

Pediatric cardiovascular safety: Challenges in drug and device development and clinical application

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Development of pediatric medications and devices is complicated by differences in pediatric physiology and pathophysiology (both compared with adults and within the pediatric age range), small patient populations, and practical and ethical challenges to designing clinical trials. This article summarizes the discussions that occurred at a Cardiac Safety Research Consortium–sponsored Think Tank convened on December 10, 2010, where members from academia, industry, and regulatory agencies discussed important issues regarding pediatric cardiovascular safety of medications and cardiovascular devices. Pediatric drug and device development may use adult data but often requires additional preclinical and clinical testing to characterize effects on cardiac function and development. Challenges in preclinical trials include identifying appropriate animal models, clinically relevant efficacy end points, and methods to monitor cardiovascular safety. Pediatric clinical trials have different ethical concerns from adult trials, including consideration of the subjects' families. Clinical trial design in pediatrics should assess risks and benefits as well as incorporate input from families. Postmarketing surveillance, mandated by federal law, plays an important role in both drug and device safety assessment and becomes crucial in the pediatric population because of the limitations of premarketing pediatric studies. Solutions for this wide array of issues will require collaboration between academia, industry, and government as well as creativity in pediatric study design. Formation of various epidemiologic tools including registries to describe outcomes of pediatric cardiac disease and its treatment as well as cardiac effects of noncardiovascular medications, should inform preclinical and clinical development and improve benefit-risk assessments for the patients. The discussions in this article summarize areas of emerging consensus and other areas in which consensus remains elusive and provide suggestions for additional research to further our knowledge and understanding of this topic. (Am Heart J 2012;164:481-92.)

“Children are not small adults” is perhaps the most popular maxim in pediatrics and for good reason: although some overlap exists between pediatric and adult cardio-

vascular safety concerns, both drugs and devices pose safety considerations far more complex than those in adult medicine. These added complexities constitute a unique range of barriers to the development of new therapeutics. Pediatric safety considerations must include not only physiologic effects but also developmental, behavioral, and psychosocial consequences for children. Despite the recent regulatory interest in pediatric cardiovascular safety, little is known about the pediatric safety of medications and devices currently in widespread use. The relatively small pediatric population limits some of the interest from industry, and there is low motivation to study off-patent drugs and devices that are currently used off-label in pediatrics. In the absence of data, much of the treatment administered to children is not evidence based, with treatment decisions often based on clinical experience, small observational studies, and extrapolation from adult data, rather than clinical trial evidence. Although most previous advances in pediatrics were obtained through this anecdotal or observational clinical use,

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changes in the regulatory environment and the rise of evidence-based medicine make this approach less acceptable in the current era. Furthermore, noncardiac medications have been found to have significant cardiovascular effects in children indicating that cardiovascular safety considerations should be integrated into development of all medications intended for pediatric use.

The Cardiac Safety Research Consortium (CSRC; www.cardiac-safety.org) was developed based on Food and Drug Administration (FDA) Critical Path Initiative principles to foster collaborations among academicians, industry participants, and regulators that address cardiac and vascular safety issues relating to the development of new medical products while remaining mindful of the need for medical innovation. Recognizing that cardiovascular safety is one of the primary barriers to development of medications and devices and that pediatric safety considerations are complex, a CSRC initiative was established to foster stakeholder discussion about pediatric cardiovascular safety. This article summarizes the discussions from the CSRC Pediatric Cardiovascular Safety meeting on December 10, 2010. These discussions provided a broad overview of pediatric cardiovascular safety issues in drug and device development as well as directions for future dialogue and research. Views expressed in this article do not formally represent the opinion or policy of any agency or organization.

Overview: pediatric therapeutics and cardiovascular safety

By definition, pediatric physiology is characterized by variability because the definition of “normal” changes as children age, including a predictable sequence of change in physiologic processes such as vital signs and somatic growth. Maturation of organ systems through infancy and childhood results in differences in pharmacokinetics and pharmacodynamics of medications, both in comparison to adults and within the pediatric age range. As such, dosing of drugs often is based on age, weight, and/or body surface area. Similarly, design of medical devices for pediatric use is affected by variation in body size, necessitating multiple device sizes to appropriately fit all patients. Once implanted, devices are impacted by somatic growth as well as by the high level and more varied types of physical activity in children.

Just as normal pediatric physiology varies from adult physiology, pediatric pathophysiology differs from adult pathophysiology. Pediatric cardiac pathophysiology comprises a wide range of diseases including congenital heart defects, acquired heart disease, congestive heart failure, systemic hypertension, pulmonary hypertension, and arrhythmias. The natural history of this broad range of uncommon pediatric cardiac diseases is

incompletely understood. Our understanding of these diseases is further obscured by the rapid pace of advances in treatment including surgical technique, nonsurgical interventions, and drug therapy, as well as a widespread practice variation within the field. The extensive variability of congenital heart defects further complicates research efforts and makes large research efforts difficult.

Both therapeutic and off-target effects of drugs carry more potential for negative impact in pediatric populations. Pediatric safety concerns encompass the entire lifespan of the human from the embryo to the geriatric population. Beginning with in utero exposure to maternal medications, critical processes of anatomical and physiologic development may be affected by the introduction of a drug or device. In addition to developmental abnormalities in structure or function, cardiac toxicities include direct myocardial cell toxicity, decreased myocardial function, induction of a proarrhythmic state, and increased risk for development of coronary artery disease. These toxicities must be considered not only concurrently with administration of the medication but also after discontinuation, as in the case of anthracycline-induced cardiomyopathy. Toxicities in children should therefore be monitored over decades. More subtle long-term effects such as increases in systolic blood pressure or heart rate caused by stimulant medications are included in cardiovascular safety concerns.

