Pediatric Trials Network (PTN)

Danny Benjamin MD PhD MPH (PI)

http://www.pediatricmedicaldevices.org/2010 Conference/Presentations/Benjamin-Pediatric Trials Network.pdf

Katherine Berezny

Duke Clinical Research Institute

J.V. Aranda, MD,PhD,FRCPC,FAAP

Professor and Director of Neonatology,
State University of New York Downstate Medical Center, New York City, NY

And

Professor of Pediatrics, Pharmacology & Pharmaceutical Sciences
NIH Pediatric Pharmacology Reseacch Unit (PPRU)
Wayne State Univ School of Medicine and College of Pharmacy
Children's Hospital of Michigan, Detroit, MI USA
Email: *jaranda@downstate.edu*

Central Park from top of the Rock

Thank You from south of the border

Pediatric Trials Network (PTN)

- What is PTN?
- What are the mandates of PTN
- What is the Organizational Structure of PTN and the Modus Operandi
- MacroTrials and Microtrials
- The Rapid Start network (RSN)
- Tasks
- Frequently asked questions- relevant to MICYRN

Pediatric Trials Network (PTN)

- ***What is PTN?***
  - What are the mandates of PTN
  - What is the Organizational Structure of PTN and the Modus Operandi
  - MacroTrials and MicroTrials
  - The Rapid Start network (RSN)
  - Tasks
  - Frequently asked questions- relevant to MICYRN

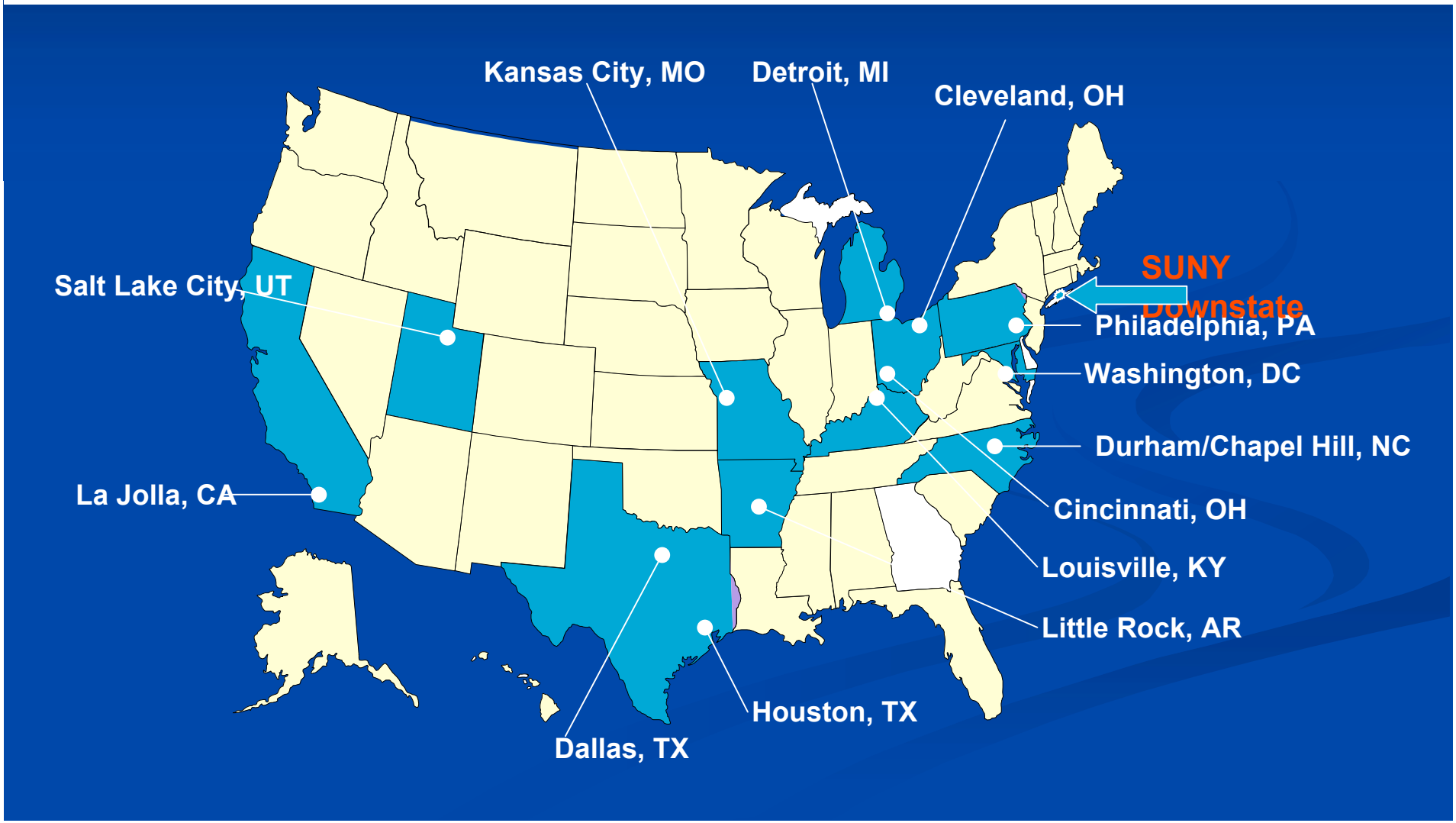
Pediatric Trials Network

Pediatric Trials Network, RFA: NIH-NICHD-CRMC-2010-02 March 2010

- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), in collaboration with the Duke Clinical Research Institute (DCRI) Pediatric Trials Network (PTN) and the PI Daniel K Benjamin Jr., MD PhD MPH,
- The main objective of the PTN is to provide an environment and an appropriate infrastructure for conducting safe and effective pediatric clinical trials for the Best Pharmaceuticals for Children Act (BPCA) drug development program and for performing ancillary activities in support of these trials (includes PK/PD, safety, efficacy etc).

