IDeA States Pediatric Clinical Trials Network for Underserved and Rural Communities

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The National Institutes of Health's Environmental Influences on Child Health Outcomes (ECHO) program aims to study high-priority and high-impact pediatric conditions. This broad-based health initiative is unique in the National Institutes of Health research portfolio and involves 2 research components: (1) a large group of established centers with pediatric cohorts combining data to support longitudinal studies (ECHO cohorts) and (2) pediatric trials program for institutions within Institutional Development Awards states, known as the ECHO Institutional Development Awards States Pediatric Clinical Trials Network (ISPCTN). In the current presentation, we provide a broad overview of the ISPCTN and, particularly, its importance in enhancing clinical trials capabilities of pediatrician scientists through the support of research infrastructure, while at the same time implementing clinical trials that inform future health care for children. The ISPCTN research mission is aligned with the health priority conditions emphasized in the ECHO program, with a commitment to bringing state-of-the-science trials to children residing in underserved and rural communities. ISPCTN site infrastructure is critical to successful trial implementation and includes research training for pediatric faculty and coordinators. Network sites exist in settings that have historically had limited National Institutes of Health funding success and lacked pediatric research infrastructure, with the initial funding directed to considerable efforts in professional development, implementation of regulatory procedures, and engagement of communities and families. The Network has made considerable headway with these objectives, opening two large research studies during its initial 18 months as well as producing findings that serve as markers of success that will optimize sustainability.

A PEDIATRIC CLINICAL TRIALS NETWORK

In 1993, Congress mandated the establishment of the Institutional Development Awards (IDeA) Program to distribute funding for biomedical and behavioral research to geographical areas that had historically received low levels of support from the National Institutes of Health (NIH).[1] The IDeA program builds research capacities by supporting basic, clinical, and translational research, faculty development, and infrastructure improvements. The IDeA program further seeks to enhance the ability of investigators to compete successfully for research funding. Historically, the major components of the IDeA program

abstract

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have been the Centers of Biomedical Research Excellence, which support a multidisciplinary research center in an IDeA state led by a NIH-funded investigator, and the IDeA Networks of Biomedical Research Excellence, which support research training of undergraduate students in eligible states.

In December of 2015, in an effort to expand pediatric-specific research capacity within IDeA states, the NIH solicited applications for funding to concentrate on building pediatric clinical trial research capacity and infrastructure to support the professional development of pediatric clinical investigators and their teams. The Environmental Influences on Child Health Outcomes (ECHO) IDeA Pediatric Clinical Trials Network (ISPCTN) (also referred to in this article as the "Network") solicitation was developed as a component of the larger ECHO initiative. Only institutional sites within IDeA states were permitted to serve as clinical sites and were required to have access to rural or medically underserved pediatric populations. Because of an emphasis on extending pediatric research to states historically underrepresented in NIH funding, sites were expected to have varying previous experience in pediatric research. Clinical site teams were expected to receive significant mentoring and growth of their research skills through the Network.

The primary aim of the ISPCTN is to enhance the competitiveness of pediatrician scientists in IDeA states to obtain funding for clinical trials research. The Network has several compelling features that make it unique, including the focus on research infrastructure specific to the conduct of trials, supervised professional training in trial implementation, and establishment of pediatric trial teams. A second aim is the Network focus on diseases and conditions that are especially relevant to pediatric populations residing in rural and medically underserved communities. The child health conditions are those included in the larger ECHO program including airway; obesity; neurodevelopment; prenatal, perinatal, and postnatal; and positive child health. Examples of disease-specific networks for clinical trials already exist,[2–6] although detailed descriptions of multisite network structures have frequently been limited to disease-specific networks largely populated with experienced centers.[7] Similarly, the Clinical and Translational Science Awards program has incorporated pediatric and child health research approximately in proportion to the US pediatric population (24%), although pediatricians are a small percentage of leadership (18%).[8] Thus, the particularly unique features of the ISPCTN to build pediatrician research expertise, while at the same time conducting clinical trials in rural and medically underserved communities, recognizes extant opportunities and gaps that will be addressed through the IDeA program. The ISPCTN's initial funding was for 4 years; thus, the identified aims provide a high bar to reach in a relatively short period of time.

The large NIH operational investment in the ECHO program has been described and encompasses the ISPCTN (see Fig 1).[9] Yet, only recently have components of the ISPCTN been identified.[10] The primary aim of this presentation is to provide a broad overview of the ISPCTN and the settings in which sites are nested. In addition, an overview of the research infrastructure and training to optimize successful implementation of pediatric trials as well as center sustainability is presented.

