# LESSONS LEARNED FROM THE NIH BPCA PROGRAM

National Academies of Sciences, Engineering, and Medicine

Committee on Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons

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# What is BPCA and Why Is It Needed?

- BPCA: Best Pharmaceuticals for Children Act 2002
- Historically inclusion of kids in drug development was avoided because of safety concerns. Kids were studied after adults, extrapolation was preferred if possible, and RCTs were limited.
- New approach needed because kids are protected **through** research not **from** research
- Great strides made in improving health and knowledge through pediatric research and care through legislative advocacy. **However**:
  - On-patent licensed drugs provide narrow indications and limited information in kids
  - Off-patent licensed drugs had limited PK, PD, safety information for kids despite having indications


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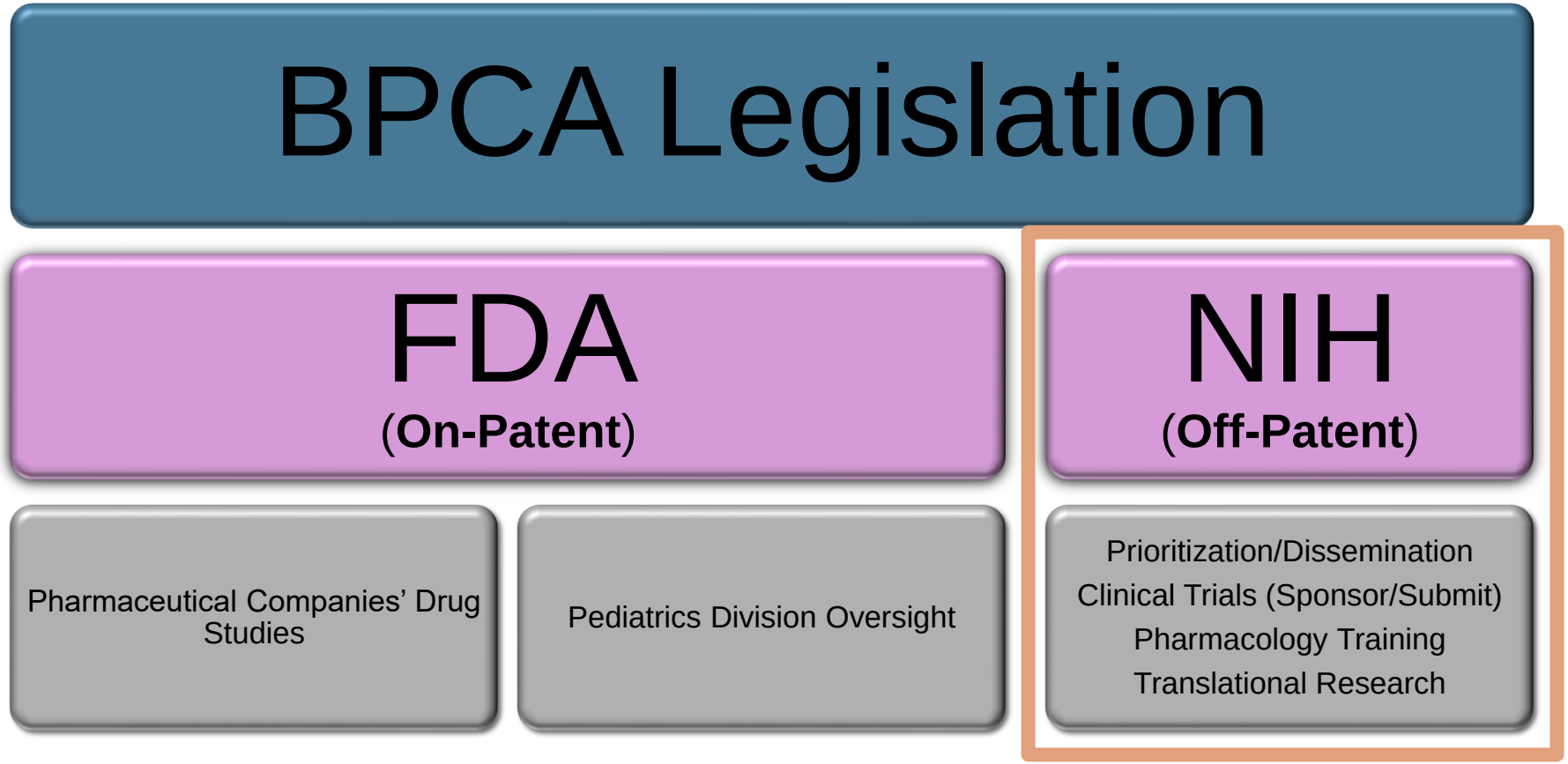
# BPCA Congressional Mandate

