

Pediatric Trials Network

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Goals for guidance and consensus

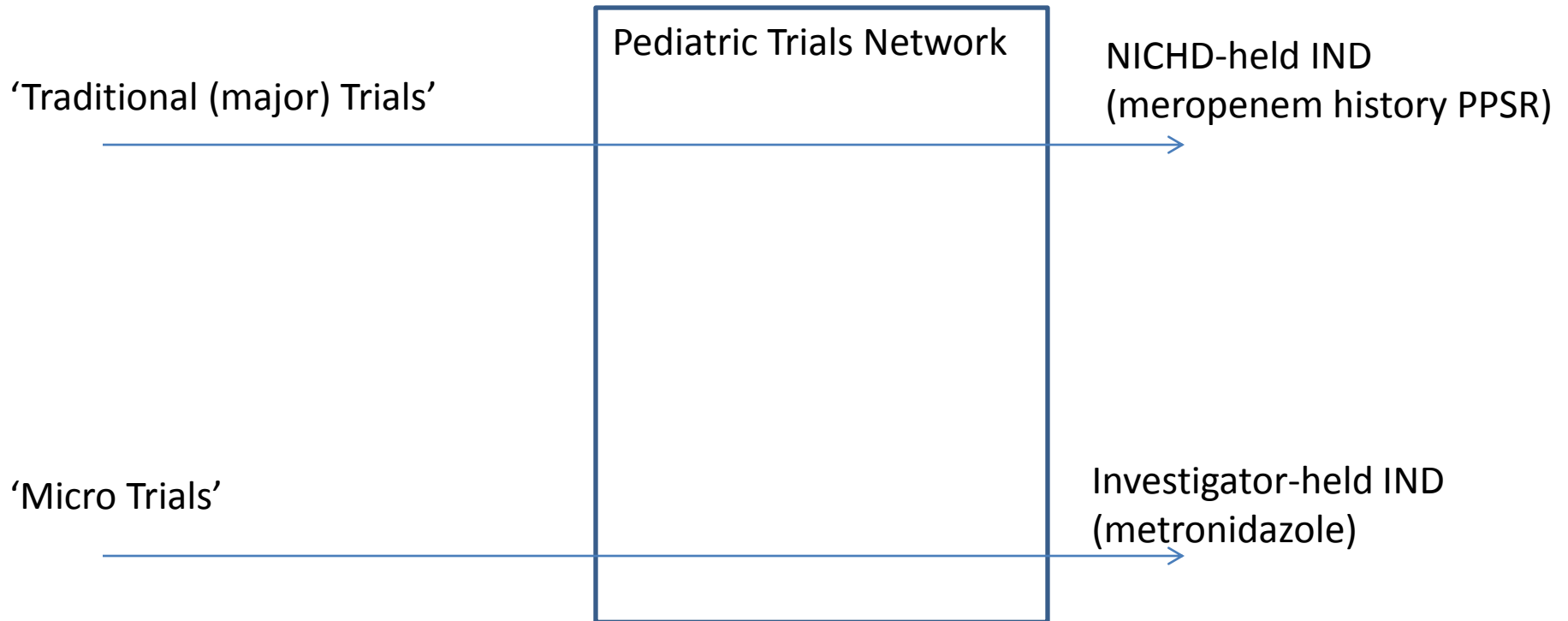
Go over

- PPSR
- Micro-trials
- Safety data and devices

Specific studies/molecules

- Metronidazole
- Hypertension

PTN as Platform



MAJOR TRIAL OPERATIONS

Major Trials: Meropenem Lessons Learned

- PPSR involvement
 - Proposed Pediatric Study Request
 - Document from the Sponsor to FDA for a Written Request
 - Format varies, but the document has the big ticket items for the trials necessary for a successful Written Request and label change
 - “Drives” funding for trials under this mechanism
- PPSR history: FDA requested 600 neonates with perforated NEC
- What we did
 - 200 infants 18 months at 25 sites
 - Included standard of care for sepsis
 - Perforated NEC 600 infants 50 sites and 10 years