WSU-SUNY Downstate NIH Pediatric Pharmacology Research Unit Network (NICHD-PPRU) 1999-2010

5-U01HD-37261-01 (PI: J. V. Aranda, MD, PhD) **$1,984,324.00 01/1/2004 – 12/31/2010(extended) 30%**
NICHD Children's Center for Clinical Pharmacology Research - Pediatric Pharmacology Research Unit Network (PPRU)
Competing Renewal - Role: PI – 30% effort (Till Nov 1st 2007; Co-PI (Nov 1,2007 – 12/31/2010 , 10% effort)



NICHD/BPCA- PTN

- **Pediatric Trials Network funded with $95M NIH grant, has FDA approval to study 4 drugs, now enrolling**
- January 13, 2011

- https://www.dtmi.duke.edu/news-publications/news/dtmi-news-archives/putting-an-end-to-2018ballpark-dosing2019-in-children
- http://bpca.nichd.nih.gov/clinical/network/index.cfm

Pediatric Trials Network (PTN)

- What is PTN?
- *WHAT ARE THE MANDATES OF PTN*
- What is the Organizational Structure of PTN and the Modus Operandi
- Tasks
- MacroTrials and MicroTrials
- The Rapid Start network (RSN)
- Frequently asked questions- relevant to MICYRN

Pediatric Trials Network

- The network conducts pediatric clinical drug trials in a variety of therapeutic areas, including but not limited to:
  - cardiovascular diseases,
  - cancer,
  - infectious diseases,
  - gastroenterology,
  - respiratory diseases,
  - neonatology, and
  - medical devices.
  - Examples will be provided

PTN Goal

- Program Management Support & Oversee Contract Transition
- Oversee Trials in Peds Device Development
- Conduct Pediatric Clinical Studies
- Develop Pediatric Formulations
- Establish Steering Committee & Protocol Development Team
- Establish/Maintain a Drug Distribution Center
- Establish Website for public & private access

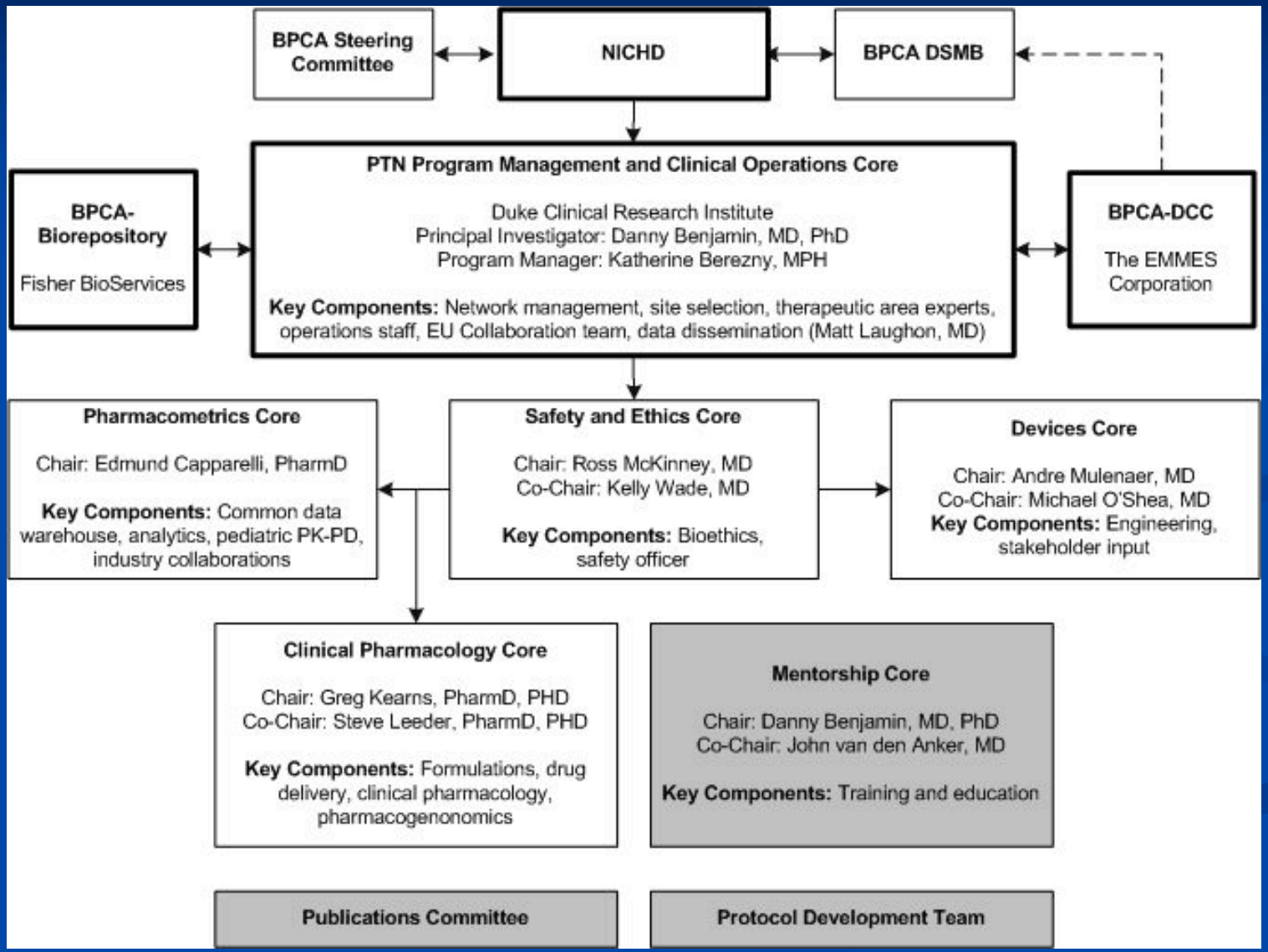
What are other mandates for PTN?

- Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the primary objective of the Pediatric Trials Network (PTN) is to create an environment in which principal investigators can manage an effective infrastructure for conducting safe and effective pediatric clinical trials and for performing ancillary activities in support of these trials.
- PTN studies product formulation, drug dose, efficacy, safety, and device development.
- Data collected from the trials will help inform pediatric drug labeling and provide regulators, pediatricians, and researchers new information on how children respond to medication.
- The primary goal is to generate the data necessary to produce evidence-based clinical practice guidelines.

