The Role of Clinical Trial Networks in Neonatal Studies

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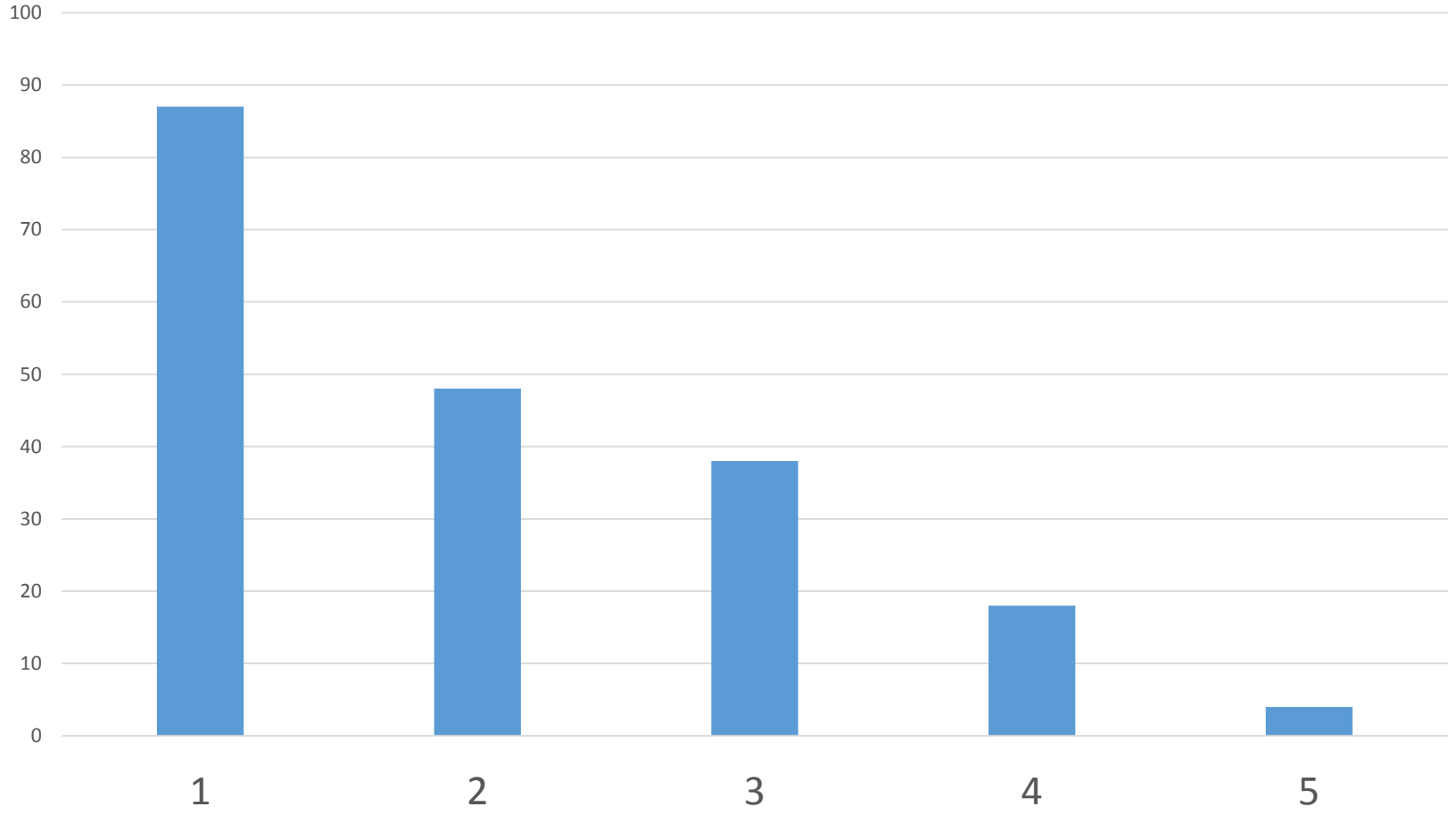
Objectives

