PEDIATRIC TRIALS NETWORK

Making drugs safer & more effective for use in the youngest patients

2021–2022

THE ANNUAL REVIEW

A MESSAGE FROM PTN LEADERSHIP

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In 2022, the **Pediatric Trials Network (PTN)** carried out its mission to improve health for all children by performing research, engaging participants, and sharing science. To date, the PTN has informed 17 label changes for drugs and devices to include dosing/usage guidance for children. Clinical study reports on several drugs were submitted to the FDA this year and will be used to inform more label changes. The PTN had five ongoing studies in 2022, which address topics like COVID-19 treatment, anesthetics, and drug dosages for participants ranging from infants, to 21-year-olds, to breastfeeding mothers. The Sildenafil study in particular has enrolled over 80 infants across two cohorts, and is expecting to open another cohort soon.

In addition to the upcoming Sildenafil cohort, the PTN is expecting to open three new studies in 2023. Two of these studies will be a bit different than what we're used to, because they will involve adult participants. One will study intravenous methadone in healthy adults (MTH02), and the other will study terbutaline sulfate in adults with asthma (TBS02). The answers learned from these clinical trials will inform the development of trials for pediatric participants. The third study enrolling in 2023 will evaluate guanfacine for children with Down Syndrome (HYP01).

Since last year's report, the PTN has released nine new publications to share these important data with the scientific community. We also developed a Results-at-a-Glance webpage to be the home of quick, easy-to-read study summaries that can be shared with the public and study participants.

Diversity and participant engagement were also a big focus of the PTN in 2022. We engaged pediatric participants by asking them what diversity in pediatric clinical research means to them, as well as directly involving them with the development of clinical trials by allowing them to provide feedback on clinical trial assent forms. We developed an anthology of creative works by pediatric trial participants to spotlight their voices and experiences. Additionally, we showed gratitude to participants and their families by developing and sending personalized thank-you notes.

Continue reading this Annual Review for more details on these accomplishments. We look forward to an exciting 2023 and thank you for your commitment to determining the safest and most effective medications and devices for children.

Danny Benjamin, MD, PhD, MPH
Pediatric Trials Network, Principal Investigator

Rachel Greenberg, MD, MB, MHS
Pediatric Trials Network, Steering Committee Chair

THIS YEAR PTN…PERFORMED RESEARCH

PTN Label Changes to Date

Under the Best Pharmaceuticals for Children Act (BPCA), the PTN works to provide the United States Food and Drug Administration (FDA) with research and data to inform label changes so that health care providers can prescribe the most appropriate doses of medications to children. As a result of research conducted through the BPCA program, led by the PTN, the following label changes have been made:

- Acyclovir
- Ampicillin
- Caffeine
- Clindamycin (2)
- Diazepam
- Doxycycline
- Lisinopril
- Lithium
- Lorazepam
- Mercy babyTAPE
- 2D and 3D Mercy TAPE
- Meropenem
- Propylthiouracil
- Pralidoxime
- Sodium nitroprusside

Ongoing PTN Studies

PTN has five ongoing studies, four of which are enrolling and one that is in the follow-up phase. Pediatric participants of these studies range in age from infants to 21 years old, and we have also enrolled breastfeeding mothers. Through these studies, PTN continues to generate evidence to advise dosing of medications commonly used in children.

- Anesthetics and Analgesics in Children (ANA)
- Commonly used drugs during lactation and infant exposure (CUDDLE)
- Long-term Antipsychotic Pediatric Safety Trial (LAPS)
- POP02
- Sildenafil II

Learn more about ongoing and completed PTN studies.

Clinical Study Reports Submitted

The PTN submitted several clinical study reports (CSRs) to the FDA to inform label changes this year.

- Levetiracetam
- Oxcarbazepine
- Furosemide
- Oxycodone
- Ondansetron
- Furosemide
- Metronidazole

Two CSRs, levetiracetam and oxcarbazepine, were based on results from the AED01 study evaluating the pharmacokinetics of anti-epileptic drugs in children with obesity. Dosing of anti-epileptics in children with obesity may vary from that in children without obesity due to altered pharmacokinetics. Inappropriate dosing may increase the risk for drug toxicity or therapeutic failure. MORE about AED01.

The oxycodone and ondansetron CSRs were results of the BMS01 study determining pharmacokinetics and safety of commonly used drugs in lactating women and breastfed infants and how these drugs are passed through breast milk. It is common for new mothers to have symptoms or medical conditions that must be treated with medicine. With these CSRs, PTN will inform doses of the drugs that are safe for both mothers and their breastfed infants. MORE about BMS01.

The furosemide CSR came from the FUR01 study, which was a randomized controlled trial evaluating the safety and preliminary effectiveness of the drug for preventing bronchopulmonary dysplasia (BPD) in premature infants. Over 60,000 infants are born ≤29 weeks gestational age each year in the U.S., and nearly 40% of those develop BPD. The condition is difficult to treat due to several comorbidities associated with it, so prevention is important. MORE about FUR01.

