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DIA

ORIGINAL RESEARCH

Pediatric Clinical Research Networks: Role in Accelerating Development of Therapeutics in Children

Rachel G. Greenberg, MD, MB, MHS[1,2] · Susan McCune, MD[3] · Sabah Attar, PhD, BEng[4] · Collin Hovinga, PharmD, MS, FCCP[5] · Breanne Stewart, RN, BSc, BScN[6] · Thierry Lacaze-Masmonteil, MD, PhD[7]

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Abstract

Background Recent decades have seen many advances in policy and legislation that support the development of drugs used by neonates, infants, children, and young people. This review summarizes the characteristics and performance of networks capable of conducting studies needed to meet regulatory requirements and make advances in pediatric drug development.

Methods Description of network goals and capabilities by network leaders.

Results In the United States, Europe, Japan, and Canada, clinical research networks have been organized to meet the needs of biopharmaceutical and academic sponsors for timely access to high-quality sites, as well as to provide advice about drug development with regard to strategic and operational feasibility. Each network addresses the specificities of its context while working toward shared principles including standards and timelines; alignment of goals and processes, while not disturbing arrangements for conducting trials that work well; wide geographic coverage; all age groups and pediatric conditions; sources of funding; sites that compete on performance; performance monitoring for benchmarking, and opportunities to optimize the allocation of resources; and education and training for network members. Facilitation in interactions among these networks is based on a single point-of-contact for each; similar approaches to strategic and operational feasibility assessment, and site selection; and collaborative approaches to education and training.

Conclusion Within five years, clinical research networks will support the needs of biopharmaceutical and publicly funded pediatric drug development through locally appropriate and globally interoperable approaches.

Keywords Pediatrics · Drug development · Research networks · Infrastructure

Introduction

Infants, children, and adolescents need access to well-evaluated therapeutics and devices. Pediatric-specific studies are essential, particularly for therapeutics, because of unique physiologic changes that occur during infancy and childhood related to the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs. For this reason, dosing and safety are not predictable in children and neonates at different developmental stages and cannot be extrapolated from adults [1]. In many cases, efficacy also cannot be extrapolated from the adult population to children and neonates [2, 3]; for example, extrapolation of efficacy is not possible for pediatric or neonatal conditions that do not occur in adults. Without pediatric-specific information on dosing, safety, and efficacy, children and neonates are at increased risk of adverse reactions (if dosing is too high) or therapeutic failures (if dosing is too low) [4, 5].

✉ Rachel G. Greenberg
rachel.greenberg@duke.edu

1 Duke Clinical Research Institute, Durham, NC, USA

2 Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA

3 Rare Diseases and Pediatrics Center of Excellence, PPD, Part of Thermo Fisher Scientific, Bethesda, MD, USA

4 Department of Women's and Children's Health, University of Liverpool, Liverpool, UK

5 Institute for Advanced Clinical Trials for Children, Rockville, MD, USA

6 Quality Management in Clinical Research (QMCR), University of Alberta, Edmonton, AB, Canada

7 Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Pediatric trials are challenging for a number of reasons, including, but not limited to (1) a small number of eligible subjects [6]; (2) ethical considerations and inability of children to volunteer for studies; (3) few clinicians with expertise in both pediatric clinical care and pediatric clinical trials; (4) high cost; and (5) willingness of pediatric clinicians to use therapeutics off-label without specific information on safety and efficacy in children. As a result, trials aimed at determining drug safety and efficacy in children can be underpowered and, therefore, unable to generate useful information [7]. Additionally, potential investigators cite the impact on non-research clinical workflow, length of patient study visits, and frequency of patient study visits as important barriers to participation in clinical research [8]. These limitations have led to early discontinuation of nearly 20% of registered pediatric studies, with patient accrual difficulties accounting for nearly 40% of study discontinuations [9].

Poor study design and implementation can lead to increased costs, primarily through prolonged enrollment. These costs need to be minimized in order to allow as many therapeutics as possible to be studied. The required combination of quality and efficiency arises from consistent approaches to study delivery, including design, implementation, and reporting. Experience shows that this consistency arises when people and organizations apply systems to optimize clinical design and implementation of research across multiple studies through clinical research networks. This paper describes current efforts by pediatric clinical research networks to optimize the delivery of clinical trials.

Strategies for Successful Clinical Research Networks

Clinical research is optimized by ensuring appropriate information and judgments contribute to the design of a clinical therapeutic development program overall, as well as to individual studies. Strong clinical research networks emphasize early engagement with experienced clinical trialists who understand therapeutic development, study design, statistics, and regulatory science. Importantly, this expertise should be integrated with clinical experience of the condition under study. Traditional research-active opinion leaders can lack the broad base of clinical practice that is needed to design a practical, multisite study within a specific geographic area or across the globe. Children, young people, and their families provide important insight into many aspects of study design and their voices need to be included in the early stages of planning therapeutic development programs. A consistent approach to incorporating these contributions early in the pediatric therapeutic development program can reduce delays and by extension, study costs. With time, such an approach can promote high-quality advice through learning across projects.

Clinical trial implementation can also be optimized by careful management of each step of a trial, from site identification through to site closure. Trial delivery is easier and more efficient if sites and sponsors can repeatedly follow the same processes. Consistency can develop within sites, between countries, and across regulatory jurisdictions, but needs support to flourish in multiple settings. Regarding site requirements for study conduct, consistency within and between sponsors is critical to improve efficiencies of pediatric programs.

Pediatric Clinical Research Networks

Several pediatric clinical research networks are operational in high-resource settings: (1) Institute for Advanced Clinical Trials for Children (I-ACT); (2) Pediatric Trials Network (PTN); (3) Maternal Infant Child and Youth Research Network (MICYRN), Canada; and (4) connect4children (c4c). Each of these networks will expand its services over the next couple of years, will remain in close contact with each other, and will have the opportunity to develop complementary ways of working together. Table 1 lists operational networks with their activities and planned status in 2022. This manuscript describes the organization, capabilities, collaborations, and future directions of these four networks.