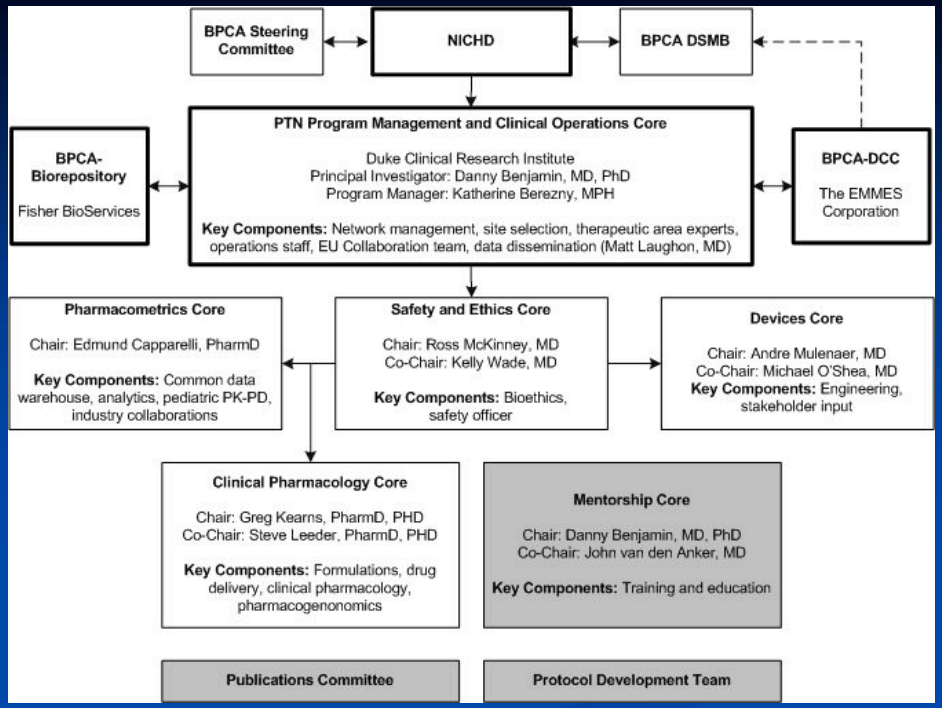
Pediatric Trials Network (PTN)

- What is PTN?
- What are the mandates of PTN
- *What is the Organizational Structure of PTN and the Modus Operandi*
- Tasks
- MacroTrials and Microtrials
- The Rapid Start network (RSN)
- Frequently asked questions- relevant to MICYRN

Structure of PTN



Major Trial Operations Steering Committee



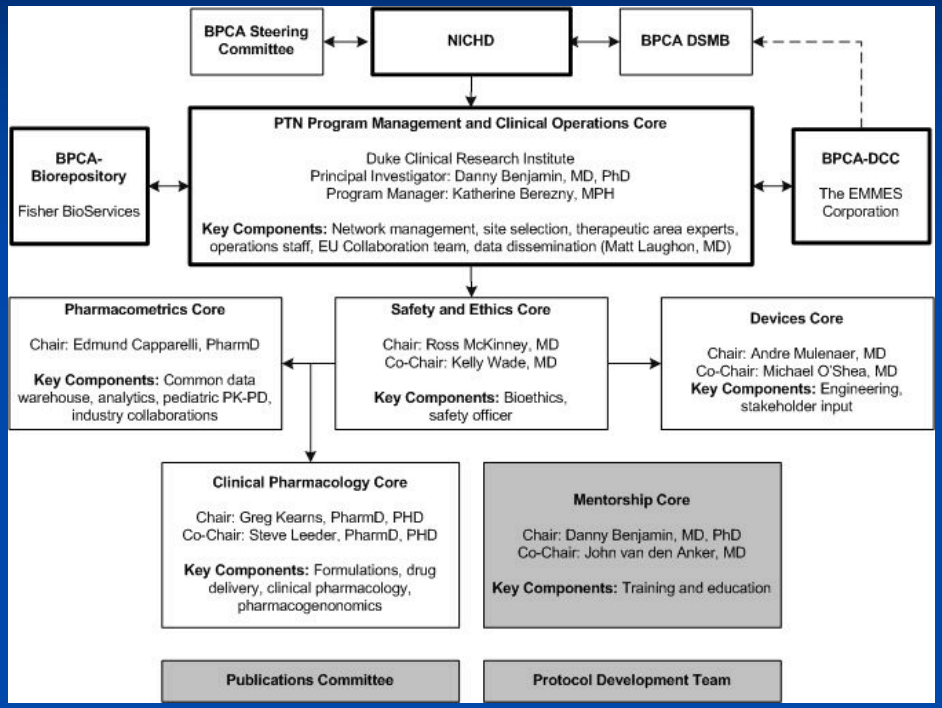
Today: Benjamin, Kearns, Capparelli, Cohen, Smith, Berezny, Wade, NICHD, EMMES, Muelenaer, van den Anker, O'Shea

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

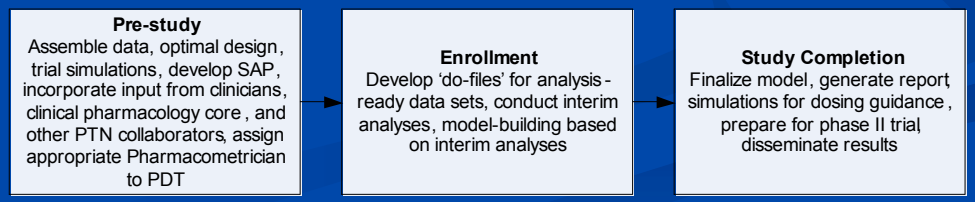
3rd Major Trial Approved, 2nd Major Trial Enrolling, 1st Major Trial Complete: Benjamin, Kearns, Capparelli, van den Anker, Wade, Muelenaer, Cohen, Smith, Berezny, Wade, O'Shea, NICHD, EMMES; drop 1st major trial leader, keep 2nd major trial leader, add therapeutic area leader from 3rd trial

Major Trial Operations
Pharmacometrics Core (UCSD, et al)

