NICHD

NEONATAL RESEARCH NETWORK

Generalizability of the Necrotizing Enterocolitis Surgery Trial (*NEST*) to Eligible, Non-Randomized Infants

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Disclosures

- Speaker: Matthew Rysavy

- Dr. Rysavy has no financial relationships to disclose or conflicts of interest to resolve.

Background: NEST

Population: Babies with birthweight <1000 g and NEC or IP needing surgical intervention
Comparison: Initial laparotomy vs peritoneal drain
Outcome: Death or NDI

Overall: 69% vs 70% (RR=1.0 [0.87-1.14])

Pre-op NEC: 69% vs 85% (RR=0.81 [0.64-1.04])
97% Bayesian posterior for benefit

Pre-op IP: 69% vs 63% (RR=1.11 [0.95-1.31])
18% Bayesian posterior for benefit

Ann Surg 2021;274:e370-80

Background: NEST

NEST enrolled 31% (n=310/992) of eligible infants

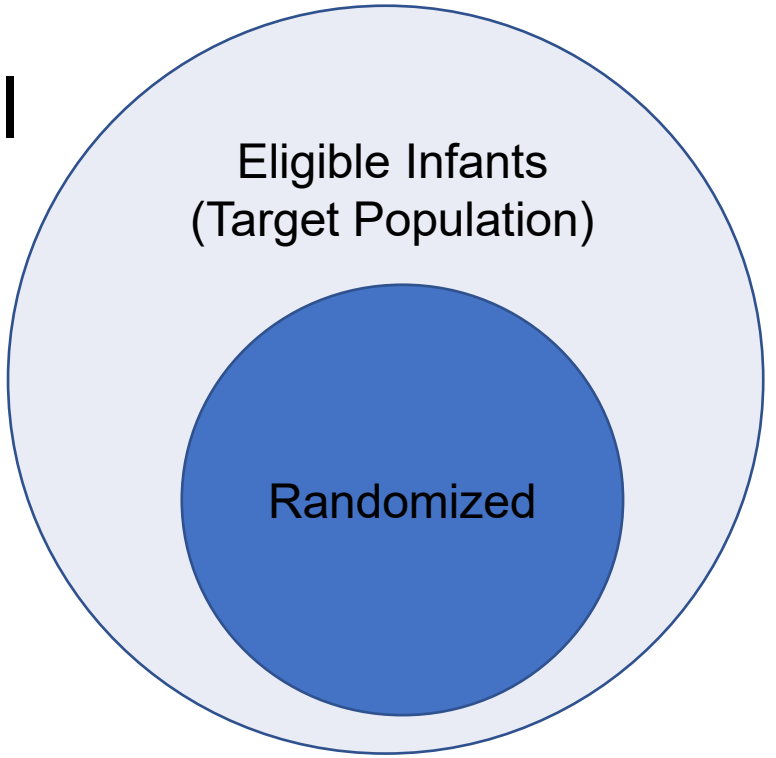
During the first years of the trial, a parallel observational study was conducted in order to understand how randomized and non-randomized infants differed.

Objective

To determine:

1) Whether infants in the target population differed from those randomized in the trial

2) How differences affect generalizability of trial results



Design

Design	RCT and nested observational study
Data sources	NEST Trial (2010-2017) and Observational Study (2010-2013)
Study infants	• Birthweight ≤ 1000 g • NEC or IP requiring surgery at ≤ 8 wk age • No major congenital anomalies
Definitions	• *Target population* = infants in NEST Trial or parallel observational study

Outcomes

Primary outcome	• Death or NDI at 18-22 months' corrected age
Definitions	• *NDI* = One or more of the following: • Moderate to severe cerebral palsy with Gross Motor Function Classification System level ≥2 • Bayley-III cognitive composite score <85 • Severe bilateral visual impairment consistent with vision <20/200 • Permanent hearing loss despite amplification

Statistical Analysis

- **Compared randomized and target populations** on characteristics and outcomes

- **Generalizability** of trial results to target population estimated using **inverse probability weighting estimators** to account for:
  - probability of being enrolled in the trial
  - probability of being enrolled during the period used to define the target population, and
  - probability of being assigned laparotomy or drain in the trial

- Trial results (from the *randomized population*) were reweighted to derive **expected treatment effect of laparotomy for the *target population*** using intention-to-treat and as-treated estimates

Covariates Used for Reweighting

Demographics	Preceding Treatments and Morbidities	Illness at Time of Enrollment
• Center • Inborn status • Sex • Birthweight • Gestational age at birth	• Antenatal corticosteroids • Pre-enrollment severe (grade 3-4) intraventricular hemorrhage • Pre-operative surgical diagnosis (NEC vs IP)	• Vasopressor or inotrope • High-frequency ventilation • Portal venous gas or pneumatosis • Abdominal compartment syndrome • FiO2 • Blood gas pH • Postnatal age

