Generalizability of the Necrotizing Enterocolitis Surgery Trial to the Target Population of Eligible Infants

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Objective The objective of this study was to evaluate whether infants randomized in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network Necrotizing Enterocolitis Surgery Trial differed from eligible infants and whether differences affected the generalizability of trial results.

Study design Secondary analysis of infants enrolled in Necrotizing Enterocolitis Surgery Trial (born 2010-2017, with follow-up through 2019) at 20 US academic medical centers and an observational data set of eligible infants through 2013. Infants born ≤1000 g and diagnosed with necrotizing enterocolitis or spontaneous intestinal perforation requiring surgical intervention at ≤8 weeks were eligible. The target population included trial-eligible infants (randomized and nonrandomized) born during the first half of the study with available detailed preoperative data. Using model-based weighting methods, we estimated the effect of initial laparotomy vs peritoneal drain had the target population been randomized.

Results The trial included 308 randomized infants. The target population included 382 (156 randomized and 226 eligible, non-randomized) infants. Compared with the target population, fewer randomized infants had necrotizing enterocolitis (31% vs 47%) or died before discharge (27% vs 41%). However, incidence of the primary composite outcome, death or neurodevelopmental impairment, was similar (69% vs 72%). Effect estimates for initial laparotomy vs drain weighted to the target population were largely unchanged from the original trial after accounting for preoperative diagnosis of necrotizing enterocolitis (adjusted relative risk [95% CI]: 0.85 [0.71-1.03] in target population vs 0.81 [0.64-1.04] in trial) or spontaneous intestinal perforation (1.02 [0.79-1.30] vs 1.11 [0.95-1.31]).

Conclusion Despite differences between randomized and eligible infants, estimated treatment effects in the trial and target population were similar, supporting the generalizability of trial results. *(J Pediatr 2023;262:113453)*.

Trial Registration ClinicalTrials.gov ID: NCT01029353

Surgical necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) affect approximately 1 in 20 extremely low birth weight infants and result in high rates of mortality.[1] Among survivors, most develop neurodevelopmental impairments (NDIs), with cerebral palsy affecting 1 in 5.[2,3]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network Necrotizing Enterocolitis Surgery Trial (NEST) was the largest randomized clinical trial to compare initial laparotomy and peritoneal drain for NEC or SIP in extremely low birth weight infants (308 infants).[4] Unlike 2 smaller prior trials comparing the same interventions, by Moss et al[5] (117 infants) and Rees et al[6] (69 infants), NEST evaluated the effect of the interventions on death or neurodevelopmental outcome at the 2-year follow-up. While there was no overall difference in the primary outcome between initial laparotomy vs drainage, the trial showed that preoperative diagnosis of NEC or SIP modified the impact of initial treatment. Despite being the largest randomized clinical trial of initial laparotomy vs peritoneal drain, NEST randomized fewer than one-third of eligible infants.

Low rates of enrollment have raised questions about generalizability of the findings from NEST as in other neonatal-perinatal trials of emergent interventions.[7,8] The NEST investigators, foreseeing the difficulty of randomizing extremely low birth weight infants in an emergency surgical setting, collected detailed observational data for eligible nonrandomized infants at study hospitals

FiO_2	Fraction of inspired oxygen
NDI	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NEST	Necrotizing Enterocolitis Surgery Trial
SIP	Spontaneous intestinal perforation

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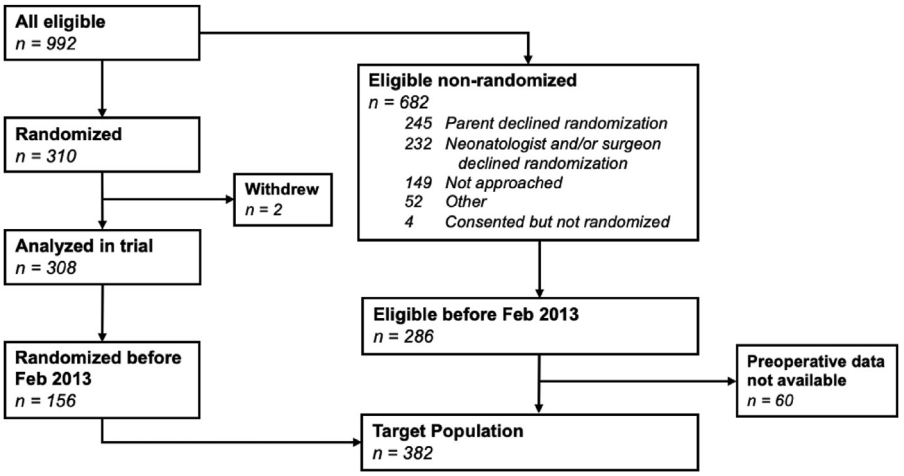

