Overview of Ongoing BPCA-Sponsored Projects

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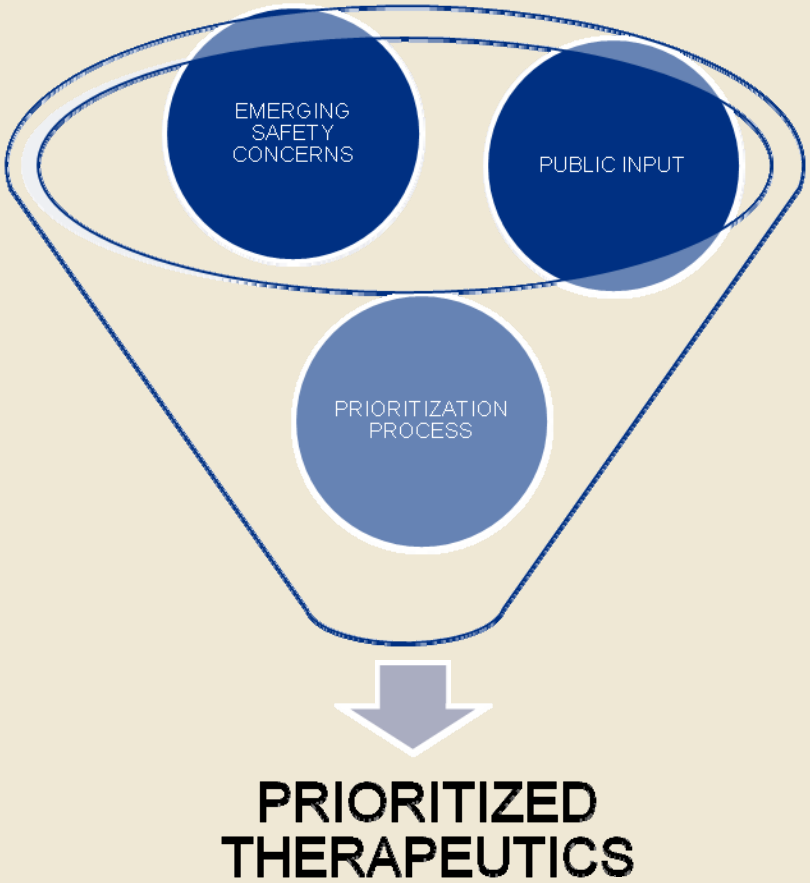
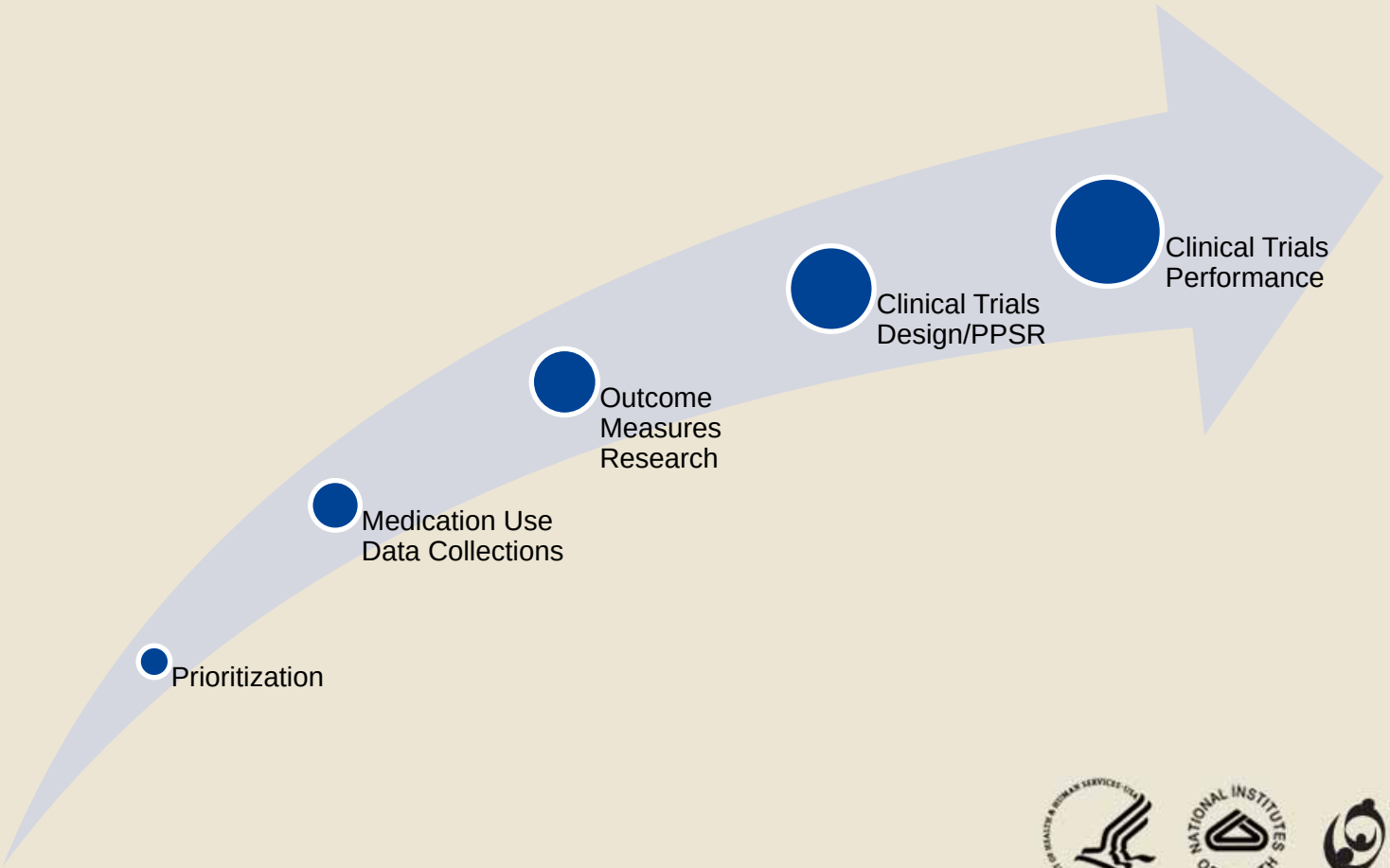
Outline