- Review barriers to antimicrobial trials in infants
- Describe potential solutions to these barriers

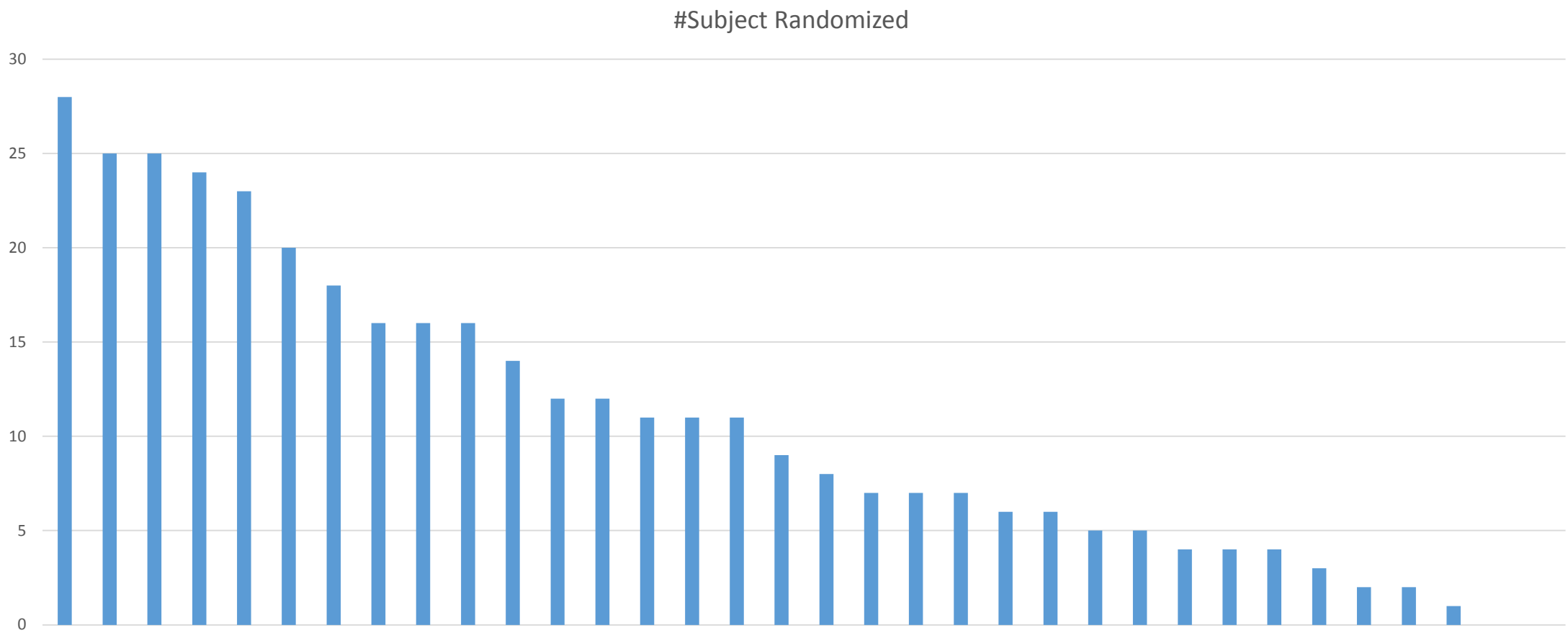
Roadblocks to Trials in Infants in the US

- Limited number of patients with the disease
- No “healthy baby volunteer”
- Low rates of parental informed consent
- Perceived study risks
- Limited blood volume
- Sick population – increases variability
- Lack of clinical pharmacology expertise
- Timing of consent
- Contamination
- Long-term follow-up
- Variability in site enrollment
- Clinician concerns/beliefs about therapies and trials
- Variability in site outcomes
- Competing research priorities

Variability in site enrollment
200 patient study (quintiles)



