Opportunities: Pediatric Trials Network

P. Brian Smith MD MPH MHS

Duke Clinical Research Institute

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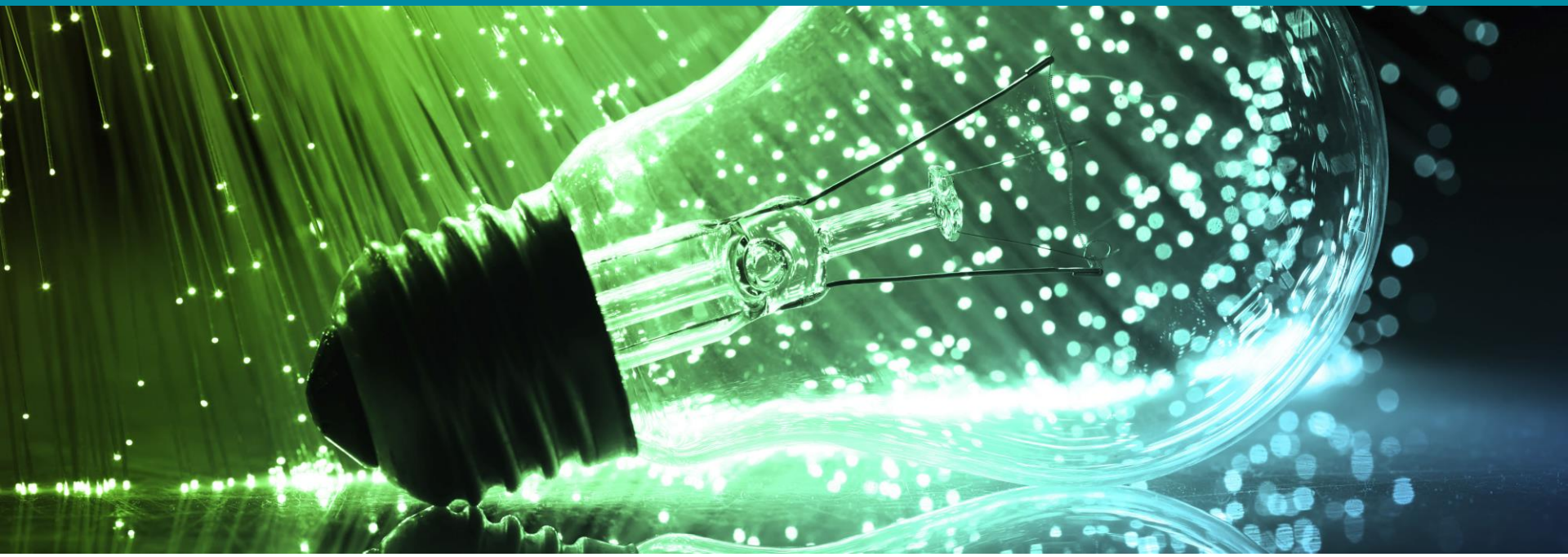
CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE



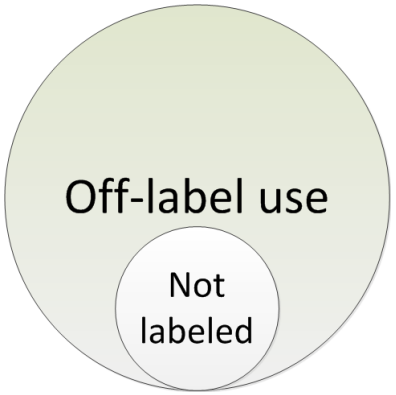
Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

The presenter is an Employee of Duke University.

100 most commonly used drugs in the NICU

- 87 not labeled for use in premature infants
- For the remaining 13, many of the exposures are off-label
  - Wrong indication
  - Wrong population
  - Wrong dose



Laughon MM, Avant D, Tripathi N, Hornik CP, Cohen-Wolkowiez M, Clark RH, Smith PB, Rodriguez W, *JAMA Pediatrics*, 2014.

