The Pediatric Trials Network: Innovating to Make Drugs Safe and Effective for Children

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BPCA Data Coordinating Center



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

What is the Pediatric Trials Network?

An infrastructure for investigators to conduct trials that improve pediatric labeling and child health

- Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- Performs studies to improve dosing, safety information, labeling, and ultimately child health
- Focus on off-patent therapeutics



Productivity Across the BPCA Mechanism: 3 Chapters

	Original BPCA 2002-2010	PTN 1.0 (2010-2018)	PTN 2.0 (2018-2024)¥	Total
Label Changes	1*	7	18	26
FDA submissions	0	10	24	34
Therapeutic areas	4	18	21	21
Trials started	4	26	10	40
Total studies**	4	38	12	54
Studies completed	1∞	33	6	40
Number enrolled	709	>7,000	>7,000	>14,000
Molecules studied€	5	40	>100®	>145

*We eventually secured 4 label changes from the trials started in this era--in 2015-2020

**The vast majority of dollars and effort is dedicated to trials, but some of the molecules require studeies that are not trials; the row "trials" is a subset of the row "total s

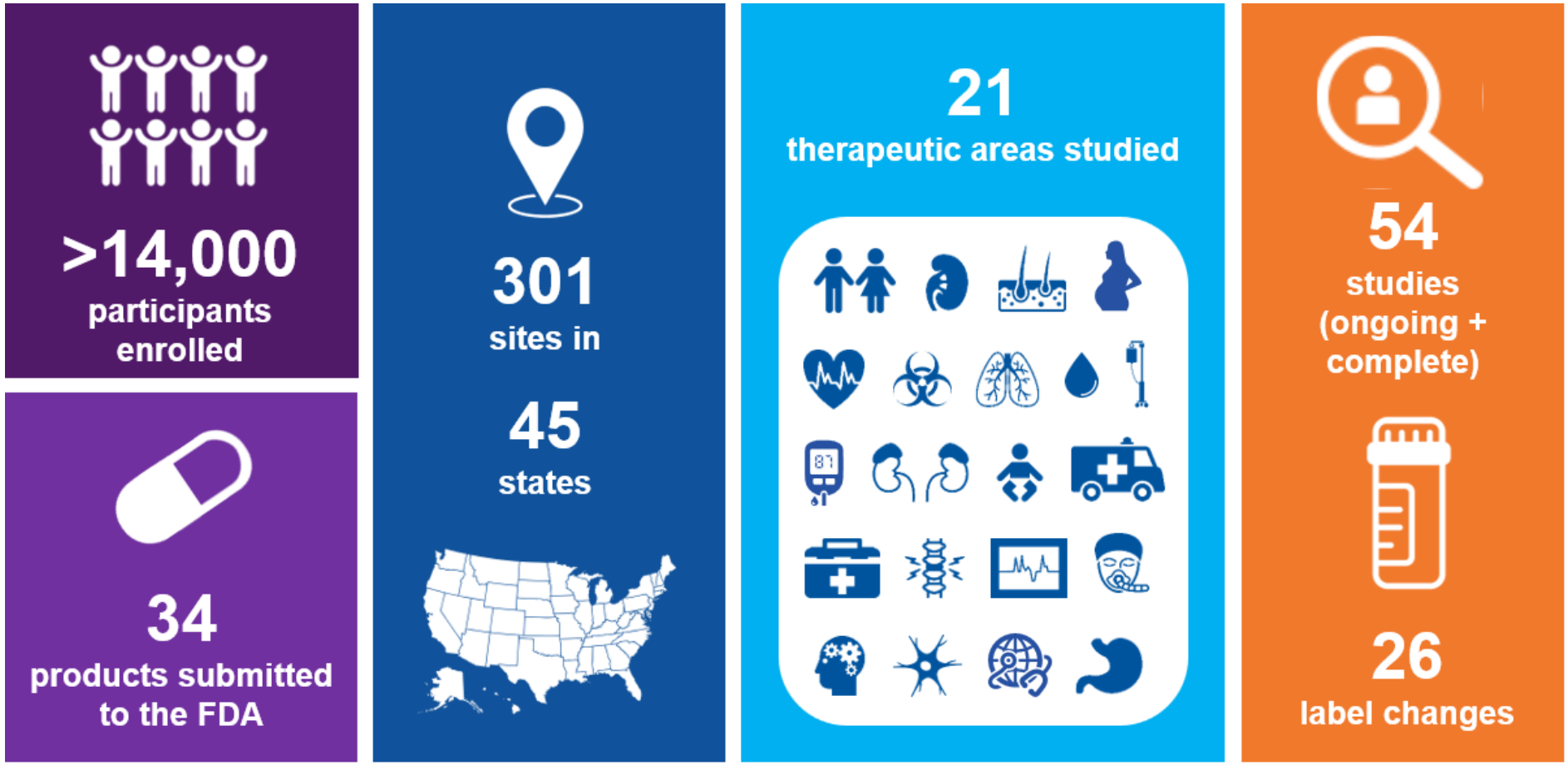
∞This trial was led by the team that successfully competed for the PTN

