SPECIAL REPORT

Recommendations to Enhance Pediatric Cardiovascular Drug Development: Report of a Multi-Stakeholder Think Tank

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Children have historically been underrepresented or, indeed, omitted entirely, in drug trials, leading to a relative dearth of evidence in support of appropriate drug treatments for many pediatric diseases.[1,2] Recent legislative initiatives in the United States and the European Union (EU) have created a system of mandates and incentives to encourage further pediatric drug development (Table 1[3–6]). Overall, these initiatives have been highly successful at shifting the landscape in drug development by making pediatric patients a priority; >600 pediatric labeling changes have been implemented in the United States over the past 2 decades, with a similar pace in the EU, since implementation of the Paediatric Regulation in 2007.[5,7,8] Nevertheless, many pediatric diseases remain relatively neglected, with many drugs still used "off-label" because studies have yet to be conducted, or because studies that have been conducted have failed to demonstrate efficacy.[9,10]

In children with cardiovascular diseases, successful drug development under the aforementioned legislative initiatives has been limited. Successful trials conducted under the regulatory incentive provisions have been primarily related to pediatric hypertension[11–20] and familial hypercholesterolemia.[21–28] Although these trials led to important changes for these particular diseases, they faced challenges related to patient recruitment, disease heterogeneity, dosing, endpoint selection, and, in general, an overall lack of experience in conducting randomized clinical trials in children. Similar challenges have limited drug development in pediatric patients with congenital or acquired heart disease, heart failure, arterial or venous thrombosis, and pulmonary hypertension. In response to these issues, a panel of experts from academia, the US National Institutes of Health (NIH), the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), industry sponsors, and advocacy groups convened for a think tank on pediatric cardiovascular drug development. The meeting was held from September 8 to 9, 2016, in Washington, DC, with the primary objective of providing recommendations to enhance pediatric cardiovascular drug development by improving trial planning, design, and execution. Herein we summarize discussions from this meeting and provide consensus recommendations.

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Table 1. Pediatric Drug-Development Legislation

Legislation	Agency	Year Enacted	Description
Pediatric Labeling Rule[3]	FDA	1994	Encouraged manufacturers to extrapolate efficacy data from adult studies with existing pharmacokinetic/pharmacodynamic data and provide safety data from children to submit for pediatric labeling.
FDA Modernization Act (FDAMA) or Pediatric Exclusivity[3]	FDA	1997	First incentive program for pediatric drug studies. Offered 6 mo additional patent protection on the moiety for on-patent agents studied as specified by the FDA.
Pediatric Rule*[3]	FDA	1998	First requirement for manufacturers to conduct pediatric studies for products being studied in adults for new indications, active ingredient and dosing regimens, or new dosage forms or route of administration.
Best Pharmaceuticals for Children Act (BPCA)[3]	FDA	2002	Extended incentives from the Pediatric Exclusivity Provision and provided financial incentives for manufacturers who voluntarily accepted and complied with FDA Written Requests to conduct pediatric studies for both on- and off-patent drugs.
Pediatric Research Equity Act (PREA)[3]	FDA	2003	Expanded upon the *Pediatric Rule, requiring manufacturers to assess safety and effectiveness of new drugs and biologics in pediatric patients. This means a supplement for a new active ingredient, any new dosage form, dosing regimen, route of administration, or indication would require pediatric studies (with some allowances for deferral or waiver).
FDA Safety and Innovation Act (FDASIA)[3]	FDA	2012	Reauthorized the BPCA and PREA as permanent and without sunset.
European Parliament Regulation No. 1901/2006 on Medicinal Products of Paediatric Use 2006[4]	EMA	2006	Required manufacturers to complete pediatric studies for any new drug following a Pediatric Investigation Plan (PIP). Upon PIP completion and approved labeling, a reward of a 6-mo extension of the Supplementary Protection Certificate (SPC) could be received. For off-patent drugs, manufactures can voluntarily develop a pediatric indication and formulation under a Pediatric Use Marketing Authorization (PUMA) and receive 10 years of marketing protection.

*The FDA's Pediatric Rule was struck down by a federal district court in 2002 with the judge holding that the agency had overstepped its authority. FDA indicates Food and Drug Administration; EMA, European Medicines Agency.

Approaches to Improving Clinical Trials in Children With Cardiovascular Disease

A number of recent pediatric cardiovascular drug trials conducted within a regulatory context have been "negative" studies, meaning that the trial did not demonstrate an effect of the treatment. Whereas negative studies may be important, informative, and clinically relevant, concern exists that some pediatric cardiovascular trials have been negative because of problems in trial design, dose selection, and/or study approach rather than absence of a treatment effect.

To better understand the potential issues, cardiovascular trials completed under an FDA-issued Written Request (WR) for potential pediatric exclusivity were reviewed during the think tank and are summarized below by therapeutic area. The goal of the think tank was to develop consensus recommendations regarding successful approaches and future strategies to avoid identified trial pitfalls. Discussions centered on trials conducted under United States regulatory guidance because of the earlier passage of pediatric legislative initiatives, but we believe our recommendations are broadly applicable to all pediatric cardiovascular trials. Summary recommendations specific to individual therapeutic areas are provided in Table 2,[29–31] with subsequent sections focusing on more generalized recommendations. Although our discussions focused on pediatric cardiovascular drug trial development, many of the recommendations pertain to other pediatric subspecialties, where similar challenges exist.

