628135]
30. Bradley JS, Sauberman JB, Ambrose PG, Bhavnani SM, Rasmussen MR, Capparelli EV. Meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in the neonate. *Pediatr Infect Dis J.* 2008;27(9):794–9. [PubMed: 18645546]
31. Benjamin DK, Jr, Smith PB, Arrieta A, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin Pharmacol Ther.* 2010;87(1):93–9. [PubMed: 19890251]
32. Smith PB, Walsh TJ, Hope W, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J.* 2009;28(5):412–5. [PubMed: 19319022]
33. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* 2003;142(1):47–52. [PubMed: 12520254]
34. US Food and Drug Administration. Guidance for Industry, Investigators, and Reviewers. Exploratory IND Studies. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf>. Accessed 6 July 2017.
35. Turner MA, Mooij MG, Vaes WH, et al. Pediatric microdose and microtracer studies using ¹⁴C in Europe. *Clin Pharmacol Ther.* 2015;98(3):234–7. [PubMed: 26095095]
36. Mooij MG, van Duijn E, Knibbe CA, et al. Successful Use of [¹⁴C]Paracetamol Microdosing to Elucidate Developmental Changes in Drug Metabolism. *Clin Pharmacokinet.* 2017. [Epub ahead of print]
37. Zhang Y, Mehrotra N, Budha NR, Christensen ML, Meibohm B. A tandem mass spectrometry assay for the simultaneous determination of acetaminophen, caffeine, phenytoin, ranitidine, and theophylline in small volume pediatric plasma specimens. *Clin Chim Acta.* 2008;398(1–2):105–12. [PubMed: 18796299]
38. Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA. Microanalysis of beta-lactam antibiotics and vancomycin in plasma for pharmacokinetic studies in neonates. *Antimicrob Agents Chemother.* 2009;53(1):75–80. [PubMed: 18955527]
39. Cohen-Wolkowicz M, White NR, Bridges A, Benjamin DK, Jr, Kashuba AD. Development of a liquid chromatography-tandem mass spectrometry assay of six antimicrobials in plasma for pharmacokinetic studies in premature infants. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011;879(30):3497–506.
40. Pullen J, Stolk LM, Neef C, Zimmermann LJ. Microanalysis of amoxicillin, flucloxacillin, and rifampicin in neonatal plasma. *Biomed Chromatogr.* 2007;21(12):1259–65. [PubMed: 17604357]

41. Patel P, Mulla H, Tanna S, Pandya H. Facilitating pharmacokinetic studies in children: a new use of dried blood spots. *Arch Dis Child*. 2010;95(6):484–7. [PubMed: 20501544]
42. US Food and Drug Administration. Guidance for Industry. Bioanalytical Method Validation. 9 2013 Available at: <https://www.fda.gov/downloads/Drugs/Guidances/ucm368107.pdf>. Accessed 6 July 2016.
43. Donnelly RF, Mooney K, Caffarel-Salvador E, Torrisi BM, Eltayib E, McElnay JC. Microneedle-mediated minimally invasive patient monitoring. *Ther Drug Monit*. 2014;36(1):10–7. [PubMed: 24365984]
44. Mooney K, McElnay JC, Donnelly RF. Parents' perceptions of microneedle-mediated monitoring as an alternative to blood sampling in the monitoring of their infants. *Int J Pharm Pract*. 2015;23(6):429–38. [PubMed: 25807981]
45. Sakaguchi K, Hirota Y, Hashimoto N, et al. A minimally invasive system for glucose area under the curve measurement using interstitial fluid extraction technology: evaluation of the accuracy and usefulness with oral glucose tolerance tests in subjects with and without diabetes. *Diabetes Technol Ther*. 2012;14(6):485–91. [PubMed: 22537393]
46. Mooney K, McElnay JC, Donnelly RF. Children's views on microneedle use as an alternative to blood sampling for patient monitoring. *Int J Pharm Pract*. 2014;22(5):335–44. [PubMed: 24308565]
47. National Institutes of Health. Pediatric Pharmacology Research Units (PPRU) Network (For Historic Purposes Only). Available at: <https://www.nichd.nih.gov/research/supported/Pages/ppru.aspx>. Accessed 4 July 2017.
48. PPRU Legacy. Available at: <http://www.ppru.org/accomplishments.aspx>. Accessed 4 July 2017.
49. Pediatric Trials Network. Available at: <http://www.pediatrictrials.org/>. Accessed 11 September 2017.
50. European Medicines Agency. Report of the 2017 annual workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/07/WC500231884.pdf. Accessed 29 August 2017.
51. US Food and Drug Administration. Global Pediatric Clinical Trials Network. Available at: <https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-17-014.html>. Accessed 22 August 2017.
52. Trial Innovation Network. Available at: <https://trialinnovationnetwork.org/elements/who-we-are/>. Accessed 22 August 2017.
53. Shah MR. Trial Innovation Network: Tackling the Critical Roadblocks in Clinical Trials. May 2017 Available at: <https://trialinnovationnetwork.org/wp-content/uploads/2017/05/Trial-Innovation-Network-Overview-5.17-FINAL-002.pdf>. Accessed 29 August 2017.
54. Redman MW, Allegra CJ. The Master Protocol Concept. *Semin Oncol*. 2015;42(5):724–30. [PubMed: 26433553]
55. Berry DA. Emerging innovations in clinical trial design. *Clin Pharmacol Ther*. 2016;99(1):82–91. [PubMed: 26561040]
56. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med*. 2017;377(1):62–70. [PubMed: 28679092]
57. National Cancer Institute. NCI-MATCH Trial (Molecular Analysis for Therapy Choice). Available at: <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>. Accessed 7 July 2017.
58. Caron H Industry Perspective on Master Protocols and Platforms. FDA Workshop on Pediatric Master Protocols. 9 2016 Available at: <http://pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/pdf/Hubert%20Caron%20iPODD%20Master%20Protocol.pdf>. Accessed 31 July 2017.
59. Fromer MJ. Accelerating Pediatric Drug Development: Master Protocols May Be a Way to Go. April 2017 Available at: <http://www.ascopost.com/issues/april-25-2017/accelerating-pediatric-drug-development-master-protocols-may-be-a-way-to-go/>. Accessed 31 July 2017.
60. Balevic SJ, Becker ML, Cohen-Wolkowicz M, Schanberg LE. Clinical Trial Design in Juvenile Idiopathic Arthritis. *Paediatr Drugs*. 2017. [Epub ahead of print]