Solution

Move primary draft from NICHD to PTN

Major Trials

Proposed PPSR

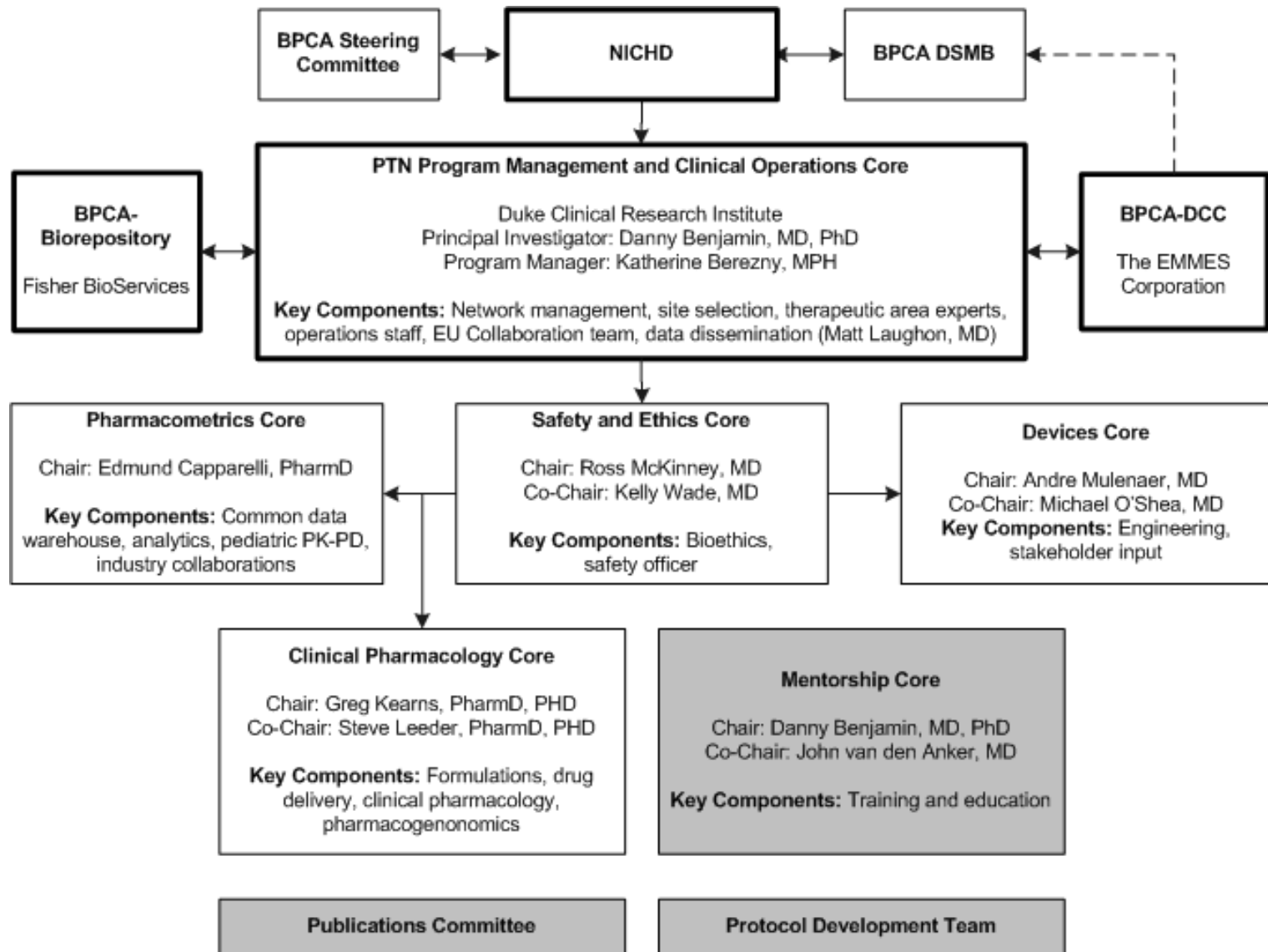
- Multiple pathways in
 - NICHD Prioritization
 - Proposals from PTN
- Request for 2 page summary: we will send out an example
- Review one month later : PTN PPSR group, with NICHD representation
- Have the investigator revise suitable for NICHD review one month later 20-30 page summary and an example will be provided
- Target submission to FDA
- 3 similar cycles per year
 - March, April, May
 - July, August, September
 - November, December, January