Figure 1. Flowchart for inclusion.

during the first half of trial enrollment. Using these data, we examined how randomized infants differed from eligible infants and whether these differences affected the generalizability of trial findings.[9]

Methods

This is a secondary analysis of NEST, which randomized 310 infants (and included 308 infants) at 20 US academic medical centers between January 2010 and March 2017 with follow-up extending through August 2019. Full elaboration of the trial design and primary trial results were published in October 2021.[4] Eligible infants weighed ≤1000 g at birth, had no known major congenital anomalies or congenital nonbacterial infection, and had a preoperative diagnosis of NEC or SIP requiring surgical intervention at ≤8 weeks of postnatal age.

Detailed observational data for eligible, nonrandomized infants were collected during the first half of trial enrollment. Observational data for nonrandomized infants included all information available for randomized infants, including preoperative diagnosis, clinical status at diagnosis, and details on treatment and outcome. In February 2013, data collection for nonrandomized infants was discontinued for logistic reasons, including cost, after randomization of 156 infants in the clinical trial. Follow-up of nonrandomized infants was completed in November 2015. NEST was approved by the institutional review board at each participating site. Infants enrolled in the clinical trial or observational data set required written informed parental consent.

For the purposes of this report, the term *target population* refers to infants randomized in the trial and eligible nonrandomized infants with observational data who were enrolled through February 2013. The target population represents the eligible population of infants at study sites around trial initiation. Further elaboration on this terminology and the methods used in this report can be found in the literature on generalizability of clinical trials to eligible populations.[9]

The primary outcome was death or NDI at 18 to 22 months of corrected age. NDI was defined as any of the following: moderate to severe cerebral palsy with Gross Motor Function Classification System level ≥2 (on a scale of 0 [normal] to 5 [most impaired]); Bayley Scales of Infant and Toddler Development, Third Edition cognitive composite score <85 (ie, >1 SD below the scale mean; mean [SD], 100 [15]); severe bilateral visual impairment consistent with vision <20/200; or permanent hearing loss despite amplification that prevented communication or understanding of the examiner. Outcomes at 18 to 22 months of corrected age were available for 295 of 308 infants (95.8%) in the NEST trial and 365 of 382 infants in the target population (95.5%).

Maternal race and ethnicity were collected by self-report using categories recommended by the National Institutes of Health[10]; these variables were included in this study because of prior findings that self-reported race was associated with participation in a neonatal clinical trial.[11] Small for gestational age was defined as birthweight <10th percentile by the infant sex-matched and gestational age–matched growth curves.[12] Antenatal steroids referred to any prenatal exposure to betamethasone or dexamethasone for fetal maturation. Postnatal steroids referred to the receipt of any systemic corticosteroid regardless of timing, dose, or duration. Early-onset sepsis and late-onset sepsis were defined by positive blood or cerebral spinal fluid cultures and diagnosed at ≤3 days or >3 days of postnatal age, respectively. Predicted risk of death or NDI at enrollment was estimated with the externally developed[1] model described in the primary trial report.[4] The model-based estimates, used for stratified randomization in the trial, accounted for gestational age at birth, birth weight, vasopressor or inotrope use, high-frequency ventilation, fraction of inspired oxygen (FiO_2), blood pH, and preoperative diagnosis (NEC or SIP).