61. Vinks AA, Emoto C, Fukuda T. Modeling and simulation in pediatric drug therapy: Application of pharmacometrics to define the right dose for children. *Clin Pharmacol Ther.* 2015;98(3):298–308. [PubMed: 26073179]
62. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics.* 2011;128(5):e1242–9. [PubMed: 22025597]
63. European Medicines Agency. Reflection paper on extrapolation of efficacy and safety in paediatric medicine development. 4 2016 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf. Accessed 22 August 2017.
64. Ford I, Norrie J. Pragmatic Trials. *N Engl J Med.* 2016;375(5):454–63. [PubMed: 27518663]
65. ADAPTABLE, the aspirin study - a patient-centered trial. Available at: <http://theaspirinstudy.org/>. Accessed 20 July 2017.
66. Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term (ADAPTABLE). Available at: <https://clinicaltrials.gov/ct2/show/NCT02697916?term=adaptable?trial&rank=1>. Accessed 20 July 2017.
67. Bender BG, Cvietusa PJ, Goodrich GK, et al. Pragmatic trial of health care technologies to improve adherence to pediatric asthma treatment: a randomized clinical trial. *JAMA Pediatr.* 2015;169(4):317–23. [PubMed: 25664620]
68. Apter AJ. Understanding adherence requires pragmatic trials: lessons from pediatric asthma. *JAMA Pediatr.* 2015;169(4):310–1. [PubMed: 25664425]
69. Steuer CE, Papadimitrakopoulou V, Herbst RS, et al. Innovative Clinical Trials: The LUNG-MAP Study. *Clin Pharmacol Ther.* 2015;97(5):488–91. [PubMed: 25676724]
70. Mulla H Understanding developmental pharmacodynamics: importance for drug development and clinical practice. *Paediatr Drugs.* 2010;12(4):223–33. [PubMed: 20593907]
71. Tomlinson G, Detsky AS. Composite end points in randomized trials: there is no free lunch. *JAMA.* 2010;303(3):267–8. [PubMed: 20085955]
72. O’Leary M, Krailo M, Anderson JR, Reaman GH. Progress in childhood cancer: 50 years of research collaboration, a report from the Children’s Oncology Group. *Semin Oncol.* 2008;35(5):484–93. [PubMed: 18929147]
73. PCORNET. The National Patient-Centered Clinical Research Network. About PCORnet. Available at: <http://pcornet.org/about-pcornet/>. Accessed 23 August 2017.
74. PCORNET. The National Patient-Centered Clinical Research Network. Demonstration Studies. Available at: <http://pcornet.org/demonstration-studies/>. Accessed 23 August 2017.
75. Wang Y, Bhattaram AV, Jadhav PR, et al. Leveraging prior quantitative knowledge to guide drug development decisions and regulatory science recommendations: impact of FDA pharmacometrics during 2004–2006. *J Clin Pharmacol.* 2008;48(2):146–56. [PubMed: 18199891]
76. Yim DS, Zhou H, Buckwalter M, Nestorov I, Peck CC, Lee H. Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. *J Clin Pharmacol.* 2005;45(3):246–56. [PubMed: 15703360]
77. Kuemmerle-Deschner JB, Horneff G. Safety and efficacy of once-weekly application of Etanercept in children with juvenile idiopathic arthritis. *Rheumatol Int.* 2007;28(2):153–6. [PubMed: 17641897]
78. Laer S, Elshoff JP, Meibohm B, et al. Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. *J Am Coll Cardiol.* 2005;46(7):1322–30. [PubMed: 16198851]
79. Rubino CM, Capparelli EV, Bradley JS, et al. Population pharmacokinetic model for gatifloxacin in pediatric patients. *Antimicrob Agents Chemother.* 2007;51(4):1246–52. [PubMed: 17220409]
80. Jorga K, Chavanne C, Frey N, et al. Bottom-up Meets Top-down: Complementary Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling for Regulatory Approval of a Dosing Algorithm of Valganciclovir in Very Young Children. *Clin Pharmacol Ther.* 2016;100(6):761–9. [PubMed: 27530217]
81. Ogungbenro K, Aarons L. Physiologically based pharmacokinetic modelling of methotrexate and 6-mercaptopurine in adults and children. Part 2: 6-mercaptopurine and its interaction with methotrexate. *J Pharmacokinet Pharmacodyn.* 2014;41(2):173–85. [PubMed: 24651962]