Major Trials

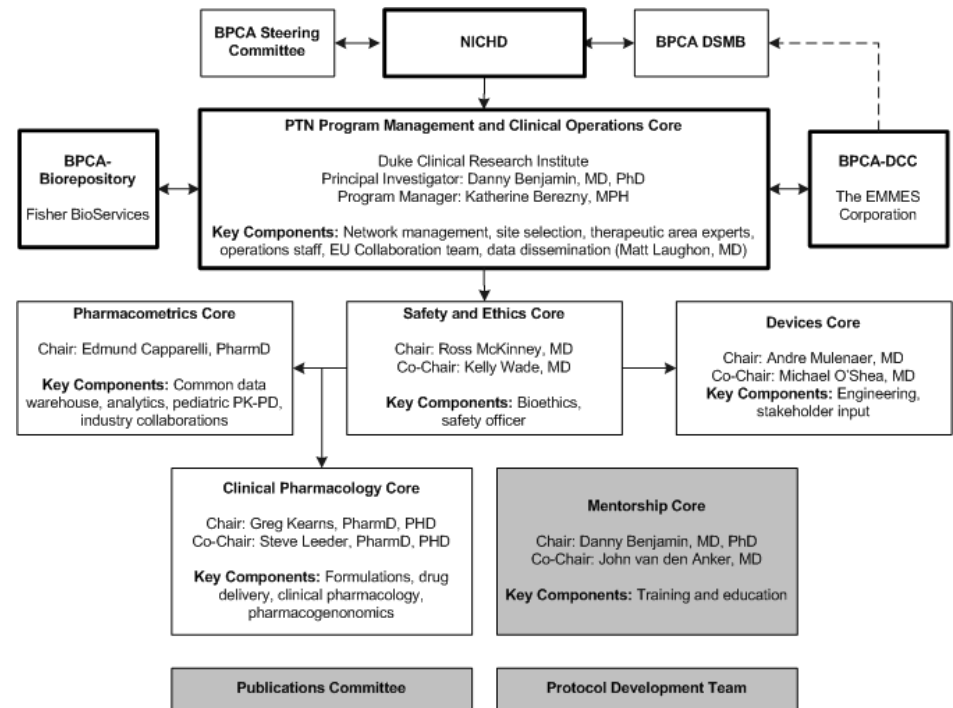
Advantages of PPSR Approach

- A team outside of NICHD is primarily responsible for PPSR, reducing central burden
- Local expertise
- Open competition and nationalize the PTN
 - Submitting team is part of move-forward strategy
 - Details of that strategy will be negotiated on case by case basis

Structure of PTN



Major Trial Operations Steering Committee



Today: Benjamin, Kearns, Capparelli, Cohen, Smith, Berezny, Wade, NICHD, EMMES, Muelenaer, van den Anker, O'Shea

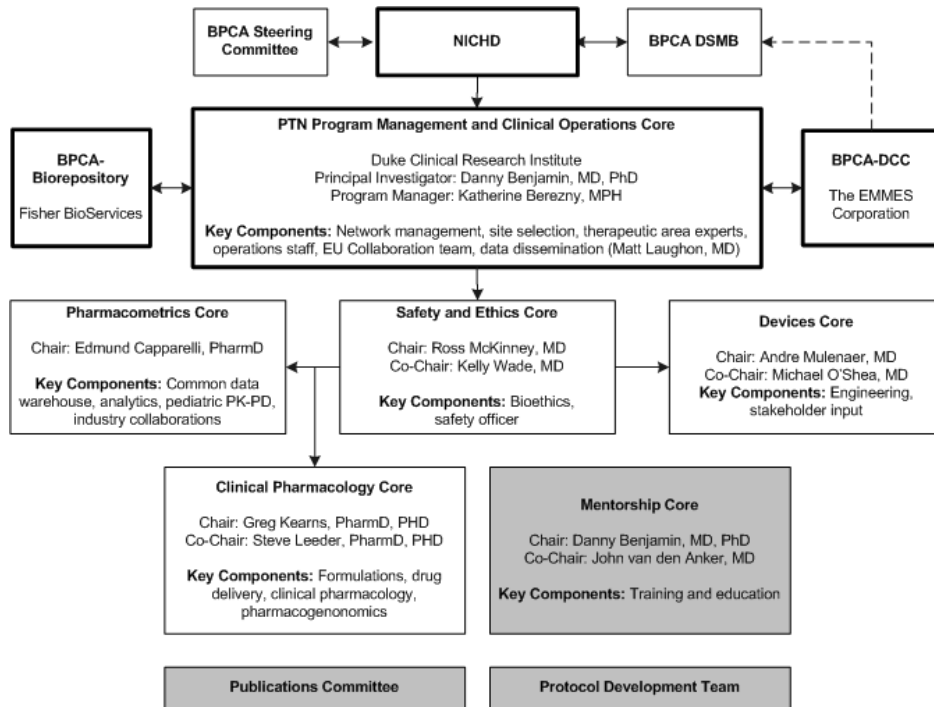
1st Major Trial Approved : Benjamin, Kearns, Capparelli, van den Anker, Wade, Muelenaer, Cohen, Smith, Berezny, Wade, O'Shea, NICHD, EMMES; add therapeutic area leader from 1st trial

