

NICHD

# NEONATAL RESEARCH NETWORK



## Changes in Patent Ductus Arteriosus Management and Outcomes in Infants Born at 26-28 Weeks' Gestation

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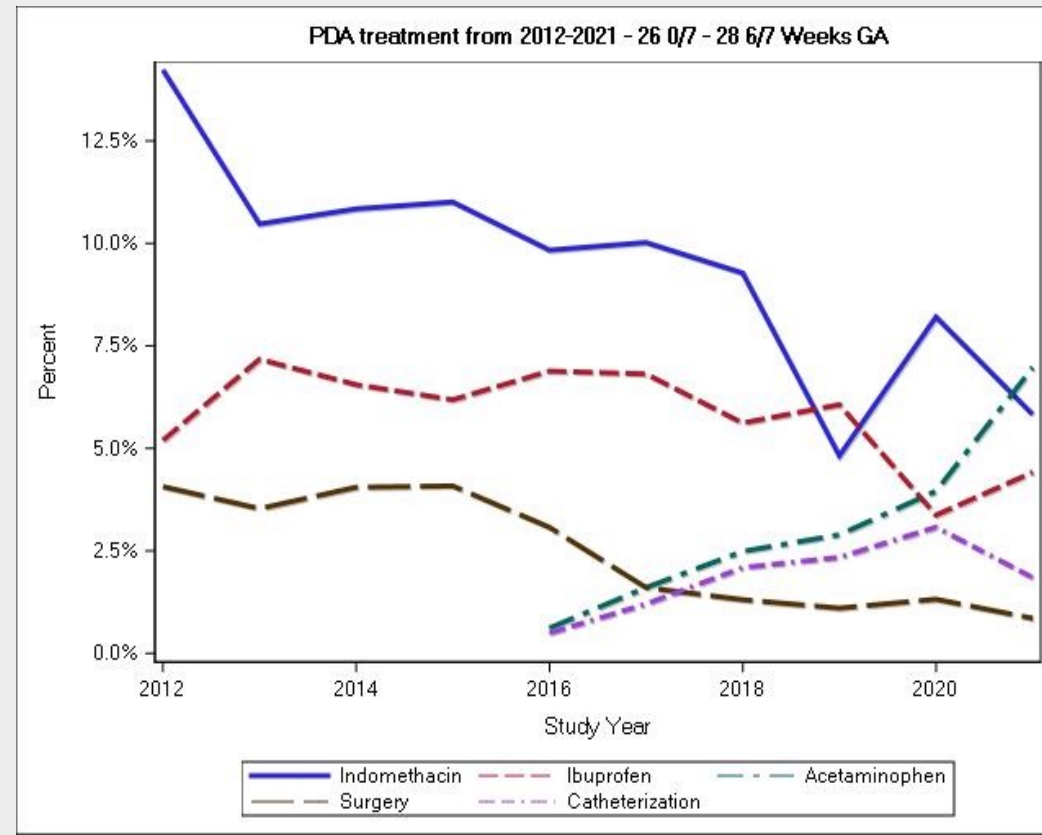
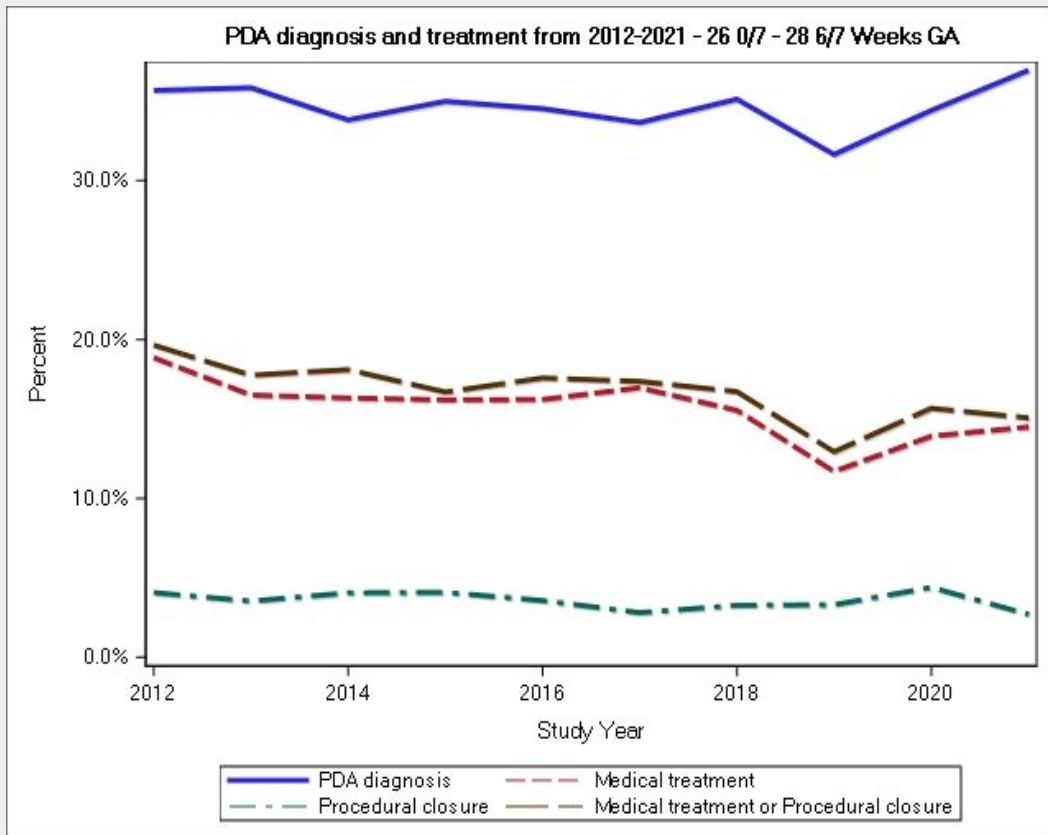