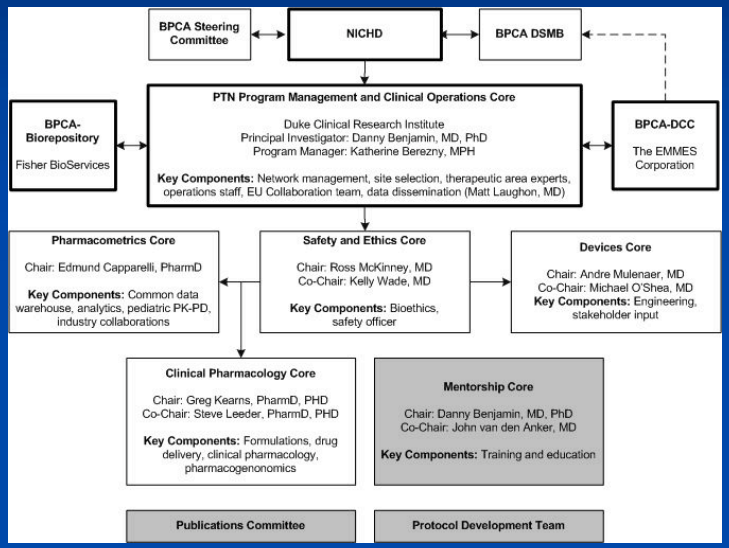


Changes from meropenem
1)Pre-trial work
2)Selection of other PK groups

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

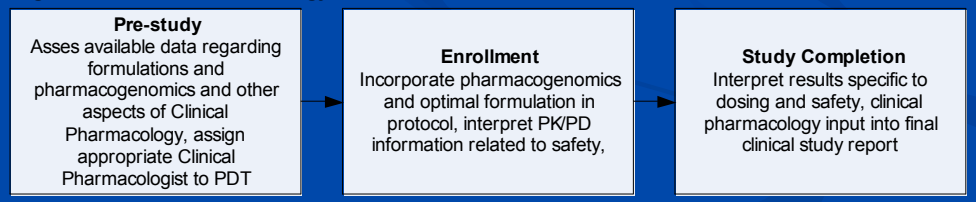
2)Formulations

3)Partnership CMH-DCRI

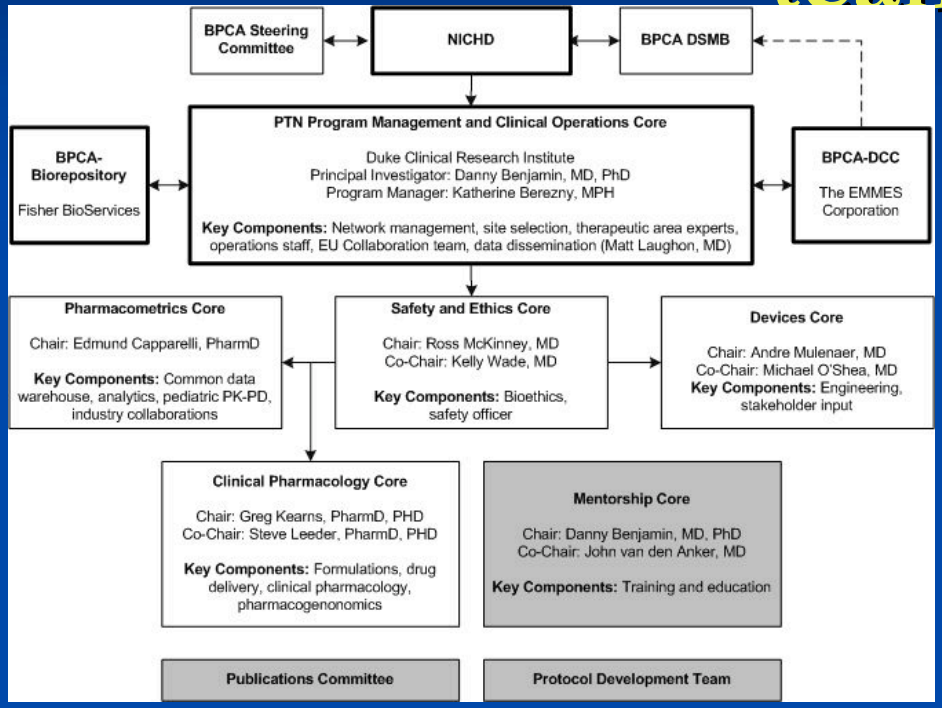
DCRI: small business, timelines, 'NICHD'

CMH: clinical pharmacology

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



Major Trial Operations
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

Pre-study
Assist in identification of PDT and Steering Committee members, logistics and administrative needs for all pre-study meetings, identify operational resources for task orders, finalize site participation list, create study plans with BPCA-DCC and BPCA-Repository

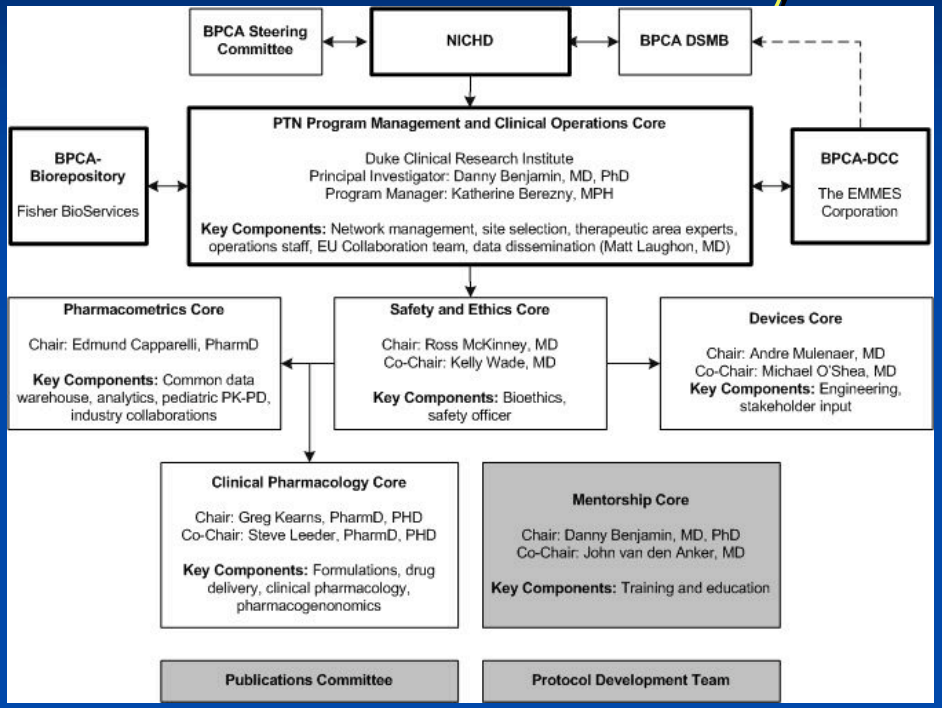
→

Enrollment
Provide study operational management as designated per task order, oversight of ongoing study activities, responsible for ensuring study timelines and financial reporting