- Overview of the Best Pharmaceuticals for Children Act (BPCA) prioritization process
- Overview of the status of BPCA clinical trials
- Update on labeling changes
- Training initiatives
- Infrastructure: Introduction of the Pediatric Trials Network (PTN)

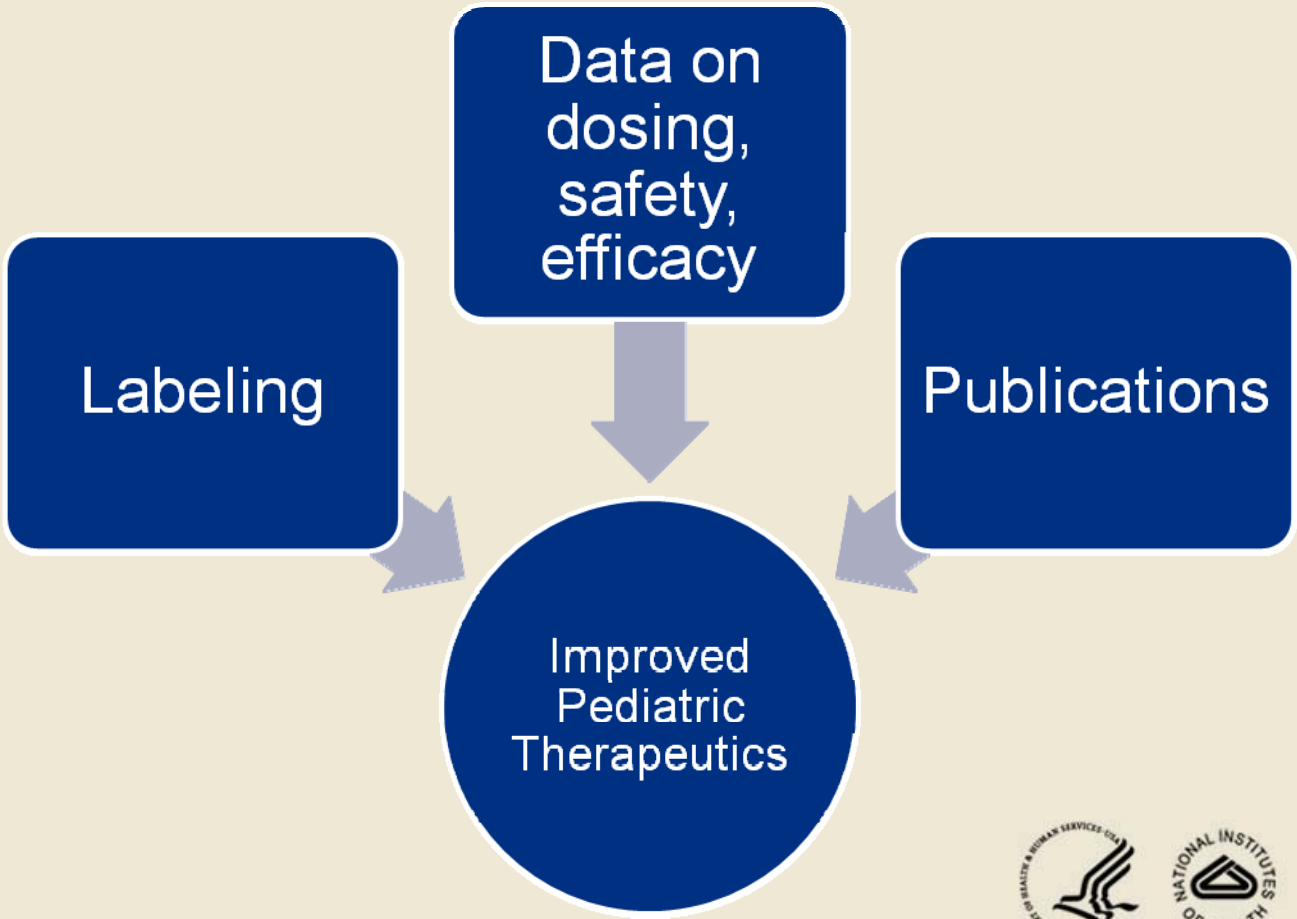
National Institutes of Health (NIH) Processes for BPCA



NIH Processes for BPCA



BPCA Process Goals



BPCA Prioritization Process

2002: Master List of All Off-Patent Drugs that lack adequate pediatric labeling

Consider for prioritizing:

- Availability of safety/efficacy data
- Are additional data needed?
- Will new studies produce health benefits?
- Reformulation?

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Drugs

BPCA Prioritization Process (continued)

2007: Therapeutic Areas

Consultation with experts in pediatric practice and research

Consider for prioritizing:
- Therapeutic gaps
- Potential health benefits of research
- Adequacy of necessary infrastructure

Develop, prioritize, publish an Annual List of Therapeutic Areas and Specific Needs

BPCA Process for Effecting Label Change

Prioritization

Written Request/PPSR

Clinical Trial

Data Submission to FDA

Label Change

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Status of Clinical Trials

Lorazepam for Sedation

- Safety, efficacy, pharmacokinetics/ pharmacodynamics (PK/PD) study in children on mechanical ventilation in the intensive care unit (ICU)
- Design: Comparison of lorazepam intermittent bolus vs. lorazepam continuous infusion vs. midazolam continuous infusion
- Study completed

Lorazepam for Status Epilepticus

- Safety, efficacy, PK study of lorazepam in children with status epilepticus
- Comparison of lorazepam and diazepam in children with status epilepticus in the emergency room
  - Exception from Informed Consent
  - United States and Canada
- Studies:
  - PK: Clinical Study Report submitted to U.S. Food and Drug Administration (FDA)
  - Clinical trial: recruitment ongoing