Site enrollment - 360 patient study



Site characteristics affecting enrollment

- Involved PI/study coordinator
- Relationship with sponsor and/or coordinating center
- Time to activation (IRB, contracting)
- Competing studies
- 24/7 coverage
- Buy-in from neonatologists, nurses

Clinician beliefs/concerns about protocols

- Furosemide
  - Not labeled for infants
  - Little evidence of efficacy or safety
  - Used routinely in infants despite many sites claiming that it is never/rarely used

Most common drugs in the NICU - ELBW (<1000 g BW) infants		
	% exposed	*FDA labeling for premature infants*
1. Gentamicin	90	Dosing
2. Ampicillin	88	None <26 weeks
3. Caffeine	70	None <28 weeks
4. Vancomycin	56	Dosing
5. Furosemide	50	No

Hsieh et al, AJP 2014.

Well maybe we use it but not at “high doses” > 1 mg/kg/day

150 NICUs with >100 infants <32 weeks gestation and < 1500 g birth weight

Furosemide dose	% of NICUs dose in any infant
≥1 mg/kg/day IV or ≥2 mg/kg PO	97%
≥4 mg/kg/day IV or ≥8 mg/kg PO	57%
≥8 mg/kg/day IV or ≥16 mg/kg PO	24%
*any dose of bumetanide	35%

SCAMP – antibiotic safety trial

Drug	Phase I (PK and Dosing)	Phase II (Safety and Efficacy)
Ampicillin	**PTN (N=28)**	SCAMP
Clindamycin	**PTN (N=28)**	SCAMP
Metronidazole	**PTN (N=24)**	SCAMP
Piperacillin-tazobactam	**CTSA supplement (N=32)**	SCAMP

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SCAMP - Study Population

- Phase 2/3 – safety, open-label, randomized, multi-center
- 300 premature infants (≤32 weeks gestation at birth) randomized 1:1:1 to drug regimen Groups 1, 2, or 3
  - Group 1 (N=100): ampicillin, gentamicin, and metronidazole
  - Group 2 (N=100): ampicillin, gentamicin, and clindamycin
  - Group 3 (N=100): piperacillin-tazobactam and gentamicin
- 50 late preterm and term infants (≥34 weeks gestation at birth) will be assigned to Group 4
  - Group 4 (N=50): metronidazole in addition to the antibiotic regimens prescribed per standard of care

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Study Drug Dosing Schemes

Drug	PNA days	GA wks	PMA wks	Weight kg	Loading dose mg/kg	Maintenance dose mg/kg	Dosing interval h
Ampicillin	≤28	≤29				50	12
	>28	≤29				50	8
	≤14	30–32				50	12
	>14	30–32				50	8
Metronidazole			<34		15	7.5	12
			34–40		15	7.5	8
			>40		15	7.5	6
Clindamycin	≤7			≤2		5	8
	≤7			>2		5	12
	>7			≤1.2		5	8
	>7			1.2 - 2		5	12
	>7			>2		5	8
Piperacillin-tazobactam*			≤30			100	6
			>30			80	6

PNA = Postnatal Age, GA = Gestational Age, PMA = Postmenstrual Age; *Dosing based on piperacillin component