→

Study Completion
Ensure final data sets are submitted to BPCA-DCC, oversee site close-out activities as necessary, participate in lessons learned, disseminate results

Major Trial Operations
Safety and Ethics



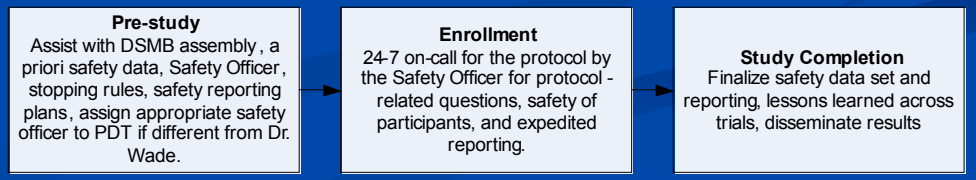
Meropenem Differences

1)Wade more as organization rather than day to day

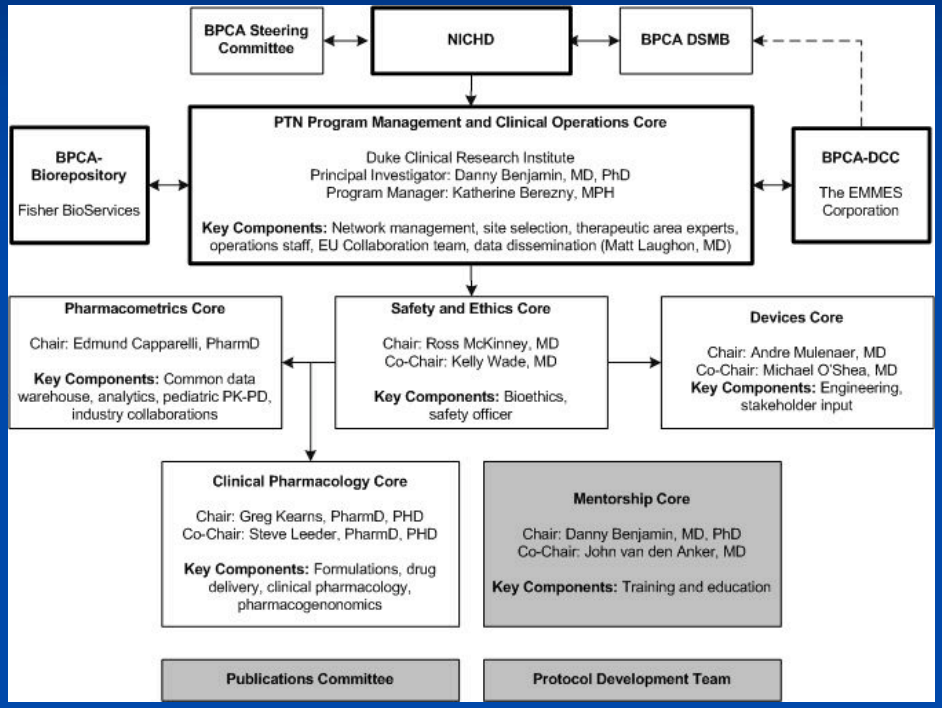
2)Safety database across trials

3)Therapeutic expertise vs. 'safety' expertise

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



Major Trial Operations Devices



Devices:

1)New from last initiative

2)Get buy-in on therapeutics operations

3)Move forward so that first request for trial ideas 2011

Figure 9: Device Core tasks for a BPCA Clinical Trial

Pre-study	Enrollment	Study Completion
Stakeholder input, product development, ensure regulatory compliance with device development, device performance validation, assign appropriate Device Core member to PDT	Ongoing review of safety data related to device performance, meet continually to discuss best practices, policies, and procedures, update guidelines as necessary	Ensure data sets are submitted to BPCA-DCC for FDA submission, participate in lessons learned, finalize best practices, policies and procedures, disseminate study results

Pediatric Trials Network (PTN)

- What is PTN?
- What are the mandates of PTN
- What is the Organizational Structure of PTN and the Modus Operandi
- Tasks

MacroTrials and Microtrials

- The Rapid Start network (RSN)
- Frequently asked questions- relevant to MICYRN

Goals for guidance and consensus

Go over

- PPSR *(PROPOSAL FOR PEDIATRIC STUDY REQUEST)*
- 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
(Proposals for Pediatric Studies Request)

- 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

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-Wolkowiez; 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

<table>
<tr><td>Protocol Title</td><td>Safety and Pharmacokinetics of Multiple Dose Metronidazole in Premature Infants</td></tr>
<tr><td>Product</td><td>Metronidazole</td></tr>
<tr><td>Objective:</td><td>Evaluate the safety and PK of intravenous metronidazole in premature infants with suspected serious infection</td></tr>
<tr><td>Secondary objectives:</td><td>Determine the correlation of metronidazole drug concentrations in plasma and dried blood spots samples.</td></tr>
<tr><td>Study Design:</td><td>Single center, open-label, PK study.</td></tr>
<tr><td>Study Population:</td><td>Up to 32 patients <32 weeks gestational age with possible serious infection. Patients will be divided into 2 groups based on postnatal age.</td></tr>
<tr><td>Number of Subjects:</td><td>Up to 32</td></tr>
<tr><td>Number of Sites:</td><td>1</td></tr>
<tr><td>Duration of Subject Participation:</td><td>Up to 15 days</td></tr>
<tr><td>Dose Schedule:</td><td>Intravenous metronidazole will be administered as follows:
<table>
<tr><th>Group</th><th>N</th><th>Postnatal Age</th><th>Loading Dose</th><th>Maintenance Dose</th></tr>
<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>
</table>
Study drug will be administered for 3-5 days.</td></tr>
<tr><td>Estimated Start:</td><td>August 2010</td></tr>
<tr><td>Estimated Finish:</td><td>August 2012</td></tr>
<tr><td>PK:</td><td>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.</td></tr>
<tr><td>Statistical Consideration:</td><td>This protocol has sufficient enrollment to provide pilot safety and PK data in premature infants .</td></tr>
</table>

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

Pediatric Trials Network (PTN)