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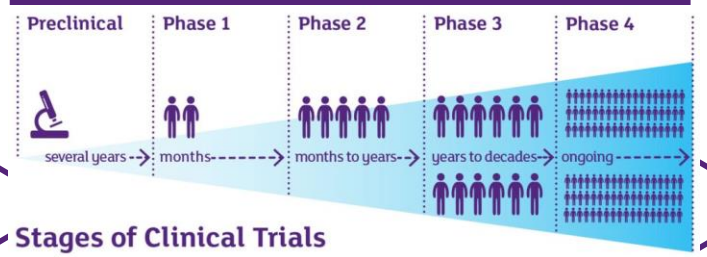
# NIH 409I Off-Patent Pediatric Drug Development Program

- Established ~2003/ Revamped in 2010

## Determining Priorities for Medications needing study


## Sponsoring Clinical Trials of Off-patent medications




## Submitting Data to FDA for Label Change

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# The Program Early On…And Now

Previous Research (clinical, preclinical)

Expert Input (Literature)

Public Health Advocacy

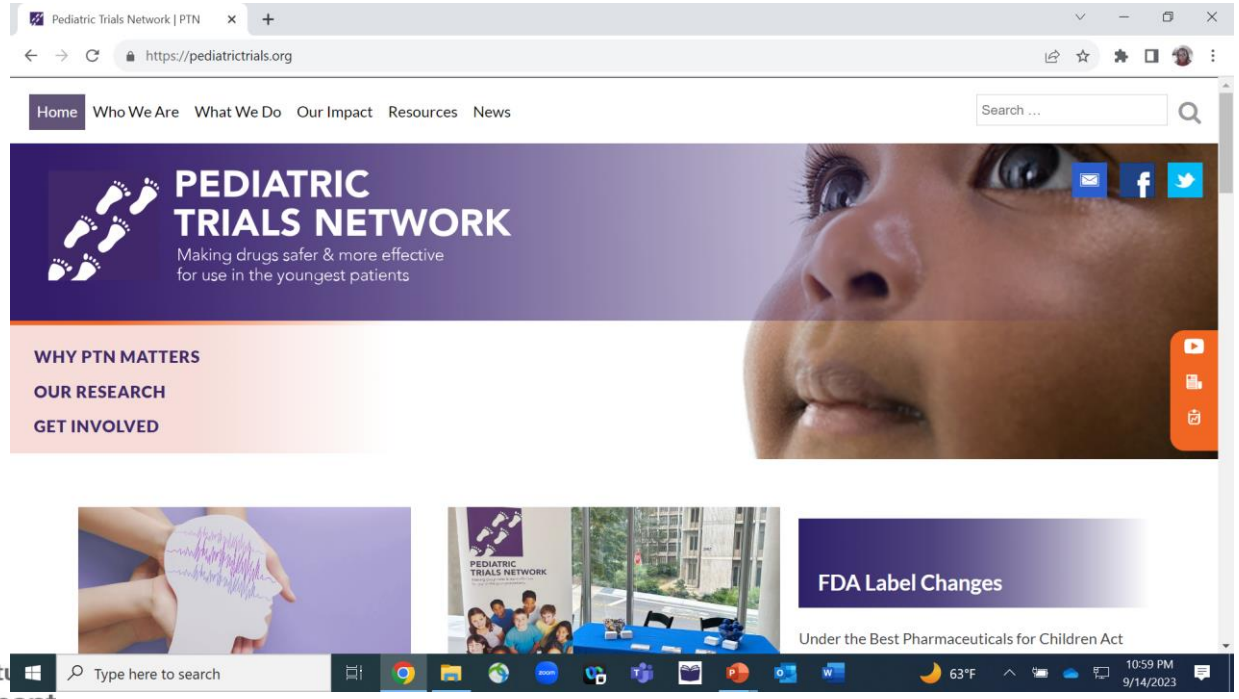
**Identified Gaps in Pediatric Therapeutics:**

