



# International network for evaluating outcomes of neonates: outputs and future directions

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**Abstract:** Ten neonatal networks from 11 countries—Australia, New Zealand, Canada, Finland, Israel, Japan, Spain, Sweden, Switzerland, the Tuscany region of Italy, and the UK—came together in 2012 to form the International Network for Evaluating Outcomes of Neonates (iNeo): an international collaboration of population-representative, national neonatal datasets. The result has been a powerful platform for epidemiological, outcomes-based, and applied health services and policy research. The network has successfully collaborated to evaluate variations in health service organization, practices, and outcomes, with an aim to harmonize processes and identify areas for quality improvement in the various countries. We have identified marked variations in outcomes such as mortality, severe neurological injury, and treated retinopathy of prematurity; and highlighted the important need for the neonatal community to harmonize criteria for diagnosing bronchopulmonary dysplasia. Despite marked changes in the respiratory management of extremely preterm neonates with the aim to avoid mechanical ventilation, judicious use of oxygen, and less invasive administration of surfactant, rates of bronchopulmonary dysplasia have continued to rise in most countries. This may be due to marked discrepancies in the diagnostic criteria for bronchopulmonary dysplasia in extremely preterm neonates. We were able to conduct a detailed survey of more than 300 neonatal units worldwide and link the responses with actual patient data to generate hypotheses to evaluate

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in future studies. Specific areas of investigation have included preventing necrotizing enterocolitis, managing patent ductus arteriosus, and managing neonates with critical events such as severe intraventricular hemorrhage. In addition, we studied the physical design of neonatal units from family-centered care delivery point of view and multidisciplinary team inclusion in care of neonates. In this review, we summarize our opportunities for improvement and future plans for the collaboration. We also highlight the challenges we face as an international collaboration, such as sustainability and funding.

**Keywords:** Outcomes; extremely preterm infants; benchmarking; variations

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## Background information

Ten neonatal networks from 11 countries—Australia, New Zealand, Canada, Finland, Israel, Japan, Spain, Sweden, Switzerland, the Tuscany region of Italy, and the UK—came together in 2012 to form the International Network for Evaluating Outcomes of Neonates (iNeo): an international collaboration of population-representative, national neonatal datasets. The result is a powerful platform for epidemiological, outcomes-based, and applied health services and policy research. Our underlying goal in building this collaboration was to improve patient-oriented outcomes for neonates born very preterm (VPT, born before 32 weeks' gestational age) and extremely preterm (EPT, born before 28 weeks' gestation) around the world.

As outlined by others in this article series, most of the networks involved in iNeo have well-established platforms for their own internal evaluation, benchmarking, and quality improvement activities. They also participate in many benchmarking activities both nationally and internationally. Since inception, iNeo has produced several high-quality outputs in the domains of outcomes evaluation, evaluation of care and practice similarities and differences between the networks, epidemiological studies, and health services evaluation. In this article we will review the salient features of these outputs and identify opportunities for the next phase in this influential international collaboration.

## Overarching network aims

As detailed in the following sections, the iNeo collaboration has made steady progress towards achieving many of its initial aims (1): these aims were to compare neonatal outcomes and health service organization for VPT neonates

at the national level; to identify differences in site-level physical, human, and environmental characteristics, as well as care practices, that underlie the outcome variations; to identify clinical and organizational practice improvements relevant to each network; to implement and continually evaluate the impact of data-informed and evidence-linked clinical and organizational practice changes in neonatal intensive care units (NICUs) within participating networks; and to train and mentor junior researchers in the conduct of neonatal-perinatal health services research.

## Network structure and organization

The iNeo collaboration was established in 2013 with funds from the Canadian Institutes of Health Research's Institute of Human Development, Child and Youth Health (2). Its purpose is to collect phenotypic information on newborns admitted to neonatal units in the participating countries, along with some maternal details, at the time of birth. As this information is already collected in local datasets, the purpose of iNeo is to first harmonize and then collectively assemble a larger pool of individual patient data from the original, population-based networks or datasets. Harmonization efforts like these have even stimulated interest and opportunities in country like China, which recently reported their first cohort data from 68 neonatal units (3-5). The underlying principles of the iNeo collaboration were to study variations in the outcomes, characteristics, practices, and cultures of the member sites; evaluate the impact of such variations on neonatal outcomes; and identify and learn from different models of health service delivery (incorporating medical and non-medical variations). The results have been published and advertised by respective network to their constituents to

implement data-linked and evidence-based practice changes where they are applicable, feasible, and sensible for their own environments.

