

COLLABORATION

Sponsors meet scientists to speed pediatric medicines development

Jonathan M. Davis,^{1*} William E. Smoyer,^{2,3} Edward M. Connor,³ W. Charles Huskins,⁴ Cindy Pastern,⁵ Mary Purucker,⁶ Elisabeth C. Schrader,⁷ Cynthia R. Jackson,^{7,8} Frederick J. Kaskel,⁹ Steven Hirschfeld¹⁰

The Point-Person Project, a child-health research initiative, enables rapid response to opportunities for participation in multicenter pediatric clinical trials.

Clinical research displays inherent inefficiencies owing to scattered infrastructure and communication channels, lack of harmonized standards for information and data exchange, and the use of customized solutions for each study (1). These bottlenecks complicate the matching and engaging of relevant investigators with clinical trial expertise and direct access to relevant patient populations. Current practice generally relies on expensive and time-consuming negotiations and contracts with multiple investigators and institutions. In some cases, outside parties negotiate with networks established for a particular patient population or disease process, but network-specific agendas and priorities can constrain collaboration (2). Child health research and development faces these as well as its own unique impediments. For example, pediatric medicine is a small market with relatively few patients, and inefficiencies exist across the entire enterprise. Clinical trials with children require stringent regulatory oversight, which, along with the small patient populations, makes safety and efficacy for new therapies difficult to establish. A general lack of training in pediatric

therapeutics development exists because of the relatively few opportunities for investigators to conduct high-quality clinical research (3). Last, priorities of the various stakeholders—academic investigators, U.S. National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), and industry—are not well aligned.

Recognizing that time and efficiency are critical resources, FinnPedMed (Helsinki, Finland) instituted a pager mechanism in 2007 to link investigators with a central point of contact so that they could respond quickly to inquiries regarding participation in clinical studies (4). This arrangement provided logistical, operational, and financial advantages for all parties. Following the lead of FinnPedMed, child health researchers at NIH Clinical and Translational Science Award (CTSA) recipient institutions (www.ctsacentral.org) initiated a pilot venture; this so-called Point-Person Project was designed to link clinical-research sponsors with subject-matter experts and relevant patient populations using a centralized portal and a network of institutional points of contact or “navigators.” These institutional navigators communicated with local investigators and determined who had sufficient interest and expertise to respond to selected clinical research opportunities. Here, we report on the program’s initial outcomes.

PROJECT PARTICIPATION

The principal investigators at the 55 participating CTSA programs designated a total of 84 point persons (PPs) with M.D. or Ph.D. degrees (scientists) (74%), nursing degrees (8%), or Master’s or other degrees (clinical research administrators or study coordinators). These individuals functioned as navigators and directed clinical-trial opportunities to appropriate investigators at their respective institutions. Pediatric clinical-trial sponsors, contract research organizations (CROs), and individual investigators

submitted trial requests (table S1) that were reviewed by senior child-health researchers and then distributed to PPs as brief protocol synopses [via the research electronic data capture (REDCap) database (Fig. 1)]. A drop-down menu at the end of the synopsis offered three options: Investigators who clicked on (i) “interested” were asked for contact information that was then forwarded directly to the clinical trial sponsor within 72 hours, with the sponsor then initiating further contact; (ii) “not interested” were asked their reason for not participating, and this ended any further contact; (iii) “need more information” were invited to participate in a scheduled group teleconference with all interested investigators, CTSA and NIH representatives, the sponsor, and any other interested parties (up to 25 to 30 individuals participated in each of these calls) so that the investigator could have his or her questions answered, obtain more information, and decide whether to participate in the trial. If the sponsor was a CRO, then specific industry representatives who contracted with the CRO to conduct the trial also participated in the call. PPs were sent surveys at the end of the one-year pilot period (table S2), and PPs from 47 of 55 (85%) participating CTSA sites returned responses. The survey questions were reviewed in advance by the Mayo Clinic Institutional Review Board and determined not to constitute research.

Twenty-four protocol-information forms were submitted over a one-year period, and a variety of diseases that affect infants and children were proposed for study (table S3), with most involving children 6 to 17 years of age. One sponsor withdrew a study after initial review and discussion with senior child-health investigators (prior to distribution) and five others were withdrawn (25% of all protocols) after investigators identified major problems with the study design. Although these five studies were granted an investigational new drug (IND) application by FDA, there were significant technical issues that made it unlikely that the trial could be successfully completed as designed. Substantial improvements in study design were then resubmitted as IND amendments to FDA.