The CSR for metronidazole was a result of the study ABS01 evaluating antibiotics for treatment of premature infants with complicated intra-abdominal infections.

These infections are common and often fatal in premature infants. Previously, the effectiveness and safety of metronidazole for this group was not known. MORE about ABS01.

Many of these drugs were also part of the POP01 study.

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THIS YEAR PTN…PERFORMED RESEARCH (continued from page 2)

Update on SIL02 Study

Sildenafil is a drug that is approved by the FDA for the treatment of pulmonary hypertension in adults. It is also used to treat premature infants at risk of bronchopulmonary dysplasia (BPD), a common chronic lung disease that can lead to life-long medical problems, prolonged hospitalization, and even death. Approximately 17,500 infants in the United States develop BPD each year, but the pharmacokinetics and efficacy for Sildenafil in this age group has yet to be defined. To inform safe and accurate dosage of Sildenafil for premature infants, PTN has already enrolled 80 infants across two study cohorts. The Sildenafil study plans to open a third cohort soon. **MORE.**

Update on HYP01 Study

The PTN study evaluating the effectiveness and dosage of guanfacine for hyperactivity in children with Down Syndrome (HYP01) is expected to begin enrollment this year. We have been hard at work selecting study sites and moving through the start-up process. This trial was developed through a collaboration between PTN and the INCLUDE initiative with the goal of enhancing clinical trial support for medication usage in children with Down Syndrome and promoting training for clinical trials involving participants with Down Syndrome. Stay tuned for more information on this study throughout 2023. MORE.

PTN Studies Enrolling Soon

- Pharmacokinetics, Pharmacodynamics, and Safety of a Single Dose Intravenous Methadone in Healthy Adult Volunteers (MTH02)
- A Prospective, Blinded, Cross-Over Trial of the Exposure-Response Relationship of Terbutaline Sulfate in Adults with Asthma (TBS02)
- Guanfacine for Hyperactivity in Children with Down Syndrome (HYP01)

ENGAGED PARTICIPANTS

PTN's Commitment to Thanking Clinical Trial Participants

The PTN recognizes the efforts of children and families involved in pediatric clinical research. To express gratitude and share study results with participants in 2022, the PTN sent thousands of thank-you notes. The messages in the thank-you notes were customized to each study. For example, if the study required blood draws, then they were explicitly mentioned so that each participant's specific contributions were acknowledged. In 2022 and beyond, the PTN is committed to thanking those who make clinical research possible.

Read more about the thank-you notes and incorporating gratitude in studies.

PTN and iCAN Research Anthology

PTN and the International Children's Advisory Network (iCAN) began the process of creating an anthology of work to showcase the importance of participation in pediatric clinical research and highlight the experiences and efforts of participants. The anthology will include personal essays, illustrations, poems, songs, and jewelry by kids across a variety of age groups who have personal experience with pediatric medicine and clinical research. It's heartwarming and eye-opening to hear the reflections of those impacted by the work of the PTN, iCAN, and pediatric clinical research as a whole. It's important to share their voice and continue engaging them in clinical research. A published version of the anthology will be made available in 2023.

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ENGAGED PARTICIPANTS (continued from page 3)

PTN's Presentation at iCAN Research and Advocacy Summit

In July, the PTN participated in the iCAN Research and Advocacy Summit in Lyon, France. The summit included a number of sessions that explored pediatric clinical research and patient engagement from unique viewpoints. The PTN presentation titled, "How You Are Making A Difference: How DCRI, PTN, and iCAN are making clinical research accessible and meaningful for participants and their families" focused on the ways the PTN and iCAN work together. The session was interactive and involved the participants reviewing a clinical trial assent and providing ways to make it more useful and understandable. The feedback was incredibly valuable to help increase understanding of research and its process for children and their parents. MORE.

PTN Video Highlights Diversity in Pediatric Clinical Trials and Voices of Participants

In March, the PTN produced a video that shows the importance of diversity and representation in pediatric clinical research. It's essential to enroll diverse participants to be certain that study results are generalizable. Having participants from different walks of life also helps raise questions and find insights that may not have previously been thought of. The video features PTN researchers as well as kids involved with iCAN who have personal experience with clinical trials. They shared why they think diversity is important and reflections on increasing diversity and lowering barriers to participation in pediatric clinical trials. The video also summarizes an analysis of representation across 33 Best Pharmaceuticals for Children Act (BPCA) studies. Study participants were found to be largely representative of the populations the PTN serves. Progress has been made to increase representation, but there's still work to be done. In the words of Imaan, a participant featured in the video, "It's not impossible. You have to want it." WATCH.