The organization, their structure, underlying population-bases, and linkages with extended datasets of the individual networks have been well characterized in a review article demonstrating the evolution of iNeo (1).

### Current collaboration

The following neonatal networks are currently participating in the iNeo collaboration: Australian and New Zealand Neonatal Network (ANZNN); Canadian Neonatal Network (CNN); Finnish Medical Birth Register (FinMBR); Israel Neonatal Network (INN); Neonatal Research Network Japan (NRNJ); Spanish Neonatal Network (SEN1500); Swedish Neonatal Quality Register (SNQ); Swiss Neonatal Network (SNN); Tuscany region of Italy (TuscanNN); and UK Neonatal Collaborative (UKNC).

### Dataset development and modification

After a detailed review of all data items collected by the participating networks, a minimum dataset was conceived in July, 2012. Variations in definitions were harmonized for inclusion in the minimum database and were mapped to the International Classification of Diseases and Related Health Problems (ICD-10) (6) and Systematized Nomenclature of Medicine (SNOMED) (7) dictionaries. The minimal dataset has been modified with the addition of some variables. The process of data collection and transfer has been streamlined and described previously (1,8). The system is organized in such a way that data are received at coordinating center from the respective countries as and when they become available. The numbers of neonates currently available from each country and certain baseline characteristics of each organization are reported in *Table 1*. Ethics approval is from local network regulatory authorities and the Research Ethics Board at Mount Sinai Hospital, Toronto, which is the coordinating center for the iNeo collaboration.

### Network outputs/achievements

The main purpose of this review is to present a succinct report of iNeo outputs and identify opportunities for the next phase of this collaboration. Key iNeo outputs are as follows:

### *Overarching project documents with report of health services organization*

After the iNeo collaboration was formed, its first act was to develop and publish a protocol. We developed a detailed plan following our mission and aims, which was first published along with the guidance document for data transfer and the data elements (8). We developed rules of engagement and conduct for different projects. There were several concerns in the initial stage of the project with regards to differences in health care services provision and health care services organization related to pregnancy and childbirth at national and even local level. The first order of the collaboration was to conduct a survey of the network directors or contact persons and collect information from the existing national documents or databases as to how neonatal-perinatal services for EPT neonates were organized within the individual countries (9). In that project, we identified that all participating countries have nationally funded maternal neonatal health care services and more than 90% of women receive prenatal care. Variations are identified and reported in *Table 1*; however, several similarities were also identified. In 2017, after an annual meeting of the collaboration directors, it was decided that the database should be expanded to collect additional details. These included data on daily processes of care and the interventions EPT neonates receive in NICU. The database was subsequently complemented with several additional variables, which were also published to ensure transparency (1).