# Disclosures

- Speaker: Dinushan Kaluarachchi MBBS
- Dr. Kaluarachchi serves as a consultant for ONY Biotech Inc.

# Background

- Management of the patent ductus arteriosus (PDA) remains controversial
- Rate of PDA treatment significantly decreased from 2012 to 2021 among infants born at 26 0/7 to 28 6/7 weeks



Kaluarachchi et al.  
J Peds 2024

# Background

- Decrease in PDA treatment is consistent with findings from other cohorts
- Conflicting data on outcomes following more conservative PDA treatment

# Objective

- Investigate the association between the secular decrease in PDA treatment rates and relevant clinical outcomes among infants born at 26 0/7 to 28 6/7 weeks

# Methods - Design

Retrospective cohort study

Preterm infants born at 26 0/7 through 28 6/7 weeks' gestation

Continuously participating hospitals in the Neonatal Research Network (NRN) between 2012 to 2021

Exclusion Criteria: Death before 12 hours, Born outside of NRN hospitals, Major congenital anomalies, Enrolled in NRN PDA trial

# Methods – Data Collection



Prospectively collected data from the NRN Generic Database



Medical PDA treatment was defined as any medication used specifically to induce PDA closure (indomethacin, ibuprofen, or acetaminophen)



Prophylactic indomethacin was also described as medical PDA treatment



Procedural PDA closure included catheter closure and surgical ligation

# Methods - Analysis

The primary composite outcome:

<b>Surgical Necrotizing Enterocolitis (NEC)</b>	<b>Grade 2-3 Bronchopulmonary Dysplasia (BPD)</b>	<b>Severe Intraventricular Hemorrhage (IVH)</b>	<b>Death</b>
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The relationship of temporal trends in PDA treatment with the primary composite outcome was analyzed using a multi-level model accounting for patient-level variables



# Methods - Analysis



A sensitivity analysis was conducted using grade 3 BPD alone instead of grade 2-3 BPD in the primary outcome (modified primary outcome)