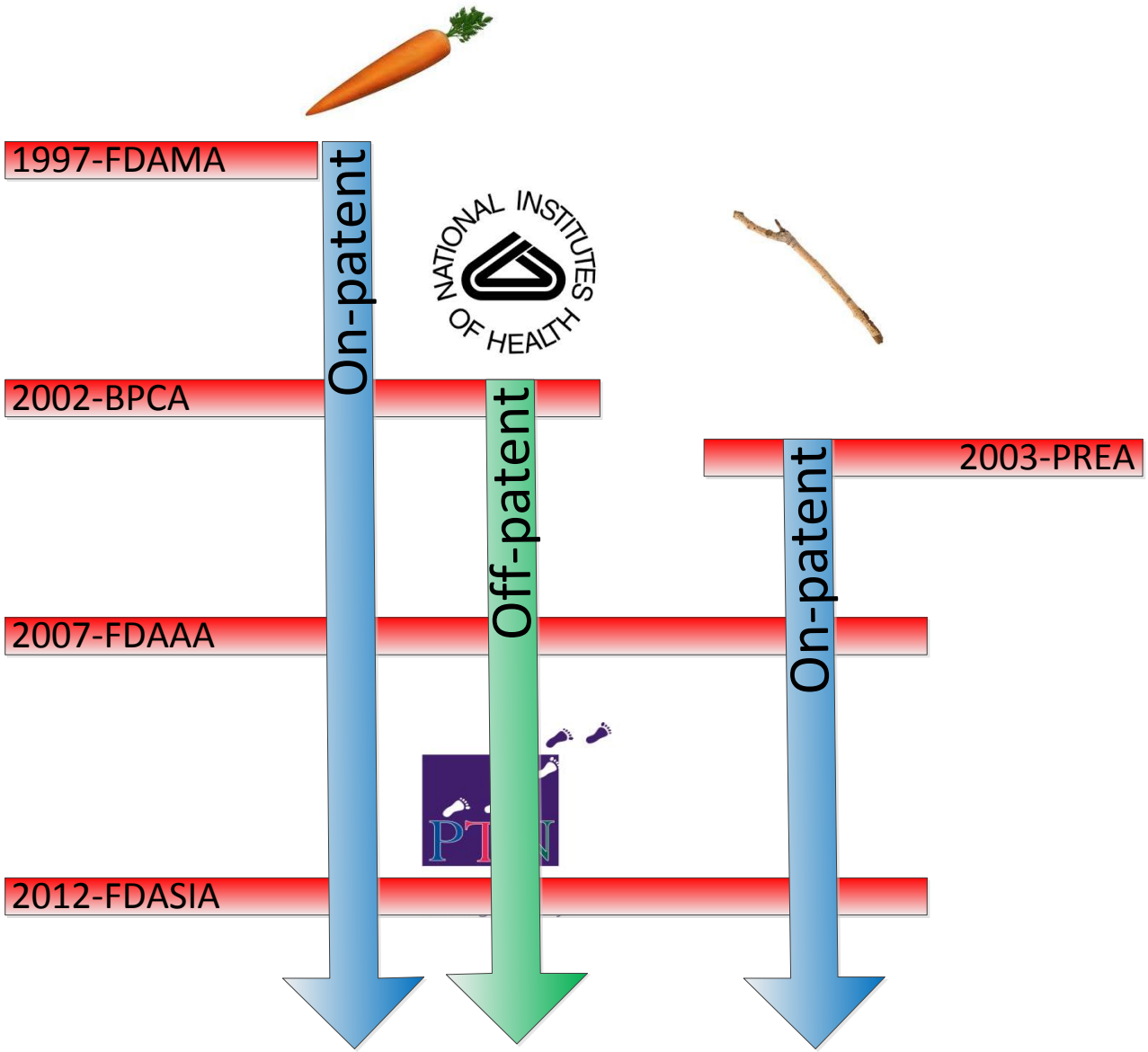
Antimicrobials use in the NICU

Rank	Medication	Exposures (/1000 infants)
1	Ampicillin	681
4	Vancomycin	91
15	Cefotaxime	43
23	Tobramycin	24
27	Fluconazole	19
28	Clindamycin	17
30	Acyclovir	16
38	Ceftazidime	12
41	Piperacillin/tazobactam	11
43	Amoxicillin	11
44	Metronidazole	11
45	Oxacillin	10
46	Nafcillin	9.0
47	Amphotericin B products	8.9

What is the Pediatric Trials Network?