Logistically, conducting clinical trials in children with uncommon diseases is complicated by small patient populations, recruitment and enrollment difficulties, higher expenses, and ethical concerns surrounding consent and assent. Given the many challenges, the paucity of pediatric trial data is not surprising. However, many medications are used clinically in children without associated pediatric clinical trials or pediatric labeling. In fact, more than 78% of cardiovascular drugs used in hospitalized children in the United States are not labeled for pediatrics or for the indication for which they are used.¹ In the absence of dosing studies and appropriate pediatric labeling, clinical practitioners often use lower doses without clear evidence of their therapeutic efficacy or safety.

Similarly, many of the devices used in pediatric cardiac surgical procedures and interventions are used off-label. Few devices are developed primarily for pediatric use due to the complex design and additional considerations for pediatrics, which require significant industry investment. In addition to the relatively low financial recovery offered by small pediatric populations, ambiguous regulatory pathways and prolonged times for device approval further discourage pediatric device development. Even devices used for appropriate indications have often not been tested in children or sized properly for children. A study of interventional cardiology procedures at a single institution found that devices were used off-label in 63%

of patients and 50% of all interventional procedures.² Thus, the current and ongoing use of drugs and devices in the absence of appropriate clinical trial data represents a critical postmarket safety issue, whereas the challenges of generating such data constitute a major barrier to the development of safer therapies for pediatric applications.

Regulatory overview for drug and device development

The US government has recognized the need to support improved pediatric research by recently passing multiple pieces of legislation. The Best Pharmaceuticals for Children Act in 2002³ provided mechanisms for conducting pediatric studies of on-patent and off-patent medications in children and offered a financial incentive for the manufacturer upon completion of the pediatric studies requested by the FDA. The Pediatric Research Equity Act (PREA) in 2003⁴ required that pediatric studies be performed for any marketing applications (new drug approvals or supplements). For those drugs approved before the Act was signed, pediatric studies are required upon approval of a new dosage form, a new route of administration, or a new indication. With concurrence by FDA, PREA allows the required pediatric studies to be deferred or waived. These key laws were reauthorized in the FDA Amendments Act of 2007. The European Medicines Agency has also started to require drug studies in children and has begun to receive pediatric investigation plans for new molecular entities. Since the passage of these statutes, many cardiovascular drugs have been successfully studied, resulting in labeling for children, including several antihypertensive and lipid-lowering medications as well as antiarrhythmic, antithrombotic, and heart failure medications. However, many drugs have failed to achieve labeling for pediatric use. Importantly, once a drug fails to achieve this labeling status, interest in further study decreases significantly.

In recognition of the pressing need for pediatric device development and surveillance, the Pediatric Medical Device Safety and Improvement Act (PMDSIA) was passed in 2007.⁵ This Act created a mechanism by which the FDA tracks the number, types of devices, and time required for approval of devices for use in children or for treatment of diseases and conditions that occur in children. As an incentive for device development, the Act allows profit for devices developed for and labeled for use in children or a pediatric subgroup that are approved under a Humanitarian Device Exemption (HDE). An HDE approval requires submission of data demonstrating that the probable benefit of use of the device outweighs its risks as well as demonstration that no comparable devices are available on the market. Devices qualify for an HDE if they are designed to treat or diagnose diseases that affect 4,000 or fewer patients annually, which is true for many pediatric cardiac

conditions. The PMDSIA requires that adverse events occurring in all devices approved for pediatric use under the HDE must be reported to the FDA's Office of Pediatric Therapeutics for review by the FDA's Pediatric Advisory Committee. The PMDSIA also allows for extrapolation of effectiveness from adults to children and from one pediatric subpopulation to another when appropriate and for longer postapproval safety studies for pediatric devices. Finally, in an attempt to encourage innovative pediatric device research, the Act also established demonstration grants for nonprofit consortia to stimulate pediatric device development.

Preclinical development

Preclinical pediatric medication development: cardiac safety models and regulatory considerations

Preclinical studies for pediatric medications include cellular models, traditional developmental toxicity studies, and juvenile animal studies. Identifying representative animal models for preclinical studies of pediatric drugs is complicated by developmental maturation. At the cellular level, there are significant developmental changes in electrophysiology, contractility, receptor coupling, drug sensitivity, and cardiac toxicity, resulting in developmental changes in physiology. Appropriate preclinical models must therefore match the specific stage of human cardiac development under investigation. Some of these parameters are known to vary between animal species, but the extent and type of variation are often unknown. There are few functional, systematic, and comprehensive studies of cardiac development over time, making the identification of an appropriate species and age of a preclinical model difficult.

In addition to choosing an appropriate animal model, it is helpful to identify preclinical biomarkers with clinical relevance. Corrected QT interval (QTc) prolongation provides a useful model to understand the difficulties in establishing the clinical relevance of preclinical biomarkers. Drug-induced QTc prolongation is a common adverse effect of drugs used in pediatric populations. However, despite a large number of drugs reported to cause QT prolongation,⁶ only a handful of cases of torsades have been reported in children.^{7,8}

Animal studies suggest that there are developmental variations in the extent of QTc prolongation, phenotype of drug-induced arrhythmias, and susceptibility to arrhythmias.

Although QTc prolongation and the incidence of arrhythmias in canine models correspond reasonably well to clinical findings in human neonates, young canines do not correlate well to children because of species-related differences.^{9,10} Further study to resolve significant knowledge gaps about electrophysiologic and inotropic changes in early animal development is warranted to identify appropriate preclinical models and biomarkers.