- What is PTN?
- What are the mandates of PTN
- What is the Organizational Structure of PTN and the Modus Operandi
- Tasks
- MacroTrials and Microtrials
- *The Rapid Start network (RSN)*
- Frequently asked questions- relevant to MICYRN

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

Pediatric Trials Network (PTN)

- What is PTN?
- What are the mandates of PTN
- What is the Organizational Structure of PTN and the Modus Operandi
- MacroTrials and Microtrials
- The Rapid Start network (RSN)
- Frequently asked questions- relevant to MICYRN

- *Tasks*

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

Pediatric Trials Network (PTN)

- What is PTN?
- What are the mandates of PTN
- What is the Organizational Structure of PTN and the Modus Operandi
- Tasks
- MacroTrials and Microtrials
- The Rapid Start network (RSN)

- *Frequently asked questions- relevant to MICYRN*

PTN – MICYRN FAO

Question : 1. Who chooses the drug to be studied from the BPCA priority list and by what criteria? Is it the PTN Steering committee who makes the choice?

Answer: Collaboration between ptn steering committee and NICHD

Question 2: Who develops the protocol? There is a protocol development Team at the bottom of the organizational structure. Is this a team that is created ad hoc by the Steering committee depending upon drug chosen?

Answer: Protocol team is created by steering committee depending on drug. the only 'rule' is that Greg Kearns, Edmund Capparelli, and I can't be protocol chairs. nor can voting members of the steering committee.

PTN – MICYRN FAO

Question 3. Who and How do you determine the funding for each project or protocol? Does the steering committee decide the level of funding together with NICHD?

Answer : Again, that is collaboration between steering committee and decided upon by NICHD. This has not been too difficult because we are starting with small trials.

Question 4. I assume that the study site selection is mainly based on the availability of the target study population and also the previous metrics (eg enrollment track records etc). Correct?

Answer: yes.

PTN – MICYRN FAO

Question 5. How is the rapid start network progressing? Will you apply this to all the study protocols of the PTN?

Answer: This is going well. and yes, to be applied to all study protocols. Metrics decreased from 90 days to 14 days

Question 6. You have European collaboration. Is this NIH funded or jointly funded by the Europeans? Is this applicable to Canada?

Answer: No European or Canadian sites in 2011. NICHD has not told us what their vision is for international sites. I would like to head that way.


Thank you –Merci Beaucoup-Gracias
May 27-29,2011

ADDITIONAL POWER POINTS FROM

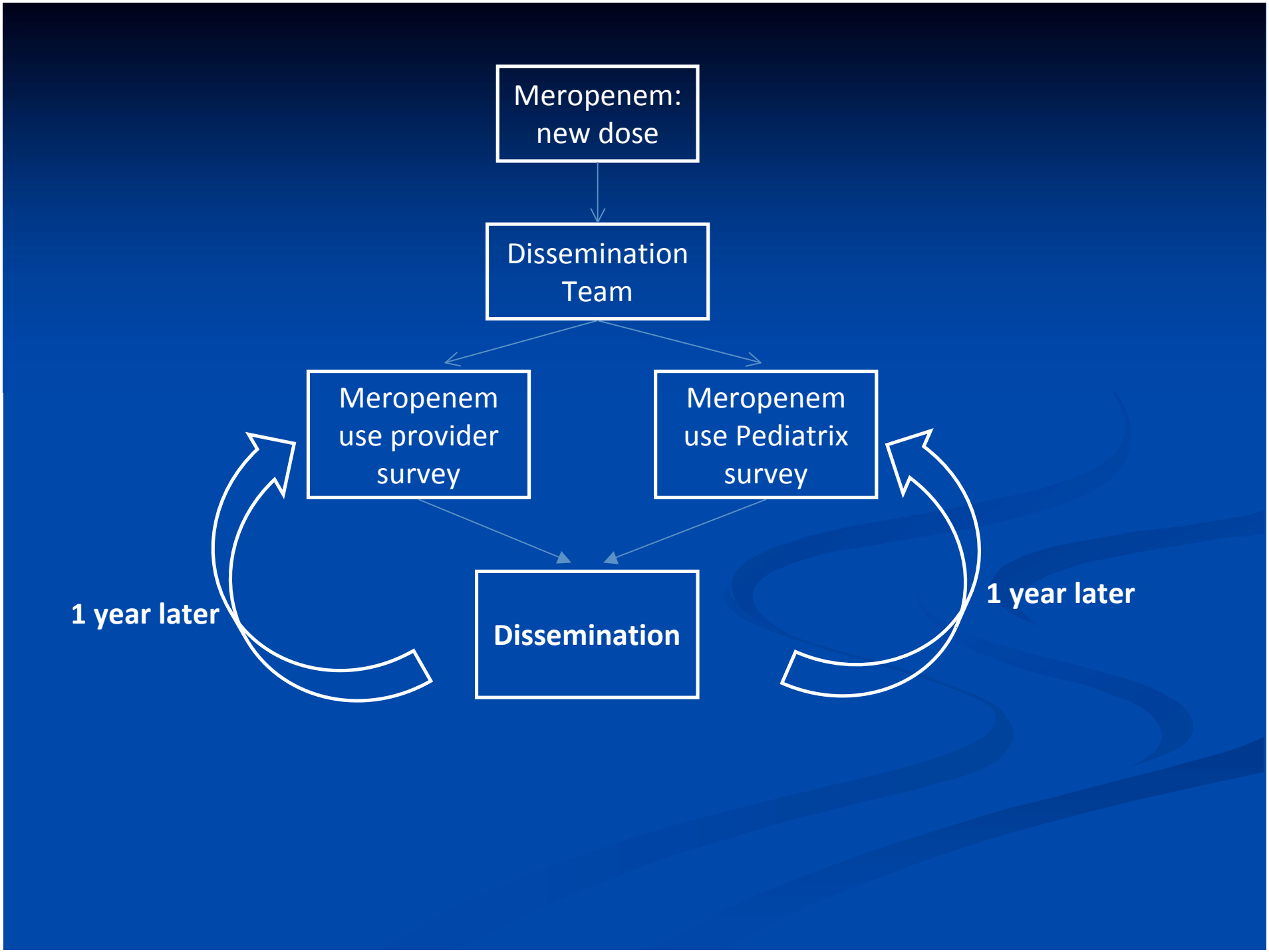
Danny Benjamin

and

Katherine Berezny

Drug Safety Discussion

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


Meropenem: new dose
Dissemination Team
Meropenem use provider survey
Meropenem use Pediatrix survey
Dissemination
1 year later
1 year later