NETWORK STRUCTURE

In September 2016, 17 institutions were awarded funding and established the ISPCTN. Furthermore, the NIH awarded a central Data Coordinating and Operations Center (DCOC) to an institution from an IDeA state, the University of Arkansas, thus completing the Network structure. The Network aims to simultaneously implement clinical trials and provide research training and opportunities for personnel, including junior investigators, study coordinators, pediatric nurses, pharmacists, advanced practice providers, and clinic managers. Enhancing research capacity at each site provides an important research entryway to populations of children in rural and underserved communities, who have historically not been included in multisite pediatric trials. To accomplish this goal, organized professional development activities through new and existing resources are shared throughout the ISPCTN. Moreover, engaging and developing a core of pediatric physician scientists and pediatric research staff is a priority for sustaining and expanding the ISPCTN. The DCOC is integrated into all activities within the Network, providing data coordination, training, and funding for clinical trials from idea conception to protocol development, trial execution data analysis, presentations, and publications.

FEATURES OF NETWORK SITES

Given the unique nature of the Network, an expectation of the NIH was that each site would bring a different level of clinical expertise and pediatric trials experience. Supplemental Table 3 reveals the states in which Network sites are located. Some sites responded to the request for applications with multiple experienced principal investigators (PIs) and some with a mentor-mentee relationship for the multiple PIs, whereas others had a single PI with coinvestigators. The nature of ongoing collaborations and characteristics within the state at Network initiation allowed some sites access to affiliated sites for collaboration in their pediatric research efforts. At Network

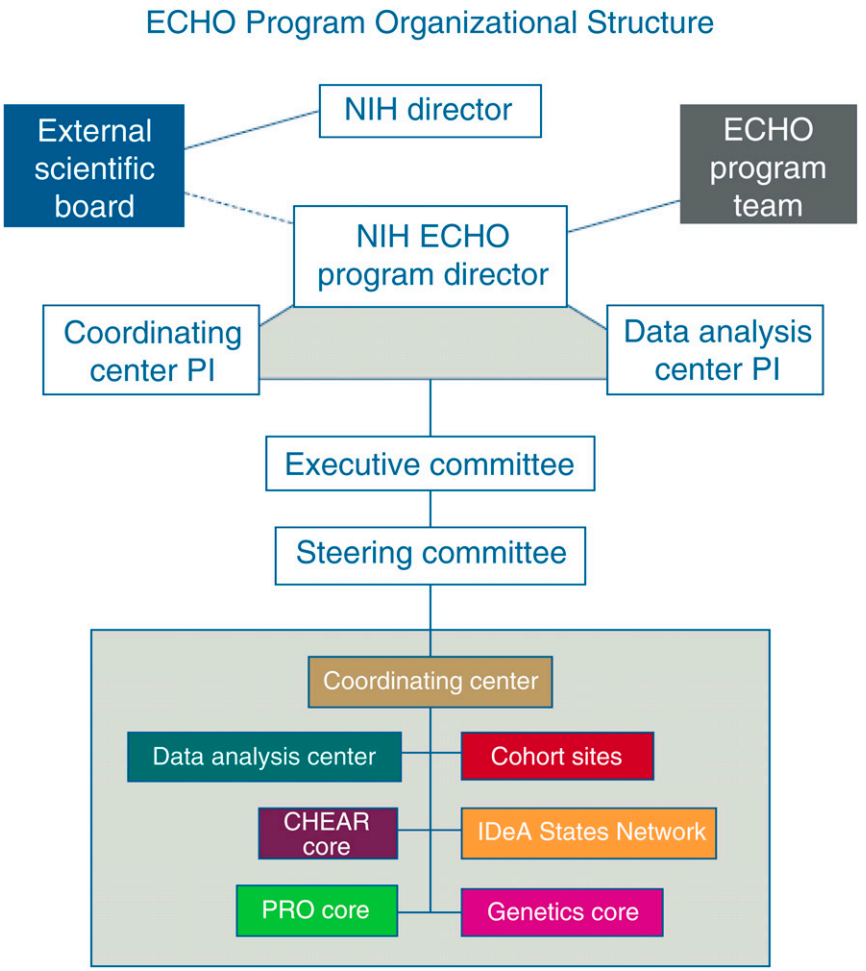

FIGURE 1
ECHO leadership structure. CHEAR, Children's Health and Exposure Analysis Resource; PRO, patient-reported outcomes.

initiation, 16 of 17 sites had developed an internal advisory committee as a means of harmonizing institutional missions. In contrast, only 6 of 17 sites had developed external advisory committees. Plans for tracking progress on the 3 primary network aims stated in the Request for Applications (enrollment of rural and/or underserved populations, community engagement, and professional development) were present at all sites. There were wide differences among sites in the presence and amount of previous experience with established pediatric networks. Previous to ISPCTN initiation, only 4 sites had previous collaborative experience with elements of the more established and larger ECHO cohorts.

