Capacity Building in a New Clinical Trials Network through Inter-Network Collaboration

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The Institutional Development Award (IDeA) is a congressionally mandated program helping to build research capacity by supporting research, faculty development, and infrastructure improvements in states with low National Institutes of Health (NIH) funding levels.[1] Children, racial, and ethnic minorities, rural populations, and patients of low socioeconomic status are underrepresented in clinical research, which limits the generalizability of results.[2-4] To address this gap, 17 institutions were awarded funding in 2016 to establish the IDeA States Pediatric Clinical Trials Network (ISPCTN) by the NIH's Environmental Influences on Child Health Outcomes Program (**Table I**).[5]

ISPCTN states encompass disproportionately rural and medically underserved populations, which are often underrepresented in clinical research studies. The ISPCTN's primary objectives are increasing representation of medically underserved and rural populations in clinical trials, applying findings from relevant pediatric cohort studies to children in IDeA state locations, and building pediatric research capacity at a national level.[5] However, at the outset, ISPCTN sites were relatively research-naïve, and institutional infrastructure for conducting research was resource limited. Challenges of performing research with limited resources include limited provider time and capacity because of competing clinical responsibilities, availability/training of study staff (eg, nurses, statisticians), access to mentorship, availability of infrastructure (eg, examination rooms and equipment), and the cost burden of research.[6,7] Evidence suggests that partnering with academic health centers possessing well-developed research infrastructure promotes early investigator growth at resource-limited institutions, and increases patient access to research in remote areas.[7-9]

In 2017, the ISPCTN partnered with the Pediatric Trials Network on an existing multicenter clinical research study, the Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care study (POP01). The Pediatric Trials Network, a coalition of over 100 academic research sites primarily in the US, was established in 2010 by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development to collaboratively design and conduct pediatric drug trials to help close information gaps regarding pediatric drug dosing, safety, and efficacy.[10] POP01 was designed by the Pediatric Trials Network to better characterize the pharmacokinetics (PK) of selected drugs in pediatric patients where limited information was available.[11] Through this collaboration between the well-established Pediatric Trials Network and the newly developed ISPCTN, the ISPCTN sought to build research capacity through a variety of mechanisms. First, ISPCTN participation in POP01, under the mentorship of the Pediatric Trials Network, would allow

Abbreviations

EHR	Electronic health record
ESI	Early-stage investigator
IDeA	Institutional Development Award
ISPCTN	IDeA States Pediatric Clinical Trials Network
NIH	National Institutes of Health
PI	Principal investigator
PK	Pharmacokinetics
POP01	Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care study
sub-Is	Sub-investigators

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for growth and development of new and established investigators and clinical research staff. Second, experiential learning from active clinical research study engagement would enhance research-related infrastructure (eg, equipment, patient recruitment procedures, standard operating procedures) at ISPCTN sites and increase site-level clinical staff interactions with clinical research team members and processes, facilitating patient recruitment and research conduct across diverse divisions/units. It was postulated that such gains would boost site-level research team confidence in conducting research.

Methods and Results

Eighteen clinical sites from within the ISPCTN participated in POP01 (1 site per ISPCTN-institution, except South Carolina, where 2 individual clinical sites participated). Four sites were active in POP01 before ISPCTN creation; the remaining 14 sites were activated between April 2018 and May 2019 through the ISPCTN and Pediatric Trials Network collaboration. A committee, led by physicians from the 4 ISPCTN sites that were already active in POP01, was formed to assist each newly activated ISPCTN site in navigating the study start-up process. In addition, the Pediatric Trials Network hosted monthly phone calls with ISPCTN principal investigators (PIs) and study coordinators to troubleshoot issues and provide a venue to share successes and challenges.

Subjects (n = 382) were recruited from ISPCTN sites to participate in POP01 as of study closure in September 2019. Each site completed a 30-question survey to enable retrospective reporting of growth in research capacity and infrastructure that occurred through collaboration with the Pediatric Trials Network. Surveys were completed with input from the ISPCTN PI, the POP01 PI, and the main POP01 study coordinator at each institution.

Between April 2018 and August 2019, there were 20 POP01 PIs from the 18 sites (2 sites changed PIs during that interval). Of these, 7 (35%) were early-stage investigators (ESIs), and 7 (35%) were new to PK research (of the 7 new to PK research, 5 were ESIs). Per NIH, an ESI is an investigator who is <10 years out of training and has not previously competed successfully as PI for a substantial NIH independent research award. Twelve sites had sub-investigators (sub-Is), with a total of 58 sub-Is working on POP01 (average of 3 sub-Is per site, 95% CI [1.32-5.12]). Of the 58 sub-Is, 29 were ESIs (50%), and 45 (78%) were new to PK research. For the 18 study coordinators, 8 (44%) were new to PK research.

