Challenges and Opportunities for Drug Development in Neonates

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DISCLOSURES

- I have no conflicts of interest to disclose
- I Chair the Neonatal Advisory Committee in the Office of Pediatric Therapeutics at FDA. My presentation reflects my own opinions and does not necessarily represent the opinions of the FDA
- I am a Director of the International Neonatal Consortium through FDA/EMA/Critical Path Institute

Newborn Intensive Care

- 6% of the 4,000,000 births each year in the US require NICU admission
- Prematurity rates (11%) - highest of any developed country
- Total cost of prematurity >$29 billion each year
- Only marginal improvements in survival and outcome in the last 20 years
- >90% of drugs used in the NICU are not FDA approved
- Smallest infants can be exposed to >60 drugs

Why is Neonatal Drug Development Difficult?

- Small market, rare diseases, high risk/liability
- Few appropriate animal models
- Variable definitions of neonatal disease
- Difficulty with study design
- Minimal agreement on outcome measures
- When to determine outcome
- Hard to establish safety and efficacy

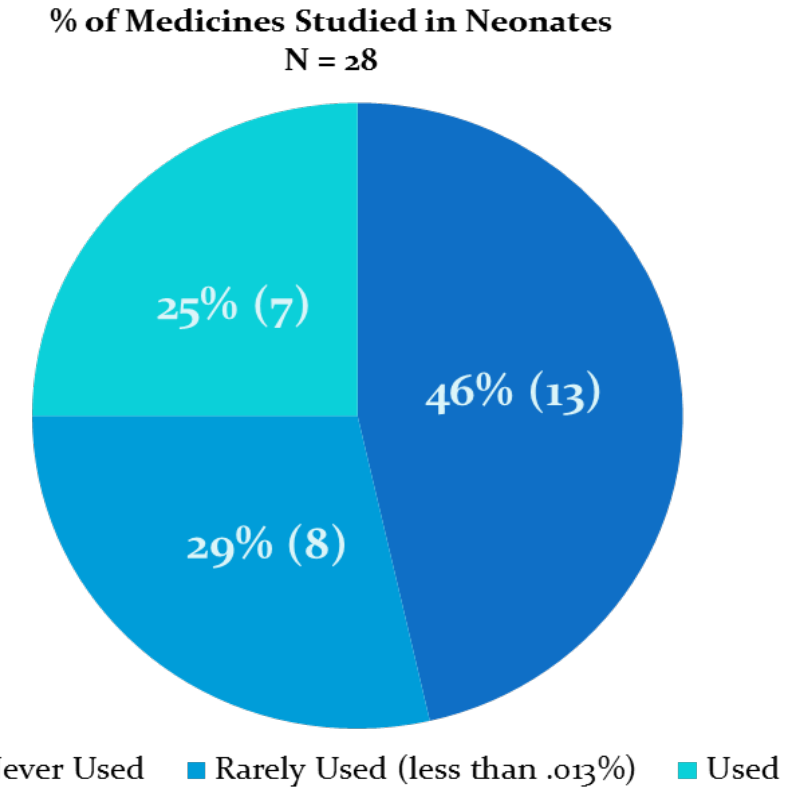
Unique Challenges in Studying Neonates

- Rapidly changing physiology
- Need to follow long term – the longer the better
- Postnatal environmental exposures (outside the NICU) become increasingly important
- Confidentiality issues (mother/neonate)
- Obtaining informed consent in the DR quickly
- Mothers/Neonates can be separated
- Limited impact of legislation on this population

Regulations Have Facilitated Pediatric Studies, But How About Neonates

Studies must be clinically relevant

- **Of 406 medicines studied in children in order to achieve 6 months of exclusivity, only 28 (7%) studied in neonates**
- **Of those 28 drugs, the majority are not used routinely in this vulnerable population**



[1]*Stiers, J., et al. Newborns, One of the Last Therapeutic Orphans to Be Adopted. JAMA Pediatr, 2014*

Pediatric Formulations

- Concerns about formulations - extrinsics (stabilizers, preservatives)
- Methadone for treatment of NAS – 15% alcohol; Buprenorphine - 30%
- Phenobarbital – 20% alcohol in elixir; 60% propylene glycol in IV preparation
- Clindamycin – benzyl alcohol

Neonatal Clinical Trials – Drugs & Devices

- Demand is increasing for trials of innovative products
- Trials are inefficient, take too long, and are expensive
- Most trials fail due to inadequate enrollment
- The trial infrastructure is fragmented, lacks sustainability
- Expertise and workforce is limited
- There are significant opportunities for change and improvement

Industry Statistics

Current State	**15**	**30%**	**4-6**	**1.5**
	Years to complete pediatric programs	Of sites never enroll a single patient	Avoidable amendments per program	Pediatric patients enrolled per site per year

Source: P.L. Simpkins, Unpublished, 2017. Analysis was completed using data from Evaluate Pharma, Drugs@FDA.gov (label) and FDA New Pediatric Labeling Information Database (pediatric label changes). Accessed February 2017. Sample size N = 114 pediatric labels. Rx products only (excludes OTC products).