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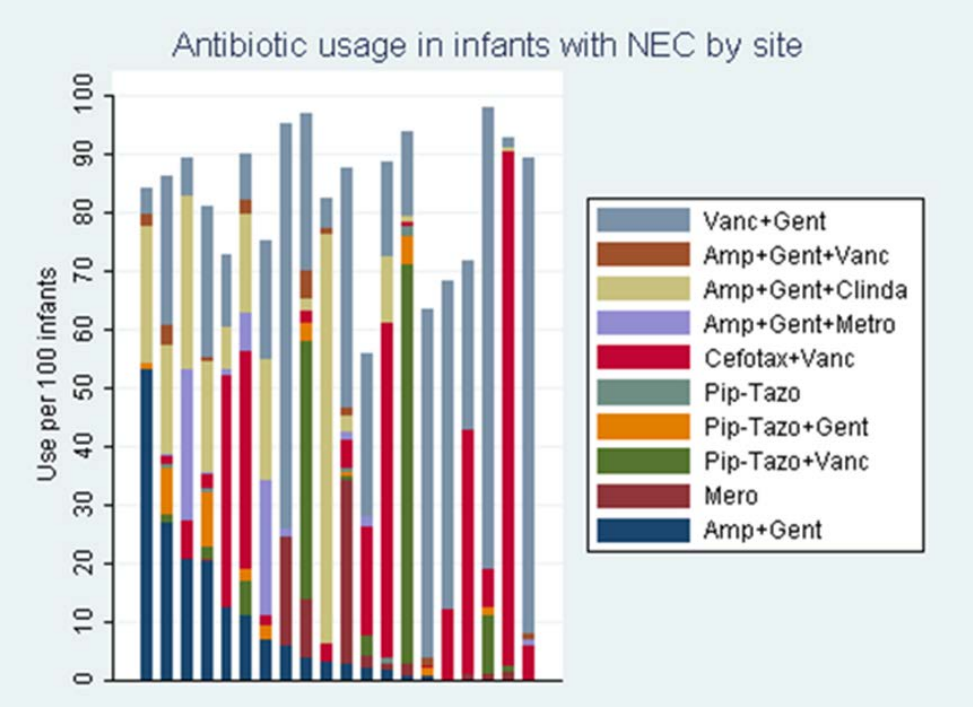
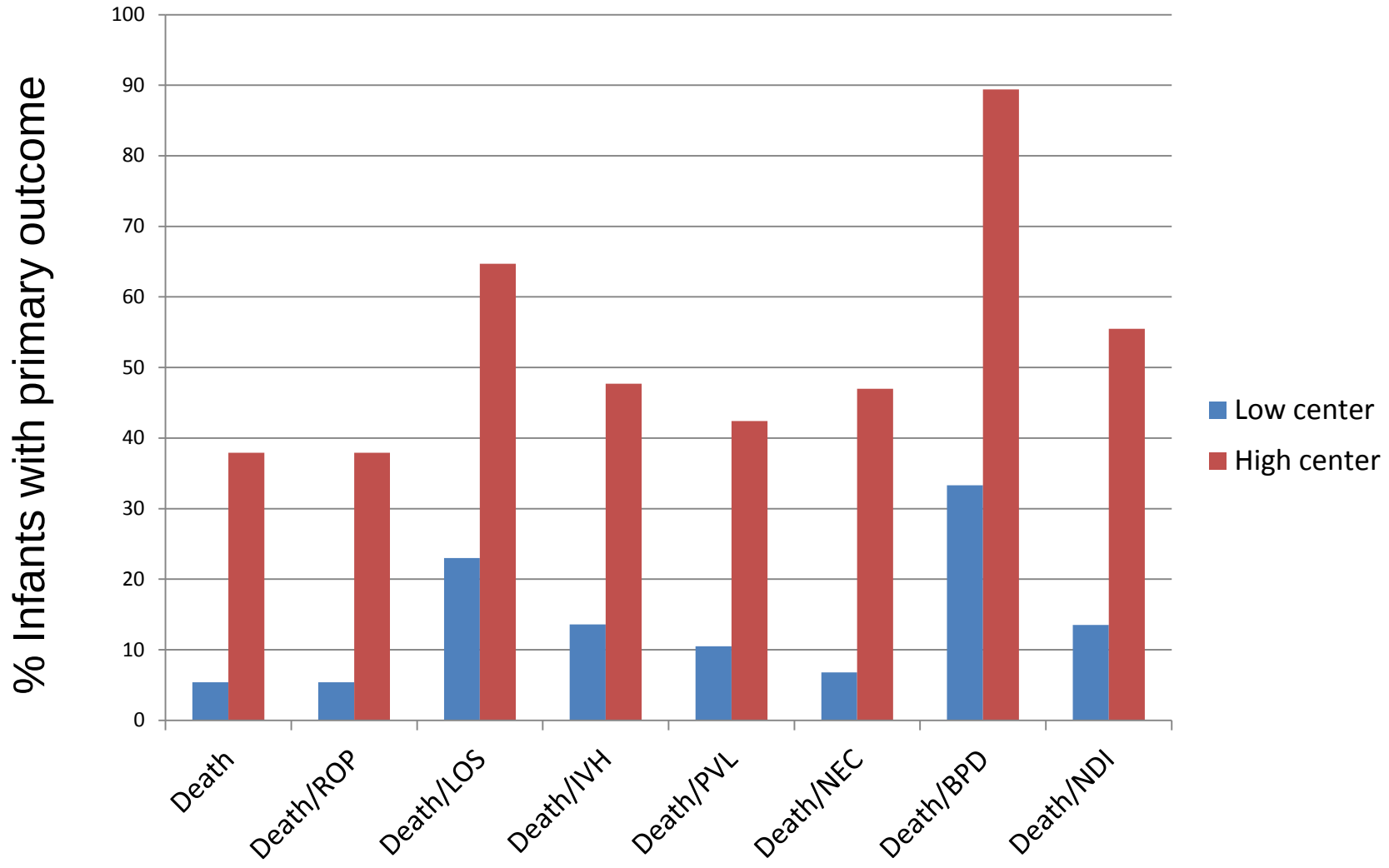
Clinician concerns