Nitroprusside

- Study of hypotensive effect of nitroprusside in children requiring blood pressure reduction
- Studies:
  - Dose-response study: completed
  - Tachyphylaxis study: recruitment nearing completion

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Baclofen

- Safety, PK/PD study of oral baclofen to reduce spasticity in children with cerebral palsy
- Studies:
  - Chart review completed
  - PK/PD study recruitment completed

Lithium

- Safety, efficacy, PK study of lithium in children with bipolar illness
- Studies:
  - PK: Clinical Study Report submitted to the FDA
  - Efficacy/safety study: recruitment ongoing

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Meropenem

- Safety, efficacy, PK study of meropenem in neonates with abdominal infections
- Study recruitment completed, data analysis ongoing

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Hydroxyurea

- National Heart, Lung, and Blood Institute (NHLBI) study of efficacy, safety, PK of hydroxyurea in young children with sickle cell disease
- Study unblinded January 2010

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Dopamine

- Co-fund with Neonatal Research Network to determine feasibility of larger efficacy/safety trial of dopamine to treat hypotension in neonates

Oncology Studies

- **Vincristine (VCR):** Studies to evaluate neurotoxicity, PK in children (National Cancer Institute [NCI]-Children's Oncology Group [COG])
- **Actinomycin-D (Act-D):** Studies to evaluate hepatotoxicity/venoocclusive disease (VOD), PK in children (NCI-COG)
  - Study 1: data extraction of National Wilms Tumor Study database for toxicity (completed)
  - Study 2: catheter-clearing experiments (completed)
  - Study 3: PK modeling of published VCR, Act-D data to design prospective PK study (completed)
  - Study 4: prospective PK study
  - Recruitment ongoing

Oncology Studies

- **Methotrexate:** Clinical studies to evaluate neurocognitive outcomes of pediatric patients with high risk acute lymphoblastic leukemia (NCI-COG)
  - Relationship of neurocognitive testing to diffusion tensor imaging-magnetic resonance imaging (DTI-MRI)
  - Longitudinal and cross-sectional
- **Daunomycin:** Disposition and response in relation to body mass index (BMI)

Isotretinoin: Proposed Pediatric Study Request (PPSR)

- **Isotretinoin**
  - Discussion at Pediatric Subcommittee of the Oncologic Drug Advisory Committee
    - Labeling for neuroblastoma (new indication)
    - Formulation
  - Written Request issued by the FDA, declined, received by the NIH
  - Primary data received from COG
  - Clinical Trials Agreement for formulation in review

Clinical Study Reports Submitted

- Lorazepam for Status PK study
- Lithium PK study

Timeline for Clinical Study Reports: Q4 2010-Q2 2011

- Meropenem
- Lorazepam for Sedation
- Baclofen PK/PD
- Nitroprusside dose-response study
- Hydroxyurea
- Daunomycin

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Labeling Changes

- Pralidoxime (listed 2006)
- Propylthiouracil

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Pralidoxime

- **FDA Approves Pediatric Use of Chemical Poisoning Treatment**

  By *U.S. Food and Drug Administration*
  Published: 2010-09-09

  The U.S. Food and Drug Administration has approved the pediatric use of Protopam Chloride (pralidoxime chloride), a drug used to treat poisoning by organophosphate pesticides and chemicals (e.g., nerve agents).

  "It can be difficult to use IV drugs in children, particularly in emergency situations, so having the new option of IM injection may help health care professionals use this medicine quickly and accurately," said Dianne Murphy, M.D., director of the FDA's Office of Pediatric Therapeutics.

  Protopam Chloride was approved by the FDA in 1964 to treat various types of pesticide and chemical poisoning in adults. The drug works as an antidote to pesticides and chemicals of the organophosphate class by slowing the attachment of the chemical to nerve endings.