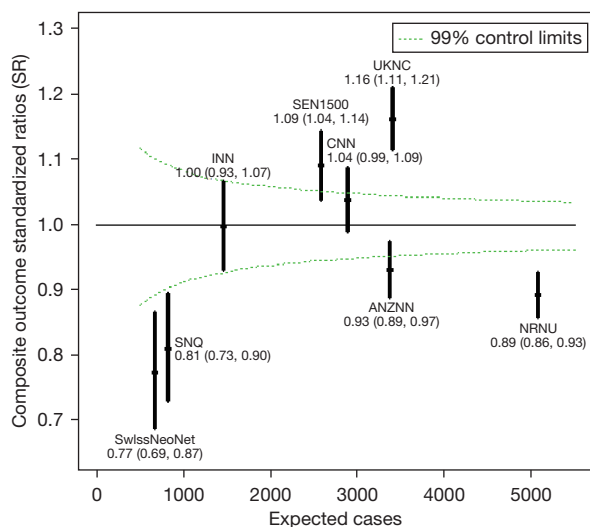
### *Evaluating outcomes*

One of the major purposes of our international collaboration was to evaluate the reasons for any variations in neonatal outcomes identified. In one of our initial papers (10), we analyzed common neonatal outcomes of preterm neonates born at 24 weeks to 32 weeks' gestation and admitted to neonatal units between the years 2007 and 2010. In that study of >58,000 neonates, we identified that the composite outcome of mortality, bronchopulmonary dysplasia (BPD: defined as need for oxygen support at 36 weeks' post-menstrual age), treated retinopathy of prematurity, and severe neurological injury varied from 26% to 42% among countries. Overall mortality in the cohort was 10%; however, it varied from 5% in Japan to 17% in Spain. The standardized ratio for the composite outcome are shown in *Figure 1*. We speculated that the differences could be due to

**Table 1** Characteristics of networks participating in the international network for evaluating outcomes of neonates

Items	ANZNN	CNN	FinMBR	INN	NRNJ	SEN1500	SNQ	SNN	TuscanNN	UKNC
Number of live births from national data (year of report)	Australia: 305,832 (2019); New Zealand: 57,753 (2020)	372,038 (2019)	46,463 (2020)	182,016 (2019)	840,832 (2020)	339,206 (2020)	113,017 (2020)	85,914 (2020)	23,462 (2019)	687,179 (2019)
Number of neonatal units contributing data to the network in 2017	29	30	31	28	219	75	38	10	20	129
Network contribution	National	National	National	National	National-partial	National-partial	National	National	Regional	National-partial
National recommendations for transfer of pregnant women	Australia: <33 weeks; New Zealand: <34 weeks	<32 weeks	<30-32 weeks	No	No	<32 weeks	<26 weeks	<32 weeks	<32 weeks	<28 weeks
Designated neonatal transport teams	Yes	Yes	No	No	No	Yes, in some regions	Yes	Yes	Yes	Yes
Average total number of neonates for whom data are contributed per year	3,896	3,658	479	1,428	4,813	2,838	1,249	871	339	9,598
Average total number of neonates per year in data who are born at 24–28 weeks' gestation	1,486	1,513	171	582	1,990	1,122	384	307	102	2,951
GA in weeks, mean (SD)	26.4 (1.4)	26.3 (1.4)	26.4 (1.4)	26.4 (1.4)	26.3 (1.4)	26.4 (1.3)	26.4 (1.4)	26.5 (1.3)	26.3 (1.4)	26.4 (1.4)
BW in grams, mean (SD)	940 (250.0)	940 (250.0)	933 (254.0)	906 (221.0)	862 (231.0)	913 (224.0)	930 (252.0)	896 (235.0)	884 (247.0)	921 (229.0)
Male sex, No. (%)	8,872 (54.3)	9,893 (54.6)	1,097 (53.5)	3,842 (55.0)	11,780 (53.8)	6,643 (53.8)	2,325 (55.1)	1,813 (53.7)	493 (53.7)	15,563 (54.0)

Last 5 rows present data for 2007–2017 for ANZNN, NRNJ, SEN1500, SNQ, and SNN; for 2007–2018 for CNN, FinMBR, and INN; for 2009–2017 for TuscanNN; and for 2008–2017 for UKNC. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; TuscanNN, Tuscany Neonatal Network; UKNC, UK Neonatal Collaborative; BW, birth weight; GA, gestational age; SD, standard deviation.



**Figure 1** Standardized ratios comparing the composite outcome of each network to all other networks combined. Vertical bars are the estimated 99% CIs of the SR. Dotted curves represent the 99% control limits expected under the null hypothesis of similar outcome rates (SR = 1). ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; INN, Israel Neonatal Network; NRNU, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; UKNC, United Kingdom Neonatal Collaborative. Adapted with permission from Shah *et al.* *J Pediatr* 2016;177:144-52.