**FDA iss… Request**

**Indust… to conduc…**

Industry responds
**No**

**Disseminate Information for Scientific Community:**
BPCA List
Publications
Conferences/Symposia

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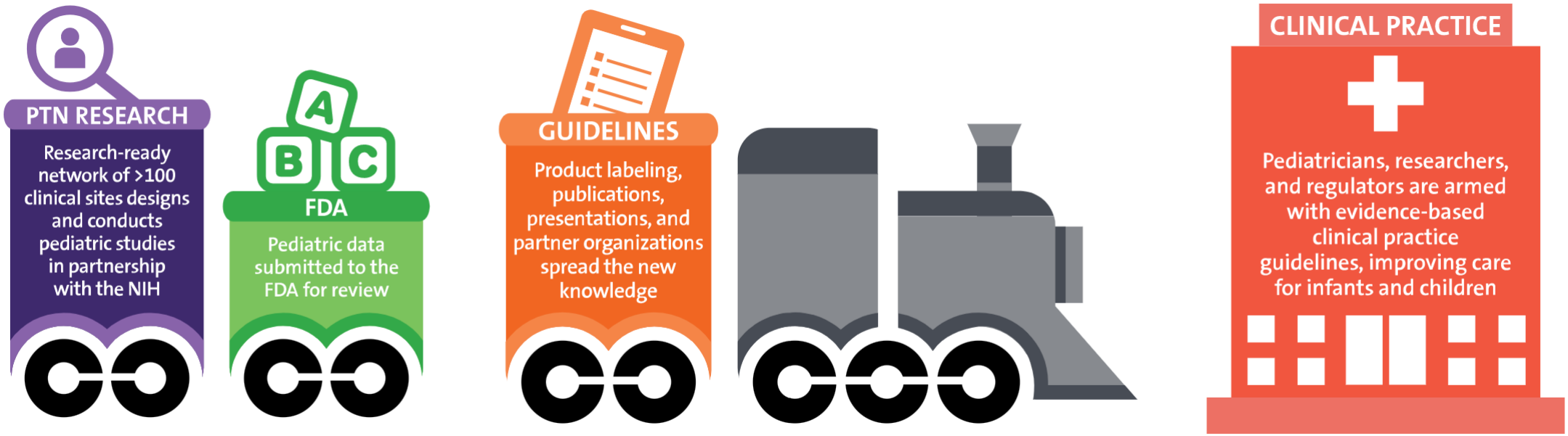
# What is the BPCA Clinical Program?

An ***infrastructure*** to conduct trials that impact pediatric labeling and ***resource*** to guide clinical practice and improve child health.

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# BPCA Clinical Program Structure

**Clinical Coordination Center**

*Duke Clinical Research Institute*

Pharmacology expertise, clinical trial design and implementation, IRB approvals, drug distribution

**Data Coordination Center**

*The Emmes Company, LLC*

Data management, regulatory support, statistical expertise, data quality and safety, site monitoring

**Logistics Support**

*Infinity Conferences Group, Inc.*

Technical expertise, website management, program dissemination

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# Pediatric Trials Network CCC Roles

**Program Management and Clinical Operations Core**

- **Protocol development**
- Network Management
- Therapeutic area experts
- Operation staff

**Site Selection**

- Potential list of investigator
- Feasibility Survey
- Site selection visits
- Official selection of sites
- Establish timelines for site activation
- Requalification if change in site PI/equipment/facilities

**Contracts**

- Responsible for all contract and budget negotiations with sites
- Provide sites a copy of executed contract(s)

**Site Training/Clinical Support**

- Provide protocol training
- Resource for clinical or protocol questions
- Conduct annual protocol training visits
- Communicate updates to sites via site wide calls, newsletters, study memos, etc.