Moving Forward

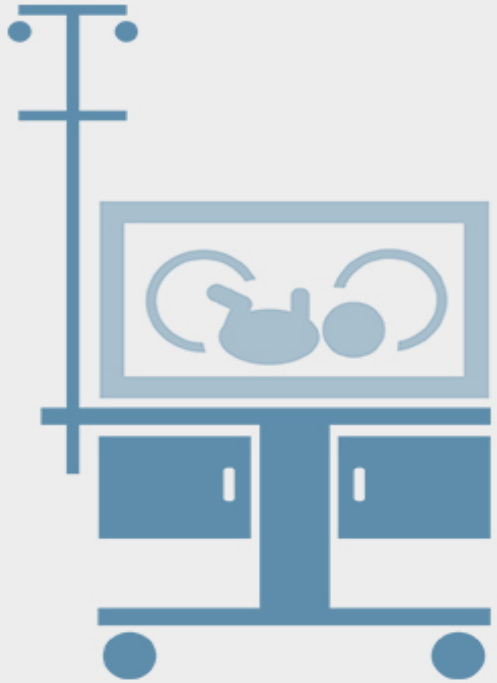
- Can we enroll every neonate in the NICU in a study protocol to optimize outcomes (similar to cancer)?
- Can we adopt uniform and better definitions?
- Can we collect standardized data?
- Can we examine global survival/outcome and adopt best practices?
- Can we establish normal laboratory values based on birth weight, gestational age, and postnatal age?
- Can we develop safer drug formulations for neonates?
- Can all key stakeholders (especially regulators) collaborate to develop the best protocols?

INC Priority Conditions

INC AND THE NICU

The International Neonatal Consortium concentrates its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of preterm birth.

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium



- NEONATAL LUNG INJURY AND CIRCULATORY FAILURE
- PERINATAL/NEONATAL INFECTIONS
- NEONATAL ABSTINENCE SYNDROME (NAS)
- RETINOPATHY OF PREMATURITY (ROP)
- NEONATAL GASTROINTESTINAL INJURY
- NEONATAL BRAIN INJURY
- DRUGS TO PREVENT PRETERM LABOR
- HEMODYNAMIC ADAPTATION (HA)

Clinical Translational Science Award Program

- Established by NIH in 2006
- A national consortium of >60 research institutions
- Under NCATS, one of 27 NIH Institutes and Centers established in 2011
- Mission: to develop innovative solutions that will improve the efficiency, quality, and impact of the process for turning observation in the laboratory, clinic, and community into interventions that improve the health of individuals and the public

CTSA Clinical & Translational Science Awards ®

Clinical Translational Science Institutes

Research Service

- Study design & analysis
- Clinical study & regulatory support
- Informatics

Conveners & Connectors

- Team Science
- Collaboration
- Multidisciplinary
- Stakeholder & community-engagement