variation in population coverage, data collection, and/or case definition; and we called for further harmonization. Once further data were available, we aimed to identify outcome trends in participating countries over the time (11). Due to significant variations in management of neonates of 22 and 23 weeks' gestational age, the collaboration has focused on neonates of >24 weeks' gestation as these neonates were universally provided neonatal care in all countries during study period. Lui *et al.* (11) evaluated >154,000 preterm neonates admitted to 529 neonatal units across iNeo countries between 2007 and 2015 (Table 2). We identified increases and decreases over the study years when the composite outcome included or excluded BPD. We also observed that this trend was consistently reduced in the later years of the study in Canada, which coincided with national quality improvement efforts. In most countries, mortality for preterm neonates was reduced over years; however, Helenius *et al.* undertook a project to understand the distribution of mortality rates in relation to gestational age (12). We studied

neonates born between 24 weeks' and 29 weeks' gestation and admitted between 2007 and 2013. The survival rate increased as gestational age increased; however, differences between the countries remained relatively similar at all gestational ages (Figure 2). We identified that standardized ratios for survival were highest for Japan and lowest for Spain, and the overall survival ranged from 78% to 93% between networks. This finding has prompted investigations at local unit and within-country levels. Moreover, prompted by the identification of between-network variation in the outcome of bronchopulmonary dysplasia, Hines *et al.* (13) undertook a systematic review of different definitions for BPD used by various investigators. We reviewed publications between 2010 and 2015 that reported on BPD as an outcome and compared the different definitions used. We noted that rates of BPD ranged from 6% to 57%, and the rate reported was entirely dependent on the definition chosen for the study. We also identified that BPD had a moderate predictive value with regards to long term pulmonary and neurosensory outcomes due to variations in the definitions. A call was made to develop a comprehensive and evidence-based definition of BPD for the purposes of benchmarking.

Another outcome with significant variability between countries was retinopathy of prematurity (ROP). Darlow *et al.* (14) studied variations in ROP rates in neonates born at 24 weeks to 28 weeks' gestation. In a study of >48,000 infants, rates of any retinopathy varied from 25% to 91% among countries in iNeo, and rates of treatment for ROP varied from 4% to 30% (Table 3).

Another commonly reported outcome of EPT neonates is necrotizing enterocolitis. Adams *et al.* (15) used a survey-linked cohort design to study the rates of surgical necrotizing enterocolitis and practices for its prevention in 9,792 infants admitted to 8 neonatal networks (Figure 3). The standardized ratio for surgical necrotizing enterocolitis was lower for Australia-New Zealand and higher for Spain compared to overall network results. In the survey of the units participating in this study, it was noted that the provision of probiotics varied from 0% to 100% among participating units, whereas feeding initiation and advancement rates were similar.

Variations in population characteristics were identified as one possible explanation for outcome differences between countries. Maternal diabetes is associated with a 2- to 3-fold increase in the rate of very preterm birth, so we explored its relationship with the outcomes of neonates born between 24 weeks' and 31 weeks' gestation in iNeo countries. Persson *et al.* (16) compared the outcomes of 3,280 neonates born to

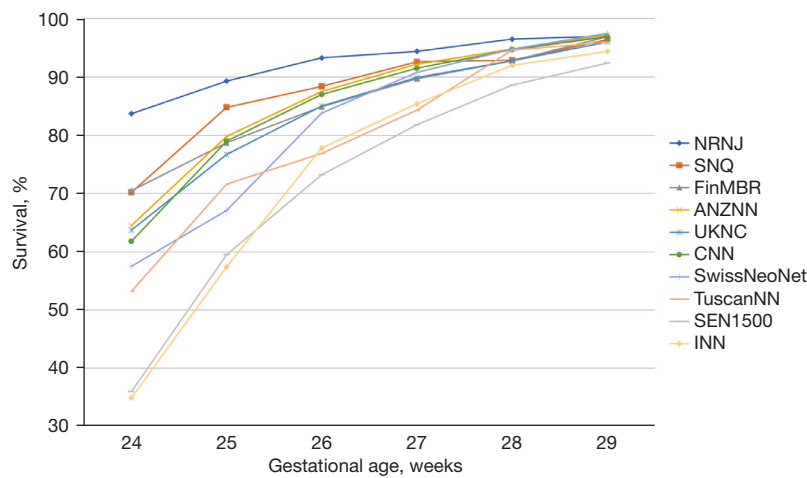
**Table 2** Rates (%) of composite adverse outcome (including or excluding BPD) over study period within each country/region