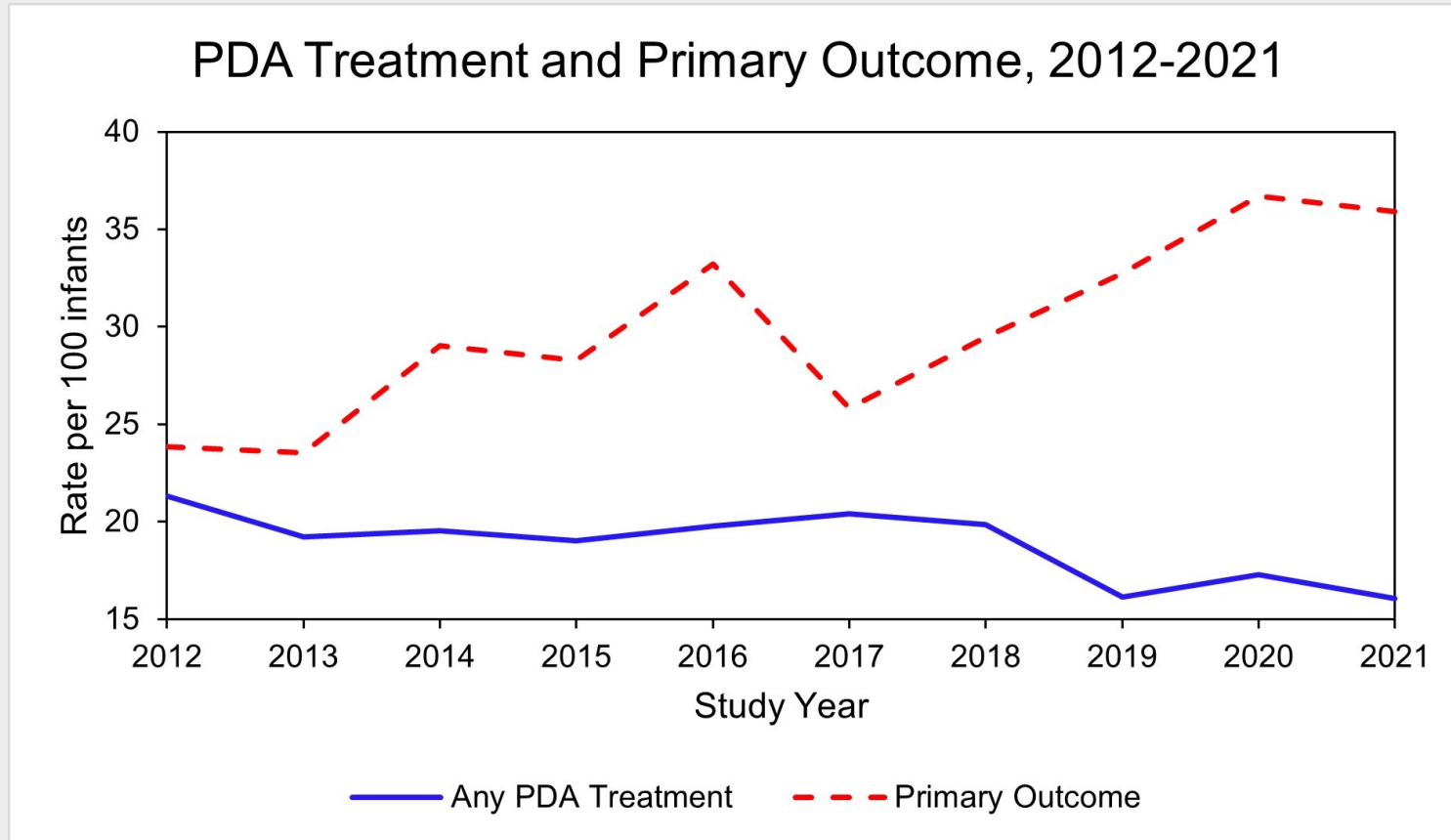
A separate analysis was stratified by hospital changes in PDA treatment

# Results – Study Cohort

- N =7864

Characteristic	Mean (SD) or Number (%)
Gestational age (weeks)	27.5 (0.9)
Birth Weight (grams)	976 (225)
Male	3973 (51)
Singleton	5820 (74)
Antenatal Steroids	7345 (93)
Small for gestational age	810 (10)

# Results -Trends in PDA treatment



# Results – Trends in the Primary Outcome

Outcome	2012	2021	P Value for Trend
<b>Primary Outcome</b>	<b>24 %</b>	<b>36 %</b>	<b>&lt;0.01</b>
Death	5%	6%	0.81
Surgical NEC	3%	3%	0.50
Severe IVH	7%	8%	0.30
<b>BPD (Grade 2-3)</b>	<b>13%</b>	<b>26%</b>	<b>&lt;0.01</b>