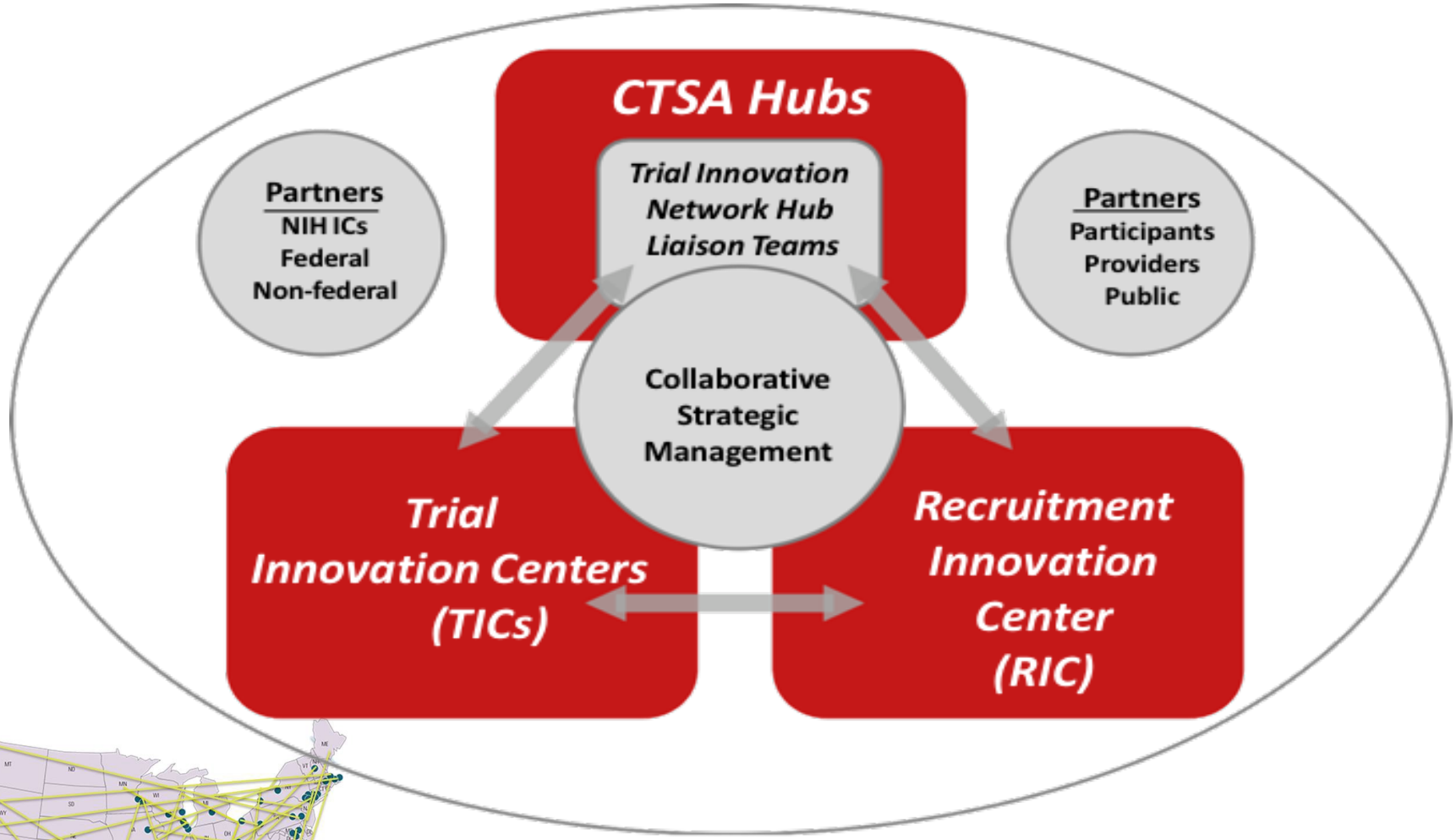
Change

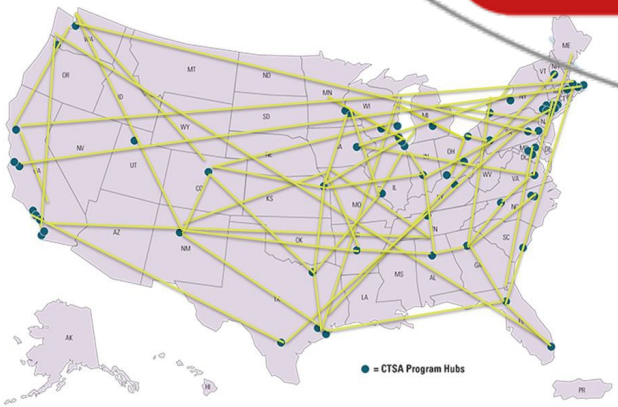
- Innovation & transformation
- Science of Science
- Process improvement
- Address roadblocks

Education

- Graduate certificate, Masters, and PhD programs
- Professional development
- Fellowship and career development programs