SHARED SCIENCE

The Work of PTN Highlighted in *Clinical Pharmacology & Therapeutics* Editorial

In June, a PTN study was highlighted as an example for diversity in clinical pharmacology in an editorial by the Editor-in Chief of Clinical Pharmacology & Therapeutics. This study used real-world electronic health record (EHR) data to develop a physiologically-based pharmacokinetic model that evaluated the disposition and dosing requirements of enoxaparin, a commonly prescribed anticoagulant medication, in children with obesity vs. children without obesity. The study found that the dosage of some drugs like enoxaparin should be adjusted based on the child's age and obesity status. The approach used in this study can be applied to other drugs to evaluate the dosage adjustments necessary for children with obesity. Clinical Pharmacology & Therapeutics published the data and results of the study in an article called Use of Real-World Data and Physiologically-Based Pharmacokinetic Modeling to Characterize Enoxaparin Disposition in Children With Obesity.

Including specific populations in clinical trials is at the very heart of the PTN's mission of making drugs and devices safer and more effective for the youngest of patients. Learning more about the implications of drug dosing for children with obesity is vital, as nearly 20% of children in the United States are classified as obese. MORE.

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SHARED SCIENCE (continued from page 4)

Results At-a-Glance

This year, the PTN developed a dedicated webpage for study Results-At-A-Glance. These summaries describe the key information, including results, of PTN studies and publications in a format that is quick and easy to read. The PTN is continuing to develop Results-At-A-Glance summaries for publications to ensure the knowledge generated from the PTN is shared, especially with study participants who make it possible. **MORE**.

Published Research (2021 – 2022)

Developing lay summaries and thank you notes in paediatric pragmatic clinical trials. Zimmerman KO, Perry B, Nsonwu A, Hanlen-Rosado E, Lane MD, Benjamin DK Jr., Becker M, Corneli A; on behalf of the Best Pharmaceuticals for Children Act — Pediatric Trials Network Steering Committee. *Health Expectations*. June 2022.

Ampicillin dosing in premature infants for early-onset sepsis: exposure-driven efficacy, safety, and stewardship. Le J, Greenberg RG, Yoo Y, Clark RH, Benjamin DK Jr., Zimmerman KO, Cohen-Wolkowiez M, Wade K. *Journal of Perinatology*. July 2022.

Use of physiologically-based pharmacokinetic modeling to inform dosing of the opioid analgesics fentanyl and methadone in children with obesity. Gerhart JG, Carreno FO, Ford JL, Edginton AN, Perrin EM, Watt KM, Muller WJ, Atz AM, Al-Uzri A, Delmore P, Gonzalez D; on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. CPT: *Pharmacometrics & Systems Pharmacology*. June 2022.

External Evaluation of Risperidone Population Pharmacokinetic Models Using Opportunistic Pediatric Data. Karatza E, Ganguly S, Hornik CD, Muller MJ, Al-Uzri A, James L, Balevic SJ, Gonzalez D; on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. *Frontiers in Pharmacology*. March 2022.

Development and Evaluation of a Virtual Population of Children with Obesity for Physiologically Based Pharmacokinetic Modeling. Gerhart JG, Carreno FO, Edginton AN, Sinha J, Perrin E, Kumar KR, Rikhi A, Hornik CP, Harris V, Ganguly S, Cohen-Wolkowiez M, Gonzalez D; on behalf of the Best Pharmaceuticals for Children Act — Pediatric Trials Network Steering Committee. *Clinical Pharmacokinetics*. February 2022.

Impact of Personal Protective Equipment on the Performance of Emergency Pediatric Tasks. Adler MD, Krug S, Eiger C, Good GL, Kou M, Nash M, Henretig FM, Hornik CP, Gosnell L, Chen JY, Debski J, Sharma G, Siegel D, Donoghue A. *Pediatric Emergency Care*. December 2021.

Capacity Building in a New Clinical Trials Network through Inter-Network Collaboration. Knight L, Pahud BA, Scheffler M, Euteneuer JC, Allen C, Ross J, Ali W, Meyer M, Purohit PJ, Zimmerman KO, Sullivan JE; on behalf of the ECHO IDeA States Pediatric Clinical Trials Network. *The Journal of Pediatrics*. January 2022.

Safety of sildenafil in extremely premature infants: a phase I trial. Jackson W, Gonzalez D, Smith PB, Ambalavanan N, Atz A, Sokol GM, Hornik CD, Stewart D, Mundakel G, Poindexter BB, Ahlfeld SK, Mills M, Cohen-Wolkowiez M, Martz K, Hornik CP, Laughon MM; on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee. *Journal of Perinatology*. January 2022.

Physiologically Based Pharmacokinetic (PBPK) Modeling of Meropenem in Preterm and Term Infants. Ganguly S, Edginton A, Gerhart JG, Cohen-Wolkowiez M, Greenberg RG, Gonzalez D; on behalf of the Best Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee. *Clinical Pharmacokinetics*. June 2021.

View a **full list of publications** from the PTN.