The current regulatory preclinical model for studying pediatric drugs provides little direct information about drug effects on cardiac development. All systemically available drugs intended for human use must undergo reproductive toxicity testing, consisting of 3 types of studies: segment I (effects on adult fertility following exposure), segment II (identification of teratogenicity or embryotoxicity), and segment III (developmental effects of exposure during late gestation and lactation). Importantly, of the reproductive toxicity studies, only segment III studies provide any postnatal information. These postnatal data are further limited because the extent of direct exposure of the juvenile animal to the drug is unknown, since it is restricted to exposure through maternal milk and plasma levels of drug in juvenile animals are rarely measured. A further constraint of these segment III studies is that outcomes focus on the neurologic and reproductive systems, providing only indirect measures of cardiovascular development and function such as weight gain. A biomarker reflective of perturbations of cardiac development would be a useful tool to incorporate into developmental toxicity studies. However, there is limited understanding of normal cardiac development in both animal and humans, making it difficult to know if standard developmental toxicity studies are predictive of adverse cardiac developmental events in humans.

In contrast to traditional developmental toxicity studies, juvenile animal studies are specifically designed to study adverse effects of direct medication administration on postnatal growth and development. Juvenile animal studies are triggered on a case-by-case basis when information from previous animal studies and adult clinical trials is judged insufficient to support a pediatric clinical trial. In these studies, medications are administered directly to juvenile animals to assess developmental toxicities or adverse effects that cannot be safely or adequately studied in clinical trials; however, cardiovascular parameters are often not included. For some drugs, these studies have demonstrated increased drug sensitivity in younger age groups, resulting in age limits for labeling. In other cases, they have uncovered toxicities unique to developing animals. Without requiring that all drugs undergo juvenile animal studies, it would be helpful to determine which signals in nonclinical and clinical studies should trigger juvenile animal studies with a focus on cardiac effects and which cardiovascular surrogates would be most useful to measure (eg, electrocardiographic, imaging with echocardiography or magnetic resonance imaging, serum markers). Consideration should also be given to whether all juvenile animal studies should routinely monitor for cardiac toxicity; this would require the identification of biomarkers or surrogates that correlate with specific cardiac toxicities or abnormal cardiac development.

Additional questions and issues regarding preclinical drug development process in children included the following:

1. *Communication and collaboration across preclinical and clinical research*: there is a need for preclinical and clinical researchers to work together to determine appropriate end points and the best methods to identify and study these findings in each setting.
2. *Potential for extrapolation from adult studies*: another option for preclinical studies in pediatric drug safety is the extrapolation of adult toxicity data, such as thorough QT studies, which document QTc prolongation in response to therapeutic medication doses as well as overdoses. Recent developments in population pharmacokinetic methods have enabled concentration-QTc modeling and simulation, which could potentially use adult data to inform pediatric clinical trial design.
3. *The role of in vitro studies*: Could in vitro studies play a role in an integrated assessment to determine whether a juvenile animal study is warranted, rather than the current paradigm of performing such studies only if safety signals are detected in reproductive toxicity studies or adult clinical trials?

Preclinical pediatric device development: design and regulatory considerations

Although pediatric device development is similar in many ways to pediatric drug development, a different set of challenges affect the variety of devices used in the treatment of pediatric cardiovascular disease. As compared with drugs, many devices are developed by small firms, making significant investments in pediatric devices risky. In addition, the market size for cardiovascular devices for children is substantially smaller than for adults. The preclinical stage closely resembles the preclinical stage of drug development, however, in contrast to medications; the rate of device technology change is rapid. Redesign of existing adult devices for pediatric use occurs before testing these devices in younger animals. Once adapted for pediatric use, in vitro assessment is relatively simple as compared with medications.

Pediatric device design varies from adult device design in a variety of ways. Importantly, industry is often unaware of the need for specific devices required for certain small pediatric populations with cardiovascular conditions. Existing adult devices may need to undergo significant redesign due to size constraints and physiologic differences in children, such as higher heart rates or different metabolic responses to materials used in devices. In addition, materials used in adult devices may not be safe over long periods of time in children. Devices often must be manufactured in multiple sizes to fit the varying sizes of pediatric patients and to accommodate their normal growth. In the congenital heart disease

population, percutaneous device delivery can be affected by prior surgical or catheterization procedures that often alter the systemic venous or intracardiac anatomy as well as the peripheral access for device delivery. For example, typical pacemaker targets such as the atrial appendage may no longer exist after palliative or corrective procedures. A final consideration for some devices is how to childproof controls that are directly accessible to the child, as in some types of ventricular assist devices.

After implantation, devices used in pediatric patients are subject to different long-term demands from those in adults. More intense and varied types of physical activity in children can put excessive physical stresses on devices. Rapid growth in children may require placement of transvenous pacemaker or implantable cardiac defibrillator (ICD) leads with additional length to allow for normal growth, resulting in less tension. Because many devices are placed for lifelong indications, durability is a key component of device design. Most pacemakers and ICDs will need to be replaced at some point during the child's lifetime because of lead fracture or malfunction, or generator depletion, making easy removal and replacement a necessary design concern. Indeed, battery life is an important consideration because pacemakers maintaining higher heart rates in children drain current more rapidly and deplete batteries more quickly.