Antihypertensive Agents

Hypertension has been a major focus in pediatric cardiovascular drug development. In the United States, 48 pediatric cardiovascular drug trials have been completed under a WR from the FDA, and 17 (35%) were for antihypertensive agents. Of the 17 different pediatric antihypertensive agents studied under a WR, 8 trials of these agents were "positive" and led to a new labeled indication for children or adolescents.[11,12,14–19,32] An additional 6 trials failed to demonstrate efficacy but resulted in the addition of safety or dosing data to the FDA label.[7] Because of the unexpectedly low success rate of these trials, analyses were conducted to determine if there might be factors in the study approach contributing to the negative trial outcomes.[33] One of the major determinants for a negative trial was dose selection; negative trials tended to have smaller

Table 2. Recommendations for Drug Development in Pediatric Cardiovascular Specialty Therapeutic Areas

Antihypertensive agents
1. Trials should consider using a placebo arm in the short-term, which has been proven to be safe in pediatric hypertension.[29] An alternative is a randomized withdrawal study, with treated patients randomized to placebo as continued treatment. 2. Trials should evaluate response on both systolic and diastolic blood pressure. 3. Future trials are needed to evaluate the differential effects of antihypertensive agents in patients of different racial and ethnic backgrounds. 4. Larger-scale trials are needed to evaluate comparative effectiveness of antihypertensive agents, as well as long-term safety and effects on growth/development.
Dyslipidemia agents
1. Trials are needed to evaluate dosing, safety, and efficacy of dyslipidemia drugs for indications other than familial hypercholesterolemia, including combined dyslipidemia of obesity and in high-risk patients (eg, type I diabetes mellitus, Kawasaki disease with aneurysms, and orthotopic heart transplantation). 2. Trials are needed to evaluate non-statin agents in children with dyslipidemia. 3. There is a need to assess the impact of lipid lowering on surrogate outcomes associated with longer-term morbidity. For example, carotid intima media thickness is an outcome measure that could be included in future trials to evaluate the impact of lipid lowering on atherosclerotic changes.
Pulmonary hypertension agents
1. Trials of targeted pulmonary hypertension agents are needed in children and adolescents. Future trials should consider the differential effects of treatment in children with differing underlying etiologies for their pulmonary hypertension. 2. Consider using time to clinical worsening or actigraphy as a primary endpoint. This endpoint has proven successful in adult pulmonary hypertension trials.[30] 3. Research is needed in children with pulmonary hypertension to evaluate the utility of promising potential trial endpoints, including: a. Parent/patient-reported trial endpoints (eg, endpoints that rely upon parental survey data). b. Novel technologies to quantify activity in patients (eg, physical activity trackers or accelerometers). c. Cardiac magnetic resonance imaging as a predictor of clinical wosening.[31]
Heart failure agents
1. Recognize the growing population of pediatric heart failure patients and include heart failure therapeutics as a priority in pediatric drug development. 2. Issue WRs in the United States before approval of adult indications, when appropriate, to expedite pediatric heart failure studies. 3. Increase focus on: a. Developing new clinically meaningful endpoints with sufficient discriminatory power. b. Engage advocacy groups for endpoint-validation studies. c. Developing targeted therapies for cardiomyopathy related to genetic disease. d. Developing therapies to support the systemic right ventricle in patients with congenital heart disease. 4. Gather pharmacokinetic/pharmacodynamic data specifically in pediatric patients with univentricular hearts, abnormal hemodynamics related to congenital heart disease, and arrhythmias in heart failure. These are all unique patient populations for which therapies are not currently evidence-based and where unique physiology may impact drug dosing and response. a. Such pediatric-specific studies could be appropriate to approach using the FDA Written Request or EMA Paediatric Use Marketing Authorization processes.
Anticoagulant agents
1. Trials should focus on high-risk childhood patient populations, potentially including single ventricle patients across the various stages of palliation, patients with Kawasaki disease and coronary aneurysms, children and adolescents with ventricular assist devices, children and adolescents with heart failure, younger children who have undergone cardiac catheterization procedures, and children who require indwelling catheters. 2. In addition to exploring drug efficacy for thromboprophylaxis, there is a need to develop agents for treatment of venous and arterial thrombosis in children and adolescents with congenital or acquired heart disease. 3. Head-to-head safety and efficacy studies are needed to compare newer anticoagulation agents with existing agents such as heparin, low molecular weight heparin, aspirin, and warfarin. 4. Attempt to define additional endpoints beyond incidence of thrombosis and bleeding that impact clinical care and patient quality of life. For example, studies are needed to validate biomarkers as surrogate endpoints; these may prove especially useful for head-to-head comparison studies.

differences in doses with potentially overlapping exposures between adjacent doses in the trial and/or lacked a placebo or very low dose comparator group. Negative trials also tended to rely upon tablet dosing, whereas positive trials used pediatric formulations, thereby allowing more precise weight-based dosing. In negative trials, blood pressure readings

tended to be obtained using automated cuffs instead of auscultation, and a reduction in systolic blood pressure was often used instead of diastolic blood pressure as the primary outcome. Finally, negative trials also tended to include more overweight patients, while positive trials had more patients with renal disease.

Antihypertensive trial designs were also evaluated. Because of early concerns regarding the use of placebo controls in children with hypertension, dose-response studies without a placebo group and randomized withdrawal designs were permitted in the WRs. Several of the early hypertension dose-response trials were "negative," meaning that they failed to demonstrate a predictable dose-versus-effect relationship, which is an identified risk when there is no placebo group and very low doses are discouraged. Subsequent analyses have demonstrated that short-term exposure to placebo is safe in pediatric hypertension trials.[29] The randomized withdrawal design is an alternative to the classic placebo-controlled design. In this trial design, all participants receive active drug and are then randomized to drug or placebo, usually with early dropout if blood pressure rises beyond a specified threshold. This design exposes patients to a brief placebo period during the withdrawal phase. This design is appealing to families, as placebo exposure is brief, and to study sponsors because it increases the likelihood of an interpretable result. However, the design is not ideal for antihypertensive agents with persistent effects.

Table 2 summarizes think tank recommendations for future antihypertensive trials. Many of the "lessons learned" from early experiences with pediatric hypertension trials, however, are not specific to hypertension trials. These recommendations have been incorporated into a broader subset of recommendations pertaining to all trials in children with cardiovascular disease (Table 3[34–36]).