Ten sites (56%) added staff, and 7 (39%) added resources specifically for POP01 participation. Added resources included refrigerated centrifuges and −70 degree Celsius freezers (to process and store blood samples), extra computers (for data entry), examination or office space, and research laboratory space (Table II). As a result of participation in POP01, 12 sites (67%) developed new workflows for processing laboratory specimens (collection, storage, shipping, etc), and 28% developed new standard operating procedures for conducting clinical research (Table III).

Fifteen sites (83%) developed a new collaboration with a clinical division, unit, or nonstudy staff to aid POP01 participation. Examples were "establishing a working relationship with physicians in the outpatient pediatric cardiology clinic to allow study staff to recruit patients for POP01" (clinical division), "working with the pediatric sedation unit in their affiliated hospital to recruit patients for POP01 who were scheduled for a procedure under sedation" (clinical unit), and "working with the inpatient pharmacy team to query the electronic health record (EHR) for a daily list of possible POP01 participants" (clinical staff). Across the 15 sites with new collaborations, 84 new relationships (average of 4 per site) were formed with 21 different pediatric clinical divisions (pediatric critical care, pediatric gastroenterology, adolescent medicine, etc), and a few nonpediatric-specific clinical divisions (day medicine, orthopedics, anesthesia). Similarly, 51 new collaborations were forged with clinical units (average of 3 per site). The 4 most common were the pediatric intensive care units, neonatal intensive care units, inpatient pediatric wards, and site-based inpatient laboratories.

Table I. The 17 institutions that encompass the ISPCTN

Alaska Native Tribal Health Consortium Anchorage, AK	University of Mississippi Medical Center Jackson, MS
Arkansas Children's Research Institute Little Rock, AK	University of Montana Missoula, MT
Dartmouth College Hanover, NH	University of Nebraska Medical Center Omaha, NE
Tulane University New Orleans, LA	University of New Mexico Health Sciences Center Albuquerque, NM
Nemours Alfred I. duPont Hospital for Children Wilmington, DE	University of Oklahoma Health Sciences Center Oklahoma City, OK
Rhode Island Hospital Providence, RI	University of South Carolina Columbia, SC
University of Hawaii at Manoa Honolulu, HI	University of Vermont Burlington, VT
University of Kansas Medical Center Kansas City, KS	West Virginia University Morgantown, WV
University of Louisville Louisville, KY	

Table II. Investment in staff and resources needed by ISPCTN sites to launch the POP01 study (n = 18 sites)

7 sites (39%) added equipment New equipment added included:	10 sites (56%) added new study staff New staff added included:
−70° C freezer	Part-time study coordinator
Refrigerated centrifuge	Full-time study coordinator
Office space	Part-time study nurse
Examination room space	Full-time study nurse
Research laboratory space	Part-time research assistant
Computer	

Table III. Development of new internal methods for the processing of laboratory specimens and SOPs for the conduct of clinical research necessary for ISPCTN site successful participation in the POP01 study

12 sites (67%) developed new methods for laboratory specimen processing New methods developed included:	5 sites (28%) created new SOPs for the conduct of clinical research New SOPs created included:
Specimen collection	Calibrating equipment
Specimen processing	Keeping temperature logs
Specimen storage	Biospecimen transport
Specimen shipping	Regulatory processes
Temperature monitoring of specimens	
Specimen documentation logs	

SOPs, standard operating procedures.

Thirty-nine new relationships were developed with clinical staff (average of 2 per site); the 3 most common were pharmacists, clinical informatics, and pediatric trainees.

Study teams at 16 sites (89%) provided an average of 3 educational sessions on POP01 (95% CI [2.11-3.77]) to a variety of nonstudy staff, primarily inpatient and outpatient nurses, institutional faculty (clinical physicians), and clinical administrative staff. Eleven sites had processes in place, some rudimentary, to query their institution's EHR for research recruitment prior to POP01; however, 16 sites (89%) developed new EHR query processes specifically for POP01 participant recruitment.

Each site was surveyed regarding how participating in POP01 had impacted the research team's confidence in conducting clinical research. A score of "0" denoted no impact, and a score of "10" denoted a very strong impact. The average score across the 18 sites was 8.1 (95% CI [7.47-8.64]).

Discussion

Clinical research networks aim to advance knowledge and health outcomes through conducting research and facilitating collaborations, education and training, study implementation, and data sharing.[12] Capacity building within a clinical research network refers to growing and enhancing investigators, study teams, organizations, and systems, with a primary goal of producing sustained change and improvement in undertaking and disseminating high-quality research efficiently and effectively.[13] A large body of literature describes capacity-building gains from forming clinical research networks.[5,14] However, no prior studies examine the impact of collaboration between a new, research-naïve network and a mature network with well-established research infrastructure on capacity building within the new network.