- Organization
- National Organizations
  - ABP
  - AAP
  - Peds Surgeons
  - NRN
  - APN
  - NANN
  - ASCPT
  - Pediatrix
  - Hospital Epidemiologists
- Dosing Guidelines
  - Pediatric Practice & Research
  - Lexicomp
  - Harriet Lane
  - Neofax
- Networks
  - AstraZeneca
  - VON/Hot Topics
  - CPQCC
  - PQCNC
  - Ohio/NY
- Conferences
  - FDA/EMA Monthly meeting
  - ESPR/International
  - PAS
- Industry/miscellaneous
  - AstraZeneca
  - Ethics

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

All Hands Meeting

May 6, 2011

Katherine Berezny

Barrie Harper

Parisa Jabbarazadegan

Maurine Morris

PTN Network

- Multiple protocols within PTN
  - Under the main PTN contract task orders are awarded
  - Protocols are across multiple therapeutic areas

    will have unique budget & task order

- DCRI is the coordinating & administrative center
  - Will develop infrastructure for PTN

    Oversee scientific and clinical aspects

PTN Network

- EMMES Corp is the Data Coordinating Center
  - Under DCRI's supervision
  - Perform monitoring, site management, data management, and statistical analysis

- DCRI will assure high quality protocols within PTN
  - Will recruit therapeutic area experts
  - Identify key collaborators
  - Sound scientific conclusions

PTN Goal

- Present lack of children's studies for therapeutics & labeling of devices
  - Prior to 1998 drug testing was not mandatory in the pediatric population
  - Few clinical trials have been performed on the safety & efficacy of most drugs
- Data collected will assist in labeling & provide info to pediatricians & researchers on drug disposition & response in children
- PTN protocols over the next 5 yrs will include a variety of therapeutics such as CV, CA, GI, infectious diseases, respiratory, device

Pediatric Regulatory Incentives

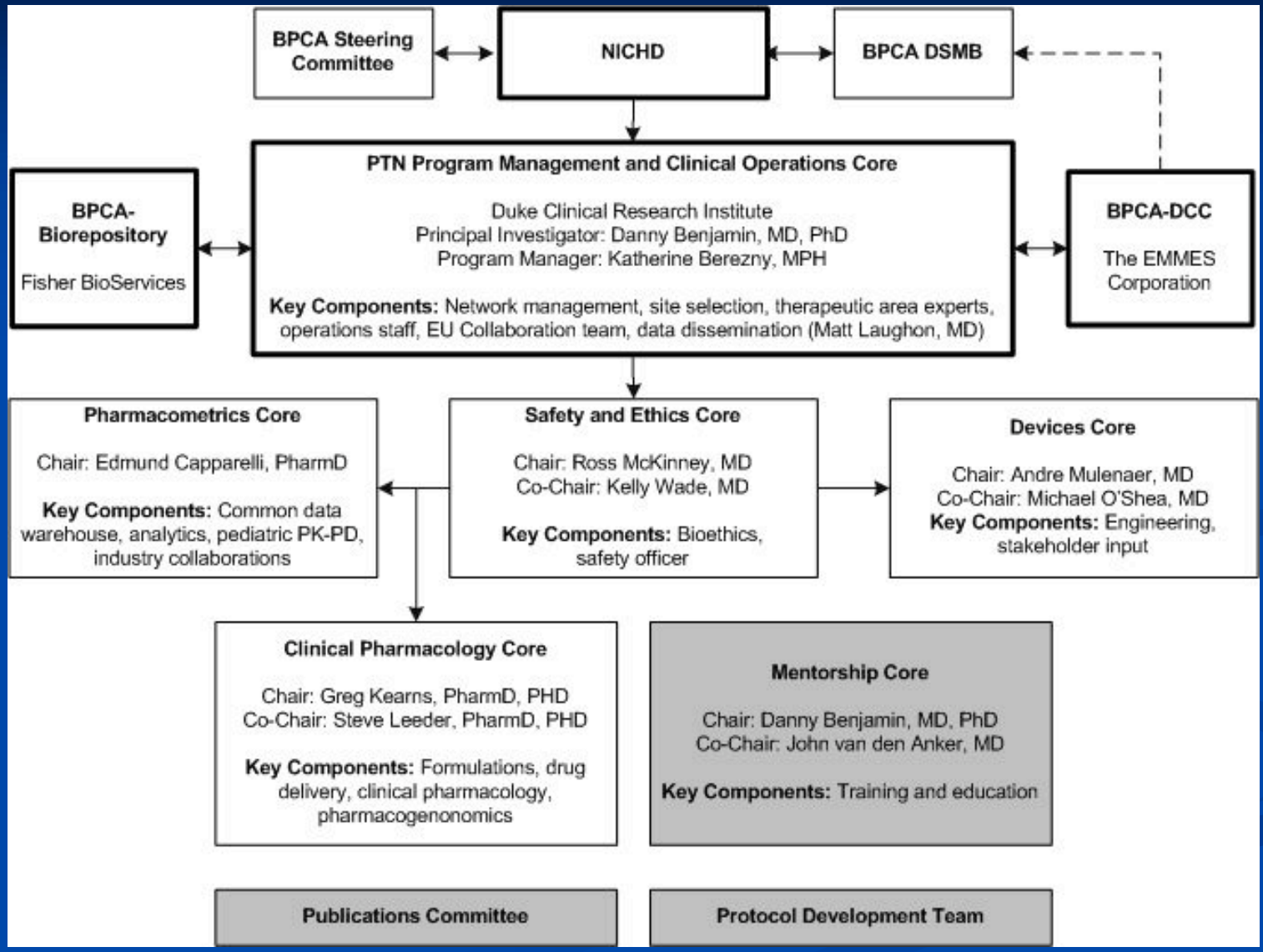
- 1997: FDAMA Pediatric Incentives
- 1998: Pediatric Rule
- 2002: Best Pharmaceuticals for Children Act (BPCA)
  - 6 months exclusivity
  - Pediatric trial does not have to be positive but "interpretable".