Network	Outcome	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	P value (Trend)
ANZNN	Including BPD	54.6	50.9	52.9	56.6	57.8	57.8	61.5	63.2	63.9	64.8	<0.01*
	Excluding BPD	28.9	26.6	26.2	26.6	25.7	23.4	24.8	27.2	25.2	24.5	0.02**
CNN	Including BPD	69.5	66.1	66.1	59.7	60.6	58.1	55.9	56.7	54.7	53.6	<0.01**
	Excluding BPD	40.3	40.7	39.7	28.8	29.5	28.8	28.7	29	26.8	29.7	<0.01**
FinMBR	Including BPD	57.9	57.2	57.0	44.7	53.5	44.2	46.9	44.9	53.2	47.1	0.01**
	Excluding BPD	32.8	31.0	37.8	26.7	29.2	22.4	26.1	28.0	24.3	23.3	<0.01**
INN	Including BPD	56.8	55.0	57.0	56.2	53.7	58.3	55.1	51.2	53.4	56.4	0.26
	Excluding BPD	46.7	44.2	46.9	46.5	41.0	47.8	43.3	41.0	38.4	40.3	<0.01**
NRNJ	Including BPD	55.9	52.9	52.9	58.1	57.5	54.6	57.5	61.1	60.6	59.7	<0.01*
	Excluding BPD	43.0	38.1	36.3	37.9	35.4	34.7	32.7	33.5	35.1	35.5	<0.01**
SEN1500	Including BPD	57.5	54.8	59.1	60.4	58.7	58	58.6	62.2	60.2	53.5	0.63
	Excluding BPD	47.3	44.3	47.2	48.6	45.9	45.6	45.9	50.8	50.3	44.0	0.44
SNQ	Including BPD	51.8	51.0	50.3	56.8	53.7	59.5	52.8	59.8	63.1	56.1	<0.01*
	Excluding BPD	31.5	30.3	32.0	37.3	32.1	31.0	29.7	30.7	34.5	31.3	0.93
SwissNeoNet	Including BPD	37.3	38.6	41.3	44.2	34.9	40.7	42.1	43.5	42.2	38.3	0.45
	Excluding BPD	28.2	25.6	27.1	29.4	23.4	21.3	24.4	24.4	24.8	21.7	0.04**
TuscanNN	Including BPD	NA	NA	60.2	58.3	58.3	61.5	59.2	55.8	40.2	51.7	0.01**
	Excluding BPD	NA	NA	50.9	50.5	47.2	47.9	48.5	50.0	36.3	46.1	0.12
UKNC	Including BPD	NA	59.7	59.8	63.1	64.3	67.6	68.1	68.9	66.3	67.4	<0.01*
	Excluding BPD	NA	31.0	29.1	31.1	30.7	32.2	31.9	32.2	30.9	31.1	0.21

\*, P value for trend increasing. \*\*, P value for trend decreasing. ANZNN, Australia and New Zealand Neonatal Network; BPD, bronchopulmonary dysplasia; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NA, not available; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish National Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscany Neonatal Network, Tuscany, Italy; UKNC, United Kingdom Neonatal Collaborative. Adapted with permission from Lui *et al.* *Semin Fetal Neonatal Med* 2021;26(1):101196. doi: 10.1016/j.siny.2021.101196.

mothers with diabetes to those of 73,080 neonates born to mothers without diabetes. We identified that gestational age and birth weight were higher in neonates born to mothers with diabetes. We also noted that mortality and composite adverse outcome rates were lower in neonates born to mothers with diabetes in unadjusted analyses; however, after adjusting for confounders, there were no significant differences in in-hospital mortality or the composite outcome between the two groups of neonates. Another maternal characteristic that has been associated with the outcomes of preterm neonates is maternal hypertension. The incidence of maternal hypertension is on the rise. Gemmell *et al.* (17) used the iNeo database to identify that the rate of

maternal hypertension among very preterm infants varied from 11% to 16%. When the outcomes of more than 27,000 neonates born between 24 weeks' and 29 weeks' gestational age and admitted between 2007 and 2010 were evaluated, maternal hypertension was associated with lower odds of mortality, severe brain injury, and treated retinopathy of prematurity: but with higher odds of BPD. The authors also identified that the diagnosis of maternal hypertension varied across countries and highlighted a need for standardized diagnostic criteria. Moreover, the paradoxical impact of maternal hypertension on neonatal outcomes emphasized the importance of studying all pregnancies rather than only studying neonates born to these mothers, as