Pediatric Trials Network (PTN)

History of Development

To address issues related to pediatric drug development, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has overseen the implementation of the 409I section of the Best Pharmaceuticals for Children Act (BPCA) mandate since 2002. The goals of the BPCA include prioritization of off-patent therapeutics for pediatric study, sponsoring of clinical trials, and training of clinical pharmacologists. The initial years of the program included data gathering (e.g., systematic literature reviews); convening expert panels; and conducting single-molecule safety, efficacy, and PK clinical trials awarded to individual academic centers. Since 2010, the program included the development and subsequent funding of the PTN [10] to develop and implement a more coordinated and succinct clinical research program focused on remaining gaps in pharmacology research in pediatrics.

Table 1 Pediatric networks involving all subspecialties and age ranges

				Available to		Scope					
Jurisdiction	Organization	Funding	Structure	Industry	Public funders	Advice about trial design	Trial conduct	Involvement of children and young people	Advice about trial supplies[a]	Status in 2021	Contact
Europeb	c4c	IMI 2 co-funding from the European Commission and 10 large pharma companies	Pan-European single contact point; components include 20 national hubs, speciality networks, and multiple sites; advisory groups are drawn from all specialties and methodologies	Yes	Yes	Through strategic feasibility advice groups	Setting standards through sites and monitoring performance	Through Young People's Advisory Groups	Through specialist trial pharmacists	Open to 6–7 proof of viability studies	Communication@conect4children.org
USA	I-ACT	FDA + memberships + industry sponsors	U.S. and international sites under a single point-of-contact; multi-subspecialty aligned consortium; advisory groups aligned with subspecialties and methodologies	Yes	Yes	Through clinical study groups and internal staff	Setting standards through sites and monitoring performance	Through engagement in patient advocacy groups	Through on staff expertise and clinical study groups	Open to multiple multi-center therapeutic and device studies	info@iactc.org

Table 1 (continued)

Jurisdiction	Organization	Funding	Structure	Available to		Scope				Status in 2021	Contact
				Industry	Public funders	Advice about trial design	Trial conduct	Involvement of children and young people	Advice about trial supplies[a]		
USA	PTN	FDA + NIH + foundation + industry sponsors	Components include study design, clinical pharmacology, regulatory science, network partnerships, sites, and education	Yes	Yes	Through clinical trialists and operational staff with pediatric experience	Selection of sites that can enroll in trials and can generate regulatory-grade data	Through partnerships with established pediatric advocacy groups	Through pharmacists and operational staff with pediatric expertise	> 35 clinical trials across 50 therapeutics	PTN-Program-Manager@dm.duke.edu
Canada	MICYRN	Children's Hospital foundations and research institutes; project-focused grants from public agencies, cost recovery services	MICYRN, an incorporated Federal non-profit charitable society is the national hub	Yes	Yes	Through method/design expert working groups	Individual site selection or through post-award service offerings either directly offered by MICYRN or provisioned through MICYRN	Through KidsCan Youth Advisory Group at British Columbia Children's Hospital	Through specialist trial pharmacists, collaboration with Industry and the Goodman Pediatric Formulation Centre	Open to 6–7 proof of viability studies and 4 emergency medicine studies	info@micyrn.ca

c4c conect4children (conect4children.org), *FDA* Food and Drug Administration, *I-ACT* Institute for Advanced Clinical Trials for Children, *IMI 2* Innovative Medicines Initiative 2, *MICYRN* Maternal Infant Child Youth Health Research Network, *PTN* pediatric trials network, *U.S.* United States

[a]Trial supplies refer to products used in clinical trials: active therapeutics, comparators, placebos. Advice includes procurement before trials and disposition during and after trials

[b]"Geographical" Europe, including 17 European Union countries, with Switzerland, United Kingdom, and Norway

Funding, Structure, and Stakeholders

The PTN is funded by NICHD under the BPCA legislation. The PTN consists of a Program Management and Clinical Operations Core, a Steering Committee (which includes thought leadership, representation from clinical sites, and patient advocates), a Data Coordinating Center (Fig. 1), and sites that enroll study participants.

Scope and Objectives

The PTN's mission is to conduct trials and other studies, primarily with off-patent drugs, that are lacking data in pediatric populations. Though these drugs may be commonly used, the exclusive right to market them has expired, so companies are not required and have no incentive to test these drugs in pediatric age groups. The PTN places particular emphasis on drugs that have been prioritized by BPCA [11]. Additionally, the PTN's program also has focused on knowledge gaps in special populations, including premature infants and children with obesity. In premature infants, PTN has studied medications for potentially life-threatening infections, as well as preventive therapies for bronchopulmonary dysplasia, a chronic lung disease affecting approximately 17,000 infants per year in the United States (U.S.). In children with obesity, PTN studies have evaluated dosing guidelines for both antibiotics and anti-seizure medications.

To accomplish these scientific objectives, the PTN Clinical Coordinating Center and Data Coordinating Center provide infrastructure to conduct multisite cooperative clinical studies that advance the knowledge of PK/PD, safety, and effectiveness of drugs in children. The Clinical Coordinating Center provides site training and management, expertise in clinical trial design and pharmacology (including PK/PD analysis), training of clinical trial and pharmacology experts, and dissemination of trial data in the form of publications and lay summaries. The Data Coordinating Center provides an electronic data capture system, statistical analysis, safety monitoring, regulatory submission to the U.S. Food and Drug Administration (FDA), and dissemination of datasets to public-facing programs as required by NICHD.