82. Ogungbenro K, Aarons L. Physiologically based pharmacokinetic modelling of methotrexate and 6-mercaptopurine in adults and children. Part 1: methotrexate. *J Pharmacokinet Pharmacodyn*. 2014;41(2):159–71. [PubMed: 24651961]
83. Hornik CP, Wu H, Edginton AN, Watt K, Cohen-Wolkowicz M, Gonzalez D. Development of a Pediatric Physiologically-Based Pharmacokinetic Model of Clindamycin Using Opportunistic Pharmacokinetic Data. *Clin Pharmacokinet*. 2017. [Epub ahead of print]
84. Mehrotra N, Bhattaram A, Earp JC, et al. Role of Quantitative Clinical Pharmacology in Pediatric Approval and Labeling. *Drug Metab Dispos*. 2016;44(7):924–33. [PubMed: 27079249]
85. Vermeulen E, van den Anker JN, Della Pasqua O, Hoppu K, van der Lee JH. How to optimise drug study design: pharmacokinetics and pharmacodynamics studies introduced to paediatricians. *J Pharm Pharmacol*. 2017;69(4):439–47. [PubMed: 27671925]
86. Cella M, Knibbe C, Danhof M, Della Pasqua O. What is the right dose for children? *Br J Clin Pharmacol*. 2010;70(4):597–603. [PubMed: 21087295]
87. Mahmood I Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. *Clin Pharmacokinet*. 2014;53(4):327–346. [PubMed: 24515100]
88. Mahmood I Prediction of drug clearance in children from adults: a comparison of several allometric methods. *Brit J Clin Pharmacol*. 2006;61(5):545–557.
89. Krueger DA, Wilfong AA, Holland-Bouley K, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. *Ann Neurol*. 2013;74(5):679–87. [PubMed: 23798472]
90. French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388(10056):2153–63. [PubMed: 27613521]
91. Momper JD, Wagner JA. Therapeutic drug monitoring as a component of personalized medicine: applications in pediatric drug development. *Clin Pharmacol Ther*. 2014;95(2):138–40. [PubMed: 24253660]
92. Krekels EHJ, van Hasselt JGC, van den Anker JN, Allegaert K, Tibboel D, Knibbe CAJ. Evidence-based drug treatment for special patient populations through model-based approaches. *Eur J Pharm Sci*. 2017. [Epub ahead of print]
93. De Cock RF, Allegaert K, Sherwin CM, et al. A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm Res*. 2014;31(3):754–67. [PubMed: 24065592]
94. Burris JF, Tortorici MA, Mandic M, Neely M, Reed MD. Dosage Adjustments Related to Young or Old Age and Organ Impairment. *J Clin Pharmacol*. 2016;56(12):1461–73. [PubMed: 27539787]
95. Sherwin CM, Sagcal-Gironella AC, Fukuda T, Brunner HI, Vinks AA. Development of population PK model with enterohepatic circulation for mycophenolic acid in patients with childhood-onset systemic lupus erythematosus. *Br J Clin Pharmacol*. 2012;73(5):727–40. [PubMed: 22053944]
96. InsightRx. Available at: www.insight-rx.com/index.html#About. Accessed 22 August 2017.
97. Mould DR, Upton RN, Wojciechowski J. Dashboard systems: implementing pharmacometrics from bench to bedside. *AAPS J*. 2014;16(5):925–37. [PubMed: 24947898]
98. Van Driest SL, Shi Y, Bowton EA, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. *Clin Pharmacol Ther*. 2014;95(4):423–31. [PubMed: 24253661]
99. Hoffman JM, Haidar CE, Wilkinson MR, et al. PG4KDS: a model for the clinical implementation of pre-emptive pharmacogenetics. *Am J Med Genet C Semin Med Genet*. 2014;166C(1):45–55. [PubMed: 24619595]
100. O'Donnell PH, Danahey K, Ratain MJ. The Outlier in All of Us: Why Implementing Pharmacogenomics Could Matter for Everyone. *Clin Pharmacol Ther*. 2016;99(4):401–4. [PubMed: 26756170]
101. Van Driest SL, McGregor TL. Pharmacogenetics in clinical pediatrics: challenges and strategies. *Per Med*. 2013;10(7).
102. Hedman M, Antikainen M, Holmberg C, et al. Pharmacokinetics and response to pravastatin in paediatric patients with familial hypercholesterolaemia and in paediatric cardiac transplant