"Create 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)
- Success - improve dosing, safety information, labeling, and ultimately child health
- PI – Danny Benjamin, MD PhD MPH – Duke Clinical Research Institute (DCRI)


1997-FDAMA
On-patent
NATIONAL INSTITUTES OF HEALTH
2002-BPCA
Off-patent
2003-PREA
On-patent
2007-FDAAA
2012-FDASIA

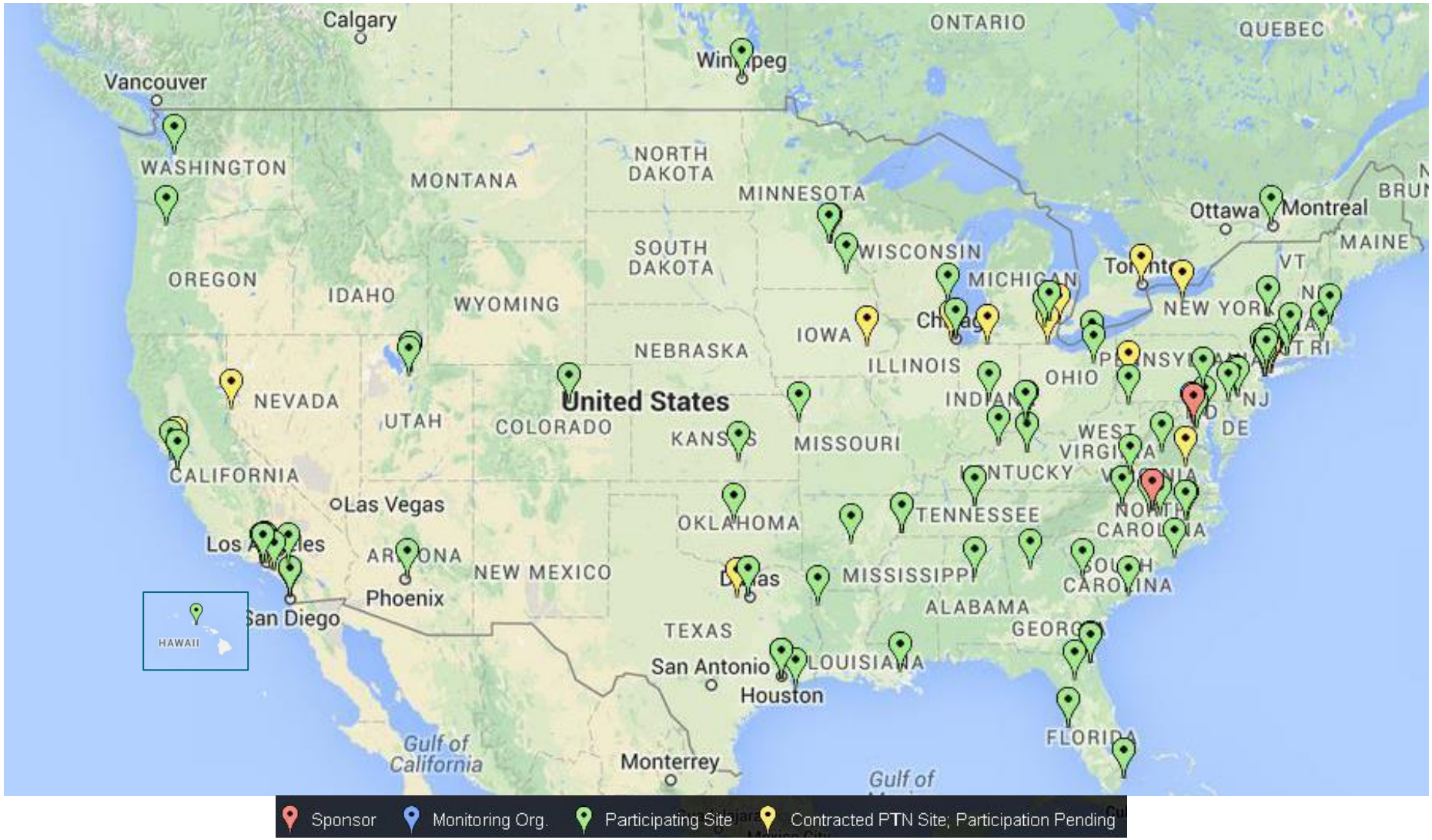
How PTN works

1. NIH develops a priority list of off-patent therapeutics
   - http://bpca.nichd.nih.gov/prioritization/status/documents/priority_list_10-26-2012.pdf
2. Investigators submit study concept sheet to PTN
3. PTN Administrative Core reviews science and feasibility
4. If approved, PTN forms protocol development team
   - protocol chair, thought leaders, pharmacologists, operations experts
5. NIH provides small amount of funding for protocol development
6. PTN sends scope of work and budget to NIH
7. PTN selects sites from rapid start network based on site study interest, site PIs, previous history of enrollment
8. PTN executes trial

