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Meeting the Demand for Pediatric Clinical Trials

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Abstract

High-quality, cost-effective pediatric clinical trials require a robust research and regulatory infrastructure and a properly trained workforce.

Therapeutic products licensed for adults are frequently used in pediatric populations without sufficient safety, dosing, or pharmacokinetic data. Nevertheless, scientists and society share the ethical responsibility of providing the resources necessary to mine the knowledge needed to guide therapeutic decisions for children (1). Today, government regulations and policies in the United States and Europe (www.aap.org) both require and provide incentives for the conduct of pediatric clinical trials, thus providing an opportunity to close the knowledge gap in pediatric biomedical innovation. However, the pediatric research enterprise must act with diligence to address deficiencies in our current preclinical and clinical research systems that often give rise to irreproducible data, which are then used to generate research hypotheses and develop treatment standards (2).

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GAINING MOMENTUM

In 2012, the U.S. Food and Drug Administration (FDA) Safety and Innovation Act (FDASIA) strengthened prior initiatives in pediatric product development and made permanent the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA), which have helped to increase the number of pediatric clinical trials. Under these programs, ~436 separate studies that enrolled ~56,000 children were performed over a 5-year period. Between 1998 and 2011, FDA issued ~340 written requests for new pediatric studies and subsequently approved more than 450 labeling changes associated with BPCA and PREA studies (www.fda.gov). In Europe, after initial implementation of the Pediatric Regulation, the majority of applications for new medicines include a pediatric plan (www.ema.europa.eu). Evidence for a more robust pediatric product–development pipeline also comes from the Pharmaceutical Research and Manufacturers of America, which reported on nearly 300 medicines in development to address health needs in children (www.phrma.org/sites/default/files/pdf/children2012.pdf). Recent initiatives to facilitate pediatric device development are also taking shape.

Because rare genetic diseases (~6,500 in total) primarily affect children, additional momentum for pediatric trials has come from the rare diseases community. Since passage of the Orphan Drug Act, more than 400 products have received orphan designation. At the federal level, the National Center for Advancing Translational Sciences (NCATS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the FDA Office of Orphan Product Development are working to advance product development for rare diseases. The International Rare Diseases Research Consortium (IRDIRC) is a collaborative initiative between the European Commission and the U.S. National Institutes of Health (NIH), with a primary goal of delivering new therapies and diagnostic aids by 2020 (www.irdirc.org). Several small specialty and large multinational pharmaceutical companies are integrating efforts in rare and orphan diseases with general pediatric drug development.

The evolution of pediatric regulations, a growing commitment to pediatric studies by sponsors, and renewed interest in therapeutics for orphan diseases have greatly increased demand for timely, high-quality, cost-effective pediatric clinical trials. To meet this mandate, we require a sustainable research infrastructure, efficient regulatory processes and review systems, and a knowledgeable workforce able to generate robust data that can be used for regulatory approval, labeling of products for children, and decision-making in clinical practice.

STRENGTHENING INFRASTRUCTURES

The current infrastructures that support pediatric clinical trials leverage the child and maternal health care delivery systems and are a mix of networks that study specific diseases. This includes existing networks redesigned to conduct these trials, new networks designed to conduct specific types of trials, and ad hoc networks formed by pharmaceutical (or other) sponsors for product-specific studies. Each component of the existing infrastructure has its strengths and weaknesses. However, the collective enterprise currently lacks the

cohesiveness, efficiency, and consistency of quality to meet the increasing demand for data sufficient to support marketing authorization or new product labeling.

Today, NIH spends ~\$3.6 billion annually for child health research, including support for ~60 specialized child- and maternal-health clinical research programs. Although this investment has firmly established a global culture of maternal-child health research, these programs remain fragmented, with inconsistency in methods, divergence in terminology, proprietary and often incompatible informatics platforms, and variability in data standards and quality. There are some notable exceptions. Pediatric HIV/AIDS and childhood cancer networks are excellent examples of networks specifically developed to ensure the consistency and validity of data needed to support therapeutics development for children with life-threatening diseases. Although these programs are highly vertically integrated, there is no readily available mechanism by which the infrastructure and resources can be exported across the spectrum of investigators and institutions working on drug development in other fields. The pharmaceutical industry, which currently funds the majority of pediatric clinical trials, provides training, quality assurance and control, data management, and other support needed to generate regulatory-compliant safety and efficacy data. But standards and processes vary among companies, and this drug-specific structure is not “institutionalized,” being repeatedly built, dismantled, and rebuilt as the demand changes.