CHARACTERISTICS OF ISPCTN STATE POPULATIONS

The 17 awardee sites are embedded within states with diverse pediatric populations (Table 1). Overall, when compared to the US population, the Network represents higher percentages for each indicator. Seven of 17 sites have high minority populations that exceed the US average; but, within the Network, significant variation exists: between 9% and 81%. The percentage of children below the poverty line varies between 10% and 30%. Metrics of child health status, such as preterm birth, percentage with low birth weight, percentage with asthma, and percentage with attention-deficit/hyperactivity disorder (ADHD), are overrepresented among ~50% of ISPCTN states compared to the US population (Table 2; preterm birth: 10 of 17 sites exceed the US average; low birth weight: 9 of 17 sites exceed the US average; asthma: 13 of 17 sites exceed the US average; ADHD: 13 of 17 sites exceed the US average). These characteristics give the ISPCTN an ability to conduct research in pediatric populations that are more diverse than what has historically been reported in pediatric clinical trials, affording the ability to undertake trials that can be more generalizable than those which are undertaken in traditional pediatric multisite networks.

RESEARCH INFRASTRUCTURE FOR PEDIATRIC TRIALS IMPLEMENTATION

The development and implementation of pediatric clinical trials has been acknowledged as particularly challenging. A lack of pediatric infrastructure has been recognized as a significant institutional barrier for some time.[11,12] Institutional capacity specific to pediatric trials rests on structures, including the physical resources for the conduct of trials as well as the unique regulatory hurdles entailed in pediatric trials.[13] The ISPCTN seeks to build these capacities within sites as well as across the network to advance improvements in children's health. Building institutional capacity has included NIH support for pediatrician scientist faculty, increasing research staff at sites, centralizing data management, and enhancing dedicated pediatric research space and equipment. These activities have been accompanied by the priority for implementing trials to improve the health and well-being of children residing in rural and medically underserved communities.

TABLE 1 ISPCTN State Characteristics

Indicator	United States	ISPCTN	Hawaii	Alaska	Montana	New Mexico	Oklahoma	Kansas	Nebraska	Mississippi	Louisiana	Arkansas	South Carolina	Kentucky	West Virginia	Delaware	Rhode Island	Vermont	New Hampshire
Child population, *n*[a]	73 399 342	9 105 248	303 414	183 816	229 434	482 153	956 486	705 961	476 841	706 141	1 095 916	703 180	1 105 945	1 008 829	364 160	203 616	205 213	115 973	258 170
Minority, %[a]	27.8	30.5	81.5	45.4	18.0	23.1	33.5	17.3	16.7	47.0	43.6	25.9	37.7	16.5	9.1	38.5	23.7	8.8	10.3
Medicaid and CHIP enrollment, %[b]	47.7	53.3	46.2	52.1	55.1	68.4	52.9	37.6	34.1	58.8	68.0	60.4	58.8	55.8	58.7	51.8	59.4	53.7	34.4
Below poverty, %[c]	14.6	14.9	10.3	10.2	14.4	20.6	16.2	12.8	12.0	21.5	19.6	18.1	16.6	18.3	17.8	12.1	13.4	11.4	8.1
Children with disability, %[d]	4.2	4.6	2.7	3.1	4.1	4.4	5.3	4.0	3.8	4.8	5.1	6.2	4.9	5.7	5.9	3.0	5.2	4.8	5.3
Children living below poverty level, %[e]	18.4	19.4	11.5	14.9	14.7	27.2	21.5	14.8	14.1	30.2	28.0	22.5	22.6	22.4	25.9	18.5	16.6	13.8	10.3

CHIP, Children's Health Insurance Program.

[a] Data are from https://www.census.gov/data/tables/time-series/demo/popest/2010s-state-detail.html#par_textimage_785300169.

[b] Number of children as of March 2019; data are from the Centers for Medicare and Medicaid Services; source: https://data.medicaid.gov/Enrollment/State-Medicaid-and-CHIP- Applications-Eligibility-D/n5ce-jxme.