Devices used for pediatric arrhythmias pose unique challenges in programming functions. In the case of ICDs, current adult-based algorithms for treatment may incorrectly interpret sinus tachycardia as a ventricular tachycardia and result in inappropriate shocks in children. Estimates of the prevalence of inappropriate shocks in pediatric patients range from 15% to 30%.¹¹⁻¹³ Aside from the psychological implications of inappropriate shocks, a review of data in the Sudden Cardiac Death in Heart Failure database showed that both appropriate and inappropriate shocks were associated with a higher risk of sudden cardiac death in adults with heart failure.¹⁴

Two ways to make pediatric device programming safer and more effective were discussed:

1. *Improved algorithms*: pediatric arrhythmia databases could be created from cardiac implantable electronic devices. These data could then be used to develop ICD algorithms specific to pediatrics. The CSRC could be helpful in compiling this type of nonproprietary information for common use.
2. *Innovations in biomedical engineering and modeling*: biomedical engineers are developing patient-specific models for origins of arrhythmia and devices targeted to treat these arrhythmogenic locations. This type of modeling has the potential to represent truly personalized medicine, which could be especially helpful in the congenital heart disease popu-

lation, given its wide variability. For example, a patient with ventricular tachycardia could have a customized defibrillator with optimum lead placement, shock waveform, and energy delivery to terminate his arrhythmia.

Clinical trial considerations

Ethical considerations of pediatric clinical trials

Although the need for sound clinical trials of pediatric drugs and devices is compelling, the logistics and ethics of designing and conducting such trials are complicated. Because the notion of experimentation on children is unsettling, careful consideration of the balance between benefits and risks of study participation is critical during the design process, according to federal regulatory guidelines. Investigators must design trials such that participation in the study group does not carry additional risk as compared with not participating. To obtain true informed consent from parents, investigators and clinicians must be candid about the limits of current clinical knowledge and practice as well as risks and benefits of the study. Clinical equipoise is a necessary component of any clinical research study. In addition to informed parental consent, children should be asked for their assent to study participation as appropriate for their developmental level.

Other ethical issues concern the role of pediatric trials in the broader fields of medical research and clinical practice. Many drugs and devices developed and tested in adults never undergo study in pediatric populations because of the relative complexity and higher cost of pediatric research, particularly with respect to the potential income from small pediatric markets. However, in some pediatric conditions, possibly related to differences in pediatric disease manifestations or outcomes, pediatric trials could occur before or concurrently with adult studies. Finally, returning to the overarching theme of the conference, it could be argued that it is unethical to use new drugs and devices in pediatric patients without recording outcomes and disseminating clinical knowledge.

Challenges of clinical trial design

Given the dangers of both off-label usage of medications and devices and off-target cardiovascular safety risks in pediatric populations, strategies to facilitate pediatric research are critical. Conducting high-quality clinical trials in children is possible with careful planning, but both industry and academia lack extensive expertise in designing and conducting trials in pediatric populations. Although pediatric trials are often designed with assumptions heavily based on adult trials, these assumptions may not apply to the unique challenges in pediatrics. Furthermore, clinical trials should be designed to meet the needs of pediatric subjects and their families. Using

preclinical data and adult trials, physicians, nurses, and parents should work together to adapt clinical trial designs to children. Modern technology should be used to collect data from children in a more effective and less invasive manner; for example, improved modeling of pediatric pharmacokinetics may enable fewer blood draws, or improved assay techniques could use alternative methods to study drug levels, such as urine samples.

After the passage of the Best Pharmaceuticals for Children Act in 2002 and the PREA in 2003, approximately half of the cardiovascular medications studied have been approved for use in the pediatric population by the FDA. Examination of drugs that failed to achieve labeling status provides insights into the challenges of designing pediatric clinical trials.¹⁵ Many of these insights are important for development of devices as well as medications; additional specific considerations for device clinical trials will be discussed in the following section.

Clinical trials of medications

Enrollment. A major challenge for pediatric clinical trials is enrollment of a sufficient number of patients. Because of the rarity of many pediatric diseases, pediatric trials are often multicenter with relatively few patients enrolled per center. This process is inherently inefficient and expensive but necessary because enrolling an inadequate number of patients may make a study uninterpretable and nongeneralizable. Effective recruitment of subjects for pediatric clinical trials may require creative approaches to study design. Although families often understand the need for clinical research, they must be assured that a trial is safe and minimizes discomfort to the patient.

An additional challenge to pediatric enrollment is maintaining clinical equipoise, a state of uncertainty on the part of the investigator regarding the comparative therapeutic merits of each arm in a trial. Referring physicians and parents should also have equipoise. However, because of the widespread use of off-label medications, both physicians and parents often have a therapeutic bias, so there may be a reluctance to enroll children in a study with a placebo arm. For example, despite conflicting data on the efficacy of angiotensin-converting enzyme (ACE) inhibitors in adults and children with mitral regurgitation, ACE inhibitors are widely used in clinical practice for this purpose. In fact, a recent Pediatric Heart Network/National Heart Lung Blood Institute study on the use of ACE inhibitors in children with repaired atrioventricular septal defects and residual mitral regurgitation found that a third of children with mitral regurgitation were already receiving ACE inhibitor treatment, making enrollment in this study almost impossible and contributing to its early termination.

Trial end points. Defining and measuring a primary end point is critical to clinical trial design. Knowledge of the natural history of the disease with respect to a

surrogate end point, if chosen, and its relationship to a clinically meaningful end point is crucial. For example, studies of ataluren, a drug hoped to improve functionality of children with muscular dystrophy, used performance on a 6-minute walk test as a surrogate end point.¹⁶ Once an appropriate end point is defined, ensuring accurate measurement is important. Multicenter trials must standardize how and when end points are measured. This may require central or core laboratory interpretation of cardiovascular safety findings (eg, echocardiography). Some studies use composite end points, combining hard end points with soft components to address broader aspects of multifaceted diseases. These soft components are subject to ascertainment ambiguity and clinical variation among centers. For example, the composite end points used for a recent study of clopidogrel include death, shunt thrombosis, or intervention at <120 days for a condition of a thrombotic nature.¹⁷ In addition to the difficulty in comparing these end points between centers, combining multiple end points complicates efforts to assess the specific effect of the intervention on each individual outcome.