The underlying current challenge is how to capitalize on strengths of existing systems but also create a sustainable and scalable infrastructure (core tools, processes, people, and data) that can meet the increasing demand for regulatory-oriented child and maternal clinical trials. This is critical if we are to fill the therapeutic knowledge gap in pediatrics and ensure that new gaps are not created. This approach has resulted in the launching of initiatives that are facilitating a more integrated and harmonized infrastructure.

CHILD HEALTH–SPECIFIC ISSUES

A core competency of any functional clinical-trials infrastructure is the generation of high-quality data that meet or exceed regulatory standards. Historically, most federally funded pediatric research programs were designed to generate data for publication rather than regulatory review, the latter a standard that needs to withstand independent validation down to individual elements. Recent developments in federal policy combined with nongovernment initiatives have generated a new paradigm in pediatric clinical research characterized by a commitment to the highest feasible data quality, the delivery of analytical datasets that can be shared among investigators and meet specifications for regulatory submission, and increasing interoperability and harmonization of pediatric research data. These efforts are part of larger initiatives to increase efficiency and remove obstacles to pediatric clinical and translational research.

Recognizing the pivotal role of high-quality data, NICHD and NCATS have cosponsored a series of workshops engaging diverse stakeholders to specifically address this issue (3). Several common themes emerged, such as the need for universal best practices in pediatric data quality; harmonization of ontology, nomenclature, and data standards; an interoperative platform for data collection, management, analysis, and validation; methodology for

information exchange with electronic health records (EHRs), research registries, and specimen and image databases; development of policies that promote culture change from parochial research initiatives to collaborative ones; and training toward competencies in clinical pediatric informatics and data quality. In parallel, two federally funded programs [the Pediatric Trials Network (PTN) and Pediatric Device Consortium (PDC)] were designed to catalyze pediatric regulatory-oriented clinical trials and product development. These programs work across therapeutic areas and provide both virtual laboratories for developing, assessing, and disseminating innovative methods and an environment for institutionalizing practices that yield high-quality data.

NICHHD established PTN (<https://pediatrictrials.org>) in 2010 under the BPCA to address knowledge gaps in pediatric therapeutics. PTN uses a contract mechanism with task orders issued for each study or activity and serves as a clinical coordination center. The PTN contract has five primary tasks: management and site performance, clinical trials performance, formulations development, clinical pharmacology study design and data analysis, and device development and validation. PTN develops study plans through the use of resources and expertise as required by the scientific needs of the relevant data gap. Affiliated locations throughout the United States are subcontracted on a project need basis, and PTN is prepared to organize, implement, and deliver data for child health–related studies independent of subspecialty or topic. Although the PTN is currently reliant on proprietary informatics platforms, this will change in future implementations.

PDC is an FDA initiative that was instituted in 2009 to facilitate the development of pediatric devices by establishing centers of excellence that provide resources and consultation for new pediatric devices and the adaptation of marketed devices for use in children (www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/default.htm). Beginning with three geographically diverse locations, PDC has now increased to seven sites funded in FY13. The PDC model is to (i) leverage expertise, facilities, and existing relationships in order to identify potential partners and (ii) issue small amounts of funding to develop devices for clinical use that may ultimately receive marketing authorization. There are no current stipulations regarding data sharing and harmonized data standards other than those that are consistent with FDA policy. PDC is designed to function as a bridge between and catalyst for the private and public sectors, commercial and not-for-profit organizations, and myriad scientific disciplines that inform medical device development for children.