[c] Data were extracted for each state. Data are from https://data.census.gov/cedsci/. See Table S1701 "PERCENT OF PEOPLE BELOW POVERTY LEVEL IN THE PAST 12 MONTHS 2017".

[d] Data are from https://data.census.gov/cedsci/. See Table S1810 "DISABILITY CHARACTERISTICS 2017".

[e] Data are from https://www.census.gov/library/publications/2018/demo/p60-263.html.

The Network has been encouraged to grow within local climates that have generally lacked research infrastructure along with pediatric researchers of various levels of trials research expertise and experience. Additionally, the Network emphasis has had to determine the priority of trials that are impactful for informing children's health. Of equal importance, Network pediatricians have been faced with building all of these facets for trial implementation within institutional environments in which resources, particularly resources for protected research time, have been sparse.

In an effort to optimize Network successes, research training for both investigators and site-level staff was an infrastructure priority. Because sites exist in settings that have historically had limited pediatric infrastructure (eg, a pediatric trials inpatient or outpatient unit), research training has been a substantial activity of the first year of ISPCTN. In some of our sites, there were few pediatric research personnel, requiring new hires and uniform training to bring a requisite minimum level of experience to support trial implementation. The DCOC brought considerable effort to the development and implementation of pediatric research training. Site infrastructure and capacity for pediatric research has been described separately.[10] However, in short, the DCOC completed a brief assessment of pediatric resources at each site and tailored this with teaching modules built to increase knowledge and expertise with elements of the pediatric research enterprises ranging from budgeting to regulatory to data management.

Recognizing a need for building site infrastructure through experience, NIH leadership encouraged collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development funded Pediatric Trials Network at the Duke Clinical Research Institute.[14] The objective of this activity was to facilitate ongoing capacity at awardee sites, especially those with limited previous research experience. The Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care was implemented across the Network because many sites had limited experience in the area of population pharmacokinetics. IPSCTN sites were thus able to build their local infrastructure to identify and recruit eligible participants, which has led to sites being invited to participate in other Pediatric Trials Network trials.

Trial development across the ISPCTN has resulted in the adoption of a centralized regulatory system. Of necessity, local site administrative research officials were requested to provide a reliance agreement, including the Streamlined, Multisite, Accelerated Resources for Trials institutional review board (IRB)[15] and, with Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care, Western IRB. Network sites that incorporated Indigenous communities additionally needed to work closely with tribal IRBs and tribal health organization research oversight committees, which served the dual purpose of community engagement and addressing regulatory concerns.[16–18]

A critical element of network infrastructure has been to master the principals of pediatric team science. Team science brings unique challenges to the pediatric research milieu. Developing a pediatric trials team is supported by ISPCTN funding, yet assembling a team and working to make a productive group of pediatric researchers is complex and time consuming.[19,20] With the ISPCTN, considerable efforts have been focused on building teams at the Network level through the implementation of working groups aligned with the ECHO priority areas

TABLE 2 Child Health Status Among ISPCTN Locations

Indicator	United States	Hawaii	Alaska	Montana	New Mexico	Oklahoma	Kansas	Nebraska	Mississippi	Louisiana	Arkansas	South Carolina	Kentucky	West Virginia	Delaware	Rhode Island	Vermont	New Hampshire
General pediatricians per 100 000 children, n[a]	—	115.9	80.6	60.2	66.6	49.6	72.5	68.5	54.5	79.1	62.3	77.8	86.4	70.7	103.8	142.0	148.5	115.6
Vaccination, %[b]	91.5	90.5	89.3	92.3	89.3	91.7	89.8	89.8	91.8	91.3	92.6	88.0	92.7	89.9	92.9	95.3	93.7	94.1
Asthma, %[c]	8.3	10.0	9.2	8.9	9.9	9.5	8.7	7.2	7.8	8.2	10.1	8.2	11.9	10.8	9.2	11.0	11.0	10.1
Overweight/ or obese, %[d]	18.5	14.0	14.0	12.0	15.0	17.0	13.0	15.0	25.2[e]	17.0	22.0	17.0	20.0	19.0	15.0	15.0	13.0	13.0
Preterm birth rate, %[f]	9.9	10.6	9.0	9.5	10.0	11.1	9.6	9.9	13.7	12.7	11.4	11.2	11.1	12.0	10.2	8.3	7.5	8.4
Low birth wt, %[f]	8.2	8.5	6.2	8.0	9.0	8.1	7.4	7.5	11.5	10.7	9.3	9.7	8.8	9.5	9.0	7.5	6.7	6.9
Infant mortality, %[f]	5.9	5.3	5.6	5.4	6.2	7.7	6.1	6.2	8.6	7.1	8.2	6.5	6.5	7.0	6.6	6.2	5.9	4.2
ADHD, %[g]	11.0	8.5	8.8	11.7	7.5	11.9	11.6	11.6	14.0	15.8	17.0	15.7	18.7	11.9	14.3	13.4	10.5	11.9
Youth reporting sadness, %[h]	30.4[i]	29.5	36.1	31.0	35.8	31.8	24.8	27.0	—	31.7	40.2	33.2	29.2	32.0	27.6	29.4	25.4	28.0