Patient Characteristics: *Birth*

	NEST Trial N = 308	Target Population N=382	Difference
Maternal age ≤ 19 y	11%	12%	-1%
Private medical insurance	31%	33%	-2%
Maternal race			
White	52%	54%	-2%
Black	42%	40%	2%
Hispanic ethnicity	24%	20%	4%
Birthweight			
< 500 g	3%	8%	-5%
500 – 750 g	57%	53%	4%
≥ 750 g	40%	40%	0%
Small for gestational age	10%	16%	-6%
Female	42%	45%	-3%
Inborn	56%	60%	-4%
Antenatal corticosteroids	83%	85%	-2%
C-section	66%	72%	-6%
5-minute Apgar ≤ 3	21%	16%	5%

Patient Characteristics: *Enrollment*

	NEST Trial N = 308	Target Population N=382	Difference
Known IVH grade 3 or 4	13%	15%	-2%
Preoperative diagnosis			
NEC	31%	47%	**-16%**
IP	69%	53%	**16%**
Abdomen compartment syndrome	2%	5%	-3%
Portal venous gas	7%	14%	-7%
Pneumatosis	15%	25%	-10%
Age at surgery			
< 7 d	38%	29%	9%
7 – 13 d	36%	31%	5%
14 – 20 d	10%	11%	-1%
21 + d	17%	29%	-12%
Any vasopressor/inotrope	40%	46%	-6%
FiO_2 (median, IQR)	0.37 (0.25, 0.60)	0.40 (0.28, 0.71)	-0.03
pH (median, IQR)	7.25 (7.16, 7.32)	7.24 (7.15, 7.32)	0.01

Reasons for Non-Enrollment

	Randomized in NEST *N=308*	Physician Declined *N=80*	Parent Declined *N=82*	Not Approached *N=47*
Birthweight				
< 500 g	3%	8%	12%	11%
500 – 750 g	57%	60%	48%	51%
≥ 750 g	40%	33%	40%	38%
Preoperative diagnosis				
NEC	31%	**61%**	43%	**63%**
IP	69%	39%	**57%**	37%
Oxygenation index (median, IQR)*	7.9 (4.8, 15.4)	13.6 (6.6, 28.9)	9.8 (6.8, 20.5)	23.5 (7.2, 43.6)
Death at follow-up	30%	57%	38%	67%
Death or NDI at follow-up	69%	76%	64%	82%
Mean predicted probability of death or NDI determined at enrollment	**67%**	**83%**	**73%**	**82%**

Outcomes

	NEST Trial N = 308	Target Population N=382	Difference
Death before follow-up	89/299 (30%)	165/369 (45%)	-15%
Death or NDI at follow-up	205/295 (69%)	264/365 (72%)	-3%

Generalizability: *ITT*

aRR (95% CI)

	NEST Trial			Target Population		
	Overall	Pre-op NEC	Pre-op IP	Overall	Pre-op NEC	Pre-op IP
Death or NDI	**1.00 (0.87-1.14)**	0.81 (0.64-1.04)	1.11 (0.95-1.31)	**0.92 (0.79-1.08)**	0.85 (0.71-1.03)	1.02 (0.79-1.30)
Death	**0.98 (0.68-1.42)**	0.75 (0.52-1.10)	1.26 (0.79-2.02)	**0.90 (0.68-1.21)**	0.83 (0.63-1.10)	1.09 (0.70-1.71)
NDI	**1.00 (0.68-1.48)**	0.89 (0.43-1.84)	1.04 (0.73-1.47)	**0.92 (0.56-1.52)**	0.86 (0.40-1.87)	0.97 (0.61-1.53)

Generalizability: *ITT*

aRR (95% CI)

	NEST Trial			Target Population		
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Generalizability: *As Treated*

Infants randomized to laparotomy:
5 received drain
1 infant no intervention (died)

Infants randomized to drain:
1 received laparotomy

Results of generalizability analysis unchanged

Conclusions

- Compared to the target population, infants randomized in the NEST Trial were:
  - Lower acuity of illness
  - More likely to have IP than NEC
- Physicians were more likely to decline consent for NEC; parents for IP
- These differences did not substantially alter *expected* trial results

Lessons Learned

- Potential value of **registry-based trial enrollment** with **complete ascertainment** of a minimal dataset for all eligible infants
- Importance of considering well-recognized (and **pre-specified**) **heterogeneity in disease** in trial analysis and interpretation
- Need for alternative methods to support enrollment in difficult trials in vulnerable populations (e.g., staged consent, “consent to continue”)

Neonatal Research Network Centers

- 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