Dyslipidemia Agents

Dyslipidemia agents, like antihypertensive agents, have been an area of focus in pediatric drug development. Of the 48 pediatric cardiovascular drug trials completed to date under the auspices of an FDA-issued WR, 8 trials (17%) were for a cholesterol-lowering indication. In each trial, the agent was specifically studied in familial hypercholesterolemia, using an established surrogate outcome (changes in lipid profiles). Impressively, all 8 studies led to efficacy-related labeling changes.[21–28] The use of a specific patient population with markedly abnormal lipid profiles has been identified as a critical feature in the success of these trials.

Whereas studies in familial hypercholesterolemia have been informative, other areas of dyslipidemia in children remain understudied, and recommendations focus on a need for further studies evaluating dyslipidemia in other high-risk patient populations (Table 2).

Pulmonary Hypertension Agents

Although pulmonary hypertension is currently listed as a "priority area of therapeutic need" by the FDA,[37] only one targeted pulmonary hypertension agent has been evaluated under the auspices of a WR. The STARTS I trial (Sildenafil in Treatment-Naïve Children, Aged 1 to 17 Years, With Pulmonary Arterial Hypertension, NCT00159913) evaluated safety and efficacy of low-, medium-, or high-dose sildenafil compared with placebo at 16 weeks after initiation of treatment, while the STARTS II safety extension trial evaluated safety of the three dosing regimens at 3 years of follow-up.[38,39] Interpretation of these trials has been controversial, and the FDA and EMA arrived at different assessments of the data presented for these trials.[40] Based on the data submitted and because of concerns with the endpoint utilized (change from baseline in peak oxygen consumption) and possible risk, the FDA did not approve sildenafil for use in pediatric pulmonary hypertension and recommended against its use, citing a lack of demonstrated efficacy and concerns regarding increased mortality with higher-dose regimens. In Europe, sildenafil was approved for treatment of pulmonary arterial hypertension in children, with a caution against using a high-dose regimen.

A major struggle in the study of drugs for the treatment of pulmonary hypertension is determining appropriate endpoints. Children with worsening pulmonary hypertension typically progress to heart failure symptoms such as exercise intolerance, but the 6-minute walk test used in adults to evaluate exercise intolerance is not validated for study in pediatric pulmonary hypertension and cannot be used in infants, young children, and those with developmental delays or certain disabilities. Cardiac catheterization performed solely for research purposes has been deemed by the FDA as too high-risk for the pediatric population, and no clear surrogate markers have been identified for pulmonary hypertension. In addition, recruiting for a study with a placebo arm in this high-risk population is challenging, if not impossible, except for add-on studies. Recently, bosentan was approved by the FDA in pediatric patients aged 3 years and older with idiopathic or congenital pulmonary arterial hypertension. However, pediatric studies are vital, and recommendations focusing on the need to develop and validate trial endpoints that are more directly applicable and meaningful to the pediatric patient population are needed (Table 2).

Heart Failure Agents

Whereas some extrapolation of adult heart failure therapies to children with acute and chronic heart failure may be

Table 3. Recommendations for Improving Pediatric Cardiovascular Drug Trials

Endpoint S+election
1. Intermediate endpoints, when used as a primary trial outcome, should predict an important clinical benefit of the drug (eg, an effect on morbidity or mortality). 2. When feasible, trials should consider evaluating multiple intermediate endpoints to confirm a true treatment response. a. The global rank endpoint assesses several intermediate outcomes that are then ranked or weighted according to clinical impact on the patient. This approach may be useful in certain pediatric cardiovascular trials as a means of improving study power while still prioritizing endpoints that are recognized as most severe.[35] 3. Pediatric quality-of-life (QOL) assessment tools, such as the Pediatric Quality of Life Inventory (PedsQL) and the Pediatric Cardiac Quality of Life Inventory (PCQLI) have been validated in children with heart disease,[36] and they may be useful as endpoints for certain trials. Parents have advocated for improvement in QOL as one of the most meaningful outcomes of an intervention in pediatric trials. 4. There is a need for further study and validation of trial endpoints that directly measure how a child functions, such as actigraphy. 5. The FDA process for "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" allows for drug approval based on a credible surrogate endpoint that is reasonably likely to predict a clinical benefit.[34] This mechanism has been underutilized in pediatric studies.
Dose selection
1. Use available pharmacokinetic (PK)/pharmacodynamic (PD) data from adult studies to scientifically inform dose selection for pediatric cohorts (ie, via application of modeling and simulation), and when possible, employ a dosing strategy based upon known exposure-response relationships (ie, a PD targeted approach). The range of doses used should consider anticipated pediatric exposures relative to what is known in adults and, in particular, those related to potential safety concerns. 2. Use established principles/methods in pediatric clinical pharmacology such as PK/PD modeling and simulation, including population PK modeling and physiologically based PK modeling when appropriate, to best-inform dose selection when factors that have the potential to alter the dose-response relationship (such as renal and/or hepatic compromise) are present. 3. Obtain pediatric-specific PK/PD data in infants and children with both active and controlled disease states whenever possible. Limit blood draw frequency and volume whenever possible. 4. Extrapolate from adult data when appropriate. Very few drug-metabolizing enzymes are controlled by growth and sex hormones, and extrapolating PK/PD data from adult studies for post-pubertal adolescents can be informative. Furthermore, inclusion of adolescents in adult trials is often appropriate. 5. In younger children, pediatric use may also be based on adequate and well-controlled studies in adults, provided that the course of the disease and the drug effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. 6. In younger children, use pediatric formulations and weight-based dosing to enable precise dosing and prevent overlap within dose ranges. Palatable liquid formulations allow for precise weight-based dosing and thus, greater ability to evaluate the dose-concentration-effect relationship. In contrast, the use of fixed dose, solid oral dosage forms have the potential to create systemic drug exposures in a pediatric patient that may not effectively mirror those in adult studies, where reliable and desirable exposure-response relationships for a given drug have been shown to exist. 7. When feasible, reassess PK/PD in phase 3 studies to link exposure to clinical outcomes. 8. When possible, avoid the development of prodrugs that rely upon metabolic conversion for activation.
Patient recruitment
1. When data are lacking, it is important to invest in preliminary studies to evaluate pediatric-specific dosing, disease natural history in children, and appropriate study endpoints. Preliminary studies can prevent inappropriate extrapolation of adult data and better inform statistical power of a trial. a. Data from existent registries and electronic health records may be useful to facilitate early discussions between sponsors and regulatory agencies and to perform simulation studies and modeling to predict the variability and appropriate powering of the study. b. During trial planning, the heterogeneity of the population being studied must be carefully considered; there may be analytic benefits to enrolling a more homogeneous trial cohort, but this also creates difficulties in recruiting patients and limits generalizability of the results. 2. Pediatric cardiovascular drug trials should strive to include subjects across age ranges, from neonates to adolescents, as variation in drug metabolism exists among these age groups. In certain cases, recruitment across each age group may not be feasible, and labeling should reflect the ages in which the drug was investigated. 3. Begin discussion of pediatric drug trials sooner in the global drug-development process with open communication between sponsors and regulatory agencies. Pushing pediatric testing partially into the premarketing space, when appropriate, could enable data to be gained earlier—before clinical equipoise, or the perception of it, is lost. 4. Perform adaptive design analyses at an appropriate point in the study to determine the variability found in the population already enrolled and the accuracy of pre-trial event rate estimates. This approach can allow the study size to be revised before the Data Safety Monitoring Board/Data Monitoring Committee has seen interim outcome data by treatment arm. Incorporating a plan for interim analysis and possible sample-size revision with a reasonable participant cap can foster appropriate budgeting. 5. Consider using focus groups to improve patient enrollment/engagement in pediatric studies. As an example, for medical devices, the FDA has recently formed the Patient Engagement Advisory Committee to help inform stakeholders of important patient-related issues such as patient preferences for study design, quality-of-life issues, unmet clinical needs, and patient-reported outcomes.