2nd Major Trial Approved, 1st trial enrolling: Benjamin, Kearns, Capparelli, van den Anker, Wade, Muelenaer, Cohen, Smith, Berezny, Wade, O'Shea, NICHD, EMMES; leader from 1st trial, leader from 2nd trial

3rd Major Trial Approved, 2nd Major Trial Enrolling, 1st Major Trial Complete: Benjamin, Kearns, Capparelli, van den Anker, Wade, Muelenaer, Cohen, Smith, Berezny, Wade, O'Shea, NICHD, EMMES; drop 1st major trial leader, keep 2nd major trial leader, add therapeutic area leader from 3rd trial

Major Trial Operations

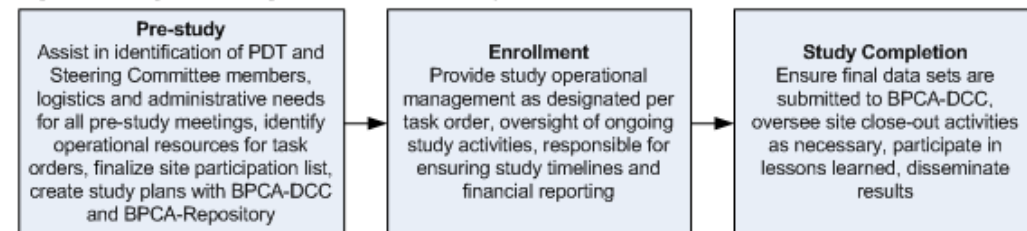
Clinical Operations Core ('DCRI team')



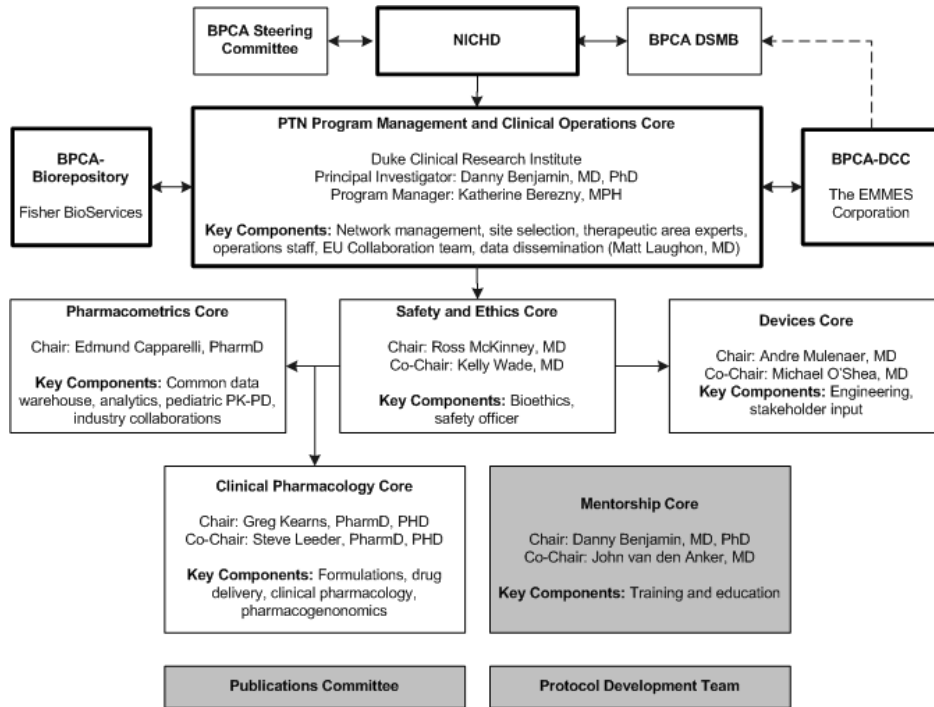
Differences from meropenem

- 1) Rapid start network
- 2) Upscale for multiple trials
- 3) European Union (van den Anker)