Working with the PTN

PTN works with sites on trial design and conduct according to mandates agreed upon with NICHD. The PTN is an open network; sites who fulfill study-specific selection criteria can participate in those studies. Additionally, the PTN

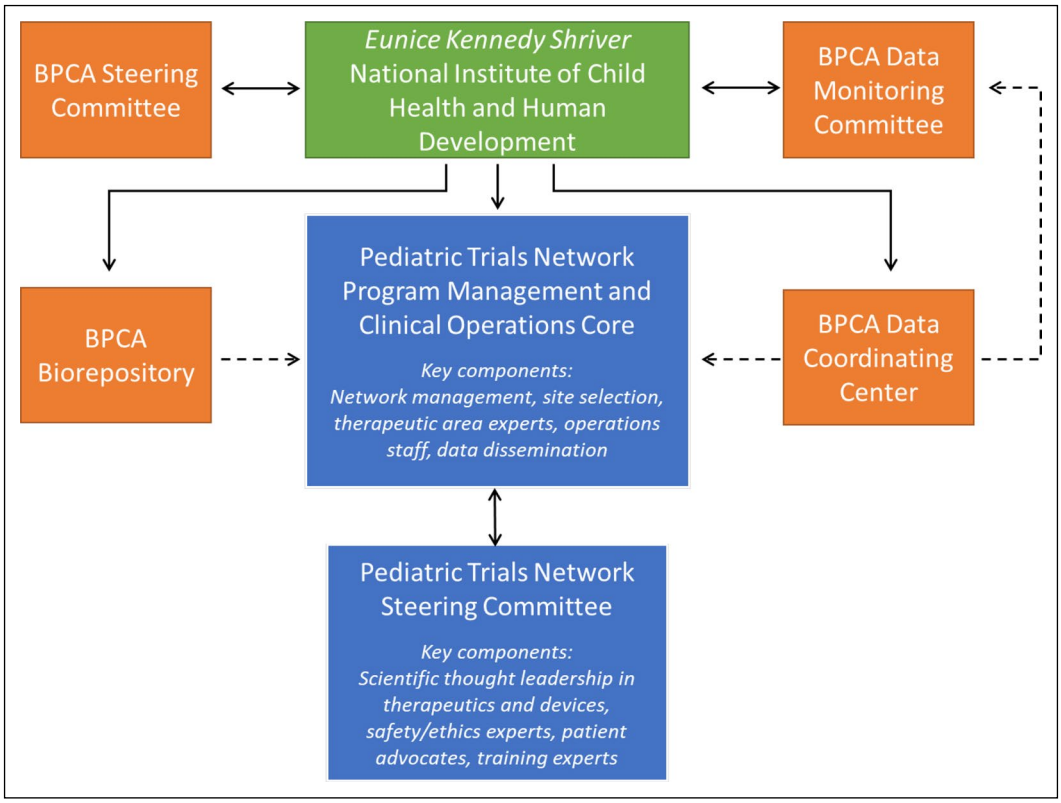

Fig. 1 Pediatric trials network structure. The PTN consists of a Program Management and Clinical Operations Core, a Steering Committee (which includes thought leadership, representation from clinical sites, and patient advocates), a Data Coordinating Center, and sites that enroll study participants. *BPCA* Best Pharmaceuticals for Children Act, *PTN* Pediatric Trials Network

accepts concept sheets by investigators inside and outside the network for protocol development consideration. Those interested in engaging with the PTN should contact PTN-Program-Manager@dm.duke.edu.

Services Offered

The PTN has contracted with > 100 sites across the U.S., plus international sites in Canada, the United Kingdom, Singapore, Israel, and Australia, to perform studies across 18 therapeutic areas. PTN studies have enrolled > 11,000 participants over a range of populations including neonates, infants, children, adolescents, and mothers. PTN studies have led to a total of 26 product submissions to the U.S. FDA, resulting in 17 label changes. PTN trials employ advanced techniques that make it possible to efficiently and safely study medicines in the youngest patients with extremely limited blood volumes, including advanced PK modeling, cutting-edge blood sampling methods, leftover samples from other laboratory tests, and mining existing clinical data. Furthermore, PTN employs multiple innovative platform protocols to capture data across a variety of drugs in an opportunistic way, including a protocol to understand transfer of drugs into breast milk. Such opportunistic protocols have facilitated quick pivots toward important drugs as needs arise, such as during the coronavirus 2019 (COVID-19) pandemic. As of September 2021, the PTN's Pediatric Opportunistic Pharmacokinetics Study (POPS) has enrolled > 300 children with COVID-19 disease or who are receiving drugs that could be used to treat COVID-19, with plans to evaluate the preliminary PK and safety of those drugs.

Past and Existing Collaborations with Other Networks

The PTN has actively engaged in collaborations with other networks in order to achieve its mission of advancing drug development in children. Together with the FDA-funded Global Pediatric Clinical Trials Network (G-PCTN), the PTN has explored site challenges in the conduct of pediatric trials. Activities with G-PCTN have also included working with I-ACT to create Good Clinical Practice training specific to pediatrics, as well as working with industry to develop tailored regulatory strategies for pediatric drug development programs. PTN has worked with the Institutional Development Award (IDeA) States Pediatric Clinical Trials Network, funded under the Environmental Influences on Child Health Outcomes (ECHO) program with the primary goal of broadening the geographic distribution of National Institutes of Health research funding. The PTN trained sites to become part of POPS, which is one of the first PTN trials performed by the IDeA States Pediatric Clinical Trials Network, giving some less experienced sites a crucial opportunity prior to participating in other trials. The PTN has collaborated with therapeutic area-specific networks, such as the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project, which focuses on health and quality-of-life needs for individuals with Down Syndrome. Finally, during the COVID-19 pandemic, the PTN has teamed up with the National Center for Advancing Translational Sciences-funded Trial Innovation Network (TIN) to support the ABC Science Collaborative [12], a program that pairs scientists and physicians with school and community leaders to help understand the most current and relevant information about COVID-19.