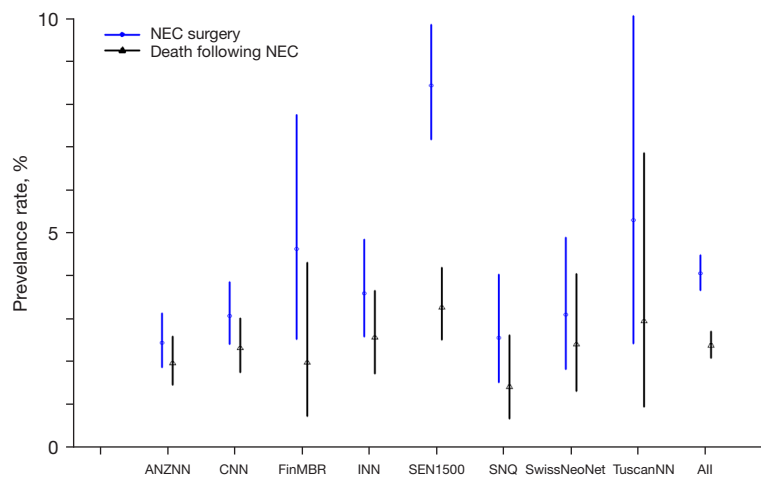


**Figure 2** Gestational-age specific survival for infants (24–29 weeks’ gestation, birth weight <1,500 g) born between 2007 and 2013 and admitted to neonatal intensive care units in the iNeo networks. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscan Neonatal Network, UKNC, United Kingdom Neonatal Collaborative. Adapted with permission from Helenius *et al.* Pediatrics 2017;140:e20171264.

**Table 3** Treatment of retinopathy of prematurity by year in individual networks (<28 weeks’ gestation)

Network	2007	2008	2009	2010	2011	2012	2013	P value for Trend
ANZNN	71 (8.2)	72 (8.3)	58 (7.4)	46 (6.1)	64 (7.8)	57 (6.9)	56 (6.6)	0.13
CNN	88 (14.8)	86 (13.2)	70 (10.8)	91 (11.6)	71 (9.8)	67 (8.8)	64 (8.9)	<0.01
INN	38 (13.9)	35 (13.0)	33 (11.4)	24 (7.8)	31 (10.7)	24 (9.3)	25 (8.3)	0.01
NRNJ	431 (36.4)	311 (26.2)	381 (30.5)	424 (30.7)	402 (29.5)	439 (31.4)	352 (28.0)	0.03
SNQ	26 (12.8)	21 (11.3)	23 (11.1)	30 (13.9)	25 (13.5)	18 (7.9)	17 (6.6)	0.02
SwissNeoNet	5 (4.0)	7 (4.7)	6 (4.2)	12 (7.3)	5 (2.8)	6 (3.1)	6 (3.9)	0.49
SEN1500	65 (14.7)	54 (11.5)	64 (12.5)	77 (15.8)	65 (13.3)	66 (12.4)	65 (13.2)	0.83
UKNC	NA	59 (5.2)	61 (5.5)	138 (9.2)	148 (8.8)	142 (8.3)	195 (11.9)	<0.01
FinMBR	11 (12.1)	8 (7.6)	19 (20.7)	8 (9.1)	14 (12.3)	11 (11.5)	7 (9.1)	0.70
TuscanNN	NA	NA	8 (13.3)	4 (8.2)	5 (10.2)	4 (7.7)	6 (10.3)	0.59
Total	735 (19.4)	653 (13.0)	723 (14.2)	854 (14.9)	830 (14.1)	834 (13.7)	793 (13.7)	<0.01

ANZNN, Australia and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NA, data not available for this year; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish National Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscany Neonatal Network, Tuscany, Italy; UKNC, United Kingdom Neonatal Collaborative. Adapted with permission from Darlow *et al.* Br J Ophthalmol 2017;101:1399-1404. doi: 10.1136/bjophthalmol-2016-310041.