2012 – Congress meets to renew/stop BPCA legislation

Program Management Support/Task Order 1

- Infrastructure (resources)
- Administrative Core
- Develop Vision and Direction of Network with Thought leaders, NICHD, DCRI faculty
- Clinical Leadership
- PTN Web site development –
  - pediatrictrials.org

Structure of PTN



Protocol Development/Task Order 2

- Development of HTN protocols in children with renal transplants
- Amlodipine PK trial
  - Phase I
  - Sample size: 26-28 patients
  - Population: Children ages 2-17 with kidney transplant and stable allograft function
  - Number of Sites: 7
  - Target to Enroll First Patient: 3rd Q 2012
  - Lisinopril PK trial (TO7)
  - Large Efficacy/safety trial of amlodipine vs lisinopril

Protocol/Task Order 3 Metronidazole

- Protocol Title: Safety and Pharmacokinetics of Multiple Dose Metronidazole in Premature Infants
- Objective: Evaluate the safety and PK of intravenous metronidazole in premature infants with suspected serious infection
- Study Population:16 to 32 participants <32 weeks gestational age with suspected serious infection. Participants will be divided into 2 groups based on postnatal age.
- Study Duration: Approximately 18 months (LPI target Dec 2011); each participant will participate in the study for up to 15 days: 2-5 days of study drug administration followed by 10 days of adverse events monitoring.
- Number of Sites: 3
- FPI: Jan 1, 2011 Enrolled to date: 10 patients

Protocol/Task Order 4 POPS

- Protocol Title: Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care
- Objectives:
  - Evaluate the PK of understudied drugs currently being administered to children.
  - Explore the pharmacodynamics (PD) of understudied drugs currently being administered to children.
  - Evaluate the influence of genetic factors, metabolic and protein profiles on therapeutic exposure.
- Study Population: up to 500 children (< 21 years of age) who are receiving understudied drugs of interest per standard of care as prescribed by their treating caregiver
- Study Duration: Approximately 4 years(LPI target May 2013); each participant will participate in the study for up to 90 days per drug
- Number of Sites: 10-20
- Target to Enroll First Patient: June / July, 2011

Protocol/Task Order 5

- Protocol Title: PK & Relative Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia
- Sample size: 40 patients
- Population: Children ages 2-17 with sickle cell anemia or sickle beta-zero thalassemia
- Number of Sites: Six
- Target to Enroll First Patient: July 1, 2011

Sickle Cell Disease

- Potentially devastating condition
  - two copies of an abnormal gene are present

    Results in a hemoglobin disorder
  - RBCs prematurely destroyed

    Leads to anemia
  - Bouts of extreme pain in long extremity bones

    May affect abdomen & face

    Fever, general body weakness or discomfort

    periods start/end abruptly after several hrs or days.

    Some >6 episodes/yr
  - Disease also associated with growth retardation

Sickle Beta Zero Thalassemia

- Similar disorder to SCD
- Child inherits one sickle cell gene and one for beta thalassemia that does not produce (any) normal adult type hemoglobin.

Hydroxyurea

- Only major drug breakthrough for SCD in past 20 yr
- Only drug FDA approved for adults with SCD
- Only drug capable of modifying factors of the disease
  - E.g., decreased bouts of pain, & cost effective
- Drug is a SOC for those with severe SCD in the US

HU PK Study

- Only limited PK studies of HU in children
- Inability of young peds to swallow capsules, a liquid formula will be manufactured for this study
- Study will evaluate PK of liquid HU in ages 2-5 and bioavailability of HU liquid compared to standard therapy in ages 5-17.
- Six sites – 40 pts
  - Enroll children over summer holiday
- DCRI services include site selection, PSSV, develop protocol/ICF & MOP, site training, inv mtg, oversee drug formulation, manuscript

Protocol/Task Order 6 Acyclovir

- Protocol Title: An Open Label Study to Describe the Pharmacokinetics of Acyclovir in Premature Infants Sample size: up to 500 patients
- Objective: To evaluate the safety and PK of IV acyclovir in premature infants with suspected systemic infections.
- Population: Infants < 45 days postnatal age, suspected to have a systemic infection divided into groups by gestational and postnatal age:
  - Group-1: 23-29 weeks gestational age, <14 days postnatal age
  - Group-2: 23-29 weeks gestational age, 14-44 days postnatal age
  - Group-3: 30-34 weeks gestational age, <45 days postnatal age
- Study Duration: Approximately 6 months (LPI target Jan 2012); each participant will participate in the study for up to 13 days: 3 days of study drug administration and 10 days of safety monitoring
- Number of Sites: 3
- Target to Enroll First Patient: June 2011

Protocol/Task Order 7

- Protocol Title: Safety and Pharmacokinetics of Multiple Dose Lisinopril in Pediatric Kidney Transplant Recipients
- Phase I
- Sample size: 24-28 patients
- Population: Children ages 2-18 with kidney transplant and stable allograft function
- Number of Sites: 7
- Target to Enroll First Patient: July 2011
- Study participation: Up to 51 days

TO7 - Lisinopril

- Lisinopril is given for the treatment of,
  - Hypertension (high blood pressure)
  - Hearth Failure
  - Heart Attack (acute myocardial infarction)
- Lisinopril is approved for adults & children/adolescents > 6 years of age
- Lisinopril is frequently given to children/adolescents for the treatment of high blood pressure

TO7 – PTN Goal /Mission

- Current Lisinopril package insert does not provide dosing guidance for children < 6 years of age
- High blood pressure is common for children/adolescents w/ kidney transplant, however, appropriate dose is not well known
- PTN hopes to generate PK data to guide dosing of Lisinopril in these vulnerable populations (since drug behaves differently in young children than it does in older children and adults)
  - Determining the levels of Lisinopril in each person
  - Finding the best effective dose

TO8 - TAPE

- Tape measure (device) to estimate patient weight
- Developed by Dr. Rahman at Children's Mercy Hospital, Kansas City
- Use in emergency setting or third world countries for quick dosing calculations
- Protocol under development

TO8 - Midazolam

- Given to children before anesthesia to cause drowsiness, relieve anxiety, and prevent any memory of the surgery or event.
- Pediatric data already exists
- Pharmacokinetic and pharmacometric experts to analyze existing data in goal of changing label to include pediatric dose.
- Use in emergency setting