Figure 3: Program Management and Clinical Operations Core tasks for a BPCA Clinical Trial



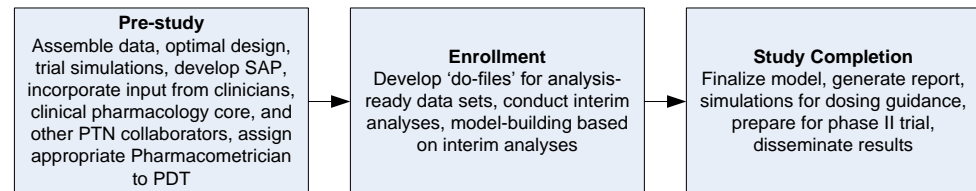
Major Trial Operations Pharmacometrics Core (UCSD, et al)



Changes from meropenem

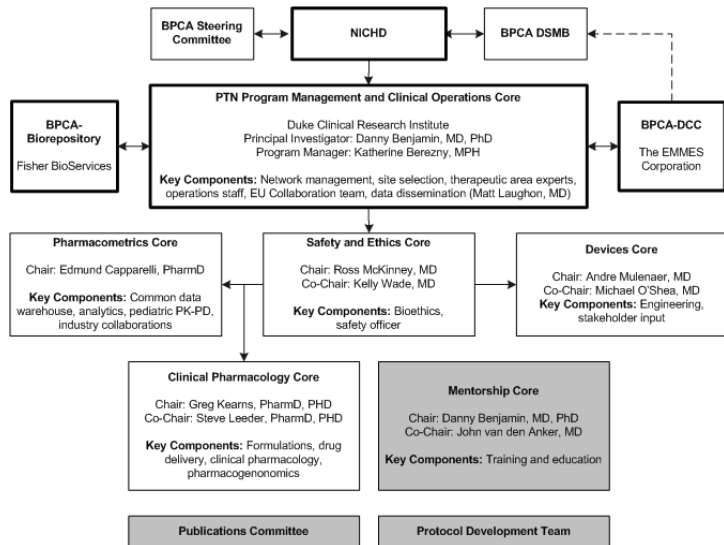
- 1) Pre-trial work
- 2) Selection of other PK groups

Figure 5: Pharmacometric Core tasks for a BPCA Clinical Trial



Major Trial Operations

Clinical Pharmacology (CMH, PPRU, et al)

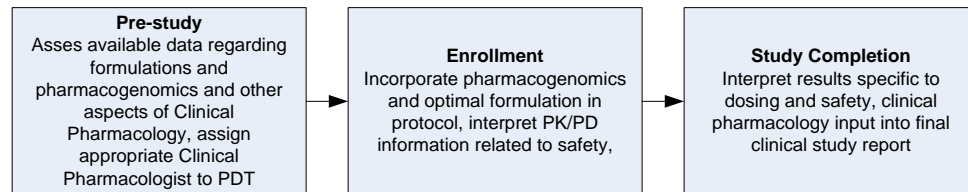


Substantively different from meropenem

- 1) Pre-award work
- 2) Formulations
- 3) Partnership CMH-DCRI

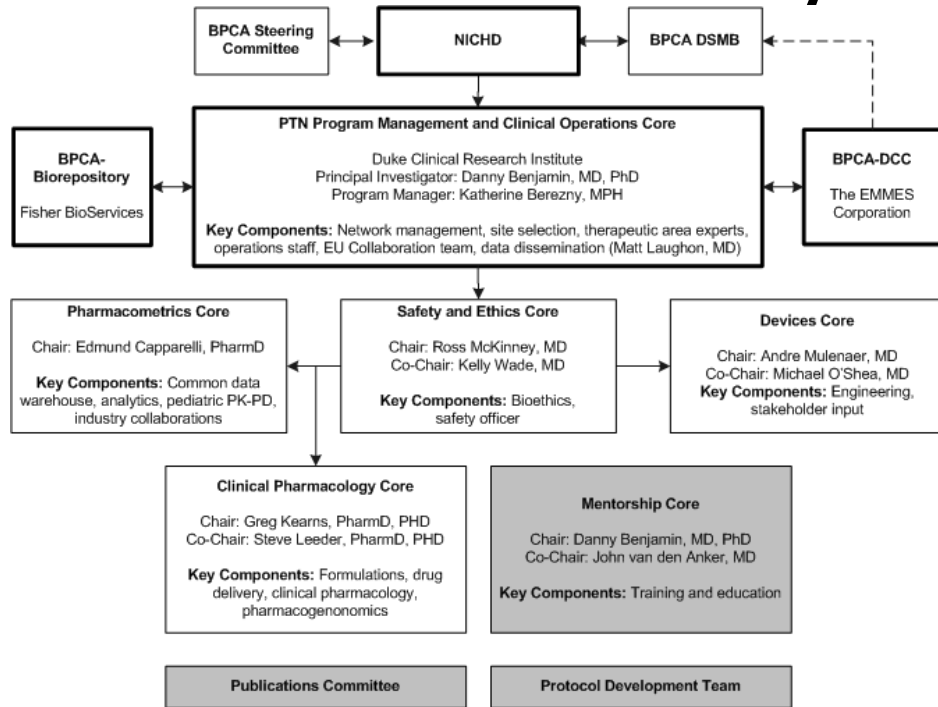
DCRI: small business, timelines, 'NICHD'
 CMH: clinical pharmacology