recipients in relation to polymorphisms of the SLCO1B1 and ABCB1 genes. *Br J Clin Pharmacol.* 2006;61(6):706–15. [PubMed: 16722833]

103. Roden DM, Pulley JM, Basford MA, et al. Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin Pharmacol Ther.* 2008;84(3):362–9. [PubMed: 18500243]
104. Chow SC. Adaptive clinical trial design. *Annu Rev Med.* 2014;65:405–15. [PubMed: 24422576]
105. US Food and Drug Administration. Guidance for Industry. Adaptive Design Clinical Trials for Drugs and Biologics. Available at: <https://www.fda.gov/downloads/Drugs/Guidances/UCM201790.pdf>. Accessed 20 July 2017.
106. US Food and Drug Administration. Guidance for Industry and FDA Staff. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. Available at: <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf>. Accessed 20 July 2017.
107. Baudouin V, Alberti C, Lapeyraque AL, et al. Mycophenolate mofetil for steroid-dependent nephrotic syndrome: a phase II Bayesian trial. *Pediatr Nephrol.* 2012;27(3):389–96. [PubMed: 21947272]
108. Thompson CG, Gay CL, Kashuba ADM. HIV Persistence in Gut-Associated Lymphoid Tissues: Pharmacological Challenges and Opportunities. *AIDS Res Hum Retroviruses.* 2017;33(6):513–23. [PubMed: 28398774]
109. Cottrell ML, Prince HM, Allmon A, et al. Cervicovaginal and Rectal Fluid as a Surrogate Marker of Antiretroviral Tissue Concentration: Implications for Clinical Trial Design. *J Acquir Immune Defic Syndr.* 2016;72(5):498–506. [PubMed: 26999532]
110. Franzen L, Windbergs M. Applications of Raman spectroscopy in skin research--From skin physiology and diagnosis up to risk assessment and dermal drug delivery. *Adv Drug Deliv Rev.* 2015;89:91–104. [PubMed: 25868454]
111. Mateus R, Abdalghafor H, Oliveira G, Hadgraft J, Lane ME. A new paradigm in dermatopharmacokinetics - Confocal Raman spectroscopy. *Int J Pharm.* 2013;444(1–2):106–8. [PubMed: 23357254]
112. Yang J, Cui Y, Zong S, Zhang R, Song C, Wang Z. Tracking multiplex drugs and their dynamics in living cells using the label-free surface-enhanced Raman scattering technique. *Mol Pharm.* 2012;9(4):842–9. [PubMed: 22352346]
113. Rosen EP, Thompson CG, Bokhart MT, et al. Analysis of Antiretrovirals in Single Hair Strands for Evaluation of Drug Adherence with Infrared-Matrix-Assisted Laser Desorption Electrospray Ionization Mass Spectrometry Imaging. *Anal Chem.* 2016;88(2):1336–44. [PubMed: 26688545]
114. Berchtold C, Bosilkovska M, Daali Y, Walder B, Zenobi R. Real-time monitoring of exhaled drugs by mass spectrometry. *Mass Spectrom Rev.* 2014;33(5):394–413. [PubMed: 24272872]
115. Lu Y, Niu W, Zou X, et al. Glass bottle sampling solid phase microextraction gas chromatography mass spectrometry for breath analysis of drug metabolites. *J Chromatogr A.* 2017;1496:20–4. [PubMed: 28365077]
116. Gorodischer R, Burtin P, Hwang P, Levine M, Koren G. Saliva versus blood sampling for therapeutic drug monitoring in children: patient and parental preferences and an economic analysis. *Ther Drug Monit.* 1994;16(5):437–43. [PubMed: 7846740]
117. Aman MG, Vinks AA, Remmerie B, et al. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. *Clin Ther.* 2007;29(7):1476–86. [PubMed: 17825699]
118. Marchei E, Farre M, Pellegrini M, et al. Pharmacokinetics of methylphenidate in oral fluid and sweat of a pediatric subject. *Forensic Sci Int.* 2010;196(1–3):59–63. [PubMed: 20096514]
119. Rauh M, Stachel D, Kuhlen M, Groschl M, Holter W, Rascher W. Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children: validation of liquid chromatography tandem mass spectrometry method. *Clin Pharmacokinet.* 2006;45(3):305–16. [PubMed: 16509762]
120. Gordi T, Hai TN, Hoai NM, Thyberg M, Ashton M. Use of saliva and capillary blood samples as substitutes for venous blood sampling in pharmacokinetic investigations of artemisinin. *Eur J Clin Pharmacol.* 2000;56(8):561–6. [PubMed: 11151745]