€Not every study results in labeling but we should describe dosing for every molecule commonly used in children

¥Includes pandemic

®This number includes molecules for which methods have been developed (e.g., PK assay; or manufacture of guanfacine) but have not yet enrolled first patient

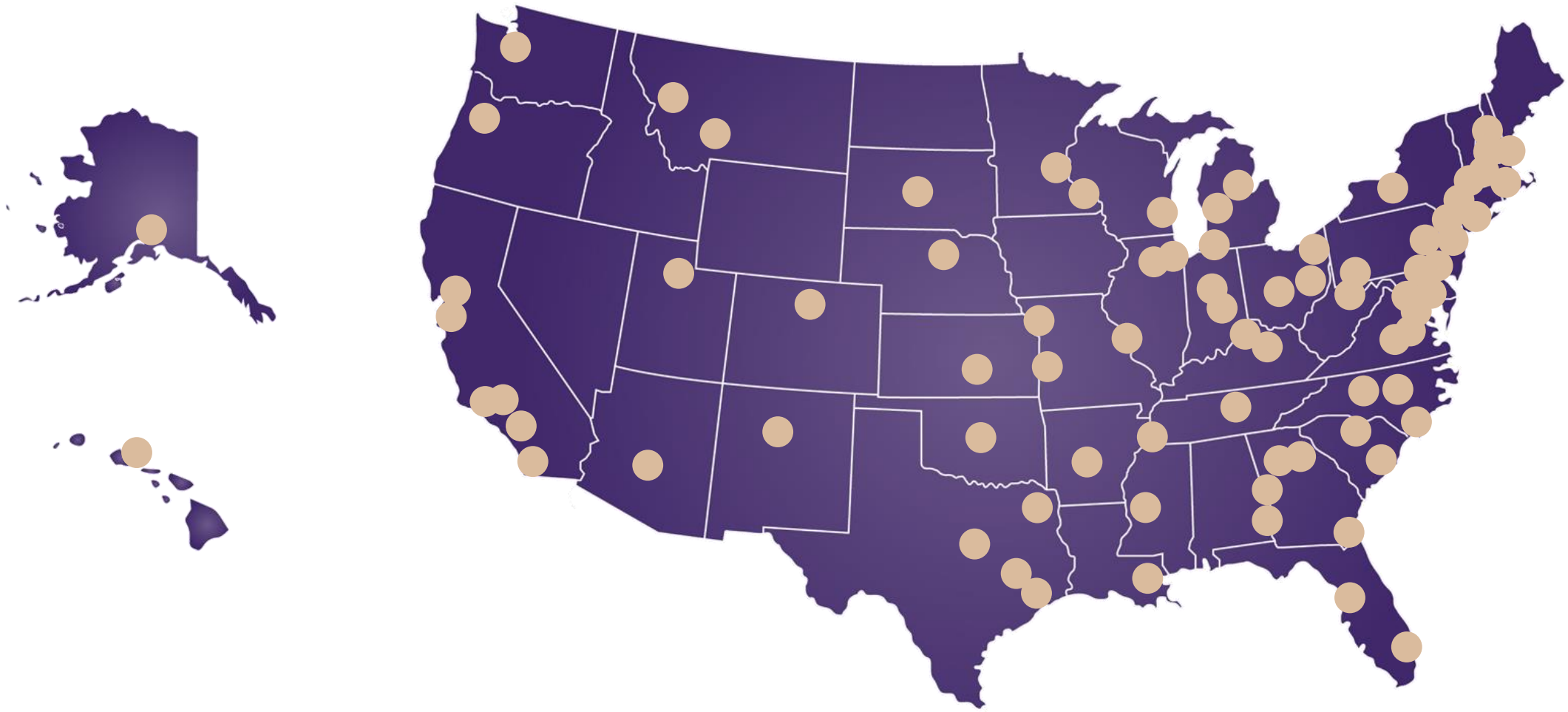
PTN Public Health Impact



Molecules studied under PTN 2010-2026

abatacept	bumetanide	dexmedetomidine	gentamicin	levofloxacin	nalbuphine	remdesivir	tocilizumab
actinomycin D	buprenorphine	dextroamphetamine	granisetron	lidocaine	nicardipine	Ribavirin	topiramate
acyclovir	bupropion	diazepam	griseofulvin	lisinopril	nifedipine	rifampin	tranexamic acid
alfentanil	caffeine citrate	Diazoxide	guanfacine	lithium	norepinephrine	risperidone	trazodone
amikacin	calfactant	digoxin	haloperidol	lopinavir/ritonavir	olanzapine	rocuronium	TMP/SMX
aminocaproic acid	canakinumab	dopamine	heparin	lorazepam	ondansetron	rosuvastatin	valganciclovir
amiodarone	cefdinir	doxycycline	hydrochlorothiazide	lurasidone	oseltamivir	ruxolitinib	valproic acid
amoxicillin	cefepime	duloxetine	hydrocodone	meropenem	oxcarbazepine	sarilumab	vancomycin
amphotericin	ceftazidime	epinephrine	hydrocortisone	metformin	oxycodone	sertraline	vasopressin
ampicillin	cidofovir	escitalopram	hydromorphone	methadone	pantoprazole	sevelamer	vecuronium