Figure 7: Clinical Pharmacology Core tasks for a BPCA Clinical Trial



Major Trial Operations

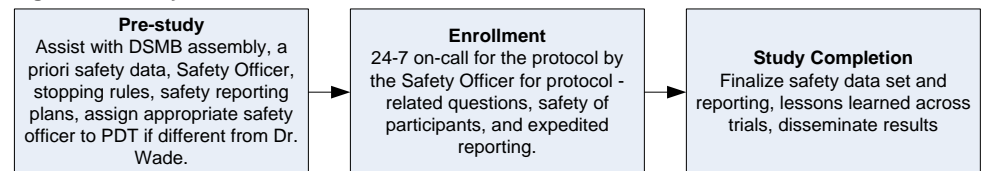
Safety and Ethics



Meropenem Differences

- 1) Wade more as organization rather than day to day
- 2) Safety database across trials
- 3) Therapeutic expertise vs. 'safety' expertise

Figure 11: Safety and Ethics Core tasks for a BPCA Clinical Trial



MICRO TRIALS

Cloud Around the Silver Lining

- BPCA renewal
- No PPSR
 - Draft PPSR 1 month
 - NICHD clearance 1 month
 - 4 months FDA turn around
 - Revisions 4 months
 - Protocol draft finalize and clearance 6 months
 - FDA turn around and revisions 4 months
 - Trial start-up 4 months
 - 24 months to first patient enrolled
- Solutions: micro trials

Micro-trials Definitions

1-log smaller than meropenem

- 25 sites
- 200 patients
- NICHD-held IND
- Established investigator
- 24 months 1st patient enrolled
- PPSR approved
- 2 sites
- 12-24 patients
- Investigator-held IND
- trainee or established
- 2 months 1st patient enrolled
- PPSR drafted

Micro-trials

Lessons Learned

- Investigator held IND
- Complete PK and safety trials for <250,000 direct costs
- Submit data to FDA and EMA
- Complete a trial in 12-24 months: piperacillin-tazobactam
- Start pre-trial work as we are negotiating PPSR

Micro-trials operations

Analogy to PPSR

- Decision of amount of funding **after** an IND is held, IRB submitted, and CRF drafter, shifting burden from NICHD to experts
- Nested within the mentorship core prior to NIH support
- PK-PD, clinical pharmacology, trial design, regulatory advice from the mentorship team
- First micro-trial
 - PI Michael Cohen-Wolkowicz; K23 HD064814-01; IND 108,209; under IRB review at Wesley (Wichita, Kansas) and IRB approved at Duke—the leading enrollers of the pip-tazo trial
- PPSR for metronidazole drafted
- Up to 32 young infants, validated assay has been developed, licensed formulation