Table I. Comparison of trial enrollment periods

Characteristics	NEST trial initiation to February 14, 2013 n = 156	NEST trial February 15, 2013 to completion n = 152	Complete NEST trial n = 308
At birth			
Maternal age ≤19 y	17 (11%)	16 (11%)	33 (11%)
Private medical insurance	42 (27%)	52 (34%)	94 (31%)
Multiple birth	44 (28%)	35 (23%)	79 (26%)
Maternal race			
White	68 (45%)	87 (59%)	155 (52%)
Black	78 (52%)	51 (34%)	129 (43%)
Other	4 (3%)	10 (7%)	14 (5%)
Maternal Hispanic ethnicity	31 (21%)	40 (27%)	71 (24%)
Gestational age at birth			
≤ 23 wk	26 (17%)	39 (26%)	65 (21%)
24-26 wk	93 (60%)	95 (63%)	188 (61%)
27-29 wk	33 (21%)	16 (11%)	49 (16%)
30+ wk	4 (3%)	2 (1%)	6 (2%)
Birthweight			
< 500 g	7 (4%)	3 (2%)	10 (3%)
500-750 g	83 (53%)	93 (61%)	176 (57%)
≥ 750 g	66 (42%)	56 (37%)	122 (40%)
Small for gestational age	22 (14%)	9 (6%)	31 (10%)
Female	67 (43%)	62 (41%)	129 (42%)
Inborn	85 (54%)	87 (57%)	172 (56%)
Antenatal corticosteroids	129 (83%)	125 (83%)	254 (83%)
Cesarean section	105 (68%)	96 (64%)	201 (66%)
5-min Apgar score ≤3	30 (19%)	34 (22%)	64 (21%)
Pre-enrollment			
Postnatal steroids	27 (17%)	47 (69%)	74 (24%)
Indomethacin	88 (58%)	68 (46%)	156 (52%)
Early-onset sepsis	2 (1%)	5 (4%)	7 (3%)
Late-onset sepsis	43 (28%)	41 (27%)	84 (27%)
IVH grade 3 or 4	13 (9%)	27 (18%)	40 (13%)
Preoperative diagnosis			
NEC	51 (33%)	44 (29%)	95 (31%)
SIP	105 (67%)	108 (71%)	213 (69%)
Interventions			
Surgery initially received			
Lap	74 (47%)	67 (44%)	141 (46%)
Drain	81 (52%)	85 (56%)	166 (54%)
Outcomes			
Death before discharge	49 (31%)	34 (22%)	83 (27%)
Death prior to follow-up	53 (34%)	36 (24%)	89 (29%)
Death or NDI at 2 y	106 (71%)	99 (68%)	205 (69%)
Survival with NDI	53 (55%)	63 (58%)	116 (56%)
Infants with primary outcome available	150 (96%)	145 (95%)	295 (96%)

IVH, intraventricular hemorrhage; *NDI*, neurodevelopmental impairment; *NEC*, necrotizing enterocolitis; *SIP*, spontaneous intestinal perforation.
The first period includes infants with trial enrollment through February 14, 2013, the day that the observational data collection for eligible nonrandomized infants was closed. The second period includes infants with trial enrollment following closure of observational data collection for eligible nonrandomized infants.

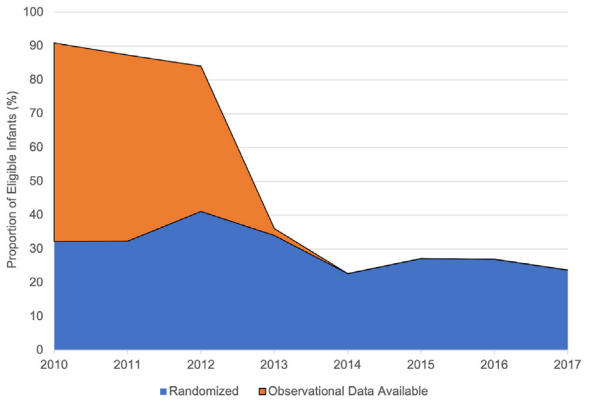

Figure 2. Enrollment in clinical trial and detailed observational dataset by year. The proportions of eligible infants randomized in NEST and with observational data collected are shown by year. Observational data for non-randomized eligible infants was stopped on February 14, 2013. *NEST*, Necrotizing Enterocolitis Surgery Trial.