anakinra	ciprofloxacin	etomidate	hydroxocobalamin	methylphenidate	paroxetine	sildenafil	venlafaxine
aripiprazole	citalopram	fentanyl	hydroxyurea	methylprednisolone	pentobarbital	simvastatin	verapamil
aspirin	clindamycin	fluconazole	Infliximab	metoclopramide	pip-tazo	nitroprusside	vincristine
atropine	clobazam	fluvoxamine	Interferon	metronidazole	poractant alfa	spironolactone	voriconazole
azithromycin	clonidine	fosfomycin	isotretinoin	midazolam	pralidoxime	sumatriptan	warfarin
baclofen	clozapine	fosphenytoin	ketamine	milrinone	pravastatin	terbutaline	ziprasidone
beractant	colchicine	furosemide	ketorolac	molindone	propofol	ticar-clav	zolpidem
bosentan	cyclobenzaprine	Gabapentin	labetalol	morphine	propylthiouracil	timolol	
Budesonide	dexamethasone	ganciclovir	levetiracetam	nafcillin	quetiapine	tobramycin	

Sites enrolling participants in PTN studies



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PTN's response to the challenges of pediatric clinical trials

Challenge	Response / Innovation
Limited blood volume	Sensitive assays and minimal sampling methods, available for other researchers
Limited number of available participants	Negotiate trial design with FDA Standard of care and adaptive design trials Pre-IND meetings for all studies Incorporation of real world data/evidence*