appropriate, there are often substantial differences between pediatric and adult heart failure. In adults, coronary artery disease and hypertension are common causes of heart failure, but in children, the most common cause of heart failure is structural heart disease.[41] Despite these differences and an unmet clinical need, only one pediatric clinical trial has been completed for an oral heart failure agent under the auspices of an FDA-issued WR. This was a multicenter, randomized, double-blind, placebo-controlled study that began in 2000 to examine the effects of carvedilol in children and adolescents with congestive heart failure (NCT00052026). Patients with heart failure caused by systemic ventricular systolic dysfunction of any etiology, including dilated cardiomyopathy and structural heart disease, were included, and the primary outcome was a composite endpoint characterizing their overall condition as worsened, improved, or unchanged. This trial demonstrated no difference in heart failure symptoms between carvedilol and placebo-treated patients.[42]

Many lessons were learned from review of the carvedilol trial in pediatric patients with heart failure, and aspects of the trial design are believed to have contributed to this being a negative trial. First, the patient population was heterogeneous, including patients with both dilated cardiomyopathy and structural heart disease-associated ventricular dysfunction (including patients with single ventricles). This was accepted at the trial's commencement because of the overall limited numbers of pediatric patients with heart failure, but the patient heterogeneity ultimately limited interpretability of the trial results, as the treatment response appeared to differ in the various patient subgroups. In addition, the doses used in the trial were extrapolated from adult data and were potentially too low in very young children. The same patient population could have been utilized before trial randomization to investigate potentially effective dosing based upon a pharmacodynamic (PD) endpoint (eg, improvement in ventricular function or changes in biomarkers such as n-terminal brain natriuretic peptide) to better inform dosing for the randomized study. Additionally, the composite endpoint that was used had not been validated in pediatric patients with heart failure. Finally, the study was underpowered because the rate of spontaneous improvement in placebo-treated patients was underestimated, possibly stemming from a lack of prior natural history data in pediatric patients with heart failure.[42] Investigating the pediatric-specific dosing, natural history, and appropriate endpoints before performing a larger, randomized trial may lead to more efficient and meaningful pediatric trials in the future.

As patients with congenital heart disease survive longer and our ability to support children through the acute clinical instability at heart failure presentation improves, the number of pediatric and adult patients with congenital heart failure will continue to climb. The "Priority List of Needs" developed by the FDA and National Institute of Child Health and Human Development (NICHD) is used to set the agenda for the NICHD's focus on Best Pharmaceuticals for Children Act (BPCA)-related activities.[37] Although not currently listed, pediatric heart failure is recognized as an issue that deserves increased attention. Recommendations for future heart failure trials focus on the overall need to recognize heart failure therapeutics as a priority in pediatric drug development, as well as areas of specific therapeutic need within the clinical spectrum of pediatric heart failure (Table 2).

Anticoagulant Agents: Planned and Anticipated Future Pediatric Cardiovascular Trials

Direct oral anticoagulants and newer, reversible antiplatelet agents that can be administered intravenously represent major breakthroughs in adult cardiovascular drug treatment. Given a significant need in pediatric cardiovascular conditions, several of these agents are currently being studied in pediatric cardiovascular trials (eg, rivaroxaban in pediatric Fontan patients [NCT02846532], apixaban versus vitamin K antagonists or low molecular weight heparin in pediatric patients with congenital or acquired heart disease [NCT02981472]), or will soon be studied. A special section of the meeting was devoted to discussion of potential trials for direct oral anticoagulants in children and adolescents with heart disease.

There are many challenges to studying these agents in children, including: (1) the heterogeneous nature of congenital and acquired heart disease that can result in both venous and arterial thrombosis; (2) the fact that coagulability often varies depending on the underlying clinical condition, thus probably necessitating separate studies for each individual condition; (3) a broad range of developmental considerations that can affect dosing and safety, such as potential adverse effects on bone development or increased fall risk in younger patients; (4) the absence of validated biomarkers and the fact that there is no clear established quantitative relationship between blood activity levels (eg, activated partial thromboplastin time levels or anti-factor levels) and clinical outcomes; and (5) challenges related to performing head-to-head studies with existing agents such as warfarin (which requires therapeutic drug monitoring) or low molecular weight heparin (which must be administered as a subcutaneous injection).