# Results – Trends in the Modified Primary Outcome

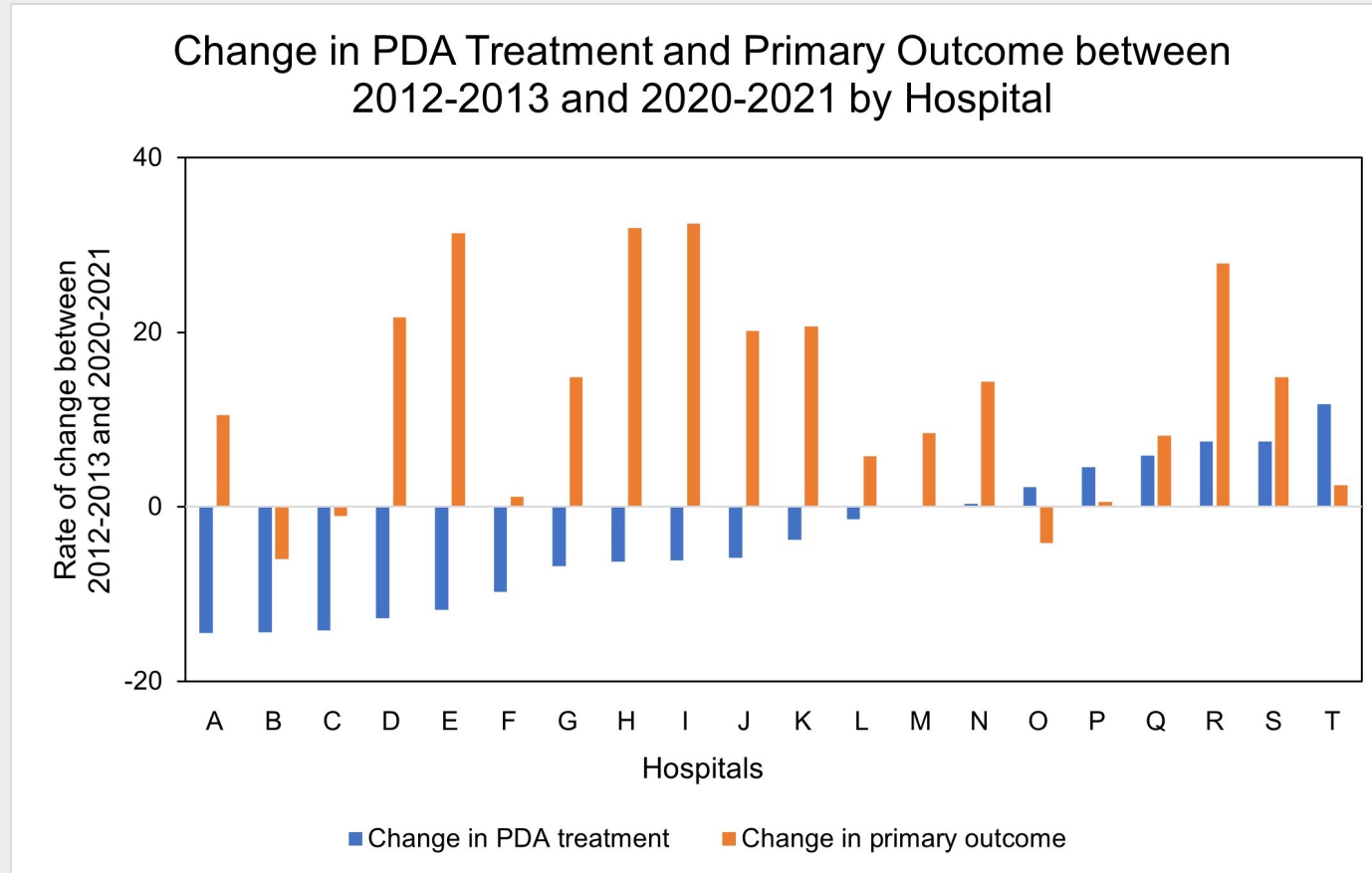
Outcome	2012	2021	P Value for Trend
Modified primary Outcome	15 %	18 %	0.38
BPD (Grade 3)	3%	4%	0.36