Real world evidence in action

- PK of ampicillin was determined by enrolling 64 infants in an open label, multi-center, opportunistic PK study
  - Safety was assessed during this study
- Safety was also assessed using Pediatrix Clinical Data Warehouse in >100,000 infants receiving ampicillin
  - Noted that higher exposure was associated with seizures
- Data submitted to FDA → label change



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ORIGINAL ARTICLES

Electronic Health Records and Pharmacokinetic Modeling to Assess the Relationship between Ampicillin Exposure and Seizure Risk in Neonates

Christoph P. Hornik, MD, MPH[1,2], Daniel K. Benjamin, Jr, MD, MPH, PhD[1,2], P. Brian Smith, MD, MPH, MHS[1,2], Michael J. Pencina, PhD[1], Adriana H. Tremoulet, MD, MAS[3], Edmund V. Capparelli, PharmD[4,5], Jessica E. Ericson, MD[6], Reese H. Clark, MD[7], and Michael Cohen-Wolkowiez, MD, PhD[1,2], on behalf of the Best Pharmaceuticals for Children Act—Pediatric Trials Network*

PTN's response to the challenges of pediatric clinical trials (continued)

Challenge	Response / Innovation
Low consent rates	Simplified trial designs Standard of care procedures Participant engagement, direct to family trials

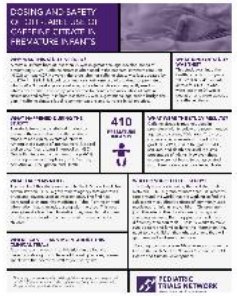


Ampicillin Results-At-A-Glance

Completed: June 1, 2022

Ampicillin, a medicine used to treat infections, is the most commonly used drug in babies born prematurely who are admitted to the hospital. At the same time, practically no one has ever figured out how the drug is processed in newborns. The goal of the "Ampicillin in Infants Study" was to find...



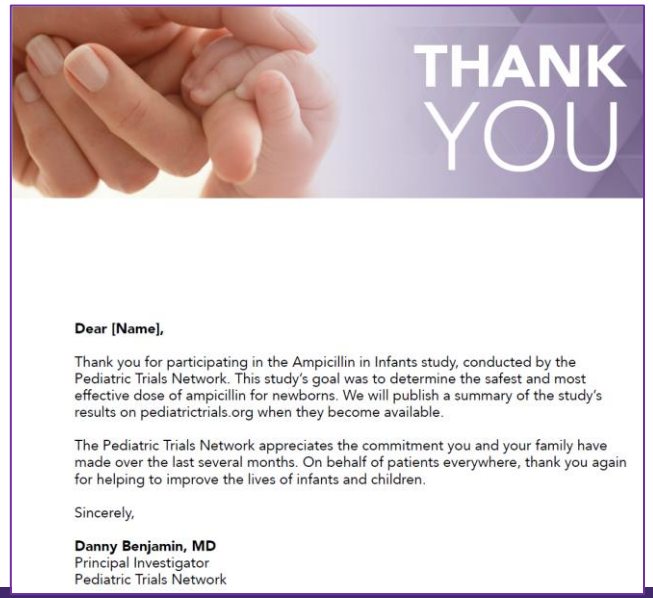


Caffeine Citrate Results-At-A-Glance

Completed: January 1, 2022

Almost all infants born at less than 29 weeks gestational age develop apnea of prematurity (AOP). Caffeine citrate is often used in the neonatal intensive care unit (NICU) to treat AOP. However, the drug label for caffeine citrate was last updated by the FDA in 1999. This label recommends...