Propylthiouracil (PTU) Hepatoxicity in Children and Recommendations for Discontinuation of Use

Rivkees SA and Mattison DR

International Journal of Pediatric Endocrinology 2009

- "The PTU problem came to attention at a recent *Eunice Kennedy Shriver* National Institute of Child Health [and Human Development] (NICHD)-sponsored workshop on October 28, 2008. Based on epidemiology and adverse event data presented, it was estimated that the risk of PTU-related liver failure leading to liver transplantation or death was about 1 in 2,000 treated children. Ten-fold more children were estimated to sustain reversible liver damage."

PTU: The FDA issues Dear Doctor Letter June 4, 2009

- FDA is notifying healthcare professionals of the risk of serious liver injury, including liver failure and death, with the use of propylthiouracil in adult and pediatric patients.
- Reports to FDA's Adverse Event Reporting System (AERS) suggest there is an increased risk of hepatotoxicity with [propylthiouracil] when compared to methimazole. Although both propylthiouracil and methimazole are indicated for the treatment of hyperthyroidism due to Graves' disease, healthcare professionals should carefully consider which drug to initiate in a patient recently diagnosed with Graves' disease. Physicians should closely monitor patients on propylthiouracil therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy. Propylthiouracil and methimazole were approved in 1947 and 1950, respectively.
- FDA has identified 32 AERS cases (22 adult and 10 pediatric) of serious liver injury associated with propylthiouracil use. Of the adult cases, 12 deaths and 5 liver transplants occurred. Among the pediatric patients, 1 case resulted in death and 6 in liver transplants.

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PTU Black Box Warning June 21, 2010

- "Physicians should closely monitor patients on propylthiouracil therapy for symptoms and signs of liver injury, especially during the first six months after initiation of therapy. Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of methimazole, and there are no other treatment options available."

BPCA Clinical Trials: Scientific Results

- Publications: 18 (plus 4 submitted)
- Abstracts: 26

BPCA Clinical Trials: Selected Publications

Lorazepam for Status Epilepticus: Publications

- Chamberlain JM, Lillis K, Vance C, et al, for the Pediatric Emergency Care Applied Research Network. Perceived challenges to obtaining informed consent for a time-sensitive emergency department study of pediatric status epilepticus: results of two focus groups. *Acad Emerg Med.* 2009;16(8):763-70.
- Chamberlain JM, Singh T, Baren JM, Maio RF. Food and Drug Administration public hearing on the conduct of emergency clinical research: testimony of Pediatric Emergency Care Applied Research Network. *Acad Emerg Med.* 2007;14(4):e41-2. Epub 2007 Feb 25. doi:10.1197/j.aem.2006.11.024.

Lithium: Publications

- Findling RL, Frazier JA, Kafantaris V, et al. The Collaborative Lithium Trials (CoLT): specific aims, methods, and implementation. *Child Adolesc Psychiatry Ment Health.* 2008;2(1):21.
- Findling RL, Landersdorfer CB, Kafantaris V, et al. First-dose pharmacokinetics of lithium carbonate in children and adolescents. *J Clin Psychopharmacol.* 2010;30(4):404-10.

Hydroxyurea: Publications

- Wang WC, Pavlakis SG, Helton KJ, et al, for the BABY HUG Investigators. MRI abnormalities of the brain in one-year-old children with sickle cell anemia. *Pediatr Blood Cancer.* 2008;51(5):643-6.
- Miller ST, Wang WC, Iyer R, et al, for the BABY HUG Investigators. Urine concentrating ability in infants with sickle cell disease: baseline data from the phase III trial of hydroxyurea (BABY HUG). *Pediatr Blood Cancer.* 2010;54(2):265-8.
- Thompson BW, Rogers ZR, Miller ST, et al. The pediatric hydroxyurea phase III clinical trial (BABY HUG): challenges of study design. *Pediatr Blood Cancer.* 2010;54(2):250-5.
- Wang WC, Ware RE, Miller ST, et al, for the BABY HUG Investigators. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet.* 2011;377(9778):1663-72.