PTN Network Steering Committee

Name	Role	
Kelly Wade, MD, PhD	Co-Chair, Safety & Ethics Core	Children's Hospital of Philadelphia, Philadelphia, PA
Michael O'Shea, MD	Co-Chair Devices Core	Wake Forest University Medical Center, Winston-Salem, NC
P. Brian Smith, MD	Network Co-Investigator	Duke University, Durham, NC
Michael Cohen-Wolkowiez, MD, PhD	Network Co-Investigator	Duke University, Durham, NC
Matthew Laughon, MD	Committee Member	UNC Memorial Hospital, Chapel Hill, NC
Ian Paul, MD	Committee Member	Penn State College of Medicine, Hershey, PA
Michael Smith, MD	Committee Member	Univ. of Louisville, Louisville KY
Anne Zajicek, MD, PharmD	Branch Chief	NICHD, Bethesda, MD
David Siegel, MD	NICHD COTR	NICHD, Bethesda, MD
Perdita Taylor-Zapata, MD		NICHD, Bethesda, MD

PTN Sites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IDAHO
WYOMING
MICHIGAN
NEW YORK
IOWA
NEBRASKA
ILLINOIS
OHIO
NEVADA
United States
UTAH
COLORADO
INDIANA
NJ
DE
CALIFORNIA
MISSOURI
KENTUCKY
Las Vegas
OKLAHOMA
TENNESSEE
NEW MEXICO
Phoenix
San Diego
MISSISSIPPI
ALABAMA
HAWAII
TEXAS
San Antonio
LOUISIANA
Houston
FLORIDA
Gulf of California
Monterrey
Gulf of
Sponsor
Monitoring Org.
Participating Site
Contracted PTN Site; Participation Pending

Pediatric Trials Network – Progress Since 2010

Contract Scope of Work

- Projects
  - 16 clinical trials
  - Phase I-II studies
- Enrollment
  - ~100 children enrolled per project
  - 1600 total enrolled
- Therapeutic areas
  - Primary contract included hypertension; but had flexibility with respect to number and type of areas
- Flexibility with respect to data submitted to FDA but reasonable goal of ~4 product submissions (by 2015)

Accomplished

- Projects
  - 30 total projects; 18 clinical trials
  - Phase I-IV studies
- Enrollment
  - Over 100 sites enrolling
  - > 5000 children enrolled
- Across therapeutic areas
    - Hypertension, Neonatology, ID, Obesity, Neurology, Psychiatry, Critical Care, GI, Pulmonary, Hematology, Oncology
- Data for 9 products submitted to FDA and >20 products with planned submission by 2017

Problem - Blood Volume Limitations

500 g, 23 week
Total blood volume
42 mL

10 - 3 mL PK samples
71% blood volume

Total blood volume
5000 mL

10 - 3 mL PK samples
0.6% blood volume

Solution - Sensitive Drug Assays

- Low volume plasma samples
  - 100 µL blood sample yields 50 µL plasma
  - Can be obtained with a heel-stick
  - 6 samples = 0.6 mL
- Dried blood spots
  - 30 µL
  - 6 samples <0.2 mL
- Multiplex assays
  - Ability to test multiple drugs simultaneously
  - Ability to test parent drug and metabolites