**Enrollment**

- Review enrollment expectations
- Gather information on challenges of enrollment
- Determine strategies for enrollment / suggest enhancements

**Vendor Management**

- Labs
- WCG – Central IRB
- Other vendors

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# Pediatric Trials Network DCC Roles

**Data Management**
- Database creation and management
- Data entry training
- Data collection
- Cleaning and analysis

**Regulatory Management**
- Regulatory document collection
- Site activation
- Informed Consent/Assent review and approval
- Trial Master File
- **Regulatory review and oversight**
- Submissions to regulatory organizations

**Safety**
- Review and oversight
- Development of the Safety Monitoring Plan
- Ongoing safety monitoring
- SAE management and reporting
- DMC management

**Site Monitoring**
- Conduct interim, closeout and for-cause visits
- Generate reports
- Work with sites to resolve action items
- Work with sites on Corrective Action and Preventive Action (CAPA) as needed
- Ensure correct implementation of study procedures

**Communications**
- Through the DCC website:
- Serves as a central location for all Network and study communications & materials
- Includes: conference calls and the dissemination of materials and correspondence (e.g., status and milestones)

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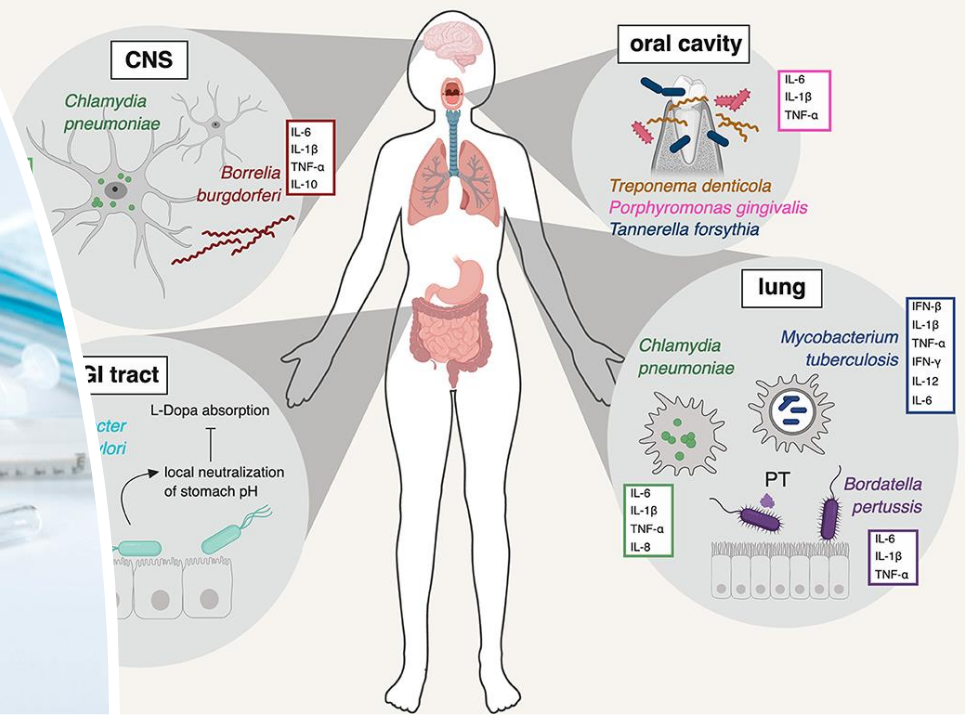
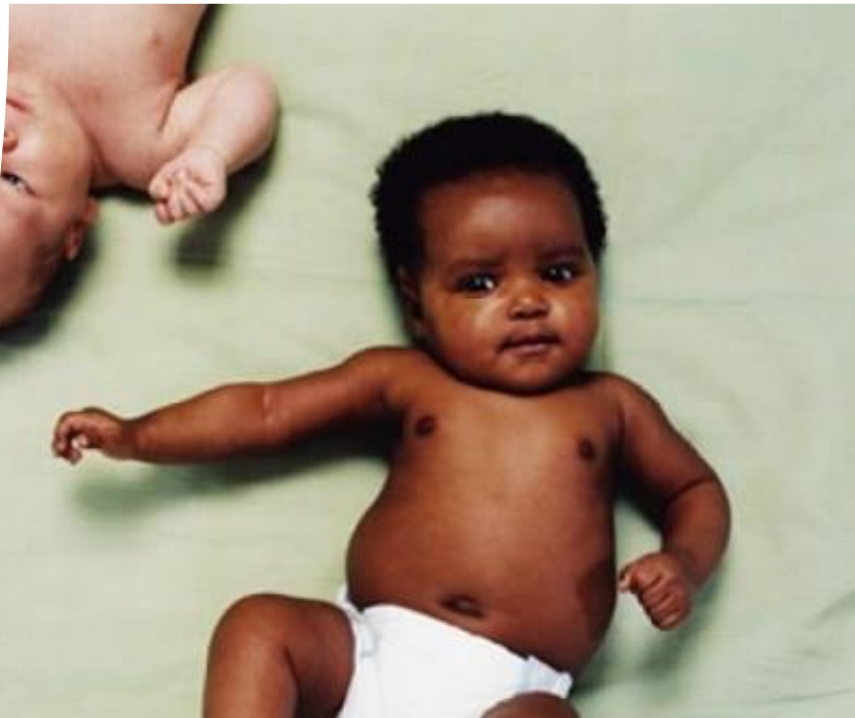
# Scope of the PTN