Recommendations for future anticoagulation pediatric trials focus on identifying sub-populations considered to be high-risk for venous or arterial thrombosis in which trials of prophylactic and therapeutic agents are needed, along with the need for head-to-head trials comparing newer anticoagulation agents with existing agents such as aspirin, heparin, low molecular weight heparin, and warfarin (Table 2).

Approaches to Improving Clinical Trials in Children With Cardiovascular Disease

Endpoint Selection

Challenges to choosing appropriate endpoints in children with heart disease include the relative rarity and heterogeneity of these diseases, frequent variability in outcomes across developmental stages, a lack of natural history data for some forms of childhood heart disease, and the fact that hard endpoints (eg, mortality or major morbidity) may take years or even decades to accrue in sufficient magnitude for an adequately powered clinical trial.

Because of these challenges, surrogate endpoints often need to be considered as trial endpoints. A surrogate endpoint is intended to predict a particular clinical benefit or harm of interest based on epidemiologic, therapeutic, pathophysiologic, or other scientific data.[43] Because many diseases in children take years or decades to manifest their long-term clinical consequences, surrogate endpoints are rarely validated. For example, while blood pressure and lipid levels are now considered validated surrogates of long-term outcomes in adults with cardiovascular disease, in the pediatric population, the outcome events of interest are typically decades away and the implications of such markers and the exact timing and cutoff values for treatment initiation are less clear. For diseases that are similar between adults and children, such as idiopathic pulmonary arterial hypertension, PD changes thought to be responsible for the benefits in adults are typically accepted as endpoints in pediatric trials. However, when diseases are dissimilar between adult and pediatric patients (eg, heart failure from structural heart disease in children versus from coronary artery disease in adults) or the relationship between PD effects and outcomes in adults are not fully understood, choosing appropriate PD or surrogate outcomes can be more difficult. In childhood heart disease it may be helpful to evaluate multiple intermediate or surrogate outcomes to determine treatment response, potentially with a higher rank or weight given to more clinically impactful endpoints (Table 3). Recognizing the challenges that exist in selecting appropriate intermediate or surrogate outcomes and the potential benefits if done properly, the FDA process for "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (under Subpart H of Code of Federal Regulations Title 21) allows for drug approval based on a credible intermediate or surrogate endpoint that is considered reasonably likely to predict a clinical benefit.[34] There was broad agreement from regulatory representatives that this mechanism is underutilized in pediatric disease and could be useful as a viable approach for drug approval in the pediatric population. Other recommendations focused on endpoint selection in children with heart disease included consideration of quality-of-life endpoints as well as novel functional endpoints such as actigraphy[44] (Table 3).

Dose Selection

Appropriate dose selection appears to have been a major problem in past pediatric drug trials and may have contributed to the high rate of negative trial results.[33] In the pediatric population, dosing is complicated by age-associated changes in the processes that govern drug disposition and action, the potential role of genomic variability associated with drug-metabolizing enzymes and/or receptors, and the impact of environmental exposures (eg, drug-drug and drug-xenobiotic interactions) on the concentration-effect relationship. Additionally, it is important to recognize that both acute and chronic manifestations of cardiac and extra-cardiac disease can compound and complicate expected age-associated differences in both drug pharmacokinetics (PKs) and PDs. Recommended approaches informing dose selection for drug-development studies in children with heart disease focus primarily on leveraging existing PK/PD data from adult studies and other patient populations, combined with established PK/PD modeling and simulation techniques (Table 3).

Patient Recruitment

Enrollment is often challenging in pediatric cardiovascular drug trials for a number of reasons: (1) the number of patients is limited; (2) there is significant disease heterogeneity; (3) obtaining informed consent/patient assent in such a vulnerable population is complicated; (4) parents may be hesitant to enroll their child in a placebo-controlled trial of a drug that is available (eg, adult indication); and (5) clinical equipoise is transient, with therapies often adopted early on by clinicians based upon preliminary evidence or extrapolation from adult studies. Although negative studies in the adult population may lead to protocol revision and a new study design, in the pediatric population there is often only one chance. While the information gleaned from a negative pediatric trial can be informative, the financial motive to conduct a revised pediatric study after the initial one failed is gone; provided the requested study was performed according to the agreed-upon terms in the WR, patent extension is granted even for a negative study.

Recruitment challenges were highlighted in the Pediatric Heart Network (PHN) study examining the effect of enalapril on left ventricular end-diastolic dimension in patients with significant left atrioventricular valve regurgitation after repair of atrioventricular septal defects (NCT00113698).[45] After 17 months, 345 patients were screened, 8 were found to be eligible, and only 5 were ultimately randomized. Upon review, several issues were identified that contributed to low patient

accrual and study termination. Although a feasibility study had been performed, the criteria used to assess disease severity were not the same as in the actual trial. In addition, there was a lack of natural history data for the disease being studied, and the assessment of degree of mitral regurgitation was, by necessity, based on data from adult patients with a different disease process because no method of assessment has been validated in children after repair of atrioventricular septal defect. This again highlighted the need for better longitudinal data on clinical course after repair of congenital heart defects, use of the actual trial criteria in the feasibility study, and pediatric-specific, validated endpoints. Finally, clinical equipoise was lost among clinicians, and there was an absence of adequate data to appropriately estimate study power.[45] In contrast, the more recent PHN Marfan trial comparing atenolol versus losartan on aortic root Z-score in children and young adults with Marfan syndrome successfully randomized 608 patients out of 1367 screened (NCT00429364).[46] The success of this trial from a patient-recruitment standpoint was attributed in part to the support of the advocacy group, The Marfan Foundation, and in part to applying lessons learned from the enalapril trial. The fact that all randomized patients received an active drug was undoubtedly advantageous.