Statistical Analysis

We compared characteristics, interventions, and the primary outcome of death or NDI at 18-22 months of corrected age for infants in the trial and the target population. Although all inferences about trial generalizability were made based on the target population, we separately described eligible but nonrandomized infants to highlight their differences from those randomized. Additionally, we compared characteristics of infants by reason for nonconsent to randomization. Reasons were coded as: at least one of the infant's physicians (neonatologist or surgeon) declined randomization; a parent declined randomization; or consent was not requested by the research team.

We estimated the effects of initial laparotomy vs peritoneal drain in the target population using weighting methods for generalizability analysis.[9,13,14] This approach assumes that randomized infants and eligible nonrandomized infants in the early part of the study would have similar outcomes with the assigned treatment given measured covariates (ie, "exchangeability") and that trial participation did not affect the outcomes except through the assigned treatment.[15] As in the primary trial publication, adjusted relative risks for the NEST trial were calculated using generalized estimating equations with a modified Poisson working model and log link and accounted for clustering by center.[4] We derived inverse probability weighting estimators for the probability of being randomized in the trial, the probability of being randomized during the period used to define the target population (trial initiation through February 2013), and the probability of being assigned laparotomy or drain, taking into account: center, inborn status, gestational age at birth, birthweight, sex, antenatal steroids, preenrollment grade 3-4 intraventricular hemorrhage, preoperative surgical diagnosis, and, around the time of diagnosis, use of a vasopressor/inotrope, use of high-frequency ventilation, presence of portal venous gas or pneumatosis, clinical diagnosis of abdominal compartment syndrome, FiO_2, blood pH, and postnatal age. Using these models to reweight (standardize) the trial population, we estimated marginal relative

Table II. Characteristics of randomized infants and the target population

Characteristics	NEST trial n = *308*	Eligible nonrandomized n = *226*	Target population n = *382*
At birth			
Maternal age ≤19 y	33 (11%)	30 (13%)	47 (12%)
Private medical insurance	94 (31%)	83 (37%)	125 (33%)
Maternal race			
White	155 (52%)	134 (60%)	202 (54%)
Black	129 (43%)	73 (33%)	151 (40%)
Maternal Hispanic ethnicity	71 (24%)	40 (19%)	71 (20%)
Gestational age at birth			
≤23 wk	65 (21%)	36 (16%)	62 (16%)
24-26 wk	188 (61%)	151 (67%)	244 (64%)
27-29 wk	49 (16%)	37 (16%)	70 (18%)
30+ wk	6 (2%)	2 (1%)	6 (2%)
Birthweight			
<500 g	10 (3%)	22 (10%)	29 (8%)
500-750 g	176 (57%)	118 (52%)	201 (53%)
≥750 g	122 (40%)	86 (38%)	152 (40%)
Small for gestational age	31 (10%)	38 (17%)	60 (16%)
Female	129 (42%)	104 (46%)	171 (45%)
Multiple birth	79 (26%)	71 (31%)	115 (30%)
Inborn	172 (56%)	144 (64%)	229 (60%)
Antenatal corticosteroids	254 (83%)	196 (87%)	325 (85%)
Cesarean section	201 (66%)	166 (74%)	271 (72%)
5-min Apgar ≤3	64 (21%)	31 (14%)	61 (16%)
Pre-enrollment			
Postnatal steroids	74 (24%)	71 (31%)	98 (26%)
Indomethacin	156 (52%)	124 (57%)	212 (58%)
Early-onset sepsis	7 (3%)	3 (1%)	5 (1%)
Late-onset sepsis	84 (27%)	73 (32%)	116 (30%)
IVH grade 3 or 4	40 (13%)	42 (19%)	55 (15%)
At enrollment			
Preoperative diagnosis			
NEC	95 (31%)	127/225 (56%)	178/381 (47%)
SIP	213 (69%)	98/225 (44%)	203/381 (53%)
Abdominal compartment syndrome	7 (2%)	15 (7%)	18 (5%)
Portal venous gas	23 (7%)	44 (19%)	53 (14%)
Pneumatosis	45 (15%)	71 (31%)	94 (25%)
Age at surgery			
<7 d	116 (38%)	43 (19%)	109 (29%)
7-13 d	110 (36%)	72 (33%)	117 (31%)
14-20 d	30 (10%)	29 (13%)	43 (11%)
21+ d	51 (17%)	77 (35%)	107 (29%)
Any vasopressor/inotrope*	123 (40%)	115 (51%)	175 (46%)
FiO_2 (median, IQR)	0.37 (0.25, 0.60)	0.45 (0.30, 0.94)	0.40 (0.28, 0.71)
pH (median, IQR)	7.25 (7.16, 7.32)	7.22 (7.14, 7.30)	7.24 (7.15, 7.32)
High-frequency ventilation*	89 (29%)	133 (50%)	155 (41%)
Initial intervention received			
Laparotomy	141 (46%)	95 (42%)	169 (44%)
Drain	166 (54%)	125 (55%)	207 (54%)
None	1 (<1%)	6 (2%)	6 (2%)
Outcomes			
Death before discharge	83/308 (27%)	109/226 (48%)	158/382 (41%)
Death before follow-up	89/299 (30%)	112/226 (50%)	165/369 (45%)
Death or NDI at follow-up	205/295 (69%)	158/215 (73%)	264/365 (72%)