Trial Innovation Network Vision and Key Partners





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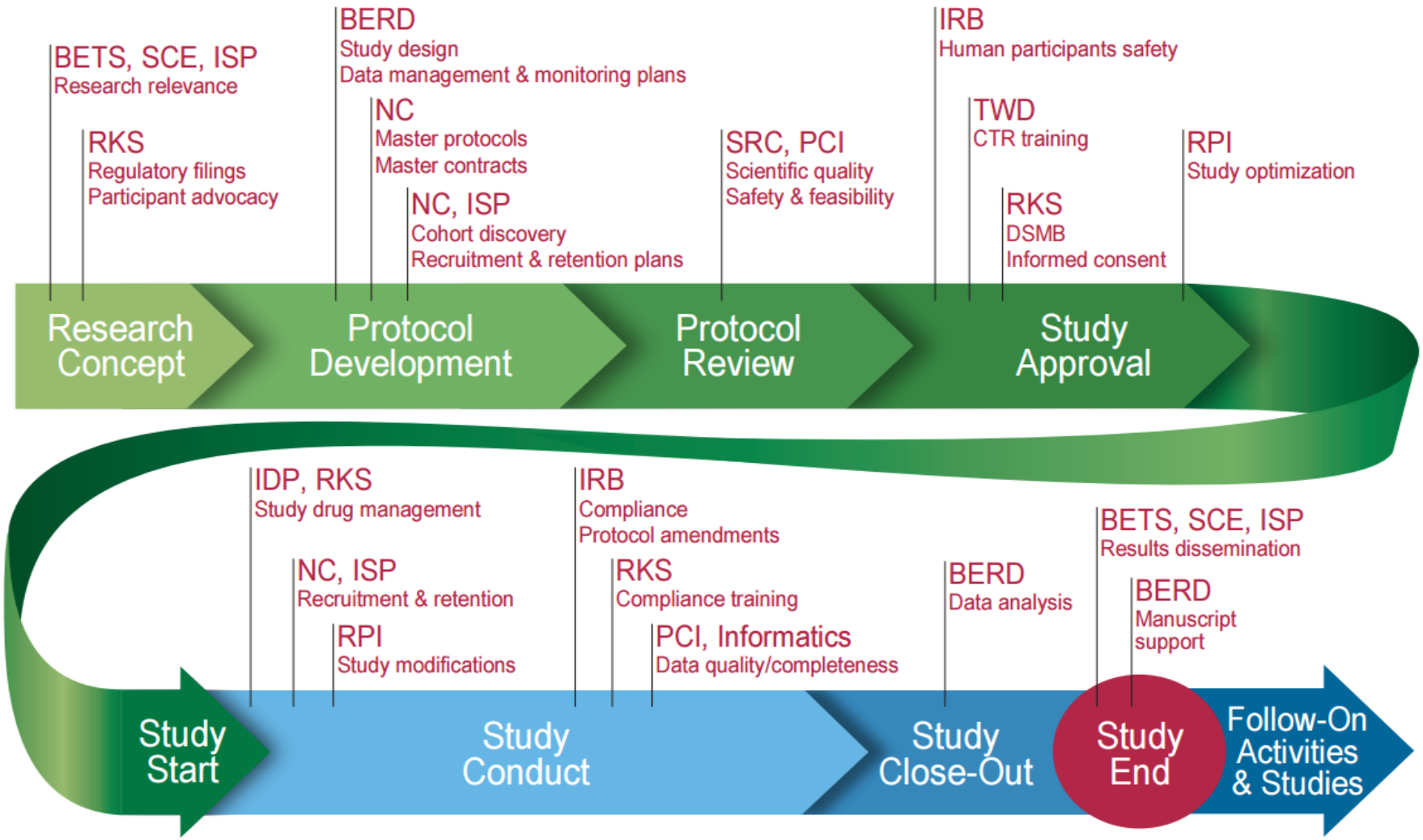
Key Clinical Research Study Quality Touchpoints



- Broadly-engaged Team Science (BETS)
- Stakeholder and Community Engagement (SCE)
- Integrating Special Populations (ISP)
- Regulatory Knowledge and Support (RKS)
- Biostatistics, Epidemiology, Research Study Design (BERD)
- Network Capacity (NC)
- Scientific Review Committee (SRC)
- Participant and Clinical Interaction (PCI)
- Institutional Review Board (IRB)
- Translational Workforce Development (TWD)
- Research Process Improvement (RPI)
- Investigational Drug Pharmacies (IDP)

Pediatric Clinical Trials Ecosystem

Japanese Pediatric Network for Drug Development

Kids CAN

NHS National Institute for Health Research
Clinical Research Network Children

c4c

PTC CRITICAL PATH INSTITUTE


Advancing
Maternal - Child Health
Sustainable
Infrastructure
Knowledgeable
Workforce
Cooperative
Networks
Efficient
Regulatory Processes