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Hydroxyurea: Publications (continued)

- Pavlakis SG, Rees RC, Huang X, et al, for the BABY HUG Investigators. Transcranial doppler ultrasonography (TCD) in infants with sickle cell anemia: baseline data from the BABY HUG trial. *Pediatr Blood Cancer.* 2010;54(2):256-9.
- Thornburg CD, Rogers ZR, Jeng MR, et al, for the BABY HUG Investigators. Adherence to study medication and visits: data from the BABY HUG trial. *Pediatr Blood Cancer.* 2010;54(2):260-4.
- Ware RE, Rees RC, Sarnaik I, et al, and the BABY HUG Investigators. Renal function in infants with sickle cell anemia: baseline data from the BABY HUG trial. *J Pediatr.* 2010;156(1):66-70.
- Wynn L, Miller S, Faughnan L, et al. Recruitment of infants with sickle cell anemia to a phase III trial: data from the BABY HUG study. *Contemp Clin Trials.* 2010;31(6):558-63. Epub 2010 Aug 24.

Vincristine and Actinomycin-D: Publications

- Skolnik JM, Zhang AY, Barrett JS, Adamson PC. Approaches to clear residual chemotherapeutics from indwelling catheters in children with cancer. *Ther Drug Monit.* 2010;32(6):741-8. Epub 2010 Oct 19.
- Mondick JT, Gibiansky L, Gastonguay MR, et al. Population pharmacokinetic investigation of actinomycin-D in children and young adults. *J Clin Pharmacol.* 2008; 48(1):35-42.
- Laër S, Barrett JS, Meibohm B. The in silico child: using simulation to guide pediatric drug development and manage pediatric pharmacotherapy. *J Clin Pharmacol.* 2009;49(8):889-904.
- Skolnik JM, Barrett JS, Jayaramana B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials : the rolling six design. *J Clin Oncol.* 2008;28(2):190-5.

Data Collections to Inform Clinical Trial Design

Neonatology: NHLBI Co-Fund for Prematurity and Respiratory Outcomes Network

- Data collection of drugs used in the neonatal ICU and following discharge for treatment of bronchopulmonary dysplasia

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Asthma Data Collection

- Collaborative Pediatric Critical Care Network data collection on medication use in children in the pediatric ICU with status asthmaticus
- Purpose: to determine the use of medications in status asthmaticus, in order to generate hypotheses that could be tested in a clinical trial

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Outcome Measures to Inform Clinical Trial Design

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Clinical and Translational Science Awards (CTSA)

- Need for outcome measures
  - Neonatology
  - Cardiovascular medicine
  - Neurology

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Snapshot of BPCA Projects
(18 recommended for funding)

Topic areas: 8 neonatology, 5 neurology, 4 hypertension/hypotension, 3 “other”; >1 topic area possible

1	Duke	Development of a PK algorithm to improve neonatal outcomes
2	UTHSC	Advanced MRI to assess neonatal care and outcome
3	Columbia	Targets and barriers for hydroxyurea use in sickle hemoglobinopathies
4	Utah	Improving management of the neonatal abstinence syndrome
5	U Pitt	Cardiac outcome measures for pediatric muscular dystrophy
6	UNC	Outcome measures for chronic lung disease of prematurity
7	U-CO	Small volume fentanyl PK/PD & PG in neonates
8	UC-Davis	Outcome measures for trials in children with autism
9	Vanderbilt	Wireless home-based tools for studying sleep in autism
10	U-MI	Pediatric Cardiac Intensive Care Data Standards Repository
11	Stanford	Methadone vs. morphine PD/PD in infants after cardiac surgery
12	Indiana	Predictors of vincristine-induced peripheral neuropathy
13	UAB	Nasal potential difference studies utilizing CFTR modulators
14	CWRU	Efficacy outcomes measures in antihypertensive trials in children
15	CWRU	Effect of BMI on exposure-response relationships to lisinopril in children
16	U-Wash	Advancing patient reported outcomes (PROs) in children with cystic fibrosis
17	AECOM	Pediatric hypertension outcome measures
18	Tufts	Improving BPD predictors and outcomes for clinical trials

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Asthma Outcomes Workshop

- NHLBI, National Institute of Allergy and Infectious Diseases (NIAID), NICHD, and external participants/experts
- March 15−16, 2010
- Purpose: attempt to develop standardized outcome measures in asthma in order to compare studies and treatments

Pre-clinical studies

- Methylphenidate
- Ketamine

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Methylphenidate and amphetamine do not induce cytogenetic damage in lymphocytes of children with ADHD.