Challenges Encountered

The PTN has had substantial success in completing regulatory-compliant trials that have led to label changes for both drugs and devices. To date, many of the successes have been for drugs in which efficacy can easily be extrapolated from adults (such as antimicrobials). For these drugs, the PTN could substantially improve public health by performing small-to-moderately sized PK and preliminary safety trials, generating important data regarding exposure that could be incorporated into drug labels. What remains more challenging is performing larger safety and efficacy trials for drugs whose outcomes cannot be extrapolated from adults. Notwithstanding the higher cost and questionable feasibility of performing such trials, groundwork is needed even prior to study design. For some drugs, natural history studies are needed to define outcomes and sample size. Biomarker qualification and development of surrogate endpoints are also critical to be able to proceed along the potential pathway for label change. The PTN is gaining experience in this area and is currently validating an endpoint for pain in young children. For several drugs, PTN is performing adult studies as requested by the FDA prior to moving to pediatric studies, which is further evidence of the lengthier regulatory pathway available for drugs in which efficacy cannot be fully extrapolated.

Historically, enrollment of racially and ethnically diverse participants has been a challenge in clinical trials of drugs and devices [13, 14]. The PTN recently evaluated 33 studies conducted from 2008 to 2020 and found that minority enrollment was comparable to, or higher than expected (based on Census data), for all groups except Asian Americans [15]. Consequently, while PTN has taken steps to ensure adequate representation of children from all racial and ethnic groups, more work still needs to be done to ensure this effort continues, particularly among minority racial and ethnic groups.

Maternal Infant Child and Youth Research Network (MICYRN), Canada

History of Development

MICYRN is a federal not-for-profit, charitable organization founded in 2006 to build capacity for high-quality, applied health research. The network links 21 maternal and child health research member organizations based at academic health centers in Canada, is affiliated with more than 30 practice-based research networks, provides support to new and emerging teams, and has established strong national and international partnerships.

Funding, Structure, and Stakeholders

MICYRN is governed by a Board, which comprised member research organizations, as well as members at large, who represent specific research foci and expertise. Regular oversight of the network is achieved through an executive team consisting of the Board chair, vice-chair, scientific directors, and executive directors. Operationally, MICYRN's national coordinating center is overseen by the executive director, and the team at the coordinating center provides logistics, communications, financial, project, and stakeholder management. On the research front, the scientific director and associate director of clinical trials oversee the development of national capabilities in multi-jurisdictional clinical trials, working closely with the clinical trials consortium (CTC) comprised scientific and operational representatives across national clinical trial units at MICYRN's member research organizations. The CTC works to prioritize areas of opportunity and also identifies key areas where setting best practices can enhance the quality and outcome of research (i.e., data management, methodology, etc.) and determine means by which to enact best practices. MICYRN also brings together the maternal-child health research institute directors and the associate pediatric chairs of research to ensure a coordinated, national voice and direction on behalf of Canada's maternal/child and youth health academic health sciences center.

MICYRN is primarily funded by the network member research organizations, with supplemental funding provided through cost recovery contracts set-up with research projects. MICYRN also has some fee-for service support agreements with other organizations.

Scope and Objectives

The mission of MICYRN is to catalyze advances in maternal and child healthcare by connecting minds and removing barriers to high-quality health research. MICYRN is working toward building a national infrastructure to attract and facilitate the conduct of maternal-child investigator-initiated and industry-sponsored, multicenter clinical trials. Although clinical trial activity is a key focus for MICYRN, the network also prioritizes quality improvement initiatives, supports training and mentorship programs for emerging investigators and new trainees, and leverages national partnerships to lead advocacy initiatives for regulatory and ethical pathways in Canada.

Working with MICYRN

MICYRN works with the Clinical Trials Consortium made up of scientific and operational leadership from member sites to identify key areas to enhance the quality and outcome of maternal-child health clinical trials. The Clinical Trials Consortium initiatives include quality improvement and performance metric collection, site standards and readiness, local capacity development, and training programs. MICYRN also works with its subspecialty networks to establish a clinical and methodological expert database following the c4c model and serves as the point-of-contact for academia and industry for study feasibility, and site identification for study participation. Organizations interested in partnering with MICYRN should contact info@micyrn.ca.

Services Offered

MICYRN functions as an academic research organization. In preparation for submission for funding opportunities such as CIHR or other funding agencies, MICYRN offers pre-award grant consultation.

MICYRN also supports post-award services [16] and helps pediatric academic health care institutions to build local capacity for clinical trial support. The post-award services include protocol development; regulatory application support; streamlining of ethics submissions; quality assurance; safety and adverse event support, including data safety monitoring board, data management, project management, placebo development, and drug procurement support.

MICYRN has partnerships with a national pharmacology working group and the Goodman Pediatric Formulations Centre (GPFC). In partnership with Clinical Trials Ontario (CTO), MICYRN was successfully awarded a $2.5 million grant from the CIHR Institute of Human Development, Child and Youth Health (IHDCYH), and the CIHR Institute of Genetics for the Canadian Collaboration for Child Health: Efficiency and Excellence in the Ethics Review of Research (CHEER). This initiative will develop a cross-provincial streamlined ethics review process for multisite studies to achieve a single ethics review for child health studies in Canada. MICYRN also plays a critical role in advocacy. Health

Canada (the National Competent Authority) now recognizes MICYRN as the national network for maternal-child health.

Past and Existing Collaborations with Other Networks

MICYRN is currently affiliated with more than 30 Canadian subspecialty networks that capture virtually all the neonatal and pediatric intensive care beds; all of the academic pediatric emergency, surgical, and anesthesia services; most subspecialty pediatric practices; and 70% of the high-risk maternity beds in the country. Additional stakeholders include the Canadian Pediatric Society, GPFC, Children's Healthcare Canada, the Pediatric Chairs of Canada, and the IHDCYH.

International Partnerships

MICYRN co-chairs the Working Group on International Cooperation of the European Network of Paediatric Research at the European Medicines Agency. MICYRN has a memorandum of understanding with I-ACT to bring industry-sponsored pediatric clinical trials for site participation in Canada. MICYRN has also signed a confidentiality agreement with c4c.