The Clinical and Translational Science Awards (CTSA) program supports 62 institutions working collaboratively to improve the quality, efficiency, and speed of translational research, including in pediatrics. It provides resources and services at individual CTSA sites, supporting the activities of child-health investigators from across the CTSA consortium. These investigator-created committees are devoted to themes such as metrics, research education and training, life-course research, rare diseases, ethics, and the development of new and existing therapeutics for pregnant women, infants, children, and adolescents. The major goals of these activities are aligned with the missions of NCATS (www.ncats.nih.gov/ctsa.html) and the CTSA consortium and include developing metrics for and improving the implementation of clinical studies that enroll children; functioning as a liaison between

investigators and sponsors seeking expertise or access to pediatric patients and trial facilities; facilitating the dissemination of best practices and study outcomes; and emphasizing public health outcomes. These groups have served as a forum for new concepts, enabled proof-of-concept initiatives, helped to organize workshops and conferences, and worked to stimulate research in the pediatric arena (Table 1). With its collaborators, NICHD and NCATS are moving forward with an emphasis on their role as a catalyst and facilitator for new ideas, processes, and partnerships that contribute to a sustainable future for maternal-child health research, consistent with recommendations made in a recent Institute of Medicine (IOM) report (4).

A common theme among these initiatives is horizontal integration of the diverse ecosystem that supports pediatric clinical trials—a goal shared by members of the international pediatric clinical trials community. Taking the perspective that clinical trial expertise is a common set of skills that can be applied across therapeutic areas, the European Medicines Agency (EMA) has taken a “network of networks” approach, and data quality and harmonization are central to this effort as well. The European Network of Pediatric Research at EMA (Enpr-EMA) is a constellation of research networks, investigators, and centers with recognized expertise in performing clinical trials in children (5). Members have scientific competencies, provide expert advice, and facilitate quality management and training to build quality into pediatric clinical trials. Enpr-EMA coordinates trials in children in order to avoid unnecessary studies and also promotes collaboration between industry and academic centers.

HARMONIZING HEALTH RECORDS

Research infrastructure typically leverages various aspects of maternal-child health care delivery systems, which are moving toward a “learning” environment in which research is more closely linked to clinical care in a process of continuous quality improvement (6). Such a learning system is made possible through data sharing, which is facilitated by EHRs. Although EHRs provide a potentially rich source of patient information on the effects of interventions, the use of EHRs for research that supports regulatory submissions has the following limitations: (i) EHR systems have been developed for clinical-care delivery rather than to support research; (ii) patient privacy restrictions; (iii) different terminologies and data architectures that limit or prevent data exchange; (iv) clinical data collection processes that are unable to accommodate research-specific variables; and (v) data flow among multiple systems (such as imaging, clinical chemistry, and anatomical pathology) is not designed for research-data capture. Despite these current limitations, EHRs will be an integral part of the learning health care system envisioned by IOM and others to integrate clinical care and research, which is a critical component of the development and conduct of clinical trials in infants and children (7).

Large-scale efforts in data harmonization have been in place for some time but have not focused on issues specific to pediatric clinical trials. To address this problem, NICHD began a terminology-harmonization effort in collaboration with the Enterprise Vocabulary Services of the National Cancer Institute that initially focused on terminology for newborn infants (8). This effort produced a pediatric terminology metastructure using a maternal-child life-

course approach and is now being incorporated into the National Children's Study and other collaborative projects. The refining of EHR systems presents an opportunity to prospectively design elements in such a way that they facilitate clinical and translational research and product development and evaluation. Such prospective opportunities are rare in the history of pediatric clinical trials. Although this will require a large initial investment, a return is likely given the time and financial costs associated with retrofitting the system later.

The goals and programs we outline here are initial steps. Sustainability is dependent on creating a virtual home for new skills and methods as well as the development of expertise in clinical and translational research and product development as a discipline. This includes not only training but also professional development, recognition of achievements, and academic rewards for conducting regulatory trials. Ultimately, it is the responsibility of those who identify the needs, design the studies, and collect and analyze the data to demonstrate to society that these efforts and resources produce benefits for all children.

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Table 1

Selected NIH-funded initiatives to facilitate child health research.

Formalize and adopt new models of the institutional review board process for multicenter clinical trials
Engage investigators in regulatory-oriented clinical trials through a structured system of contacts at institutions in the consortium
Decipher obstacles to the recruitment of pediatric subjects into clinical trials
Develop metrics for pediatric clinical trials
Advance education in child and maternal product development