IVH, intraventricular hemorrhage; *NDI*, neurodevelopmental impairment; *NEC*, necrotizing enterocolitis; *FiO_2*, fraction of inspired oxygen; *SIP*, spontaneous intestinal perforation.
*Variable definitions differ slightly from **Table I** of the primary trial report[4] and include any use between diagnosis and surgical intervention.

risks of the primary outcome for initial laparotomy compared with peritoneal drain in the target population. Following the primary trial report,[4] which showed a statistically and clinically significant interaction between preoperative diagnosis and treatment effect, we estimated treatment effects stratified by preoperative diagnosis of NEC and SIP.

The primary analysis was conducted to estimate the effect of treatment assignment (ie, intention-to-treat).[4,16] In a sensitivity analysis, using the same methods, we estimated the effect of treatment receipt (ie, per-protocol effect), as some infants in the trial did not receive the assigned intervention.[17] Statistical analyses were performed using SAS, version 9.4, and R, version 4.1.3.

Results

The NEST trial included data for 308 randomized infants.[4] During the first half of trial enrollment, detailed data were collected for 382 eligible infants (156 randomized and 226 nonrandomized — 86% of the 442 eligible infants during this

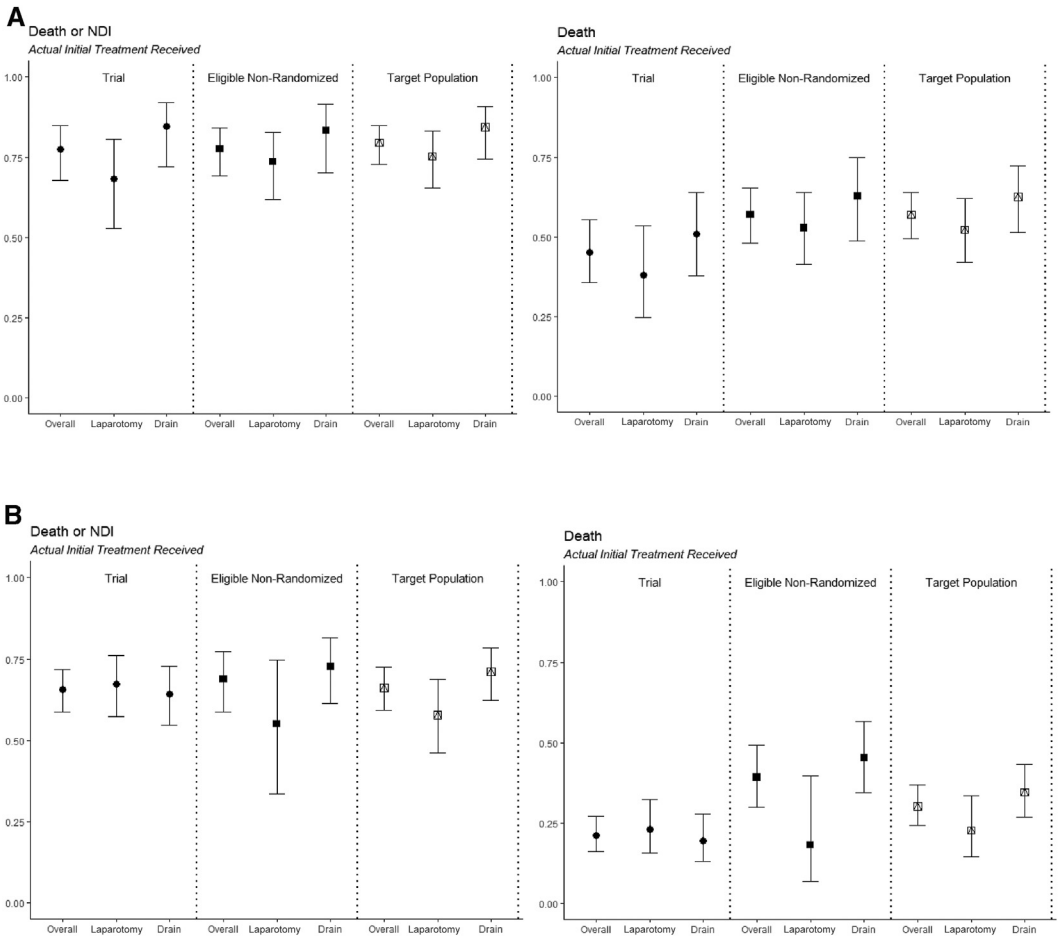

Figure 3. Unadjusted outcomes in trial infants, eligible non-randomized infants, and target population. Panels **A** and **B,** show the proportions of infants with death or neurodevelopmental impairment (NDI) and death in 3 groups of patients (the clinical trial; eligible nonrandomized patients; and the target population) based on preoperative diagnosis and treatment received. Outcomes for each group are shown with 95% CI.

period), who comprised the target population (**Figure 1**). Details on infants randomized to the study during the period of observational data collection for nonrandomized infants compared with those randomized in later years are shown in **Table I**. The rate of randomization of eligible infants did not change substantially throughout the study, including after the closure of the observational data collection for nonrandomized infants (**Figure 2**).