Defining adverse events. Electrocardiographic adverse events pose a particular problem in pediatric clinical trials because normal electrocardiogram (ECG) values are based on relatively small studies in children. There is a clear need for a data warehouse of ECGs representing children stratified by age, sex, race, ethnicity, and pubertal status to better characterize normal values. Technical issues with standardizing ECGs in infants and children, such as appropriate lead placement on patients of varying sizes, will complicate efforts to build larger databases. A similar database of Holter monitor data would help characterize common normal rhythm variations in children such as sinus arrhythmia or second-degree Mobitz type 1 atrioventricular block; understanding the prevalence of these arrhythmias is important to determine whether they truly represent adverse events. In addition, the relevance of ECG parameters such as prolonged QTc to clinical outcomes is not clearly understood in children.

Example of multicenter pediatric oncology clinical trials. The Children's Oncology Group (COG) provides an example of using collaborative research efforts to surmount obstacles in pediatric clinical trial design to make significant differences in clinical care of rare diseases. Formed by the merger of previous oncology research collaboratives, COG has helped to dramatically increase survival rates of most childhood cancers. More than 60% of children with cancer are enrolled in clinical trials.¹⁸ Hundreds of thousands of childhood cancer survivors continue to be observed by COG.

Given the diversity of centers and diseases under study, COG has adopted a standardized way to measure safety in its clinical trials, the Common Terminology Criteria for Adverse Events, developed by the National Cancer

Institute.¹⁹ These criteria describe each adverse effect such as complete atrioventricular block and grade its functional severity on a scale of 1 to 5, with 5 always signifying death. This standardized language of adverse events facilitates an overview of the adverse effects from new treatments and provides a common language for researchers to use. However, most of the toxicities are those noted in adults rather than focusing on developmental toxicities that may be more prevalent in pediatrics.

Efficacy and dose-response studies. The FDA generally requires 1 to 2 adequate and well-controlled clinical studies to establish efficacy and to achieve labeling status for all medications, with exceptions for studies with particularly compelling findings or drugs intended to prevent irreversible harm. However, for pediatric use, the FDA may allow extrapolation of a drug's efficacy from adults to children, thus potentially eliminating the need for efficacy studies. To extrapolate, the FDA requires that both the disease and the response to treatment are sufficiently similar in adults and children. The degree of similarity determines the type of additional studies needed; for example, if efficacy can be extrapolated, pharmacokinetic studies need to be performed in children to determine an appropriate dose to achieve therapeutic levels, in addition to safety studies. If one is not certain whether extrapolation is appropriate, one adequate and well-controlled efficacy trial in addition to dose-response and safety studies may be sufficient.

If extrapolation is not possible, 1 to 2 adequate and well-controlled efficacy trials are typically required. Previous clinical trials in children have illustrated that pharmacodynamic and pharmacokinetic studies are important precursors to pediatric efficacy studies. Because of the development-related changes in absorption, distribution, metabolism, and clearance of drugs in children, adaptation of adult dosing is often problematic. Preliminary data from pharmacodynamic and pharmacokinetic studies should therefore be used to choose a dose for the efficacy study. Subtherapeutic dosing leads to a failed efficacy study, whereas overdosing may result in high rates of adverse events.

Once efficacy is established either through extrapolation or specific pediatric efficacy studies, additional studies regarding dosing and safety may be required to obtain labeling status, depending on the adult data available. Pharmacodynamic and pharmacokinetic data should be used to guide dose-response studies, which aim to determine the physiologic response to different drug dosages. The goal of this type of study is to demonstrate the correlation between increasing medication dose and physiologic response. A key component of a dose-response trial is the inclusion of a placebo arm; without these data, the trial may be uninterpretable and non-generalizable if there is no significant difference between

the doses studied. Doses must be sufficiently different from each other and cover an appropriate range to evaluate the full dose-related response curve. Computer modeling has improved the ability to predict suitable drug dosing in recent years. Most dose-response studies are performed in children aged 6 to 16 years, and if effective, the drug is labeled for the age group in which it was tested. Although pharmacokinetic data may be available for younger age groups, these groups cannot be included in the labeling, unless appropriate clinical trials have been performed in the specific population.

Extrapolation case example: fenoldopam. Fenoldopam provides a useful example of extrapolation of adult data to enable pediatric dosing to be included in labeling. After studies proving efficacy in adults, a multicenter, pharmacokinetic/pharmacodynamic randomized trial was performed in Tanner Stage 1 children (ages 2-12 years). The trial was conducted in 2 phases: a double-blind, placebo-controlled, dose-ranging study followed by an open-label dose titration of intravenous infusion to achieve the intended effect, induced hypotension during surgery. Based on this study, pediatric dosing results and dosing recommendations were included in fenoldopam's labeling.