- Leaders in practical innovation in pharmacology focused trials
  - Master Protocols
  - Opportunistic Designs (POPS, CUDDLE)
- Various clinical settings
  - Inpatient
  - PICU
  - Outpatient
  - NICU
- Special populations
  - Neonates
  - IDeA states
  - Children with Down syndrome
- Therapeutic agnostic







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# BPCA Programmatic Successes Since 2002

## BPCA 2002 – 2007

- 57 priority pharmaceuticals identified
- 6 Clinical Studies performed
- 0 FDA submissions
- 2 label UPDATES

## BPCA 2007 - 2012

- 40 priorities identified
- 10 clinical studies performed
- 3 (Legacy Trials)
- 1 Label change

## BPCA 2012 – 2017

- 36 priorities identified
- 13 Clinical Studies performed
- 7 FDA CSR submissions
- 4 Label changes

## BPCA 2017 – 2023

- 33 priorities identified
- 17 Clinical Studies performed
- 13 FDA CSR submissions
- 12 Label changes

To Date:
160+ Priorities

46 CTs
62 INDs
1K, 1Q
26 CSRs
19 Labels

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# **BPCA** by the Numbers

**>12,500**
participants enrolled

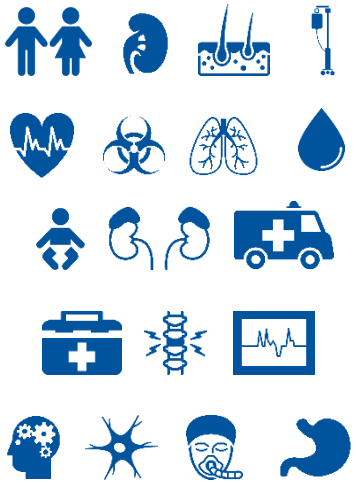
**26**
products submitted to the FDA

**301**
sites in

**45**
states and

**4**
foreign countries

**20**
therapeutic areas studied



**46**
studies

**19**
label changes

**>100**
publications

**>200**
methods developed

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# BPCA Contribution to Pediatric Drug Development

