Opportunities: Pediatric Trials Network

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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

# Antimicrobials use in the NICU

<table>
<thead>
<tr>
<th>Rank</th>
<th>Medication</th>
<th>Exposures (/1000 infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ampicillin</td>
<td>681</td>
</tr>
<tr>
<td>4</td>
<td>Vancomycin</td>
<td>91</td>
</tr>
<tr>
<td>15</td>
<td>Cefotaxime</td>
<td>43</td>
</tr>
<tr>
<td>23</td>
<td>Tobramycin</td>
<td>24</td>
</tr>
<tr>
<td>27</td>
<td>Fluconazole</td>
<td>19</td>
</tr>
<tr>
<td>28</td>
<td>Clindamycin</td>
<td>17</td>
</tr>
<tr>
<td>30</td>
<td>Acyclovir</td>
<td>16</td>
</tr>
<tr>
<td>38</td>
<td>Ceftazidime</td>
<td>12</td>
</tr>
<tr>
<td>41</td>
<td>Piperacillin/tazobactam</td>
<td>11</td>
</tr>
<tr>
<td>43</td>
<td>Amoxicillin</td>
<td>11</td>
</tr>
<tr>
<td>44</td>
<td>Metronidazole</td>
<td>11</td>
</tr>
<tr>
<td>45</td>
<td>Oxacillin</td>
<td>10</td>
</tr>
<tr>
<td>46</td>
<td>Nafcillin</td>
<td>9.0</td>
</tr>
<tr>
<td>47</td>
<td>Amphotericin B products</td>
<td>8.9</td>
</tr>
</tbody>
</table>
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
2002-BPCA
2007-FDAAA
2012-FDASIA
2003-PREA

On-patent

Off-patent

Pediatric Trials Network
Leading the Way
How PTN works

1. NIH develops a priority list of off-patent therapeutics

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

[Map of the United States with markers indicating PTN Sites, Participation Sites, and Contracted PTN Sites.]

- Sponsor
- Monitoring Org.
- Participating Site
- Contracted PTN Site, Participation Pending
**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

Total blood volume
5000 mL

10 - 3 mL PK samples
71% blood volume

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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Sample Size</th>
<th>Purpose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>60-200</td>
<td>Safety</td>
<td>3-8 million</td>
</tr>
<tr>
<td>III</td>
<td>&gt;300</td>
<td>Efficacy</td>
<td>&gt;20 million</td>
</tr>
</tbody>
</table>
Solution

Opportunistic

Phase I - PK/PD

Phase II - Safety

Extrapolation
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.


- **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.


- **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

- Diuretics in NICU: retrospective review: 2 sites, 679 infants. Protocol Chair: Matt Laughon, UNC. Complete. CSR submitted to FDA.
- 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


- Clindamycin/trimethoprim-sulfamethoxazole: submission of PK data from POPS.


Thank you.

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