Randomized infants, compared with the target population, were more likely to have NEC (31% vs 47%) and die before discharge (27% vs 41%), as shown in **Table II**. Death or NDI were similar between randomized infants and the target population (69% vs 72%). Outcomes stratified by preoperative diagnosis and intervention are shown in **Figure 3**.

Table III shows infant characteristics by reason for nonrandomization. A physician declined consent for 35% of eligible nonrandomized infants (80 of 226); a parent declined for 36% (82 infants); and 21% (47 infants) were not approached by the research team. In addition, 6% (14 of 226 infants) had other reasons for not obtaining consent, including 5 who died after identification but before consent could be discussed. In 1% (3 of 226 infants), consent for randomization was initially granted by the parents but the infant was not randomized in the trial because the parent or surgeon withdrew prior to intervention. Infants whose physicians declined enrollment and who were not approached by the research team had greater severity of illness based on higher rates of death at follow-up and greater respiratory and hemodynamic support indices. Physicians were more likely to decline randomization for infants with preoperative diagnosis of NEC than with SIP (61% vs 39%); parents were more likely to decline randomization for infants with preoperative diagnosis of SIP than with NEC (57% vs 43%).

In generalizability analyses based on the intention-to-treat principle (based on assigned treatment, as used in the primary trial report), the estimated effect of laparotomy vs peritoneal drain in the target population was similar to that in the trial (**Table IV**). A total of 7 infants did not receive the assigned intervention: 5 trial infants randomized to initial laparotomy received initial drain

Table III. Characteristics by reasons for non-randomization in the target population