Given all these challenges, recommendations for improving patient recruitment in pediatric drug trials were discussed, including appropriate timing of studies, processes for acquiring preliminary data, and the use of more flexible analytic approaches (Table 3).

Novel Trial Designs

Traditionally, randomized, double-blind, placebo-controlled trials have been recognized as the gold standard in trial design. However such trials can be challenging to effectively develop in the pediatric population for a number of reasons, including lengthy patient accrual time, hesitance to include a placebo arm in pediatric trials, cost, and challenges related to the small and diverse pediatric cardiovascular disease patient population, including costs and difficulties developing appropriate endpoints. To address these concerns, several novel trial designs were discussed as well as their advantages and disadvantages (Table 4). Think tank participants agreed that novel designs should be considered more often in pediatric cardiovascular drug development to overcome challenges associated with clinical trials in our unique patient population and to improve the potential for meaningful outcomes. Adaptive trial designs that incorporate prospectively planned

Table 4. Trial Designs

Design	Description	Advantages	Disadvantages
Factorial	Patients are given treatment A, treatment A and B, treatment B only, or placebo.	Enables investigators to compare individual treatment response and determine if treatments have additive effects.	Requires a large sample size.
Crossover	Patients receive drug A or drug B. This is followed by a washout period, and the subject is then given the alternative drug.	Enables use of a smaller sample size and permits within-subject analysis.	Potential for clinical deterioration during the washout phase could limit recruitment, increase the rate of study withdrawal, and affect assessment of drug efficacy.
N-of-1 Clinical Trial (Multiple Crossover)	An individual patient is randomized to receive different treatments (drug or placebo) with intervening washout periods.	Enables identification of a subset of responders with individualized therapeutic responses. Has a favorable cost profile.	Results from individuals may be patient-specific and difficult to generalize.
Randomized Discontinuation (Withdrawal)	All patients receive the study drug in the first phase. In the second phase, only responders are randomized to placebo or continuation of the same treatment.	Includes only those patients with the greatest chance of benefit and is optimal for studying long-term, non-curative therapies. Close monitoring allows for early detection of clinical worsening before severe consequences.	For select drugs and diseases, withdrawal can precipitate clinical deterioration (eg, because of rebound hemodynamic effects such as hypertension or pulmonary hypertension), which may be minimized by slow tapering.
Adaptive	Prospectively planned interim analyses are used to potentially modify an ongoing trial (eg, adjust sample size, change eligibility criteria, permit early stopping).	Potential to make trials more efficient, more likely to demonstrate an effect of the drug if one exists, or more informative (eg, by providing broader dose-response information).	May introduce bias into the study, power calculations must account for “multiple looks” at the data.

interim analyses to potentially modify an ongoing trial were also discussed. Adaptive designs can potentially improve trial efficiency, increase the likelihood that a trial demonstrates an effect of the drug if one exists, and increase the informative potential of a trial. However, caution must be exercised to avoid introducing bias into the study, and power estimates must be adjusted for multiple looks at the data.[47] Finally, it must be recognized that some pediatric cardiovascular diseases are so rare that they do not lend themselves to inclusion in traditional pediatric clinical trials. Potentially, for these rare diseases, a variation of the N-of-1 trial design (multiple crossover design, Table 4) could be considered as a mechanism for better understanding treatment response.

Leveraging Existing Resources

There are fewer pediatric cardiovascular trials than in other pediatric specialties, and many important diseases remain understudied.[48] It is therefore important to both increase the number of trials and conduct them with efficiency and at a reasonable cost. There are many potential resources that can be leveraged to facilitate improved efficiency and cost effectiveness of clinical trials, including clinical registries, trial networks, electronic health information, and advocacy groups (Table 5). Specific strategies are discussed below:

Using Existing Registries to Design, Plan, and Conduct Clinical Trials

The "trial-within-a registry" concept has been previously used for several large adult trials and represents a potentially transformative approach that leverages existing registry infrastructure to allow for a more efficient trial at a potentially significantly reduced cost.[49,50] Existing registry data can be coupled with advanced statistical modeling approaches (eg, Monte Carlo trial simulations and/or Bayesian modeling) to determine the optimal trial design, inclusion cohorts, trial endpoints, and analytic approaches. The PHN has used this approach recently to plan a large clinical trial, using data from

Table 5. Resources for Pediatric Cardiovascular Drug Trials

Resource	Advantages	Examples
Registries	Enable utilization of existing registry infrastructure and data and can allow optimization of trial design. Can identify patients for inclusion in studies, patient characteristics that can be used in patient selection, and patient cohorts of particular interest. Study endpoints and analytic endpoints can be identified at potentially decreased cost.	-Congenital Cardiac Anesthesia Society Database -Congenital Heart Surgeons Society Database (CHSS) -Congenital Cardiac Catheterizations Project on Outcomes (C3PO) -Extracorporeal Life Support Organization (ELSO) -European Association for Cardio-Thoracic Surgery (EACTS) Congenital Heart Surgery Database -Improving Pediatric and Adult Congenital Treatments (IMPACT) -Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID) -Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) -Multicenter Pediatric and Adult Congenital Electrophysiology Quality Registry (MAP-IT) -North American Kawasaki Disease Registry (NAKDR) -Pediatric Cardiomyopathy Registry (PCMR) -Pediatric Heart Transplant Study (PHTS) -Pediatric Cardiac Critical Care Consortium (PC4) -Pediatric Health Information System (PHIS) Database -Registry of the International Society for Heart and Lung Transplant -Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD) -Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension (TOPP) Registry -United Network for Organ Sharing (UNOS)
Networks	Promote collaboration among clinical sites, increased patient enrollment, centralization of infrastructure, and standardization of study protocols and data analysis.	-Alliance for Adult Research in Congenital Cardiology -Bench to Bassinet Program -Congenital Heart Disease Genetic Network Study (CHD GENES) -National Pediatric Cardiology Quality Improvement Collaborative (NPCQIC) -Pediatric Heart Network (PHN) -Pediatric Trials Network (PTN)
Advocacy Groups	Provide insight on study feasibility, barriers to enrollment, and impact of outcomes on patients and their families. Promote study enrollment, provide fundraising, and may even collect data into private registries.	-Children's Heart Foundation -Children's Heart Association -Kids With Heart -Mended Little Hearts -The Marfan Foundation -Parent Project Muscular Dystrophy -Pediatric Congenital Heart Association -Sisters by Heart -Sudden Arrhythmia Death Syndromes (SADS) Foundation