Challenges Encountered

Canada lags behind the U.S. and Europe in the number of therapeutic agents approved for use in general pediatric populations. The net result is that physicians in Canada routinely resort to prescribing medications for off-label use without appropriate evidence-based justification. Another fundamental challenge is the lack of dedicated research infrastructure funding for Canada. MICYRN currently heavily relies on foundations and philanthropy. For future sustainability, MICYRN is actively working to secure funding from sources such as the federal government or national granting agencies.

Finally, one of the most notable challenges in Canada for drug development is that regulatory decisions are independent from price, cost, access, and reimbursement processes. Manufacturers in Canada are not obliged to submit pediatric data to Health Canada as part of a New Drug Submission Process unless a specific pediatric indication is being pursued, even when pediatrics can use or anticipate to use the drug (Pediatric Rule). On a positive note, Health Canada has plans to modernize the clinical trials framework [17] to adopt a risk-based approach that will allow greater flexibility in the evaluation of innovative therapies and off-label drugs. MICYRN is providing feedback to Health Canada on this initiative from the collective perspective of maternal-child health.

Institute for Advanced Clinical Trials for Children (I-ACT)

History of Development

In 2014, Critical Path Institute's Pediatric Trials Consortium engaged stakeholders (clinicians, patients, sponsors and regulators) to produce an Advisory Report that outlined the development of a new organization tasked with improving the efficiency of conducting pediatric clinical studies. I-ACT, an independent 501(c)3 non-profit, was launched in 2017 in alignment with the Advisory Report. I-ACT's strategic and operational plan focuses on creating an integrated resource for pediatric product development with sustainable infrastructure to support all phases of pediatric clinical investigations.

Funding, Structure, and Stakeholders

I-ACT was established to be an independent, impartial entity focused on advancing pediatric clinical trials that support regulatory approval and labeling of new products. To accomplish this, I-ACT regularly obtains input from multiple stakeholders including clinicians and patient families/advocates, the FDA, and sponsors. The Institute's employees include a senior management team, project managers, trial site support staff, and medical/scientific experts.

The I-ACT site network comprised affiliated pediatric hospitals and private practices that have been identified based upon their ability to function as clinical trial sites capable of delivering high-quality data. Each site is represented by two research leaders who serve as representatives on I-ACT's Best Practice, Education and Training Committee, which creates educational programming, tools, and resources to enhance trial conduct throughout the network. I-ACT also established the framework and leadership for a site-level quality improvement program aimed at improving efficiency of trial conduct (Pediatric Improvement Collaborative for Clinical Trials & Research [PICTR®]). PICTR includes (1) an educational component in which site staff learn quality improvement principles; (2) a system for data collection on standardized metrics; (3) ongoing mentored performance improvement projects aimed at improving study start-up (e.g., Institutional Board Review, contracting and budgeting) times and subject recruitment; and (4) a community forum for I-ACT network site staff to share experiences and outcomes to drive sustained innovation.

I-ACT's medical and scientific staff comprised experts in pediatric drug development. Additional expertise has

been recruited from experienced pediatric subspecialists connected to trial sites within I-ACT's network. The Institute also has established partnerships with multiple patient advocacy groups that are consulted for patient protocol acceptability and feasibility. I-ACT has partnered with multiple real-world data sources to provide tools to aid in regulatory filings and to assist in the development of more feasible pediatric clinical trials. I-ACT is funded through federal and private grants, sponsor and individual memberships, and fee-for-service work obtained from sponsor consultations and requests.

Scope and Objectives

I-ACT's main objective is to advance pediatric clinical trials and to support efforts that improve the process for regulatory approval and labeling of new products. Sites are established and continually developed to ensure that they can perform in accordance with regulatory requirements. I-ACT provides advice and guidance through consultations from sponsors engaged in designing pediatric development plans and clinical trials. Finally, I-ACT plays an important role in contributing to pediatric drug development innovation by organizing and leading non-proprietary projects aimed at addressing challenges identified by the stakeholder community.

Working with I-ACT

I-ACT works with sponsors from the private and public sectors to cultivate clinical trials of innovative products for children of all ages, specifically, promoting and advancing innovation in clinical trial design and conduct. I-ACT functions as a public–private collaboration using a variety of flexible methodologies. Those interested in engaging the Institute as a partner in pediatric product development initiatives should contact info@iactc.org.

Services Offered

First, the I-ACT site network includes 84 clinical trial sites that have been involved in 18 clinical trials. The Institute works with sponsors to identify suitable sites for their studies and helps facilitate early engagement. Second, I-ACT has an extensive list of pediatric subspecialty and regulatory experts under contract to act as consultants on regulatory strategy, protocol feasibility, and study design. I-ACT has provided advice and guidance in more than 25 clinical trials/programs, and conducted 12 advisory boards for sponsors during its first 4 years. Third, I-ACT collaborates with stakeholders to encourage innovation in pediatric drug development. One area of focus has been the development of adaptive platform trials. For example, I-ACT has advanced a Duchenne Muscular Dystrophy (DMD) platform trial through several regulatory meetings including a type B meeting with the FDA in which the elements of the trial and the governance of the platform were discussed. I-ACT also has successfully convened stakeholders at two Pediatric Research and Innovation Forums. These forums have engaged clinicians, scientists, regulators, sponsors, and patient advocates to address and develop recommendations around topics aimed to encourage improvements in pediatric drug development. Fourth, I-ACT's quality improvement project, PICTR, educates I-ACT sites on quality improvement processes and how to identify actionable adjustments to current practices that will substantially improve clinical trial site performance. The Institute also mentors sites on process improvement projects and encourages network sites to collaborate and disseminate best practices. Fifth, I-ACT's National Leaders' program has improved trial recruitment and retention for multiple pediatric clinical trials. Finally, I-ACT has access to multiple pediatric real-world data sources that can be used to help with regulatory submissions, assessing protocol feasibility and improving protocol design. I-ACT is collaborating with the Critical Path Institute to develop a neonatal real-world data warehouse to address neonatal clinical trial planning that includes electronic health care data from I-ACT sites.