Pediatric dose formulation. Regardless of whether extrapolation is possible, many medications must be reformulated for children who cannot swallow pills. Therefore, appropriate dose formulation is a key design consideration unique to pediatrics. The ideal oral preparation for children would be effective and well tolerated with good stability and palatability (including acceptable taste, after-taste, and smell). Liquid formulations enable more precise weight-based dosing, but stability and bioequivalence testing of liquid formulations requires additional time and expense. The importance of this time and expense is illustrated by clinical trials of antihypertensives, in which liquid formulations were not developed, instead using extemporaneous preparations, which may have resulted in imprecise dosing and contributed to the inability to show an effect.¹⁵

Pediatric clinical trial case example: carvedilol in pediatric heart failure study. A study examining the use of carvedilol in pediatric congestive heart failure illustrates the interactions between challenges in pediatric clinical trial design. This study represented the first placebo-controlled multicenter trial of heart failure therapy in pediatrics. Carvedilol was given to 161 children and adolescents with chronic symptomatic heart failure due to systemic ventricular systolic dysfunction of any etiology, including dilated cardiomyopathy or structural heart disease (including single ventricle physiology). The primary outcome was a composite end point characterizing their condition as worsened, improved, or unchanged. The drug failed to show a significant effect in the intervention group.²⁰

Multiple study design factors may have affected the outcome, including the heterogeneous mixture of underlying causes for systolic dysfunction, the primary inclusion criterion. The composite end point used in the study had not been validated in pediatric heart failure studies and may be inappropriate for use in children. In addition, the study used a dose extrapolated from adult data rather than establishing an appropriate age-related dose; further studies have indicated that both age and weight may affect the efficacy of this drug and that the study doses may have been too low. Finally, the study's power was calculated based on adult data, which greatly underestimated the rate of spontaneous improvement in many forms of pediatric cardiomyopathy, as demonstrated by the placebo group. Additional challenges included poor clinical trial infrastructures at many of the sites involved and the lack of hard end points to characterize pediatric heart failure. Despite the many shortcomings of the carvedilol study, numerous lessons were learned and it continues to inform the design of future pediatric cardiovascular clinical trials.

Clinical trials of devices

As in the development of medications, the FDA has the ability to allow extrapolation of device efficacy from adults to children. Devices generally require only one full study for approval rather than the 2 generally required for drugs. In addition, 3 separate risk-based regulatory classes exist as compared with only 1 for medications. Class I devices including items such as tongue depressors are low risk. Class II devices such as electrocardiographs and hearing aids involve intermediate risk. Class III devices are implantable or life-sustaining devices and carry the highest risk.

In contrast to medications, device clinical trials are more difficult because academic centers and institutional review boards often do not have a clear understanding of the process of device development. Clinical trials of different types may be required depending on the extent of product redesign and the applicability of adult data to pediatrics. Owing to the nature of device design, device trials diverge from drug trials; rather than determining effect, device trials confirm efficacy in humans, evaluate safety, and determine potential for risk and performance variability. In clinical trials and the postmarketing phase, practitioner or operator technique has a large effect on results; further, device performance can be observed more readily than medication effects.

Further points raised in the discussion of clinical trial considerations included the following:

1. *Knowledge gaps*: registries should be developed to define the natural history of pediatric cardiovascular diseases to identify appropriate clinical end points and to better evaluate the incidence of cardiovascular adverse events.
2. *Practice variation*: registries could be used to characterize technique and practice variation, which could improve standardization of treatment protocols and improve the use of composite end points across multiple centers.
3. *Need for collaboration in research*: participants agreed that all parties involved (including academia, industry, regulators, caregivers and parents) should work to develop a culture similar to COG to stimulate and standardize clinical trials in the pediatric population.
4. *Monitoring of trials and adverse events*: exploration of use of a common terminology criteria for adverse events should be considered; further, the appropriateness of the current grading system for different age groups should be determined. The Pediatric Heart Network, a research collaborative, has developed its own dictionary of adverse events including serious adverse events which could be used more widely or adapted to other pediatric cardiology clinical trials.²¹

Postmarket surveillance of cardiovascular events caused by medical products

Postmarketing surveillance plays a key role in pediatric drug and device safety. In fact, given the wide variability of pediatric disease and small patient populations, postmarketing data may be the best data stream to capture some of the complexities of pediatric practice. These complexities include off-label usage of drugs and devices as well as identification of cardiovascular safety issues. Indeed, much of our knowledge about the off-target cardiovascular effects of medications such as anthracyclines comes from postmarketing data.

Medications

Because of the small size of most pediatric drug studies, infrequent adverse effects often cannot be reliably detected in clinical trials, thus making postmarketing surveillance essential. The FDA requires that drugs approved for pediatric labeling undergo a 1-year postmarketing surveillance process followed by review by the FDA's Pediatric Advisory Committee. New or more severe adverse effects in pediatric populations have been detected in 10% to 20% of all medications studied. Adverse effects detected by postmarketing safety reviews, such as prolongation of the QT interval associated with cisparide use,²² have been added to the labeling specifications for the drug.

In addition to mandated review by the Pediatric Advisory Committee, the FDA also uses passive surveillance for medication-related adverse events. This process is driven, in part, by the Adverse Events Reporting System (AERS), scientific literature, various advisory committees,

and other outside inputs. The largest passive surveillance system in the United States, AERS is a voluntary computerized reporting system whose limitations include underreporting, biased reporting, incomplete information in reports received, and the absence of a denominator or comparison group for events. Despite these limitations and the crude technique inherent to data mining, AERS has identified some important public health concerns, particularly for events that have a short latency period such as the sudden cardiac death associated with psychotropic medications, certain antihistamines, or gastrointestinal drugs, or possibly with stimulant medications.

Possible triggers for practitioners to report an adverse event to AERS include adverse events associated with the drug's indication for use, an apparent causal association between the drug and the adverse event, and media coverage of adverse events related to the drug. The FDA follows up on key reports but is unable to investigate all reports submitted to AERS.

Pediatric drugs with off-target effects on the cardiovascular system

The following examples illustrate both immediate and long-term safety impacts of specific drugs on the pediatric cardiovascular system. Many of these effects have become apparent only after marketing of these medications.