—, not applicable.

[a] Data are from the Pediatric Physicians Workforce Data Book 2017–2018.

[b] Measles-mumps-rubella vaccination coverage among children 19–35 mo in 2017; source: https://www.cdc.gov/vaccines.

[c] Data are from the Centers for Disease Control and Prevention; source: https://www.cdc.gov/asthma/most_recent_data_states.htm.

[d] Data are from the Centers for Disease Control and Prevention; source: https://www.cdc.gov/healthyschools/obesity/obesity-youth.htm.

[e] Data are from the Mississippi Obesity Action Plan 2018; source: https://msdh.ms.gov/msdhsite/_static/resources/6164.pdf.

[f] Data are from the National Center for Health Statistics, 2016 and 2017; source: https://www.cdc.gov/nchs.

[g] Data are from the National Survey of Children's Health 2011; source: https://www.cdc.gov/ncbddd/adhd/stateprofiles.

[h] Data are from CDC *MMWR Youth Risk Behavior Surveillance: United States, 2017*, Table 43: Percentage of high school students who felt sad or hopeless, by sex, sexual identity, and sex of sexual contacts.

[i] Median reported.

(airway; obesity; neurodevelopmental; prenatal, perinatal, and postnatal; positive child health). Yet, recognizing that many sites include minority communities, including Indigenous communities, an emphasis of ongoing Network development has been the inclusion of community stakeholders. Sites have actively sought community stakeholder input, primarily through the development of community advisory committees, and the Network has capitalized on these site activities with a stakeholders' working group as part of regular steering committee meetings.

As with any new research network, prioritizing the development of local and network leadership and creating a time line for trial implementation have been considerable. The Network has created a steering committee, leadership committee, and publication and presentations committee that manage scientific decision-making, study implementation, results dissemination, and professional development. The NIH ECHO office has developed responsibilities for appointing and administering an independent protocol review committee and data and safety monitoring board. The protocol review committee reviews all finalized protocols for both scientific fidelity and feasibility and makes recommendations to the NIH ECHO director.

ISPCTN PROFESSIONAL DEVELOPMENT

Professional development through supervised training in clinical trial implementation remains a primary goal of the Network. The Network's steering committee meetings have provided one venue for this training, exemplified in didactic sessions for enhancing research team engagement and educational presentations on team science. Building on these in-person trainings, the DCOC created web-based trainings for both

pediatrician scientists and pediatric research staff. Domains for training have included regulatory concerns in the conduct of research with children, community engagement, data management, and critical elements of clinical trials (eg, trial phases). To date, the DCOC has created 25 trainings that are nested in these domains. These have been webcast and are available via archive on the ISPCTN Portal. Live participation has ranged considerably, with up to 70 participants for any 1 didactic session. In addition to these professional development series, local sites have required competency-based training, including that offered through a site's workforce development program associated with the local translational science center and/or Good Clinical Practice training. Only recently has there been recognition for standardized training for federally funded clinical trials with the implantation of the Enhancing Clinical Research Professionals' Training and Qualifications project.[21,22]

SUSTAINABILITY AND MARKERS FOR SUCCESS

Network sustainability rests on a foundation of trials that impactfully address high-priority child health, trial implementation and completion, community engagement support, dissemination of findings, and translation to public policy. Initial successes of the Network include the Advancing Clinical Trials in Neonatal Opioid Withdrawal Current Experience study, Vitamin D Oral Replacement in Asthma, and the Advancing Clinical Trials in Neonatal Opioid Withdrawal initiatives (eating, sleeping, consoling for neonatal opioid withdrawal in a randomized blinded trial to shorten pharmacologic treatment of newborns with neonatal opioid withdrawal syndrome). These studies were developed in the initial 18 months of the ISPCTN and include presentations and articles that have been produced. Already, the network goal of enhancing competitiveness of pediatrician scientists to obtain clinical trials funding has been achieved with modest success, with collaborations that have led to federal grant applications. Along with these Network activities, particular attention has been focused on community support, particularly critical in rural and underserved communities that include Indigenous people. Taken as a whole, these sustained efforts by ISPCTN investigators may be expected to make for a robust and sustainable clinical trials network that will inform the health of children for generations to come.