Witt KL, Shelby MD, Itchon-Ramos N, et al.

J Am Acad Child Adolesc Psychiatry. *2008 Dec;47(12):1375-83*

- RESULTS: Sixty-three subjects enrolled in the study; 47 subjects completed the full 3 months of treatment, 25 in the methylphenidate group and 22 in the amphetamine group. No significant treatment-related increases were observed in any of the three measures of cytogenetic damage in the 47 subjects who completed treatment or the 16 subjects who did not.
- CONCLUSIONS: Earlier findings of methylphenidate-induced chromosomal changes in children were not replicated in this study. These results add to the accumulating evidence that therapeutic levels of methylphenidate do not induce cytogenetic damage in humans.

Infrastructure

- Training
- Clinical Trials
  - Study design
  - Patient recruitment
  - Data analysis
  - Formulations

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Training

Training: T32 National Institute of General Medical Sciences (NIGMS) Co-fund

- Clinical Pharmacology Training Program:
  - Mayo Clinic
  - University of California, Los Angeles (UCLA)
  - University of California, San Francisco (UCSF)
  - Jefferson University
  - University of Pennsylvania
  - Vanderbilt University
  - University of Chicago

Training: F31 NIGMS Co-fund

- Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Predoctoral Fellows in Pharm.D./Ph.D. Programs (F31)
- Expiration date: May 08, 2013
- Application submission/receipt date(s): Standard dates apply

Training: T32 in Pediatric Clinical Pharmacology

- Postdoctoral Research Training in Pediatric Clinical and Developmental Pharmacology (T32)
- Program Announcement (PA) Number: RFA-HD-10-005

Infrastructure

- Need for infrastructure for all aspects of pediatric clinical trials performance
  - Management (site performance)
  - Study design/clinical pharmacology
  - Recruitment
  - Formulations
  - Data analysis
  - Device development/validation

Pediatric Trials Network

- Awarded September 28, 2010
- Duke University
  - https://www.fbo.gov/index?s=opportunity&mode=form&id=cf49c1b60b546914941b266295b24c84&tab=core&_cview=1
- Cores:
  - Management
  - Clinical trials performance
  - Formulations development for clinical trials
  - Clinical pharmacology study design and analysis
  - Device development (validation)

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Pediatric Trials Network

Potential Therapeutic Areas

- Cardiovascular diseases
- Infectious diseases
- Respiratory diseases
- Gastroenterology
- Pediatric oncology
- Neonatology

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Formulations

- Baclofen
- Hydroxyurea

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NIH-FDA Formulations Platform

- Interagency Agreement with FDA 2010−2011
- Develop an open-source, technically feasible platform based on chemical structure, to produce orally dissolvable solid dosage forms that are stable at high temperatures/humidity, taste-masked, with good oral absorption, in suitable dosage increments, with minimal excipients

Work in Progress

- New clinical trials under the PTN
- Use of formulations platform to provide open-source information to manufacturers
- Meeting with CTSA sites on outcome measures grants
- Synthesis and analysis of BPCA clinical trials data

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Frequently Asked Questions

Frequently Asked Questions

- **Will the Listing Process continue?**
  - Yes, the listing process will continue but on a smaller scale.
- **How will the prioritization process work with the PTN?**
  - Recommendations for prioritized therapeutic areas and drugs will be further prioritized by the PTN for feasibility and other considerations.
- **How can I participate in the PTN?**
  - If you are interested in participating in pediatric research studies being conducted under the PTN, please visit the BPCA Web site for additional information.
- **Is the PTN the only way clinical trials will be performed?**
  - Yes, drug trials will be done through the PTN. However, NICHD will continue to collaborate with other NIH Institutes and Centers and with other government agencies.

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