Past and Existing Collaborations with Other Networks

I-ACT has agreements with c4c's Belgium Hub (Belgian Pediatric Clinical Research Network [BPCRN]), MICYRN, and Japan Pediatric Society Pediatric Drug Development Network (JPEDNet) to assess trial feasibility, as well as identify site willingness and ability to participate in sponsored trials. The Institute collaborates with these networks to define clinical trial site standards, performance metrics, and educational efforts. I-ACT has involved these networks in its multi-stakeholder meetings to optimize the sharing of information across a broad range of experienced investigators and experts. I-ACT also partnered with PTN and Duke Clinical Research Institute (DCRI) to develop Good Clinical Practice training modules.

Challenges Encountered

The need for establishing I-ACT was clearly articulated by all stakeholders five years ago; since then, substantial progress has been made in developing a site network, as well as completing pre-competitive and product development projects. As a new entity, I-ACT was built from the ground up and has spent time putting in place the necessary expertise and infrastructure to serve as a value-added collaborator with sponsors and the rest of the pediatric product development community. As a public–private

collaboration working primarily in the innovative drug development space (on-patent drugs), the organization needed to establish a track record and proof-of-principle for impact in helping to advance product development for children. Working with founding sponsors, mostly large biopharmaceutical companies, has positioned the Institute well and provided the opportunity to refine its processes and pressure test its systems and approach.

Public sources of funding were critical to the Institute's early years. An FDA grant provided much-needed support soon after I-ACT was founded; this grant played a critical role in creating the network and PICTR. The next important step after start-up is sustainability. I-ACT continues to foster a path toward ongoing growth and sustainability by attracting interest from a broader range of sponsors and collaborators (e.g., small- and mid-sized biopharmaceutical sponsors and public–private grants). The public–private collaboration is necessary to improve drug development for children, yet each collaboration brings its own unique challenges and opportunities. As a result, the Institute has developed a flexible approach to engagement with a strong focus on measuring and ensuring impact and productivity. The full value and impact of I-ACT's contribution to the field may take several years to transpire. In the interim, I-ACT is becoming a fully sustainable organization that is a major force in advancing innovative drug development for children.

connect4children (c4c)

History of Development

The European Union Paediatric Regulation was introduced in 2007, to ensure that new and existing drugs took into account the requirements for children [18]. In 2017, the 10-year review of the Pediatric Regulation identified barriers to the conduct of clinical trials, including delays in setting up and completing pediatric trials [19]. The Collaborative Network for European Clinical Trials for Children (c4c) aims to address some of these difficulties by building capacity for national coordination of pediatric research across Europe [20].

Funding, Structure, and Stakeholders

The c4c consortium comprised 10 large pharmaceutical companies and 34 non-industry partners including academia, hospitals, third-sector organizations, and patient advocacy groups.

Scope and Objectives

The goal of c4c is to develop and evaluate specific processes and aspects of a Europe-wide clinical trial infrastructure to meet the needs of children involved in clinical trials. After the end of the c4c grant in 2024, a new legal entity will continue the work that c4c has developed.

Governance and Oversight

As a grant-funded project, c4c governance is led by a General Assembly made up of all beneficiaries of the grant. The General Assembly has delegated authority to the Project Steering Committee, which oversees the operations of the network.

Working with c4c

The c4c consortium works with industry and academic members on trial design and conduct, education and training, and data standards. When the successor organization opens in 2024, the services will be available to all organizations that are willing to pay. Interested organizations should contact Communication@conect4children.org.

Past and Existing Collaborations with Other Networks

The academic members of the c4c include 21 National Networks and six Specialty Networks. c4c is also represented in the European Joint Programme on Rare Diseases and the European Network of Paediatric Research at the European Medicines Agency. c4c has clinical data agreements in place with I-ACT, PTN, and MICYRN. c4c is working with I-ACT and MYCRN on metrics and standards for sites working in pediatric clinical trials. c4c is working with the European Joint Programme for Rare Diseases (EJP-RD) and European Rare Disease Research Coordination and Support Action (ERICA) on education, site standards, and data models in view of the overlap between pediatrics and rare diseases.

Services Offered

The services offered by c4c are being evaluated to test the viability of the network. c4c is funding three non-industry trials and is working with five industry trials. c4c takes an iterative approach to the development, as well as rolling out procedures and services with specific underlying principles: (1) co-creation of all processes with industry and academic partners to take into account heterogeneity across industry sponsors and academic organizations; (2) consultation across all consortium members, National Hubs, and sites to ensure country specificities are incorporated

into guidance and processes, where possible; (3) feedback mechanisms to review the rollout and timely revisions to the process to incorporate feedback; and (4) underpinning metrics to ensure real-time process quality management and intervention.

Single Point-of-Contact

c4c provides a single point-of-contact service for all trial-related support, processes, and queries. Designed as a customer-facing service, single point-of-contact has responded to 28 service requests, with > 3000 queries since May 2019, with an average response time of two days.

Expert Advice

c4c has established a cohort of > 300 experts across clinical subspecialties, including methodology experts, as well as patient and parent representatives. The established procedures include a centralized contracting procedure to ensure a timely response (Fig. 2).

Beginning in 2019, c4c has included experts in the standing expert groups; since including experts, c4c has handled 26 advice requests. Processes have been put in place to ensure that costs are in line with fair market value and adherence to the European Federation of Pharmaceutical Industries and Associations Code of Practice for industry sponsors. Patient and public involvement activities are offered to all requests and undertaken as an ad-hoc service.

Site Identification and Feasibility

c4c has implemented streamlined processes to ensure qualitative and timely feedback on feasibility of sites. The core elements of the feasibility service that have been deployed in the proof of viability studies include (1) confidentiality disclosure agreements: site identification through a centralized database including more than 240 sites; (2) utilization of pre-agreed contractual templates across sponsors, national hubs, and sites allows efficient set-up of confidentiality disclosure agreements per sponsor per trial within 30 working days; and (3) protocol-specific feasibility: processes established to provide timely qualitative responses with country-specific input.