ECHO COHORT COLLABORATION

A long-term goal of the ECHO program is to inform the ISPCTN's development of pediatric clinical trials that advance understanding of children's health as well as generate solution-oriented research. ECHO components include a coordinating center, data and analysis center, patient-centered outcomes, health exposures and analysis resources, genetics, and analytic results from the ECHO cohorts themselves. ECHO cohorts aim to create a large database from aggregation of over 50 000 children, and this process includes the challenges of transmitting, harmonizing, and prioritizing data across the entire range of extant data, such as participant and family characteristics, clinical outcomes, environmental exposures, genetics, and metadata elements. The bidirectional synergy between ECHO components and the ISPCTN is critical for the long-term success of the entire program and creates a roadmap for future partnerships.[23–25]

Collaborations between the ISPCTN and ECHO cohorts may take several forms. ISPCTN investigators are represented on cohort working groups, enhancing crosstalk between the ECHO components. ISPCTN representatives contribute to ECHO-wide committees, including the Executive Committee, Policy Implementation and Evaluation Committee, and ECHO Discovery Editorial Board, and educational and dissemination platforms. ISPCTN and DCOC representatives attend ECHO Steering Committee meetings, contributing to both tabletop and programmatic discussions. Lastly, ISPCTN collaborates with the other components of the ECHO program in the selection and mentoring of competitively awarded, internally funded pilot projects through the ECHO Opportunities and Infrastructure Fund. The Opportunities and Infrastructure Fund is an NIH-funded grants mechanism for early investigators to support projects for the introduction of new research, tools, and technologies within the ECHO program.

LIMITATIONS

Although ambitious in the aims for the initial years of funding, the Network has only begun to develop and implement pediatric effectiveness trials. Network successes have included methodologic discussions of clinical trial design, including those used in public health service delivery research (eg, stepped-wedge design[26,27]) that are being implemented with trials becoming activated. Network investigators will need to consider additional clinical trial designs that inform pediatric health practice as well as those that include dose finding, drug pharmacokinetics, and efficacy monitoring, such as adaptive designs that inform communities and pediatric health providers.[28–30] Other novel trial methods and designs, such as value of information methods and platform designs, will need to be considered.[31–33] Moreover, professional development activities that educate pediatric researchers about trial designs will need to be

included in future Network activities.[34]

CONCLUSIONS

The NIH ECHO initiative has taken a novel approach to promoting pediatric research that informs children's health care and seeks to positively influence future child health, particularly those children residing in rural and medically underserved communities. The ISPCTN represents a novel network with a focus on overlapping child health domains, including positive child health, and serves as a testing ground for findings from ECHO cohorts that are distilled into high-impact pediatric clinical trials. This Network is unique because the sites for pediatric trials are being established within states with historically low NIH funding success. Moreover, the sites are predominantly nested adjacent to or within largely rural communities, in which significant health disparities exist. Importantly, with the inclusion of rural communities, the findings from trials conducted within the Network are expected to be generalizable to all children.

In the creation of the ISPCTN, the initial challenges to Network functioning required the development of leadership and communication structures that could optimally guide the implementation of pediatric trials and support structures for sites to increase capacity to conduct trials. With this challenge was a core mandate to build a new generation of geographically distributed pediatrician researchers. The process of building a new Network with issues of both infrastructure gaps and trial prioritization has involved the need to rise above a series of high hurdles, a task that the ISPCTN teams have successfully completed. The development of a considerable infrastructure necessary to successfully implement pediatric trials should be recognized as a significant achievement for the initial years of NIH support. In this overview of the initiation and development of the ISPCTN, we provide not only the opportunity to conduct and disseminate pediatric clinical research to a geographically diverse population of children but also a useful roadmap for future networks that might impact children throughout the United States.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
DCOC: Data Coordinating and Operations Center
ECHO: Environmental influences on Child Health Outcomes
IDeA: Institutional Development Awards
IRB: institutional review board
ISPCTN: Institutional Development Awards States Pediatric Clinical Trials Network
NIH: National Institutes of Health
PI: principal investigator

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