Micro-trials

Metronidazole

Protocol Title	Safety and Pharmacokinetics of Multiple Dose Metronidazole in Premature Infants															
Product	Metronidazole															
Objective:	Evaluate the safety and PK of intravenous metronidazole in premature infants with suspected serious infection															
Secondary objectives:	Determine the correlation of metronidazole drug concentrations in plasma and dried blood spots samples.															
Study Design:	Single center, open-label, PK study.															
Study Population:	Up to 32 patients <32 weeks gestational age with possible serious infection. Patients will be divided into 2 groups based on postnatal age.															
Number of Subjects:	Up to 32															
Number of Sites:	1															
Duration of Subject Participation:	Up to 15 days															
Dose Schedule:	<p>Intravenous metronidazole will be administered as follows:</p> <table border="1"> <thead> <tr> <th>Group</th> <th>N</th> <th>Postnatal Age</th> <th>Loading Dose</th> <th>Maintenance Dose</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>8-16</td> <td><14 days</td> <td>15 mg/kg</td> <td>7.5 mg/kg q24 hours</td> </tr> <tr> <td>2</td> <td>8-16</td> <td>≥14 days</td> <td>15 mg/kg</td> <td>7.5 mg/kg q12 hours</td> </tr> </tbody> </table> <p>Study drug will be administered for 3-5 days.</p>	Group	N	Postnatal Age	Loading Dose	Maintenance Dose	1	8-16	<14 days	15 mg/kg	7.5 mg/kg q24 hours	2	8-16	≥14 days	15 mg/kg	7.5 mg/kg q12 hours
Group	N	Postnatal Age	Loading Dose	Maintenance Dose												
1	8-16	<14 days	15 mg/kg	7.5 mg/kg q24 hours												
2	8-16	≥14 days	15 mg/kg	7.5 mg/kg q12 hours												
Estimated Start:	August 2010															
Estimated Finish:	August 2012															
PK:	Blood samples will be obtained at various time points around the first dose and at steady state (doses 3-5). PK parameters will be estimated by non-compartmental analysis using WinNonLin software.															
Statistical Consideration:	This protocol has sufficient enrollment to provide pilot safety and PK data in premature infants.															

Strengths of the micro-trials approach

- New investigator pipeline
- New 'blood' into PTN
- Open competition
- Trials are peer-reviewed
- Data submitted for labeling, regardless
- Publications (Benjamin et al) generalization of knowledge
- Improved dosing, pediatric public health, regardless
- Small investment per trial
- Strong start
- Supplemental trials

Subsequent micro-trials

- Increased capacity, institutions, pipeline
- Goal of 2-4 new trials per year
- Linked to a new PPSR that for which the draft has been approved
- We suspect that we will need a PK trial prior to the main trial of the PPSR for either regulatory, ethical, or patient safety reasons
- Improve dosing and public health

Major Trial

HTN PPSR precursor

- Team: Howard Trachtman, et al
- Patient population options
 - Obesity: many trials already completed
 - Neonatal: few trials completed to date, but heterogeneous population
 - ***Renal transplantation: no trials completed***
- Sample size, primary endpoint
 - 100 patients each arm in a two-arm trial
 - Change in GFR at 12-24 months
- Agents
 - Calcium channel blocker amlodipine
 - vs. ACE or ARB
- Secondary endpoints
 - Safety, proteinuria, etc