Problem – Children/Parents do not like needle sticks

Solution - Minimal Risk Methods

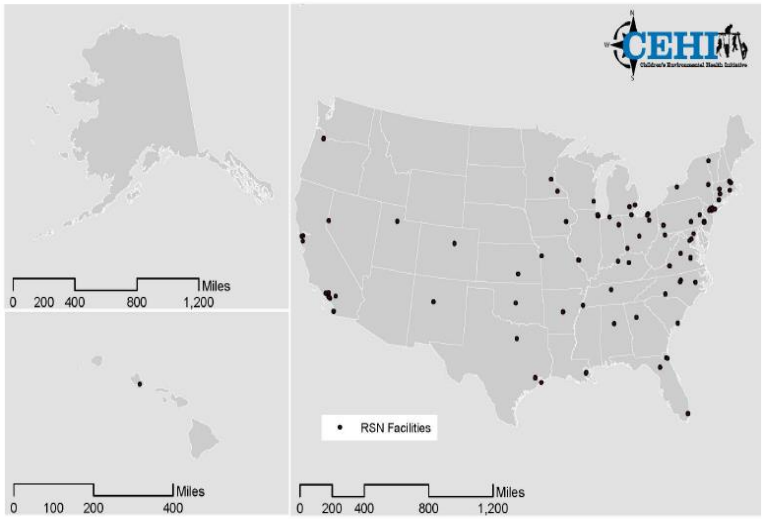
- Sparse sampling
  - Sampling windows
  - Sampling can occur during normal, standard of care lab draw times
  - Population PK analyses
- Scavenge sampling
  - Samples obtained from leftover blood in clinical labs

Problem: Site Contracts

- Contracts take 6-12 months depending on site

Solution: Duke Clinical Research Institute Rapid Start Network

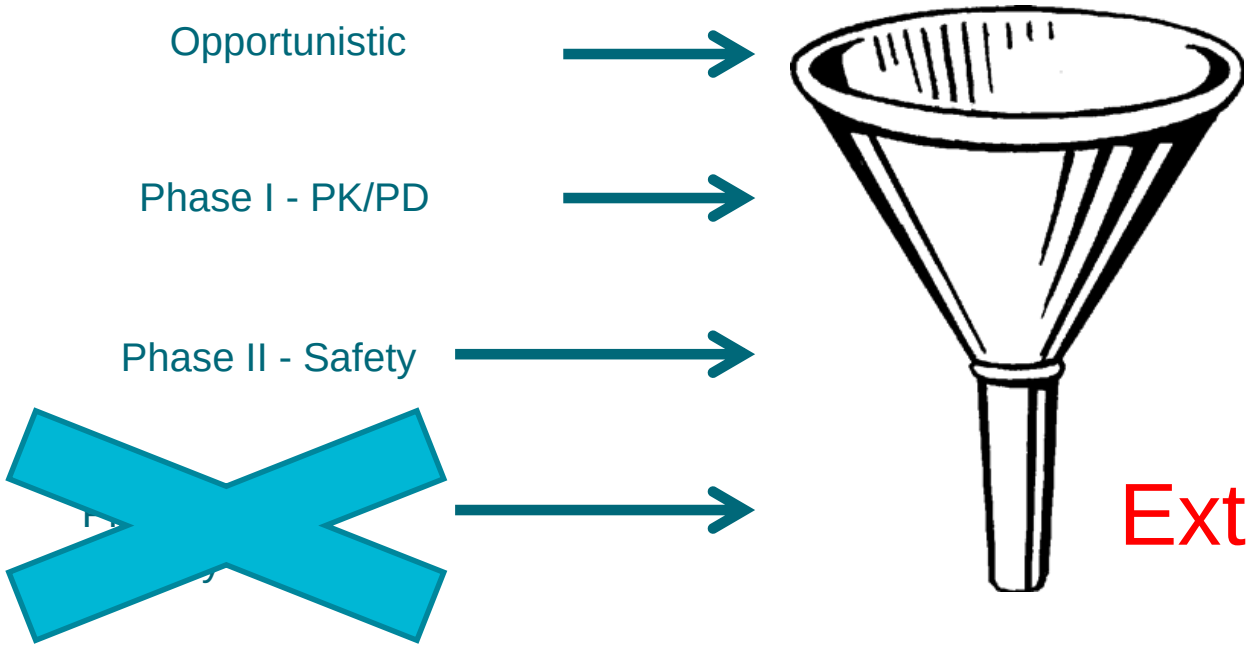
- Master service agreement, each study addendum
- 120 sites
- Strengths
  - Develop site metrics – data collection, enrollment
  - PI training
  - Contract metrics from >4 months to 4 weeks



Problem – Funding: Limits of the mechanism

II	60-200	Safety	3-8 million
III	>300	Efficacy	>20 million

Solution



PTN - Lessons Learned

- Have frequent discussions with FDA/NIH
- Keep protocol simple
- Make inclusion criteria “inclusive”
- Minimize exclusion criteria
- Minimize blood draws
- Use labs/procedures done per standard of care
- Work with experienced sites