**Figure 3** Necrotising enterocolitis surgery prevalence rate and 95% confidence interval by network for 2014 to 2015. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NEC, necrotising enterocolitis; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscan Neonatal Network. Adapted with permission from Adams *et al.* BMJ Open 2019;9:e031086.

**Table 4** Outcomes in triplets compared to singleton preterm neonates <29 weeks' gestation

Outcomes	Triplet neonates, N=6,079	Singleton neonates, N=18,232	Unadjusted odds ratio (95% CI)	Adjusted odds ratio <sup>†</sup> (95% CI)	Adjusted odds ratio <sup>‡</sup> (95% CI)
Composite outcome <sup>§</sup> , n (%)	1305 (23.4)	3,941 (24.0)	0.97 (0.89, 1.06)	0.91 (0.83, 1.01)	1.00 (0.90, 1.11)
Mortality before discharge, n (%)	360 (5.9)	1,138 (6.2)	0.95 (0.81, 1.10)	0.83 (0.70, 0.98)	1.08 (0.90, 1.30)
Severe neurological injury, n (%)	343 (6.2)	1,094 (6.7)	0.92 (0.80, 1.07)	0.91 (0.78, 1.06)	1.12 (0.94, 1.33)
Treated retinopathy, n (%)	181 (3.0)	522 (2.9)	1.04 (0.85, 1.28)	0.99 (0.80, 1.22)	1.05 (0.83, 1.32)
Bronchopulmonary dysplasia, n (%)	717 (12.7)	2,130 (12.6)	1.01 (0.90, 1.13)	0.97 (0.86, 1.09)	0.94 (0.83, 1.07)

<sup>†</sup>, Adjusted for maternal hypertension and birth weight z-score. <sup>‡</sup>, Adjusted for maternal hypertension, cesarean birth, antenatal steroid administration, and birth weight z-score. <sup>§</sup>, Composite outcome was defined as mortality or severe neurological injury or treated retinopathy or bronchopulmonary dysplasia. CI, confidence interval; N, number in group; n, number in category. Adapted with permission from Shah PS *et al.* Pediatrics 2018;142(6):e20181938.

there is potential for missing an intrauterine pregnancy loss.

The large international database maintained by iNeo has also allowed us to explore the possibility of understanding rare exposures. We compared the outcomes of 6,079 triplets born between 24 weeks' and 32 weeks' gestation to those of a matched cohort of 18,232 singleton infants (18). We identified no difference in the composite outcome of mortality, severe neurological injury, treated retinopathy of prematurity, and BPD (Table 4), and the results were robust when they were evaluated only for triplets born at 24 weeks to 28 weeks' gestation. Norman *et al.* (19) compared the outcomes of 609 infants with severe congenital heart disease to those of 76,371 neonates without diagnosis of congenital

heart disease and found that in-hospital mortality was significantly higher in those with CHD, with an odds ratio of 2.3 [95% confidence interval (CI): 1.61–2.37]. The large database allowed us to compare the outcomes of different types of severe congenital heart diseases. We noted that mortality was higher with all types of congenital heart disease; however, the highest odds ratios were associated with congenital heart disease causing congestive heart failure. We also identified that rates of CHD and neonatal outcomes differed significantly between countries.

One of the major difficulties in evaluating and benchmarking outcomes between centres or between countries is the variability in severity of illness. It is argued



that severity of illness varies between the units or countries and complicates outcomes comparisons unless it is adjusted for. Since no uniform severity of illness criteria are used by iNeo countries, we evaluated the universally recorded Apgar score at 5 minutes after birth as a surrogate marker of severity of illness to understand its relationship with neonatal mortality and severe neurological injury (Shah *et al.* 2021; submitted). In a study of 92,412 neonates, we identified that mortality decreased as 5-minute Apgar score increased from 0 to 10. Moreover, lower Apgar scores were associated with higher odds of severe neurological injury, but this relationship was not linear across the spectrum of Apgar scores.