Fifty-five of the 62 CTSA programs participated in the PP project, with a total of 289 responses (range 0 to 18 per site) received; 129 (45%) were initially interested, 93 (32%) needed more information, 64 (22%) were not interested, and 3 sites were

¹Department of Pediatrics, The Floating Hospital for Children and the Tufts Clinical and Translational Science Institute, Boston, MA 02111, USA. ²Center for Clinical and Translational Research, Nationwide Children’s Hospital, Columbus, OH 43205, USA. ³Clinical and Translational Research Institute, Children’s National Medical Center, Washington, DC 20010, USA. ⁴Division of Pediatric Infectious Diseases, Mayo Clinic, Rochester, MN 55905, USA. ⁵CTSA Consortium Coordinating Center, Vanderbilt University, Nashville, TN 37232, USA. ⁶National Center for Advancing Translational Science, Bethesda, MD 20892, USA. ⁷Pediatric Center of Excellence, Quintiles, Inc., Durham, NC 27703, USA. ⁸Department of Pediatrics, Division of Pediatric Infectious Diseases, Duke University Medical Center, Durham, NC 27710, USA. ⁹Department of Pediatrics, Montefiore Medical Center, New York, NY 10467, USA. ¹⁰National Institute for Child Health and Human Development, Bethesda, MD 20892, USA.

*Corresponding author. E-mail: jdavis@tuftsmc.com

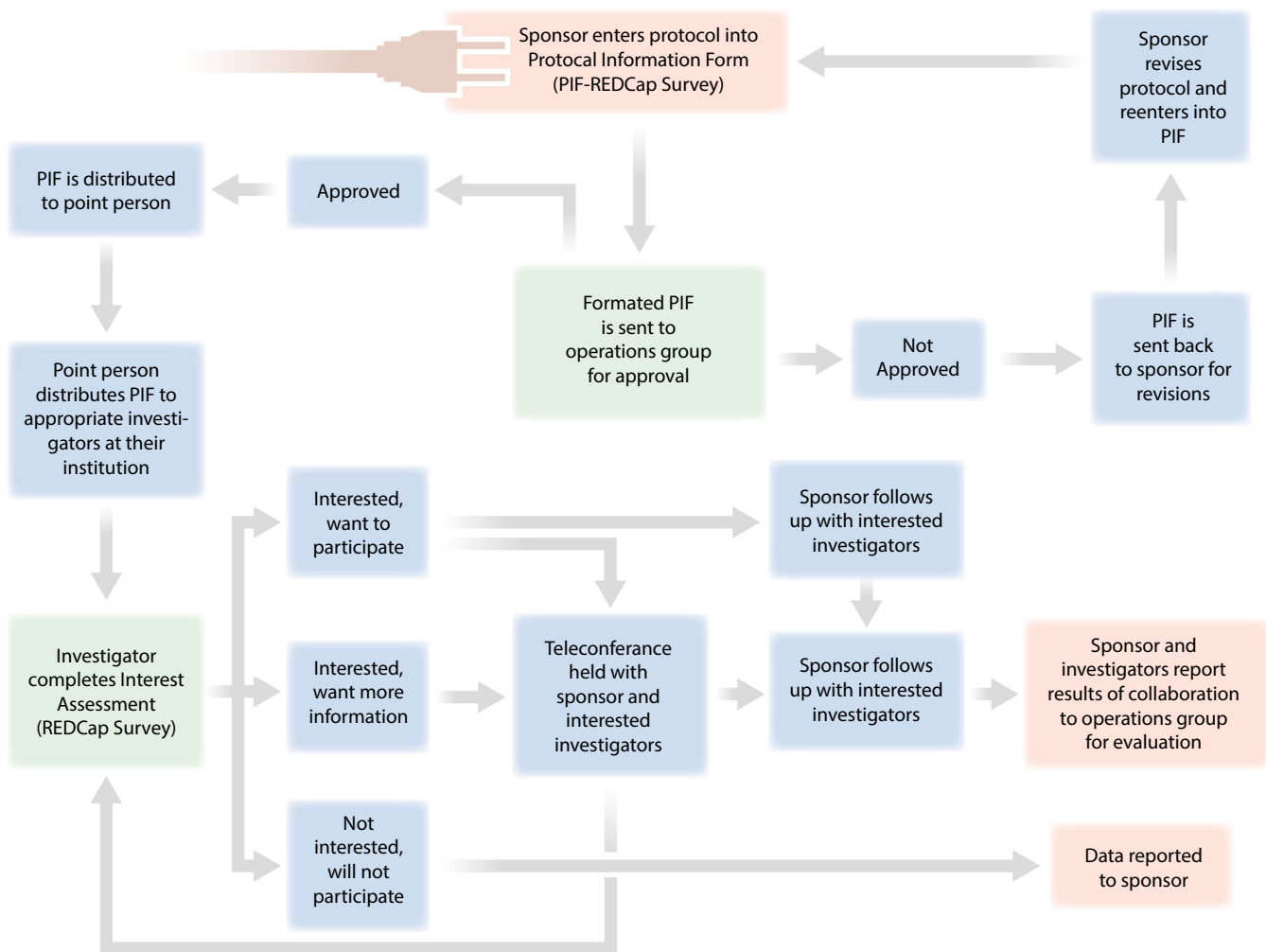


Fig. 1. Pointing the way toward pediatric therapies. Flow diagram of processes associated with protocol submission for the PP project.