Case example: cardiovascular safety of anthracyclines. Anthracyclines are an effective class of chemotherapeutic drugs that were subsequently found to produce significant cardiomyopathy in many patients. First noted to be associated with congestive heart failure in the 1960s, follow-up studies of cancer survivors have shown that anthracyclines have a dose-dependent effect with significant variation between patients.²³ Lifetime doses of anthracyclines therefore guide echocardiographic screening protocols in patients with oncologic disease. Given the remarkable improvement in survival of pediatric oncologic diseases, this long-term morbidity issue has become increasingly important.

Case example: cardiovascular safety of stimulant medications. Stimulant medications, used in the treatment of attention-deficit hyperactivity disorder (ADHD), are known to have subtle cardiovascular adverse effects, and concerns have been raised that they may increase the risk of sudden cardiac death.²⁴⁻²⁶ As sympathomimetics, stimulants cause small increases in heart rate and systolic and diastolic blood pressures at all therapeutic doses and in all age groups; some patients have more dramatic increases than others. Clinical trials may underestimate cardiac toxicities of these medications, particularly if the studies are not designed to assess long-term cardiovascular effects.²⁷ The physiologic significance of these small increases, particularly over the course of decades of treatment, is unknown.

Case reports of sudden cardiac death have heightened concerns about the use of stimulants and resulted in warnings about misuse and resultant cardiovascular adverse reactions. Although the initial series of sudden death case reports reviewed by the FDA was dominated by children with underlying structural heart disease, a subsequent case-control study showed that stimulants may increase the risk of sudden cardiac death even in subjects without structural heart disease.²⁴ The possible connection between stimulant medications and sudden cardiac death may be confounded by additional factors. For example, people with ADHD have high rates of psychiatric comorbidities such as anxiety or mood disorders, known to increase the risk of sudden cardiac death in adults, although this risk is unknown in children. The risk of sudden cardiac death may also be caused by specific genetic variants that may result in differential metabolism of stimulants, particularly when used in conjunction with other medications. Studies have shown that polymorphisms in the cytochrome P-450 CYP2D6 pathway affect hemodynamic responses to atomoxetine, with poor metabolizers exhibiting greater increases in heart rate and blood pressure.²⁸ Additional risks posed by stimulant medications include the risks of long-term treatment, the use of anesthetics in children on stimulants, and their potential for teratogenicity. However, because of the consequences of untreated ADHD for children and young adults, including impaired school performance and an increased tendency for risk-taking behaviors,²⁹ the benefits of stimulants continue to outweigh the risks in most clinical scenarios.

Case example: cardiovascular safety of psychotropic medications. Antidepressant and antipsychotic medications have also been found to have cardiovascular adverse effects. Tricyclic antidepressants have a variety of cardiac effects including multiple arrhythmias. Although less proarrhythmic, serotonin selective reuptake inhibitors affect ion channels, potentially resulting in ECG changes and arrhythmias. In utero exposure to paroxetine has also been connected to persistent pulmonary hypertension of the newborn. In addition, serotonin selective reuptake inhibitors may have additional indirect cardiovascular effects through interactions with other drugs or in cases of overdose. Atypical antipsychotics such as risperidone and quetiapine have been shown to cause QTc prolongation, ventricular arrhythmias, and sudden cardiac death in adults.³⁰

Potential areas for research and collaboration identified by participants in the CSRC meeting included the following:

1. *Reexamination of preclinical testing:* for medications demonstrated to have adverse cardiovascular effects in humans, determination of whether there were important preclinical safety signals that could help guide optimization of such testing.

2. *Creation of a data “warehouse” or registry on ADHD drug effects:* a registry to study the long-term effects of sympathomimetics from childhood into adulthood should be formed because the significance of increases in heart rate and blood pressure over long periods of time is unknown.
3. *Collaborative efforts to indentify cardiovascular drug effects, both short and long terms in children:* of a new model for long-term studies of drugs in children in a partnership between academia, government agencies, and industry should be developed.

Devices

Similar to medications, surveillance is the primary mechanism for monitoring device safety after marketing. Passive medical device reporting via the FDA's Manufacturer and User Facility Device Experience database captures several hundred thousand voluntary reports annually, primarily from manufacturers, but only 5% of these represent pediatric reports. In addition to the passive surveillance of Manufacturer and User Facility Device Experience, the FDA has a more intensive effort to identify adverse events through the Medical Product Safety Network (MedSun) that enrolls a subset of user facilities for more intensive collaborative reporting. Launched in 2002 by the US FDA's Center for Devices and Radiological Health, the primary goal for MedSun is to work collaboratively with the clinical community to identify, understand, and solve problems with the use of medical devices. More than 350 health care facilities, primarily hospitals, participate in the MedSun network including 22 acute care general children's hospitals and 2 acute care pediatric specialty hospitals. KidNet is a subgroup of MedSun focusing on identifying, understanding, and solving problems with medical devices used in neonatal and pediatric intensive care units. As part of the active surveillance component of the MedSun program, participants agree to respond to periodic rapid response surveys focusing on a specific product. To date, no active surveys have been published regarding cardiac devices in children. Both of these mechanisms address issues such as manufacturing defects, software glitches, and packaging errors that can be identified by a few events.

The FDA mandates postmarketing studies to address low-frequency events such as procedural failure and complications. One type is postapproval studies, which are conditional for approval of class III (highest risk) devices. Device-specific registries can fulfill the need for a postapproval study. Section 522 postmarket studies,³¹ which are typically ordered “for cause” for devices expected to have significant pediatric use, are required for clearance in class II devices or approval of class III devices.