Characteristics	Randomized in NEST n = *308*	Physician declined n = *80*	Parent declined n = *82*	Not approached n = *47*
Maternal age ≤19 y	33 (11%)	8 (10%)	8 (10%)	7 (15%)
Private medical insurance	94 (31%)	28 (35%)	41 (51%)	13 (28%)
Maternal race				
White	155 (52%)	51 (65%)	53 (65%)	23 (49%)
Black	129 (43%)	23 (29%)	18 (22%)	23 (49%)
Maternal Hispanic ethnicity	71 (24%)	16 (21%)	14 (18%)	5 (11%)
Gestational age (mean, SD)	24.9 (1.8)	24.8 (1.4)	25.0 (1.8)	24.9 (1.5)
Birthweight				
<500 g	10 (3%)	6 (8%)	10 (12%)	5 (11%)
500-750 g	176 (57%)	48 (60%)	39 (48%)	24 (51%)
≥750 g	122 (40%)	26 (33%)	33 (40%)	18 (38%)
Inborn	172 (56%)	49 (61%)	52 (63%)	34 (72%)
5-min Apgar ≤ 3	64 (21%)	8 (10%)	11 (13%)	9 (19%)
Preoperative diagnosis				
NEC	95 (31%)	49 (61%)	35 (43%)	29 (63%)
SIP	213 (69%)	31 (39%)	47 (57%)	17 (37%)
Any vasopressor/inotrope*	123 (40%)	41 (51%)	39 (48%)	24 (51%)
High-frequency ventilation*	89 (29%)	47 (59%)	33 (40%)	27 (57%)
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)
Mean predicted probability of death or NDI determined at enrollment	67%	83%	73%	82%
Death at follow-up	89/299 (30%)	45/79 (57%)	29/77 (38%)	30/45 (67%)
Death or NDI at follow-up	205/295 (69%)	59/78 (76%)	49/76 (64%)	37/45 (82%)

NDI, neurodevelopmental impairment; *NEC*, necrotizing enterocolitis; *SIP*, spontaneous intestinal perforation.
An additional 14 of 226 eligible nonrandomized infants had other reasons for not obtaining consent, including 5 who died after identification but before consent could be discussed. Three infants had consent initially granted but subsequently withdrawn by parent or physician prior to randomization.
*Variable definitions differ slightly from **Table I** of the primary trial report[4] and include any use between diagnosis and surgical intervention.
†Oxygenation index was calculated as [FiO_2 x mean airway pressure]/P_aO_2.

and 1 infant received no intervention (died following consent and randomization but before intervention); 1 infant randomized to initial drain received initial laparotomy. In the sensitivity analysis, generalizability analyses for the effect of receiving treatment (per-protocol analysis) produced estimates similar to those for the effect of treatment assignment.

Discussion

Our study found important differences between infants randomized in NEST and the target population, including in preoperative diagnosis and the risk of death but not death or NDI. Randomized infants, on average, had lower severity of illness and were less likely to die before follow-up than infants in the target population. Nevertheless, generalizability analyses suggest that a trial randomizing infants representative of the target population would not be expected to have substantially different results.

Our findings highlight the difficulty of randomizing extremely preterm infants in a clinical trial of an emergency intervention, which has been detailed by others.[18-21] The proportion of eligible infants randomized in NEST (31%) was similar to recent important trials of emergency interventions in extremely preterm infants. The landmark Surfactant, Positive Pressure, and Oxygenation Randomized Trials

Table IV. Effect of initial laparotomy vs peritoneal drain on death or NDI in the trial and target population

Intention to treat	NEST trial			Target population		
aRR (95% CI)	Overall	NEC	SIP	Overall	NEC	SIP
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	1.00 (0.69-1.45)	0.77 (0.52-1.13)	1.28 (0.79-2.06)	0.91 (0.69-1.21)	0.83 (0.63-1.11)	1.09 (0.70-1.71)
Survival with 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)
Per protocol*	**NEST trial**			**Target population**		
aRR (95% CI)	Overall	NEC	SIP	Overall	NEC	SIP
Death or NDI	0.97 (0.84-1.12)	0.79 (0.62-1.01)	1.09 (0.90-1.32)	0.90 (0.78-1.05)	0.85 (0.71-1.03)	0.96 (0.74-1.26)
Death	1.04 (0.70-1.56)	0.79 (0.53-1.18)	1.37 (0.80-2.36)	0.90 (0.68-1.19)	0.84 (0.63-1.12)	1.02 (0.67-1.56)
Survival with NDI	0.92 (0.62-1.36)	0.81 (0.39-1.66)	0.96 (0.67-1.38)	0.89 (0.54-1.46)	0.85 (0.39-1.85)	0.91 (0.57-1.46)