Rapid Start Network

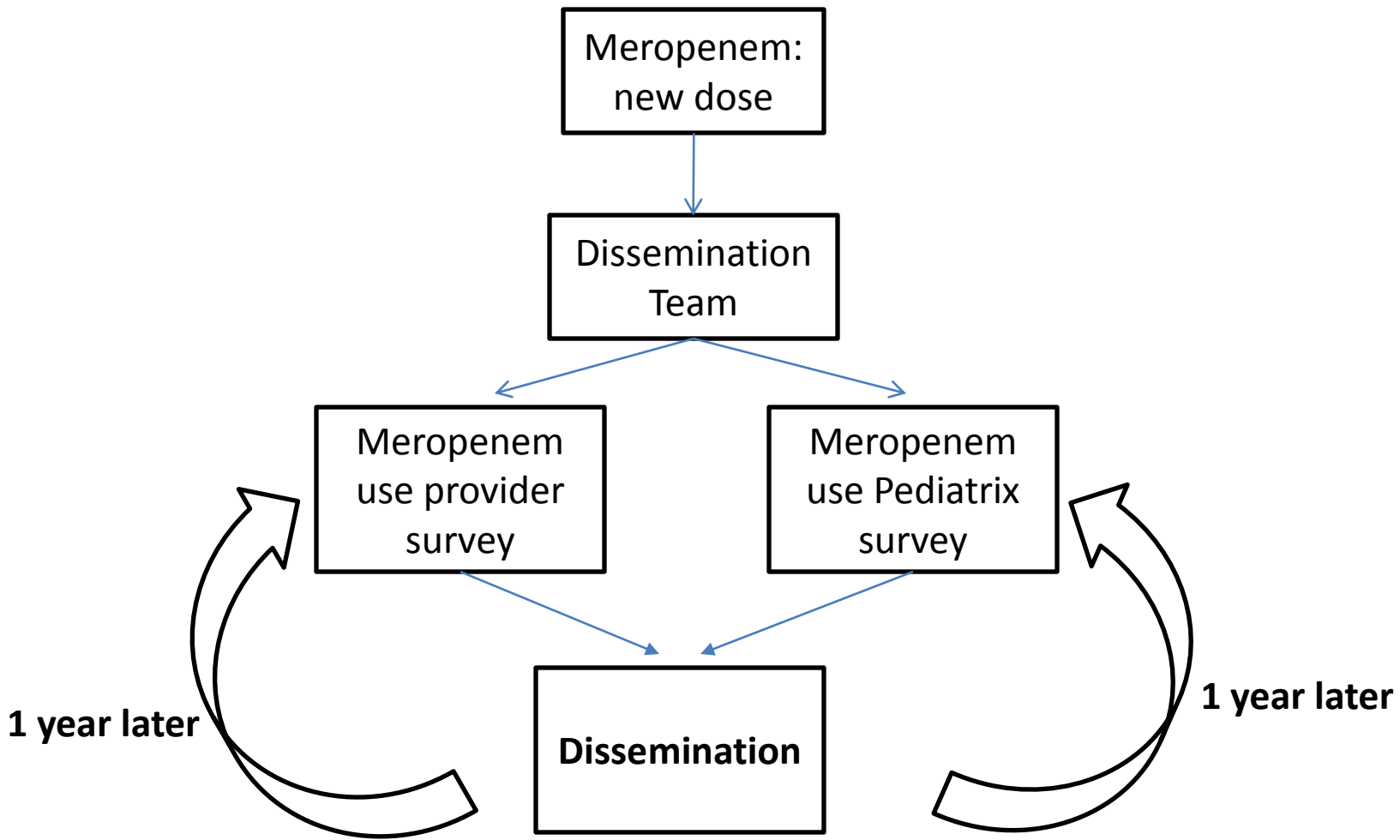
- Industry-sponsored Rapid Start Network (RSN)
 - Rationale and History
 - Master service agreement, each study addendum
 - Strengths
 - Across institution
 - Contract metrics 4 months to 4 weeks
- Rapid Start Network Federally Funded Contracts (RSN-FFC)
 - Differences between NIH and Industry

Task Orders

- Task Order 1
 - Formation of the PTN and administrative
- Task Order 2
 - Develop PPSR for hypertension
- Task Order 3
 - PK trial metronidazole
- Task Order 4 in concept phase
 - Opportunistic studies
 - 15 sites year one, add sites each of next 3 years
 - Common PK protocol: standard of care and obtain samples
 - Competition for spots
 - Posted on website and emailed to call recipients
 - January Task Order finalized, protocol out to sites by June 2011

Drug Safety Discussion

- Initiative at Duke
- Registry outcomes
 - Brian Smith
- Devices
 - Andy Muelenare
 - Mike O'Shea



Organization	Responsible Party
National Organizations	
ABP	Bose
AAP	Sullivan
Peds Surgeons	Blakely
NRN	Higgins
APN	Buus-Frank
NANN	Buus-Frank
ASCPT	Mehta
Pediatrix	Clark
Hospital Epidemiologists	Weber
Dosing Guidelines	
Pediatric Practice & Research	Mehta
Lexicomp	Aliaga
Harriet Lane	Aliaga
Neofax	Young
Networks	
AstraZeneca	Benjamin
VON/Hot Topics	Soll
CPQCC	McCaffrey
PQCNC	McCaffrey
Ohio/NY	McCaffrey
Conferences	
FDA/EMA Monthly meeting	Laughon
ESPR/International	Benjamin
PAS	Laughon
Industry/miscellaneous	
AstraZeneca	Benjamin
Ethics	Weber/Aliaga
Twitter/Facebook	Aliaga
Traditional Media	UNC/Duke PR

Summary Accomplishments and Short term goals

- October 2010
 - First PPSR drafted
 - Hypertension team has concept sheet
 - First IND, first IRB approval
- Short term goals
 - First patient enrolled December 2010
 - Hypertension and other PPSR
 - Task Order 4
 - Broader network participation