Table 6. Recommendations for Enhancing Pediatric Cardiovascular Drug-Development Processes*

1. Enhance access to and utilization of appropriate expertise to increase the amount of scientific advice and to ensure input from academic experts. Ideally this should occur before pediatric study decisions and preferably with sponsor participation during the discussion. Mechanisms for accomplishing these objectives include:
   a. Engagement of content experts as sponsor consultants early in the drug-development timeline.
   b. Increasing representation of pediatric cardiologists on the FDA and EMA advisory boards/committees. *Currently the FDA is seeking nominations for academicians to serve on the pediatric advisory committee. Think tank participants and other members of the pediatric cardiology community are encouraged to submit nominations via the FDA website: (https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm116527.htm).
   c. Prioritizing the training of the next generation of pediatric clinical trialists and clinical pharmacologists through increased exposure and education in clinical trial design and conduct, including regulatory and ethical aspects. Supporting seminars focused on clinical research skills and early career development for trainees and junior faculty with increased input from industry and regulatory agencies is recommended.
   d. Encourage less formal interactions among clinical experts, sponsors, advocacy groups, and regulatory agencies to identify unmet needs and design feasible development programs.
2. Improve the timeliness of feedback to sponsors from the FDA and EMA, especially for rejected study plans, or for plan amendments.
3. Increase communication and collaboration between the FDA, EMA, and industry sponsors via:
   a. Beginning discussion early in the drug-development timeline and increasing communication if/when issues arise to facilitate a joint timeframe for study modifications.
   b. Attempt to align FDA and EMA study requirements and, importantly, study endpoints.
4. If FDA and EMA requirements are not aligned, promote increased feedback from the agencies to sponsors.

*Recommendations do not reflect official opinions of the US National Institutes of Health, the US Food and Drug Administration (FDA), or the European Medicines Agency (EMA).

the Pediatric Cardiac Critical Care Consortium registry to estimate numbers of eligible patients at Network sites.

Recognizing the Invaluable Role Pediatric Trial Networks Can Serve in Facilitating Trial Initiation and Execution

The PHN represents the most obvious example within pediatric cardiology and was created and funded by the National Heart, Lung, and Blood Institute in 2001 to improve outcomes in patients with cardiovascular disease. The PHN facilitates collaboration among clinical sites, centralization of infrastructure, and standardization of study protocols. This network has completed more than 20 studies in children with cardiovascular disease, including 4 randomized controlled trials.[51] The PHN is interested in and has begun several industry collaborations that may lead to advances in treatment for children with heart disease (eg, NCT02741115, NCT02201342, and NCT03013751 examining udenafil dosing, safety, and efficacy in adolescent survivors of the Fontan procedure; NCT02981472 comparing safety and PKs of apixaban versus vitamin K antagonists or low molecular weight heparin in pediatric patients with congenital or acquired heart disease; and NCT02956590 assessing the effect of pitavastatin versus placebo in obese adolescents). In addition to the PHN, the NICHD-sponsored Pediatric Trials Network (PTN) was established under the framework of the BPCA to study formulation, dosing, safety, and efficacy of off-patent drugs in children. Finally, industry sponsors often invest heavily in developing a trial network for any given study. Unfortunately, the network is usually dissolved upon trial completion. With logistical and financial support, these networks could be appropriately developed with an integrated sustainability model to facilitate future trials.

Including Advocacy Groups in Drug-Development Discussions

Advocacy groups can be tremendously helpful in drug-development trials but remain a frequently overlooked resource. Advocacy groups can inform researchers on the feasibility of proposed studies, identify barriers to enrollment, and give input on the significance of proposed outcome measurements. Additionally, advocacy groups can significantly boost enrollment, provide financial support for research through fundraising, and even collect data into their own registries.

Drug-Development Processes in the United States and Europe

Regulatory agencies in the United States and EU share the same goal of promoting safe and informative medical products in the pediatric population. While many similarities exist, differences in study plan development, trial timelines, and study review between regulatory agencies can complicate the process of designing and completing studies in the small population of pediatric patients with cardiovascular disease. Below we highlight some of these process-related similarities

and differences, and recent progress in harmonizing approaches. Table 6 provides specific recommendations from non-governmental participants for further enhancing these drug-development processes for pediatric cardiovascular diseases.

Study Plans

In both the United States and EU, a system of mandates and incentives are used to stimulate pediatric drug research.[3,4] Mandates include requirements for pediatric study of new drugs being introduced to the market (with some exceptions, such as orphan drugs in the United States), and incentives exist in the form of patent and/or exclusivity extension if pediatric studies are appropriately conducted and consistent with the health authority agreements. The scope and approach to these pediatric drug studies must be outlined and agreed upon upfront. However, the processes differ. EMA requirements specify developing a single, comprehensive study plan known as a Paediatric Investigation Plan (PIP) that outlines studies for all new agents, new indications, or new dosage forms to be studied in children in order to obtain patent extension.[52] In contrast, the FDA requirements separate the processes for mandated versus incentivized studies.[53] A Pediatric Study Plan (PSP) for studying the drug in the pediatric population for the same indication must be developed for agents that fall under the Pediatric Research Equity Act (eg, for new agents, new indications, new dosage forms, etc,), while a WR under the Best Pharmaceuticals for Children Act outlines studies that are incentivized by extension of exclusivity and can include use of an agent in pediatric diseases that are different from the adult indication[s]).[54]