already participating in the proposed clinical trials (1%). Of the 16 protocol summaries submitted by a CRO, contact was made with 69 investigators, including 39 who had not worked with the CROs previously. Confidentiality agreements were sent to 67 investigators and completed by 54 (81%). Clinical trial site information forms were sent to 40 sites and completed by 20 (50%). Sixteen of these sites were involved in selection, start-up, or enrollment of at least 1 protocol by the end of the one-year study period, and ~15 children had already been enrolled in at least one clinical trial. After a review of the complete protocol, 50% of investigators who initially responded positively were no longer interested because of concerns about enrolling enough patients ($n = 21$), lack of support staff ($n = 17$), a lack of interest in industry-sponsored trials ($n = 14$), complexity of study design ($n = 13$), competing trials ($n = 5$), and concerns about safety ($n = 3$).

The PP Project platform was also used for investigator-initiated clinical studies examining rare diseases. One submitted proposal resulted in investigators at 11 sites expressing interest in participating in a clinical trial. These scientists established a research group and published a detailed manuscript on plastic bronchitis (5). Subsequently, a full clinical trial protocol was developed and an IND application submitted.

PROJECT IMPACT

From the survey responses received from PPs at 85% of the participating CTSA sites, we note the following benefits of the program: (i) increased awareness of planned clinical studies, (ii) ability to discuss the trial protocol with the sponsor and ask questions before deciding to participate in the trial, (iii) ease of disseminating information to potential investigators, (iv) development of new scientific collaborations, (v) identifi-

cation of design weaknesses before further resource commitment and implementation, and (vi) opportunities for new and established investigators to participate. Challenges included: (i) identifying appropriate investigators in a timely manner, (ii) ensuring that all paperwork was handled properly and expeditiously, (iii) lack of structured institutional support and follow-up, (iv) highly specialized or difficult protocols, and (v) ensuring a short turnaround time.

Although the PP program linked investigators with a sponsor or other investigators, it was intentionally limited in scope and did not extend beyond arranging initial connections between relevant stakeholders. There was no planned implementation program to either carry out studies or provide structured input for protocol development. The power and efficiency of the program could be increased substantially if there was linkage to an integrated full-service

clinical trial infrastructure for study implementation. Once interest is expressed by the investigator, it still takes time to complete other trial-related procedures before the trial could begin to enroll patients (6). This time lag resulted in only 16 (40%) sites being involved in selection, start-up, or enrollment of at least one protocol by the end of one year. This experience highlights opportunities to further streamline the clinical trials process (www.nichd.nih.gov/about/meetings/2009/Pages/42309.aspx).

In 25% of discussions, the sponsor withdrew a protocol that received an IND from FDA after identifying significant methodological problems. This observation reinforces the need for early involvement of experienced physician-scientists to provide expertise in the design and operational aspects of multicenter trials. Further, in some cases, investigators who were initially interested in participating in a trial were no longer interested after they had reviewed the complete protocol because of inadequate numbers of eligible subjects, study design issues, or safety of the study drug. Such findings highlight the potential advantage for sponsors to engage qualified experts early in the clinical trial design process in order to jointly develop a protocol that is more likely to result in successful enrollment and completion of the trial. Many investigators decided not to participate in industry-sponsored clinical trials even though the studies were designed to provide the data needed to potentially support the use of these drugs in children. U.S. federal law (for example, the FDA Safety and Innovation Act) (7) requires that all new drugs developed by industry sponsors include a pediatric component if the potential for benefit

exists. The law was enacted to ensure that children, especially newborn infants, have a permanent place on the agenda for drug research and development. If insufficient numbers of investigators agree to participate in these studies, both patients and the industry will suffer. For most academic investigators, participation in industry trials requires a significant time commitment but rarely produces publications or contributes toward promotion or other academic achievements. In addition, most academic investigators do not have sufficient training in regulatory science and Good Clinical Practice to be comfortable with current regulatory requirements. Thus, important opportunities exist to leverage the PP program to become a multifaceted clinical trial-training platform that develops the next generation of child-health investigators.