121. Sowunmi A, Gbotosho GO, Happi CT, et al. Therapeutic efficacy of artesunate-amodiaquine combinations and the plasma and saliva concentrations of desethylamodiaquine in children with acute uncomplicated *Plasmodium falciparum* malaria. *Am J Ther*. 2013;20(1):48–56. [PubMed: 21192244]
122. US Food and Drug Administration. White Paper: FDA and Accelerating the Development of the New Pharmaceutical Therapies. Available at: <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm439082.htm#7>. Accessed 25 Oct 2017.
123. Cote TR, Xu K, Pariser AR. Accelerating orphan drug development. *Nat Rev Drug Discov*. 2010;9(12):901–902. [PubMed: 21119719]
124. Sharma A, Jacob A, Tandon M, Kumar D. Orphan drug: Development trends and strategies. *J Pharm Bioallied Sci*. 2010;2(4):290–299. [PubMed: 21180460]
125. Tambuyzer E Rare diseases, orphan drugs and their regulation: questions and misconceptions. *Nat Rev Drug Discov*. 2010;9(12):921–929. [PubMed: 21060315]
126. Bai JP, Barrett JS, Burckart GJ, Meibohm B, Sachs HC, Yao L. Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants. *AAPS J*. 2013;15(2):447–454. [PubMed: 23334978]
127. Yang Q, Wang H, Maas JD, et al. Paper spray ionization devices for direct, biomedical analysis using mass spectrometry. *Int J Mass Spectrom*. 2012;312:201–7. [PubMed: 22350566]
128. Dullet NW, Geraghty EM, Kaufman T, et al. Impact of a University-Based Outpatient Telemedicine Program on Time Savings, Travel Costs, and Environmental Pollutants. *Value Health*. 2017;20(4):542–6. [PubMed: 28407995]
129. TytoCare. Available at: <http://www.tytocare.com/>. Accessed 19 September 2017.
130. Goldman JL, Davis HM, Zhou H, Kearns GL. Association of Infliximab Clearance and Resting Energy Expenditure in Children. *Clin Pharmacol ther*. 2011;89:S36–S37. Abstract OII-A-3.

Table 1:

Overview of Current Strategies to Optimize Pediatric Clinical Pharmacology Research

Outcome	Innovative Approaches	
	Early Phase	Late Phase
Clinical Trial Optimization		
<i>Optimized Data Collection and Use</i>	Bioanalytical Optimization	Pragmatic Trial Designs Electronic Health Records
<i>Reducing Participant Risk</i>	Opportunistic Designs Sparse/Scavenged Sampling Microdosing	Efficacy Extrapolation
<i>Increased Efficiency and Reduced Costs</i>	Master Protocols	Master Protocols
<i>Increased Enrollment and Collaboration</i>	Research Networks	Research Networks
Simulation and Modeling		
<i>Optimized Study Design</i>	Clinical Trial Simulations	Clinical Trial Simulations
<i>Predict Effects of Organ Dysfunction</i> <i>Predict Enzyme/Transporter Ontogeny</i>	PBPK	PBPK
<i>Individualized Dosing</i>	Population PK Bayesian Analyses	Concentration-Guided Trials Population PK Bayesian Analyses