Set-up and Conduct of Trials

Trial-specific services during set-up and conduct of trials across c4c (Fig. 3) leverage on the network-building activities of 20 national hubs include continued relations with sites and national stakeholders, knowledge of the research landscape, training and network support, performance management, and quality improvement.

Education and Training

c4c has established a learning platform, which includes specific courses that have been designed and conducted utilizing consortium members' expertise. An Education Board, which reports to the Project Steering Committee, reviews the relevance and quality of these courses. The courses that are currently being piloted through the national hubs and sites for the subset of academic trials that are being supported by c4c are shown on their web site [18].

Trial Data

The terminologies used in clinical trials are inconsistent, making data reuse difficult. c4c has developed a cross-cutting pediatric data dictionary, which is a centralized

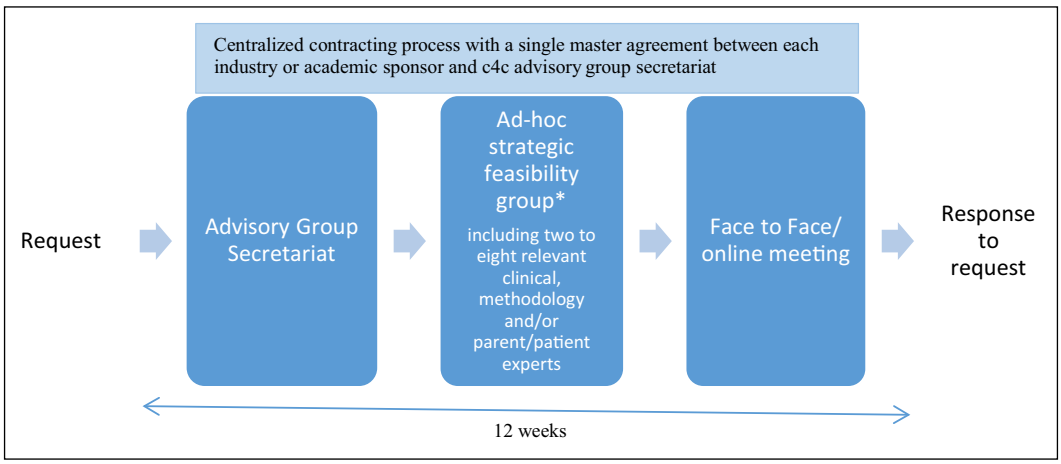

Fig. 2 c4c centralized contracting process for strategic feasibility. c4c's established procedures include a centralized contracting procedure to ensure a timely response. *c4c* conect4children

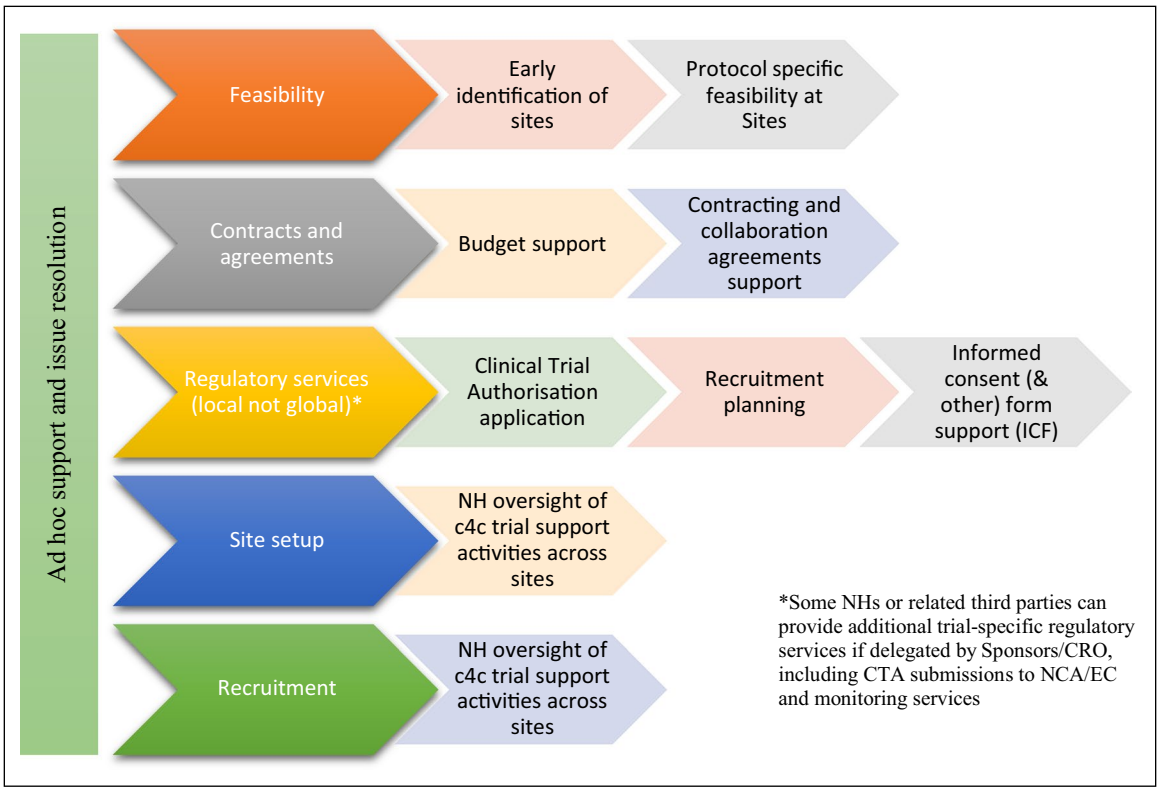

Fig. 3 c4c national hub support for trial activities. c4c has trial-specific services that support resolution during set-up and throughout the conduct of trials. *c4c* conect4children, *CRO* clinical research organization, *CTA* clinical trial agreement, *ICF* informed consent form, *NCA/EC* National Competent Authorities/Ethics Committees, *NH* national hub

repository of information about specific data. For example, a data dictionary may show data meaning, relationships, origin, usage, and format. c4c is working closely with Clinical Data Interchange Standards Consortium (CDISC) to develop a Therapeutic Area User Guide for pediatrics, which will help all pediatric studies using CDISC to generate more standardized and interoperable data.