Sustainability of the PP program will depend on the establishment of a virtual home for the development of expertise in clinical and translational research and product development as a discipline (1). To further optimize this potential, other key foundational activities that might be feasible include establishment of integrated infrastructure that provides trial planning, development, and implementation services that are not linked to specific diseases or conditions; formal training in clinical trial methods; and improved processes for collaborative study design among industry sponsors, regulatory agencies, and academic investigators. Ultimately, it is the responsibility of those who identify the medical needs, design the studies, and collect and analyze the data to demonstrate to society that these efforts and resources produce benefits for children.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/7/279/279fs11/DC1

Table S1. Protocol synopsis

Table S2. REDCap survey questions

Table S3. Studies involving specific disease processes

REFERENCES AND NOTES

1. E. M. Connor, W. E. Smoyer, J. M. Davis, A. Zajicek, L. Ulrich, M. Purucker, S. Hirschfeld, Meeting the demand for pediatric clinical trials. *Sci. Transl. Med.* **6**, 227fs11 (2014).
2. M. A. Turner, M. Catapano, S. Hirschfeld, C. Giaquinto, Global Research in Paediatrics, Paediatric drug development: The impact of evolving regulations. *Adv. Drug Deliv. Rev.* **73**, 2–13 (2014).
3. J. M. Davis, E. M. Connor, A. J. Wood, The need for rigorous evidence on medication use in preterm infants: Is it time for a neonatal rule? *JAMA* **308**, 1435–1436 (2012).
4. M. Korppi, P. Lepola, K. Vettentranta, S. Pakkala, K. Hopppu, Limited impact of EU paediatric regulation on Finnish clinical trials highlights need for Nordic collaboration. *Acta Paediatr.* **102**, 1035–1040 (2013).
5. J. Racz, G. Mane, M. Ford, L. Schmidt, J. Myers, T. J. Standiford, K. R. Schumacher, C. Fifer, M. W. Russell, K. A. Stringer, Immunophenotyping and protein profiling of Fontan-associated plastic bronchitis airway casts. *Ann. Am. Thorac. Soc.* **10**, 98–107 (2013).
6. D. M. Dilts, A. B. Sandler, S. K. Cheng, J. S. Crites, L. B. Ferranti, A. Y. Wu, S. Finnigan, S. Friedman, M. Mooney, J. Abrams, Steps and time to process clinical trials at the Cancer Therapy Evaluation Program. *J. Clin. Oncol.* **27**, 1761–1766 (2009).
7. C. P. Milne, J. Davis, The pediatric studies initiative: After 15 years have we reached the limits of the law? *Clin. Ther.* **36**, 156–162 (2014).

Competing interests: E.M.C. serves as a consultant for Pro-sensa, Sarpeta, NEA, 3-V Biosciences, and Janssen and as CEO/CMO of ReveraGen. **Funding:** Supported by award numbers UL1TR001064, UL1TR000075, UL1TR000073, UL1 TR000135, and UL1TR001070 from the NIH NCATS. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of NCATS, FDA, or the Eunice Kennedy Shriver NICHD. 10.1126/scitranslmed.aaa2045

Citation: J. M. Davis, W. E. Smoyer, E. M. Connor, W. C. Huskins, C. Pastern, M. Purucker, E. C. Schrader, C. R. Jackson, F. J. Kaskel, S. Hirschfeld, Sponsors meet scientists to speed pediatric medicines development. *Sci. Transl. Med.* **7**, 279fs11 (2015).

Science Translational Medicine

Sponsors meet scientists to speed pediatric medicines development

Jonathan M. Davis, William E. Smoyer, Edward M. Connor, W. Charles Huskins, Cindy Pastern, Mary Purucker, Elisabeth C. Schrader, Cynthia R. Jackson, Frederick J. Kaskel and Steven Hirschfeld

Sci Transl Med 7, 279fs11279fs11.
DOI: 10.1126/scitranslmed.aaa2045

ARTICLE TOOLS	http://stm.sciencemag.org/content/7/279/279fs11
SUPPLEMENTARY MATERIALS	http://stm.sciencemag.org/content/suppl/2015/03/16/7.279.279fs11.DC1
REFERENCES	This article cites 7 articles, 2 of which you can access for free http://stm.sciencemag.org/content/7/279/279fs11#BIBL
PERMISSIONS	http://www.sciencemag.org/help/reprints-and-permissions

Use of this article is subject to the [Terms of Service](#)

Science Translational Medicine (ISSN 1946-6242) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. 2017 © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works. The title *Science Translational Medicine* is a registered trademark of AAAS.