# Results – Association of Annual PDA Treatment on Outcomes

Outcome	Odds Ratio (95% CI)	P Value
<b>Primary Outcome</b>	0.85 (0.77-0.94)	<b>&lt;0.01</b>
<b>Grade 2-3 BPD</b>	0.85 (0.76-0.94)	<b>&lt;0.01</b>
Death	0.98 (0.91-1.06)	0.63
Surgical NEC	0.97 (0.86-1.10)	0.68
Severe IVH	0.95 (0.90-1.01)	0.08
Grade 3 BPD	0.98 (0.91-1.07)	0.68

Multilevel model was clustered by birth year and adjusted for hospital, small for gestational age, exposure to any antenatal corticosteroids, gestational age, late onset sepsis, infant sex, Vitamin A, surfactant, post natal steroids and any mechanical ventilation.

# Results – Outcomes stratified by Hospital Trends in PDA Treatment



Change is calculated as the difference in proportion from 2012-2013 to 2020-2021

# Results – Outcomes stratified by Hospital Trends in PDA Treatment

Characteristic	More Decrease (6*)	Less Decrease (7*)	Increase (8*)	P value
PDA Treatment	↓ 12 %	↓ 5 %	↑ 7%	<0.01
Primary Outcome	↑ 10%	↑ 18%	↑ 10%	0.66
Grade 2-3 BPD	↑ 10%	↑ 21%	↑ 11%	0.49

\* Number of hospitals

Change is calculated as the difference in proportion from 2012-2013 to 2020-2021



# Results - Summary

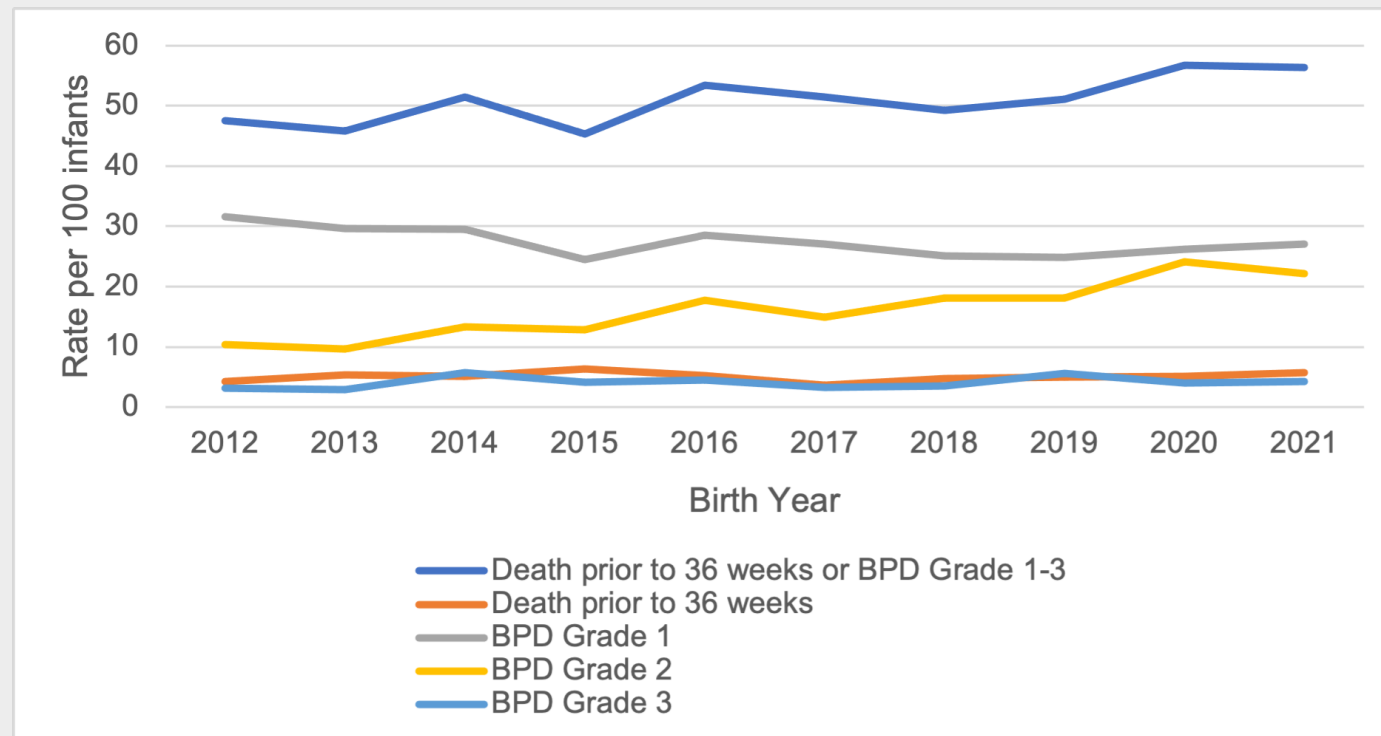
- Association between the temporal decrease in PDA treatment and an increase in grade 2-3 BPD from 2012 to 2021
- No changes were observed in death, surgical NEC, severe IVH or grade 3 BPD
- Grade 2-3 BPD increased regardless of trends in PDA treatment at hospital level