Information System

The c4c Information System has been developed to support the operational elements of the above functions. All of the services offered by the Information System will be available to organizations that have contracts with the organization succeeding c4c.

Sustainability

Through the development and implementation of activities described above, the ultimate goal of c4c is to develop a sustainable set of key services. The nature of these services is being informed and evaluated through proof of viability trials, but the mechanisms for sustainability have not yet been defined in advance and will be identified based on the needs of key stakeholders (e.g., investigators, sites, contract research organizations, and trial sponsors). Work on the business model and legal structures for a successor organization is under way, with the hope of setting up an independent legal entity before the end of the funded c4c consortium in 2024.

Challenges Encountered

Variability of practice, procedures, and governance across the different European countries has been an anticipated challenge from the outset. Broadening the design elements to take a ground-level approach, as well as extending the consultation during the design and pilot stage of the services and processes led to more cohesion. Aspects outside of c4c's scope, such as ethics regulations of individual countries, national and regional laws, etc., will inform other research harmonization initiatives. Furthermore, c4c has been flexible in its implementation of services, taking into account the heterogeneity across and within the different sponsor organizations. These responsive tailored efforts, combined with engaging global sponsors' teams and national representatives (e.g., affiliates, sub-contracted clinical research organizations), have been invaluable to inform collective

learning across the national hubs and the central c4c coordination function.

Discussion

Networks have some similar characteristics. Table 1 lists a number of global networks where sites have been identified and processes have been instituted to facilitate pediatric clinical trial implementation. While each global area faces unique considerations, there are some common approaches to network development: (1) shared standards for site identification, provision of shared resources for documents, data acquisition, data analysis, and regulatory-ready submissions; (2) developing process interoperability, while not disturbing clinical care or the individual sites, including potential disruption of national, international, or other global requirements or previous relationships; (3) expanding global platforms and protocols to facilitate trial execution; (4) including all therapeutic areas and pediatric ages in the consideration of studies; (5) providing leadership by individuals with expertise in both pediatric clinical care and pediatric clinical trials; (6) launching quality improvement projects across the sites; and (7) advancing education and training, particularly with respect to Good Clinical Practice as required by the regulatory agencies.

Over the past 5–10 years, there has been a significant increase in the number of established global pediatric networks. Importantly, these networks should develop processes for collaboration rather than competition. Furthermore, network-developed resources should provide basic standardized approaches that can be shared across networks. Nevertheless, one must remain mindful that there are global differences with respect to standard of care, ethical approaches, and regulatory requirements. Some of the considerations for establishing consistency across networks include (1) identifying a single point-of-contact that will be used for enquiries to that network about trial design and/or implementation; (2) recognizing therapeutic areas of excellence at each of the sites so that protocol support can be accomplished by the sites with the most experience, thereby potentially improving the feasibility of trials; (3) improving processes to improve collaboration across trial networks, especially for rare diseases; (4) understanding the operational feasibility at each of the network sites, recognizing the resources required to undertake multiple studies simultaneously; (5) using collaborative approaches to education and training, as well as the development of programs, to educate the patient communities about clinical trials and the development of therapies for children; (6) creating and implementing data standards/data dictionaries across networks, particularly with respect to adverse event reporting; and (7) employing collaborative approaches to trial challenges including patient enrollment, trial visits, and trial follow-up.

Future Directions

Network access to multiple sites will be particularly useful with respect to natural history studies to define outcomes and sample sizes, biomarker development for enrichment of study populations and the potential development of surrogate endpoints, and access to a racially and ethnically diverse population of trial participants.

A number of new networks are being established with a plan to scale up activities in the therapeutics and devices space. In the next 2–3 years, these networks will expand collaborations with established networks, thereby broadening engagement with multiple stakeholders in the pediatric therapeutic development process. Patient and parent advocacy groups are critical to providing input on clinical trial designs and identification of patients for potential studies.

Each network needs to develop its own basis for individual and collective sustainability. Sustainable funding will cover the costs of the work, incentives to maintain capability/quality at the site level, and support for the coordination of each network. Additional support is necessary for the implementation of individual trials. Sources of sustainable funding include industry (subscriptions and/or fee-for-service) and public funders (governments or insurers). Importantly, sites need to identify internal resources and understand their limitations with respect to the number of trials that they can support.

While the core activities of networks and their services users are consistent, there is substantial diversity in how services are accessed and used. While each network and their users need to maintain internal consistency with governance and other standards, flexibility is needed to work effectively. Service users will not benefit from working with networks unless the service users can adapt to touch points, communication, and sequencing of operations that underpin the efficiency and effectiveness of the networks.

Conclusion

There is a significant need to develop new therapies for pediatric diseases and to establish safety, efficacy, and dosing for products that are used off-label in children. Global pediatric clinical trial networks have been established and provide efficiency across sites by leveraging therapeutic area centers of excellence, and developing standardized approaches to good clinical practice, data acquisition, data analysis, and regulatory document submission. Networks are also able to identify ethical and clinical standard of care approaches that differ across countries and regions. As an increasing number of

global pediatric trial networks are being developed, collaboration across networks will be of utmost importance to reduce duplication of effort, especially in the area of pediatric rare diseases. Such collaboration could be achieved through regular global meetings and conferences to discuss projects underway and future visions. Networks will need to engage additional stakeholders, including patient-parent advocacy groups, pharmaceutical industry partners, clinical research organizations, and funding/regulatory agencies to maximize the potential for effective and efficient pediatric therapeutic development.

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Declarations

Conflict of interest
All authors have no relevant conflicts of interest.

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