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Direct-to-Family trial program

An example



iPERSONAL

Individual Patient Exposure and Response in Pediatric Lupus

- Nation's first direct-to-family trial for pediatric lupus
- A single virtual site conducted study activities across 12 states
- Exceeded enrollment goal in this rare pediatric disease in the first 10 days

Next steps

- PTN is planning a study of methotrexate in children with juvenile idiopathic arthritis (JIA)
- Home-based study will improve research access and decrease participation burden
- PTN has developed an application to study the drug under FDA guidance with goal of changing the drug label

PTN's response to the challenges of pediatric clinical trials (continued)

Challenge	Response / Innovation
Onerous contracting / start-up	Opportunistic studies Platform trials

- Platform trials (master protocols): answer more than one question at a time
  - Platform trial: multiple treatments or diseases are evaluated within the same protocol
  - Basket trial: one therapy is tested on more than one disease
  - Umbrella trial: multiple therapies are tested for a single disease

- Three stages of research
  1. No one can do this
  2. We cannot do this
  3. We have always done this

Summary of Platform Trials That We Have Designed, Completed Enrollment, and Submitted Data to FDA

- **POPs**: PK and a modest amount of safety; now PK-PD
  - Child receiving molecule per standard of care; consent for 1 to 5 drops of blood during standard of care laboratory
  - PTN uses POPS as a funnel: 33,000 biologic samples, >100 validated assays (>200 methods), >50 analyses completed
    - Screening of: Investigators, Sites (300 across PTN trials), Molecules (145), Populations
    - Emerging and difficult populations—neonates (2,700 samples), ECMO (2,000), obesity (6,000), breast feeding (3,000), COVID
- **CUDDLE** (Breast Milk Study): PK and a modest amount of safety
  - Mothers receiving medicine per standard of care—sample from mother's blood, breast milk, and infant's blood
- **SCAMP:** Safety and efficacy of antibiotics in premature infants
  - Preterm infants with complicated intra abdominal infection randomized to 5 different molecules, at doses stratified by postmenstrual age
- **LAPS:** Long-term safety of anti-psychotic medicines

Pediatric Trials Network
Molecules from Platform 2018-2024

POPS: Pediatric Opportunistic PK Study
NCT04278404
CUDDLE: Mother-infant dyads, breast milk
NCT03511118
SCAMP: complicated abdominal infections in infants
NCT01994993
LAPS: Long term anti-psychotic safety study
NCT03522168

ECMO: extra-corporeal membrane oxygenation
NCT01431326
ANA: Anesthetics and Analgesics
NCT03427736
POPS for Children with Obesity
NCT04278404
AED: Anti-epileptic drugs used in obese children
NCT02993861
Anti-Staph Trio: antibiotics to treat S. aureus
NCT01728363
Dosing of Therapeutics in COVID
NCT04278404