# Discussion – Association Vs Causation

- Should be interpreted with caution
  - Increase in BPD is out of proportion to decrease in PDA treatment
  - Grade 2-3 BPD increased equally at hospital level

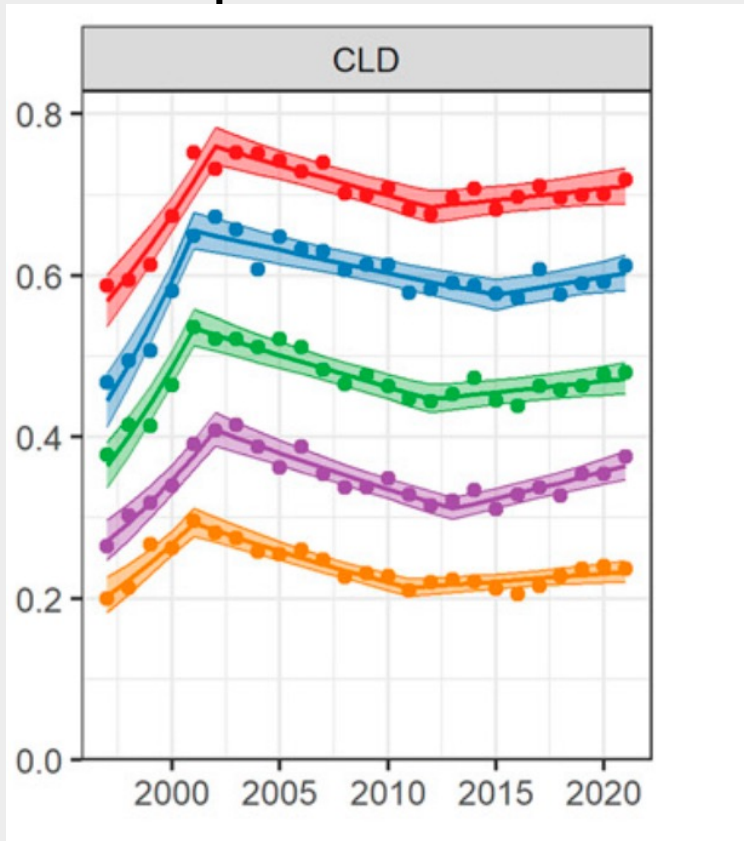
# Discussion – Increase in BPD

- Concerning trend
- Restricted to Grade 2



# Discussion – Increase in BPD

- Consistent with data from other networks (VON)
- Remains unexplained



Horbar et al.  
Pediatrics 2024

# Limitations

- No standardized echocardiography protocol across NRN sites
- Details of significance or duration of PDA exposure were not available
- Timing of diagnosis or treatment were not recorded
- Residual confounding possible

# Conclusions

- Temporal decrease in PDA treatment was associated with an increase in grade 2 BPD
- This relationship does not adequately explain the concerning increase in grade 2 BPD
- Evaluation of current practices and development of new therapeutic strategies for prevention of BPD are needed

# Neonatal Research Network Centers (2011-2016)

- Brown University
- Case Western Reserve University
- Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of California – Los Angeles
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- Wayne State University

# Neonatal Research Network Centers (2016-2023)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- University of Utah