NDI, neurodevelopmental impairment; *NEC*, necrotizing enterocolitis; *NEST*, Necrotizing Enterocolitis Surgery Trial; *SIP*, spontaneous intestinal perforation.
Adjusted relative risks (aRR) and 95% CI are for the comparison of initial laparotomy vs peritoneal drain. Results weighted to the target population were estimated using the probability of being enrolled in the trial, the probability of being enrolled during the period used to define the target population, and the probability of being assigned laparotomy or drain, taking into account: center, inborn status, gestational age at birth, birthweight, sex, antenatal steroids, pre-enrollment grade 3-4 intraventricular hemorrhage, preoperative surgical diagnosis, and, around the time of diagnosis, vasopressor/inotrope receipt, high-frequency ventilation, presence of portal venous gas or pneumatosis, abdominal compartment syndrome, FiO_2, pH, and postnatal age. aRRs for the NEST Trial (intention to treat) were published in the primary trial report.[4] aRRs for the target population represent the treatment effect had the target population been enrolled in the trial.
*In the analysis by received treatment (per protocol), 1 infant was randomized but no intervention was performed; this infant was excluded from the analysis.

randomized 30% (1316 of 4369) of eligible infants.[7] In the Australian Placental Transfusion Study, in a subset of participating hospitals in New Zealand and Australia where comprehensive data on eligible infants were available, 18% (535 of 3024) of the target population was randomized.[8] A recent study of pediatric clinical trials showed that 60% (418 of 696) of trials published in 2009, 2010, or 2016 did not clearly report consent rates.[22] Given inadequate reporting of consent rates and lack of information on the characteristics of eligible nonrandomized infants, it is unknown how often neonatal trials are affected by questions of generalizability that may impact application to clinical practice.

In the eligible population for which we had data, 127 of 382 (33%) eligible patients were not given the opportunity to participate in the trial due to the physician or research team not approaching parents for consent to randomize. More efficient and effective strategies for supporting research participation are needed to ensure that diverse and representative populations participate in clinical trials.[23,24] Such strategies could include promotion of clinician understanding and engagement in research protocols[25]; processes to minimize delays in clinical intervention related to study participation[26]; and modifications to the consent process to accommodate the needs of parents in high-stress situations.[27,28] Notably, it is unknown whether parents not approached learned their children were eligible for a clinical trial or how they perceived (or would have perceived) not having the opportunity to participate. We are unaware of research on this aspect of conducting neonatal RCTs.

To our knowledge, this is the first use of generalizability methods in the neonatal clinical trial literature. Similar methods have been used in other areas of medicine[29,30] and provide the opportunity to estimate treatment effects for eligible patients not enrolled in a clinical trial in order to support the interpretation and implementation of trial findings. The results derived from generalizability methods rely on specific causal and modeling assumptions and should not be considered equivalent to conducting the actual clinical trial in other infants.[31] However, the selection of patients into a clinical trial through nonrandom processes (eg, approaching for consent) substantially reduces the likelihood that trial participants represent an intended target population.[32] Generalizability methods make formal and explicit the assumptions made by clinicians and others who apply clinical trial findings to patient care.[33]

Limitations of this study include that data were not available for the complete cohort of eligible infants and that observational data collection for nonrandomized infants was stopped midway through the trial. Notably, the proportion of eligible infants consented for randomization did not change substantially over time. We attempted to account for any potential differences in patient characteristics of infants between the first and second half of the trial by using inverse probability weighting estimators for the probability of the infant being randomized during the first half of the trial.

Strengths of this study included the detailed available data, including preoperative diagnosis and extensive clinical data collected at the time of diagnosis and eligibility, to permit comparison of eligible non-randomized and randomized infants. NEST is the largest clinical trial of interventions for NEC or SIP in extremely preterm infants and required nearly a decade to complete; another clinical trial on this question would be costly and difficult to conduct. Using available patient data, our generalizability analyses add value and context to aid clinicians in implementing the NEST findings.

In conclusion, despite differences between randomized infants and the target population, the estimated treatment effect in the target population was similar to that in the trial, supporting the generalizability of the NEST trial results. ■

Declaration of Competing Interest

The authors declare no conflicts of interests.

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Data Statement

Data sharing statement available at www.jpeds.com.

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