- Support drug dosing that is <50% different than protocol dose
- Support one arm over another for a particular infant
- Number of blood draws



Week of Life	Mean	Min	Max
1	39	7	100
2	32	2	122
3	28	1	110
4	20	1	115
5	14	1	61
6	12	1	60
7	9	1	66
8	9	1	70
9	8	1	67
10	7	1	44

Variability in Outcomes – 25-27 week infants, Neonatal Research Network, 2002-08



Smith, Pediatrics, 2012.

NICHD - Neonatal Research Network

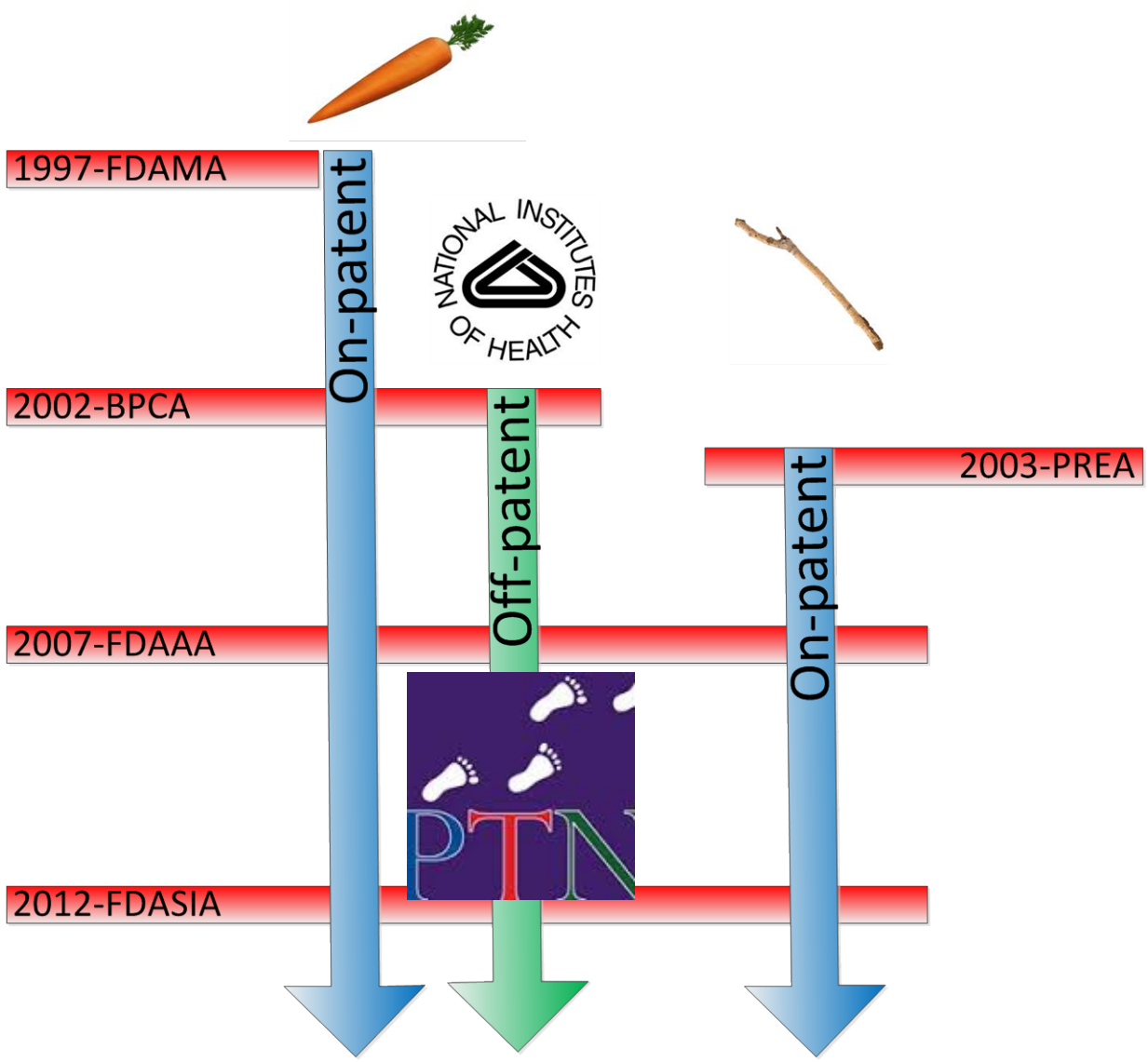
- 15 center (~40 NICUs)
- Primary focus on premature infants
- Barriers to antimicrobial studies
  - Have never done one
  - 14 active trials
  - Number of studies in queue ahead of new studies
  - Co-enrollment is an issue

NICHD -Pediatric Trials Network (PTN)

“Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health.”

- Study age-appropriate drug dosing, efficacy, safety, and device validation
- Success - improve dosing, safety information, labeling, and ultimately child health
- PI – Danny Benjamin, MD PhD MPH – Duke Clinical Research Institute (DCRI)

PTN


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

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 - Innovation