PTN Update

- Metronidazole: 3 sites, 24 premature infants at risk for NEC. Protocol chair: Michael Cohen-Wolkowiez. Enrollment and analysis complete, CSR submitted to FDA, published PIDJ.
- Acyclovir: 3 sites, 32 infants with suspected HSV. Protocol chair: Brian Smith. Enrollment and analysis complete, CSR submitted to FDA, published PIDJ.
- TAPE weight estimate device: 3 sites, 625 children. Protocol chair: Sue Rahman, Children's Mercy Hospital, Kansas City, MO. Enrollment and analysis complete. CSR submitted to FDA, FDA cleared the 510(k) application, published Ann of Emer Med.
- Hydroxyurea: 8 sites, 40 children. Protocol chair: Kathleen Neville, Children's Mercy Hospital, Kansas City, MO. Enrollment and analysis complete. CSR submitted to FDA, published J Clin Pharm
- Opportunistic (POPS): 36 sites, 2000 children. Protocol chair: Michael Cohen-Wolkowiez/Chiara Melloni. Enrolling (>2000 enrolled to date).
- Lisinopril PK: 8 sites, 26 children with kidney transplants and HTN. Protocol chair: Howard Trachtman, NYU Langone Medical Center. Enrollment and analysis complete. CSR submitted to FDA, published CPT

PTN Update

- Midazolam meta-analysis: Update label to include treatment of seizures in children 2 years and older using available data. Protocol chair: Brian Smith. Analysis in progress.
- Ampicillin meta-analysis: 1 site, 64 infants, PK analysis in combination with 2 retrospective studies. Protocol chair: Michael Cohen-Wolkowiez. Data collection and analysis complete, CSR submitted to FDA, published AAC.
- Obesity informatics: Database of published PK studies relevant to pediatric obesity. Protocol chair: Kevin Watt. Complete, published JAMA Peds.
- Staph microtrials: 12 sites, 63 infants, 3 anti-staph drugs. Protocol chair: Matt Laughon, UNC. Complete, published AAC
- Sildenafil: 9 sites, 41 infants with pulmonary hypertension or lung disease. Protocol chair: Matt Laughon, UNC. Enrolling.
- Clindamycin obesity: 6 sites, 23 children. Protocol chair: Michael Smith and Janice Sullivan, University of Louisville, KY. Federated IRB. Complete. CSR submitted to FDA.

PTN Update

- Methadone PICU: 5 sites, 26 subjects. Protocol chair: Kevin Watt. Complete.
- Diuretics in NICU: retrospective review: 2 sites, 679 infants. Protocol Chair: Matt Laughon, UNC. Complete. CSR submitted to FDA.
- Piperacillin-tazobactam, clindamycin, metronidazole, ampicillin safety in infants with complicated intraabdominal infections (SCAMP): 50 sites, 374 subjects, Protocol Chair: Michael Cohen-Wolkowiez. Enrolled 150 subjects.
- Pantoprazole obesity: 4 sites, 41 children. Protocol chair: Greg Kearns, Children's Mercy Hospital, Kansas City, MO. Complete.
- Pediatrix meta-analysis of safety of 11 drugs: Retrospective data analysis; database includes >300 sites and >800,000 infants. Protocol chair: Brian Smith. Analysis complete. Published Peds, EHD (2), PIDJ, JPGN, J Perin, A J Perin
- Fluconazole safety meta-analysis: 33 sites, 361 infants enrolled in an earlier RCT. Protocol chair: Brian Smith. CSR submitted to FDA.
- Baby Tape: 8 sites, 2000 subjects. Protocol chair: Sue Rahman, Children's Mercy Hospital, Kansas City, MO. Complete

PTN Update

- Caffeine therapy for apnea of prematurity: retrospective safety, PK, and efficacy. Protocol chair: Kelly Wade, CHOP, data collection for 400 infants
- Furosemide for the prevention of bronchopulmonary dysplasia: 20 site, 120 subjects. Protocol Chair: Matt Laughon, UNC. Enrolling.
- Clindamycin/trimethoprim-sulfamethoxazole: submission of PK data from POPS
- Timolol for infantile hemangioma: 10 sites, 100 subjects. Protocol chair: Beth Drolet, Children's Hospital of Wisconsin. Protocol development.
- Antiepileptic obese children: 6 sites, 72 subjects. Protocol Chair: Kanecia Zimmerman, Duke. Protocol development.

Thank you.

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

P. Brian Smith MD MPH MHS

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brian.smith@duke.edu