Key regulatory challenges for postmarketing device surveillance include increasing the capacity to actively monitor more devices and synthesize information from

various sources. The FDA is currently working to develop a database of unique device identifiers. This database would improve understanding of the risk-benefit ratio of devices and potentially facilitate tracking of devices and outcomes and adverse event reporting. To increase its active surveillance capacity, the FDA established the Sentinel Initiative, with the goal of forming an integrated national infrastructure of electronic health data systems.³² The Sentinel Initiative will enable observational data to be used for prospective, real-time active surveillance, providing access to information on subgroups, special populations, and long-term outcomes. Information would be exchanged with major stakeholders including academia, health care providers, and health insurance providers. Lastly, the FDA has partnered with the National Institutes of Health, Centers for Medicare and Medicaid Services, industry, the academic medical community, and the Mechanical Circulatory Support Database to develop the Inter-agency Mechanically Assisted Circulatory Support (INTERMACS) Registry, a postmarket ventricular assist device registry that includes a dedicated pediatric arm (www.intermacs.org).

Postmarketing device registries

With the exception of academic registries, current device registries are small and typically based on procedures rather than products, with specific device identification usually considered additional information. The FDA is working to link registry information with claims data using probabilistic information to better characterize the denominator of adverse events. The FDA may also help by creating a compendium of registries or fostering the development of new registries. For example, the FDA partnered with the American College of Cardiology National Cardiovascular Data Registry to develop the ICD registry, which includes pediatric implantable defibrillators. The FDA and the National Cardiovascular Data Registry also joined the American College of Cardiology, the Society of Thoracic Surgeons, the Society for Cardiovascular Angiography and Intervention, and American Academy of Pediatrics to form the IMPACT registry of outcomes after hemodynamic and interventional catheterizations for congenital heart disease (www.ncdr.com).

Regulatory pathways: device development

Participants in the CSRC subgroup meeting agreed that the current regulatory pathways for pediatric medical devices are suboptimal. Given the difficulties in developing pediatric devices, novel regulatory pathways are needed, including simplified processes of adapting adult devices for children. Ideally, these pathways would be selected based on a unique and indication-specific review of adult data, international data, and device design for each individual device. In addition, participants in the meeting discussed the current HDE model for regulation,

which is still not viable for very small disease populations. A middle ground of regulation and clinical development paradigms is needed between the extremes of a single device for a single patient model and the current HDE model. One suggestion for facilitating the approval of pediatric medical devices was to publish case studies on the pathway used by a single device or class of devices because groups working in the preclinical space often are unaware of the regulatory pathway required for device approval. The group also agreed that more frequent meetings between academia, industry, and regulatory committees might help identify issues in pediatric device design and develop approaches to move the entire field forward in the preclinical space.

Case example: AdvaMed Heart Valve Workshop

A useful model of the process of adaptation of adult devices for pediatrics was provided by the AdvaMed Heart Valve Workshop, a collaboration among academic, industry, and regulatory communities. This group established preclinical, clinical, and postmarketing paradigms for maximizing existing adult data to accelerate development of smaller heart valves for children. In this model, pediatric valve design hinged on scaling down approved adult devices while using the same materials and taking a total product life cycle approach to evaluation. The preclinical testing paradigm developed by this workshop is similar to the adult pathway. Clinical input on different stresses placed on pediatric valves should guide additional testing needs. The valve size representing the “worst-case” test conditions should be used when testing for structural performance, fatigue, and dynamic failure; however, sewing ring integrity must be confirmed in all sizes. Animal studies as well as biocompatibility and sterilization testing were deemed unnecessary if the same materials and design are used. The clinical paradigm recommended testing each valve size in 15 patients, establishing efficacy with hemodynamic data and basing safety on key adverse events. Finally, under this paradigm, postapproval study through registries played a critical role, given limited clinical experience with new device sizes.

Priorities and next steps

Future directions

The CSRC think-tank dialogue clearly identified the need for collaboration including all stakeholders committed to advancing pediatric cardiovascular safety. Initial efforts will likely be small steps such as leveraging current efforts like the IMPACT registry and compiling existing data from the FDA.

An important point made by a patient representative in attendance at the meeting is the need to mobilize and use families to improve pediatric research and ensure cardiovascular safety of drugs because parents are likely to be the first to be aware of and report any unusual drug effects.

Raising awareness about the need for research and funding both within and beyond the congenital heart disease community may facilitate important scientific efforts and drug and device development for this population.

Multiple important issues in pediatric cardiovascular safety were identified and discussed at this meeting. Each of these issues deserves further in-depth discussion and could represent topics for future collaborative work between pediatric clinicians, the FDA, and industry under the umbrella of the CSRC (eg, research projects, white papers, focused think tanks, etc) or external to it.

Consensus goals

- 1 Facilitate collaboration between preclinical and clinical researchers to define and validate appropriate biomarkers for pediatric trials.
- 2 Develop new paradigms for pediatric clinical trials that are designed to fit the unique needs of children and their families rather than following standard adult trial designs.
- 3 Improve current and establish new registries, including the following:
 - a Registry of the natural history of specific congenital and pediatric heart diseases, which includes drug and device treatment outcomes as well as the effects of all medications (These data could identify clinical end points that could inform preclinical markers for future medication and device development.)
 - b Long-term registries spanning pediatric and adult populations to track long-term effects of using noncardiac medications as well as medications currently used to treat adult cardiac conditions but used off-label in pediatrics
 - c Device registries incorporating pediatric-specific data such as congenital heart disease diagnoses and pediatric age groups.
 - d Linkage of current cardiovascular registries
- 4 Improve existing regulatory and incentive pathways for pediatric device design to encourage development.
- 5 Explore novel approaches for pediatric drug and device development that provide appropriate evidence of benefit while minimizing potential risks.

Disclosures

The opinions and conclusions expressed in this article are solely the views of the authors and do not necessarily reflect/represent regulations and policies of the Food and Drug Administration, Health Canada, or the authors' affiliated organizations.

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