- Diverse Study Designs (shared thru publications)
  - Small PK (5) ACY01,CLN01,MET01,MTH01,PAN01
  - Mid- range PK/Dose Finding/Safety Studies (8) AED01, *Baclofen*, DGX01, HTN01, HUB01, SIL01, STA01, TBS01, *Meropenem, SNP1*
  - Safety Studies (5) ABS01, FUR01, LAP01, SIL02, SIL03
  - Efficacy (7) TIM01, *Status 1 & 2, COLT 1 & 2, Sedation, SNP2*
  - Master Protocols (5) ANA01, BMS01, BMS02, POP01, POP02
  - Device Studies (4) TAP01, TAP02, TAP03, Positron
  - Retrospective Chart Reviews (5) ABS02, ACY02, AMP01, CAF01, DPD01

*Italics indicates Legacy (non-PTN) study*

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# POP02: PK, PD, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care

- Example of a Master Protocol design used by the Network.
- The study began in 2020; Enrollment goal is 5000 total patients across cohorts and drugs of interest.
- Eligible patients can be enrolled if given one of the following drugs per standard of care for a qualifying diagnosis:

  - Aminocaproic acid
  - Amiodarone
  - Bosentan
  - Budesonide
  - Cefdinir
  - Cefepime
  - Ceftazidime
  - Clindamycin
  - Clobazam
  - Dexamethasone
  - Dexmedetomidine
  - Dextroamphetamine/ Amphetamine
  - Fosfomycin
  - Furosemide
  - Gabapentin
  - Guanfacine
  - Hydrocortisone
  - Labetalol
  - Meropenem
  - Metformin
  - Milrinone
  - Nalbuphine
  - Nicardipine
  - Nifedipine
  - Oseltamivir
  - Oxycodone
  - Risperidone
  - Sertraline
  - Sevelamer Carbonate / Sevelamer Hydrochloride
  - Spironolactone
  - Terbutaline
  - Tranexamic acid
  - Voriconazole
  - Zolpidem
  - Azithromycin
  - Lopinavir/Ritonavir
  - Ribavirin
  - Tocilizumab
  - Anakinra
  - Aspirin
  - Canakinumab
  - Colchicine
  - Interferon
  - Remdesivir
  - Ruxolitinib
  - Sarilumab

# BPCA Contribution to Pediatric Drug Development

- 30+ Datasets on NICHD Data and Specimen Hub (DASH)
- >100 publications in various journal
- >100 Drug Methods developed (available on PTN website)
- Study summaries and Patient testimonials (available on PTN website)

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# What we have learned

- Kids need to be at the table (at least thought of in early phases)
- Sustainable Infrastructure important to success
- Innovative and Practical approaches to trial designs work (de-risk trials)
- Clear and frequent communication/collaboration with FDA necessary

# What still needs to be done…

- **Maximize and Leverage the Legislative and Regulatory Wins:**
  - More Focused legislations such as RACE
  - Evidence generation for off-label use
- **Address Remaining Challenges:**
  - Studies in Special populations, including neonates and orphan designations
  - Limitations in patient and staffing numbers, continuing the pipeline of experts
  - EHR reform for real-world data (RWD)/real-world evidence (RWE) to FDA
- **Potential Solutions and Priorities**:
  - Monetizing the benefits of research in kids
    - Maximizing the inclusion of kids holistically in the discussion and design of research
  - Training the next generation
    - Improve the pipeline of researchers, clinicians, and patient advocates
    - Training programs that are multi-dimensional including hubs affiliated with NIH networks, industry, FDA fellowships,
  - See Research as a Partnership
    - What is important to the community? Include from the beginning and report back
    - Leveraging existing data and resources to minimize the burden of trials (decentralized trials)
    - Consider Precision medicine approaches

# More information

- www.Pediatrictrials.org
- www.bpca.nichd.nih.gov

- Perdita Taylor-Zapata, MD. Program Director
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