In the first year of ISPCTN activities, collaboration with the Pediatric Trials Network through participation in POP01 provided an opportunity for network-to-network mentoring, within-network mentoring, and ISPCTN site engagement in research activities. Under the Pediatric Trials Network and ISPCTN leadership guidance, ISPCTN sites completed critical study start-up milestones including obtaining institution review board approval for a research study, participating in site qualification and site initiation visits, and identifying investigators to perform the study at each institution. POP01 participation allowed research-naïve sites to learn about local resources, identify and fill gaps in their research capacity, and practice clinical research workflows such as patient identification/recruitment, specimen processing, and data management.[5] All this was aided by Pediatric Trials Network-hosted monthly site-wide phone calls for continued mentoring, troubleshooting, and sharing of successes and challenges.

The growth of ESIs and the development of new skill sets for experienced investigators and study coordinators are pivotal factors for sustaining a research program. The substantial number of ESIs at ISPCTN sites and the number of study team members who were new to PK research will enhance maturation of these investigators, staff, and sites into strong clinical research entities.

In academic centers whose primary missions are clinical and teaching, the organizational culture may impede initiating and sustaining research programs.[15,16] Through POP01 participation, ISPCTN sites developed new relationships with myriad clinical divisions/units/staff while working on patient recruitment and study-related procedures. In doing so, nonstudy physicians and clinical teams interacting with PIs and research staff became more familiar with research-related workflows and practices. Although not all these relationships may be long-lasting, these initial interactions may lead to collaborations with those same people/units on future research studies. In addition, exposing clinical physicians to research within their practice settings may spark individual interest in a clinical research career path.

We examined the effects of network-to-network collaboration and mentoring on the growth of research capacity and infrastructure within a newly formed clinical research network. Collaboration of the ISPCTN with the Pediatric Trials Network on this multi-site clinical research study allowed for substantial growth of site-level teams and resources. These results reveal the positive impact of inter-network collaboration and mentoring and may assist future fledgling networks in developing capacity-building efforts that are practical, effective, and efficient. ■

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References

1. Gorospe JR. Institutional Development Award. National Institute of General Medical Sciences, U.S. DHHS, Oct 5, 2012. www.nigms.nih.gov/Research/DRCB/IDeA/Pages/default.aspx. Accessed August 7, 2020.

2. Cohen E, Uleryk E, Jasuja M, Parkin PC. An absence of pediatric randomized controlled trials in general medical journals, 1985-2004. J Clin Epidemiol 2007;60:118-23.
3. Bourgeois FT, Murthy S, Pinto C, Olson KL, Ioannidis JPA, Mandl KD. Pediatric versus adult drug trials for conditions with high pediatric disease burden. Pediatrics 2012;130:285-92.
4. Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer 2008;112:228-42.
5. Snowden J, Darden P, Palumbo P, Saul P, Lee J, IDeA States Pediatric Clinical Trials Network. The ISPCTN: building research capacity among the rural and medically underserved. Curr Opin Pediatr 2018;30:297-302.
6. Safdari R, Ehtesham H, Robiaty M, Ziaee N. Barriers to participation in medical research from the perspective of researchers. J Educ Health Promot 2018;7:22.
7. Armstrong LJ, Finny P. Building research capacity in resource-poor settings: triumphs and challenges. Natl Med J India 2016;29:295-7.
8. Macleod MLP, Dosman JA, Kulig JC, Medves JM. The development of the Canadian Rural Health Research Society: creating capacity through connection. Rural Remote Health 2007;7:622.
9. Birden HH. The researcher development program: how to extend the involvement of Australian general practitioners in research? Rural Remote Health 2007;7:776.
10. England A, Wade K, Smith PB, Berezny K, Laughon M, Best Pharmaceuticals for Children Act - Pediatric Trials Network Administrative Core Committee. Optimizing operational efficiencies in early phase trials: the pediatric trials network experience. Contemp Clin Trials 2016;47:376-82.
11. Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care - Full Text View - ClinicalTrials.gov. http://clinicaltrials.gov/ct2/show/NCT01431326%20.
12. Li G, Wu Q, Jin Y, Vanniyasingam T, Thabane L. Key factors of clinical research network capacity building. J Venom Anim Toxins Incl Trop Dis 2018;24:15.
13. Capacity Building in Research. How to Note: A DFID Practice Paper, Department for International Development, June 2010. assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/187568/HTN_Capacity_Building_Final_21_06_10.pdf. Accessed August 14, 2020.
14. Ali R, Finlayson A, INDOX Cancer Research Network. Building capacity for clinical research in developing countries: the INDOX cancer research network experience. Global Health Action 2012;5:1.
15. Feldman AM. Does academic culture support translational research? Clin Transl Sci 2008;1:87-8.
16. Somkin CP, Altschuler A, Ackerson L, Geiger AM, Greene SM, Mouchawar J, et al. Organizational barriers to physician participation in cancer clinical trials. Am J Manag Care 2005;11:413-21.