- Data access
- Federated IRB
- Master contracts
- Partnerships with funding, etc.
- Neonatal studies

- Master protocols
  - POPs
  - Multi-arm PK/PD studies
  - Multi-arm safety studies
  - Antipsychotics
  - Anesthesia

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PTN – Progress Since 2010

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

Antimicrobials: PK trials

Rank	Medication	Exposures (/1000 infants)
1	Ampicillin	681
2	Gentamicin	676
4	Vancomycin	91
15	Cefotaxime	43
23	Tobramycin	24
27	Fluconazole	19
28	Clindamycin	17
30	Acyclovir	16
38	Ceftazidime	12
41	Pip/tazo	11
43	Amoxicillin	11
44	Metronidazole	11
45	Oxacillin	10
46	Nafcillin	9
47	Amphotericin B	9
48	Amikacin	9

Hseih, A J Perin, 2014.

Enrollment – PTN SCAMP

- Goal –50 sites, 350 participants
- Eligible participants: 1.2 participants/site/month
- Enrollment: 0.2 participants/site/month = 17% of eligible participants

Enrollment – PTN Furosemide Safety Trial

- Goal – 25 sites, 120 participants
- Eligible participants: 5 participants/site/month
- Enrollment: 0.2 participants/site/month = 4% of eligible participants