Product	Therapuetic area	IND	Start Up	Enrolling	CSR at FDA	Label negotiations	Next milestone
Ampicillin	Infectious Diseases	125,250					Label change 2018
Lithium	Psychiatry	73,844					Label change 2018
Mercy BabyTAPE	Devices	K191174					Label change 2019
Acyclovir	Infectious Diseases	106,153					Label change 2019
Doxycycline	Infectious Diseases	133,951					Label change 2020
Caffeine citrate	Neonatology	125,696					Label change 2020
TMP-SMX	Infectious Diseases	113,645					Label change 2020
Clindamycin	Infectious Diseases	115,396					Label change 2020 & 2021
Diazepam	Neurology	131,971					Label change 2021
Rifampin	Infectious Diseases	130,531					Label change 2023
Levetiracetam	Neurology	139,604					Label change 2023
Fluconazole	Infectious Diseases	76,813					Label change 2024
Oxycodone	Lactation/Pain	135,227					Label change 2024
Oxcarbazepine	Neurology	139,604					Label change 2024
Furosemide	Neonatology/Pulm	120,933					Label change 2024
Metronidazole	Infectious Diseases	108,209					Label change
Ondansetron	Lactation	135,227					Label change
Topiramate	Neurology	139,604					Label change
Nifedipine	Lactation/Cardiology	135,227					DASH submission
Valproic acid	Neurology	139,604					DASH submission
Timolol	Dermatology	129,154					DASH submission
Digoxin	Cardiology	141,063					DASH submission
Hydromorphone	Anesthesiology/Pain	136,790					CSR completion
Pip-tazo	Infectious Diseases	108,209					CSR completion
Aripiprazole	Psychiatry	132,329					CSR completion
Risperidone	Psychiatry	132,329					CSR completion
Sertraline	Lactation/Psychiatry	135,227					CSR completion
Azithromycin	Lactation/ID	135,227					CSR completion
Tranexamic acid	Lactation/Hematology	135,227					CSR completion
Escitalopram	Lactation/Psychiatry	135,227					CSR completion
Labetalol	Lactation/Cardiology	135,227					CSR completion
Metformin	Lactation/Endo	135,227					CSR completion
Ciprofloxacin	Lactation/ID	135,227					CSR completion
Methadone	Anesthesiology/Pain	119,459					CSR completion
Sildenafil	Neonatology/Pulm	226,396					Enrollment completion
Terbutalline	Pulmonology	144,549					Enrollment completion
Ketamine	Anesthesiology/Pain	136,790					Enrollment completion
Ketoralac	Anesthesiology/Pain	136,790					Enrollment completion
Morphine	Anesthesiology/Pain	136,790					Enrollment completion
Amoxicillin	Lactation/ID	135,227					Enrollment completion
Buprenorphine	Lactation/Pain	135,227					Enrollment completion
Buproprion	Lactation/Psychiatry	135,227					Enrollment completion
Citalopram	Lactation/Psychiatry	135,227					Enrollment completion
Cyclobenzaprine	Lactation/Pain	135,227					Enrollment completion
Duloxetine	Lactation/Psychiatry	135,227					Enrollment completion
Gabapentin	Lactation/Pain	135,227					Enrollment completion
Hydrocodone	Lactation/Pain	135,227					Enrollment completion
Leviteracetam	Lactation/Neurology	135,227					Enrollment completion
Paroxetine	Lactation/Psychiatry	135,227					Enrollment completion
Trazodone	Lactation/Psychiatry	135,227					Enrollment completion
Venlafaxine	Lactation/Psychiatry	135,227					Enrollment completion
Guanfacine	Psychiatry	154,035					Enrollment start
Bumetanide	Pulmonology	174,270					Enrollment start
Methotrexate	Rheumatology	173,907					Enrollment start
Urgent PC	Devices	Q220378					Enrollment start

Platform Trials Lessons Learned: Infrastructure, Stakeholders, and Partners

- Sites face the challenges of keeping a team together and financial ~~gap~~ chasm
- Infrastructure and Collaboration
  - POPS1 in 2010, extensive pediatric-specific site infrastructure for opportunistic studies
  - Limited compensation, but the prospect of 20 or 50 or more therapeutics meant that each site could support a full-time coordinator
- Key stakeholder input
  - Families, child advocates, professional societies, AAP, NIH, FDA, investigators, and sites
- Industry and NIH more broadly:
  - Economics of 2 or 3 molecules vs. 20 or 30 molecules
  - Flexibility of sponsors (agencies or companies) and stakeholders is central

ICAN
International Children's Advisory Network

Platform Trials Lessons Learned: Flexibility

- Flexibility to fill critical knowledge gaps:
  - Opportunistic protocols can be designed to allow for studying variations in PK based on subgroup – i.e. patients on continuous renal replacement therapy, patients with obesity, those with potential drug-drug interactions, etc.
  - Flexibility in sampling schemes depending on the properties of the molecules of interest: the four antiepileptics in AED01 had wide variations in PK properties and the protocol allowed for varying sampling schemes

- Industry application
  - Flexibility and compromise around protocol details and sampling schemes, balancing the sites and disease, and the other partners

Platform Trials Lessons Learned: Ability to Pivot

- Molecules in common clinical use
  - When drugs are rarely prescribed, potential problem in most other designs
  - COVID-19 pandemic, added 15 drugs for COVID and MISC
  - 33 sites; enrolled the first child patient in 6 weeks
  - Some worked; and some failed
  - Additional sites cost more on the front end but key to success