Timelines

Partly because of differences in study plan requirements, there are also differences in the timelines for development of pediatric studies. In the EU, PIPs are requested for new drugs or new indications when adult PK studies are completed. The early timeline is intended to ensure appropriate planning is underway (eg, development of pediatric formulations) to help align adult and pediatric study plans, and also to avoid loss of equipoise. If needed, deferrals are permitted to allow more adult data to be collected before pediatric study initiation.[52] In the United States, PSPs are required to be submitted before the start of pediatric clinical studies and no later than 60 days after the end of phase 2 meetings, if applicable.[54] The timing of WR proposals has evolved; previously, WRs were often not issued by the FDA until after the agent had already entered the market for an adult indication. More recently, the FDA is placing an emphasis on defining potential product use and applicability for issuing a WR in pediatrics before receipt of the initial adult application, though no formal legislative timeline exists. All told, the process-related differences in timelines for study development can make it challenging for sponsors to develop alignment between their EU and United States drug-development programs and sometimes result in significant delays before study initiation.

Expert Review

Within a highly subspecialized therapeutic realm such as pediatric cardiology, expert input into study design is essential. A consensus recommendation from the think tank was that sponsors should seek to involve subject matter experts early in the time-course of trial development. While both the EMA and FDA have mechanisms for expert input into the study designs in the form of the Pediatric Committee (PDCO) at the EMA and both the Pediatric Review Committee (PeRC) and review division involved with the class of products at the FDA, none of these committees has a specific pediatric cardiovascular focus; rather, they rely upon one or two member representatives or external subject matter experts to provide input across the broad spectrum of pediatric cardiovascular disorders.

Cost Incentives

In both the United States and EU, financial incentives are leveraged to encourage clinical trials in children. In the United States, industry sponsors may be rewarded with 6 months of patent extension if studies are conducted as outlined in a WR. In the EU, similar financial incentives can be attained via extension of the “Supplementary Protection Certificate.” These incentive programs have certainly bolstered pediatric drug development. In 2013, the McKinsey Center for Government analyzed the economic impact of pediatric exclusivity in the United States, reporting an additional $71 billion in incremental revenue for pharmaceutical companies since 1997.[55] While financial incentives to study drugs in the pediatric population exist, one concern is that they are skewed toward drugs with large profit margins. This was demonstrated by Li et al in an analysis of costs associated with studies conducted for pediatric exclusivity. In this 2007 report, the cost of conducting trials for pediatric exclusivity for a single agent ranged from $5278 408 to $49 641 232, and the net economic return (ie, estimated patent extension benefits minus trial costs) ranged from -$8946 033 to $242 403 765, depending on total sales.[56] Thus, a “blockbuster” drug has a significantly greater potential financial incentive, while drugs that are effective in adults but have significantly smaller profit margins may have trial costs that outweigh potential benefits. These drugs may be less likely to be tested in the pediatric population. It should be noted that

both the United States and the EU have programs to support development of "orphan" drugs that are developed to treat rare diseases or conditions.

Harmonizing Regulatory Processes

Whereas there are important process and timing-related differences between the United States and EU regulatory requirements, the regulatory agencies share the same goal of developing safe and effective medical products for children. Realizing the potential benefits and efficiency of a more harmonized approach, the EMA and FDA have been communicating via monthly teleconferences called the Pediatric Cluster.[57] In these meetings, which were first implemented in 2007, PIPs, PSPs, and WRs are discussed. The focus of discussion is typically on trial design, safety, and endpoints. The Pediatric Cluster has been quite effective in improving communication between the FDA and EMA, with joint discussions on more than 413 products.[57] The EMA and FDA recently published a review of the similarities and differences in the pediatric programs and the programs in place to address harmonization of pediatric studies.[58] Nonetheless, a need remains to align PIPs and PSP/WRs *earlier* in the planning process to prevent trial delays. Moreover, in the United States, the FDA and NIH both play important roles in pediatric drug development. Combining the experience and expertise from each institution to better inform the other could enable a much more streamlined approach and greater number of drug-development trials in pediatric cardiovascular disease. This concept holds promise, as think tank representatives from both the FDA and NIH expressed interest in increased collaboration.

Educating the Next Generation of Clinical Trialists

Pediatric trainees often receive relatively little exposure and/or training in clinical trial design and conduct, including regulatory and ethical aspects. There is a need to prioritize training of the next generation of pediatric clinical trialists and clinical pharmacologists in order to build upon progress made in pediatric drug development. Moreover, there is a need for greater exposure of all pediatric trainees to clinical trial methodologies. Lack of exposure likely has downstream effects, including reduced likelihood and/or willingness to recruit patients to clinical trials or to implement changes in practice based on well-designed trial results. Since 2009, the PHN has offered a biannual Clinical Research Skills Development Seminar for pediatric trainees and junior faculty. Responses to these seminars have been overwhelmingly positive, and think tank participants agreed that more are needed, ideally with increased input from industry and regulatory agencies.

Summary

Significant progress has been made in pediatric drug development, with over 600 pediatric labeling changes implemented in the United States over the past 2 decades. Many lessons have been learned throughout this endeavor to make pediatric patients a priority in drug development, yet a tremendous need remains for pediatric drug trials across pediatric subspecialties. The Pediatric Cardiovascular Drug Development Think Tank brought together leaders from academia, the NIH, FDA, EMA, industry, and advocacy groups to discuss ways to improve clinical trials as well as the broader process of drug development in pediatric patients with heart disease. Recommendations summarized in this white paper should be considered by regulatory agencies, industry sponsors, and other stakeholders as they plan pediatric drug-development programs and future pediatric drug trials. Ongoing discussion and processes are needed to ensure sustained collaboration between the various stakeholders.

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None.

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