- Industry and NIH more broadly
  - Some molecules will be more ‘popular’ than others (Industry)
  - A subset of sites might be crucial for some molecules more so than others
  - Going beyond traditional large centers (NIH)

Platform Trials Lessons Learned: Looking Forward

- Lessons from BPCA are uniquely positioned to innovate in clinical trials; these lessons learned can be applied to not just molecules, but other care questions
- "Reverse engineering" studies:
  - Start with a professional guidance document (e.g., osteomyelitis, traumatic brain injury, or neonatal HIE), usually ~20 recommendations
  - Select all the recommendations with low or very low quality of evidence
  - First randomize at the site, because children get sick at night & you don't want to fail
  - Then stack subsequent interventions with different questions at different times
  - E.g., severe traumatic brain injury,
    - what is target intra-cerebral pressure (ICP) monitoring;
    - then randomize at the individual: if ICP exceeds limits, do you use salt or mannitol to reduce ICP;
    - then, if you fail first line therapy, what do you do; primary endpoint 12 months after injury
    - then, how best to improve cognitive outcomes 12-24 months after injury

Recent challenges

- PTN is funded through a federal contract
- In 2025, PTN experienced a >40% cut to the program
  - 4 trials in start-up phase were halted
    - Including the methotrexate direct-to-family trial
- In 2026, additional cuts:
  - An ongoing trial has been terminated
    - Enrollment will stop in 29 states
    - There are 39 drugs for which the PTN will not be able to provide appropriate dosing information for one or more subgroups of children. Subgroups include:
      - Children younger than 2 years old
      - Premature neonates
      - Critically ill children (e.g., children on extra corporeal membrane oxygenation)
      - Obese children
  - 800 blood samples from 325 children will be wasted

Beyond clinical trials: Training the next generation

- Over 300 trainees have accessed PTN resources and data since 2011
- National program with trainees from over 35 states

- Early career faculty: lead trials to link to K23, bridge to R01, or link R01
- Subspecialty fellows and PHD students: secondary analyses (PBPK, popPK)
- Residents, medical, college, and high school students: PK analyses, trial modeling, pharmaco-epi, and epi-studies in preparation for future studies

- https://dcri.org/education/dukes-star-program
- STAR Summer program
  - Senior faculty pool time and resources into common program
  - Crash course in clinical research (IRB, ethics, stats, clin pharm etc.)
  - Near-peer mentorship











STAR
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Acknowledgements / collaborators

PTN Steering Committee

Duke Clinical Research Institute

Texas Christian University

MUSC Health
Medical University of South Carolina

SickKids
THE HOSPITAL FOR SICK CHILDREN

PennState

Tulane
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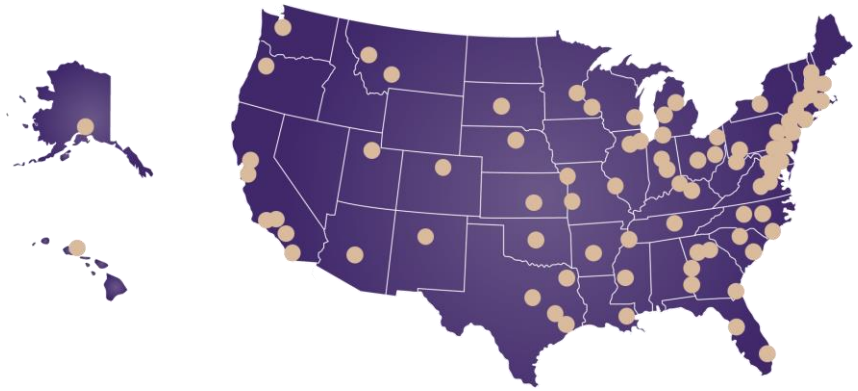
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Emmes

Enrolling Sites



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Thank you

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