### ***Understanding outcome variations by evaluating practice variations using a survey and survey-linked cohort study design***

After identifying outcome variations between the countries, the participants of the iNeo collaboration were determined to understand the reasons behind the variations. One of the basic dimensions in assessing system-level change in outcomes within any network is to identify improvements in outcomes over time and reduce unexplained variation in outcomes between similar constituents within the network. Lui *et al.* (20) evaluated outcome variations within units in each network over time in a study of 110,000 infants born at 23 weeks to 28 weeks' gestation and admitted to 569 NICUs in 10 countries between 2007 and 2016 (Table 2). The inter-center variability in outcomes over years within individual countries increased in Australia-New Zealand, Spain, and Switzerland. Such analyses provide information crucial for identifying variations in unit-level practices as well as system capacity.

These variations were assessed in a systematic fashion after asking each unit to complete a detailed survey of physical factors, human resources, system-level factors, management practices, and availability of resources. The pre-piloted questionnaire was designed to obtain details relating to the situation in the unit in the year 2015. Shahroor *et al.* (21) evaluated health care personnel variations in responding units and identified that, of 325 units, 43% had team-based care models of practice and 59% (27–100% variation between countries) had in-house presence of neonatologists 24 hours per day. Regarding nursing presence, a 1:1 ratio of nursing personnel to unstable and complex care need patients was available in 52% of the units, whereas a 1:2 ratio of nursing personnel

to neonates requiring multisystem support was available in 59% of the units. Other types of personnel were available in various proportions of the units, as follows, with marked variability even within countries: respiratory therapist (15%), pharmacist (40%), dietitian (34%), social worker (81%), lactation consultant (45%), parent buddy (6%).

Parents have been identified as an integral part of the care provider team for EPT neonates. Lehtonen *et al.* (22) evaluated facilities supporting parental presence in the infant's room 24 hours per day in participating neonatal units. Of the 331 units that responded to a survey, only 13% had facilities accommodating infant-parent rooms in their NICUs. When patient-level data were linked for 159 units in 7 networks, we identified that 28% of the cohort was cared for in the units with infant-parent rooms. Infant outcomes are reported in Table 5. These findings highlighted the importance of family-centered care for EPT neonates, for whom the length of stay in the NICU is dependent on unit practices, discharge support, and community services organization. Seaton *et al.* (23) reviewed data from 28,204 neonates born at 24 weeks to 28 weeks' gestation to understand between-country variations in length of stay for surviving neonates. Observed median length of stay was the longest in Japan (21 days longer) and was shortest in Finland (5 days shorter) than the reference country, Sweden. The factors associated with longer length of stay were country of birth, lower gestational age, multiplicity, and male sex. It was possible that differences in mortality may partially explain the longer length of stay in Japan; however, other factors could also play a role.

Several clinical practices were evaluated to identify variations between units in the management of EPT neonates. Beltempo *et al.* (24) evaluated practice variations in the respiratory management of EPT infants born at <29 weeks' gestation. In a survey of 321 units, it was identified that a neonate of 23 weeks or 24 weeks' gestation with increasing respiratory distress on continuous positive airway pressure support will be managed by most units with intubation and mechanical ventilation. However, for a neonate at 25 weeks to 26 weeks' gestation in a similar situation, the management strategies varied significantly between the units within each network. For infants of 27 weeks and 28 weeks' gestation, there was even more variation, with certain units providing mechanical ventilation, continuing continuous positive airway pressure support, intubation-surfactant administration-extubation, and less invasive surfactant administration. Darlow *et al.* (25) evaluated survey responses from 329 units about

**Table 5** Patient-level characteristics comparing neonatal intensive care units with or without infant-parent rooms

Outcomes	Unadjusted OR (95% CI)	Adjusted OR <sup>†</sup> (95% CI)	Adjusted OR <sup>‡</sup> (95% CI)
Composite of mortality or any morbidity	0.95 (0.84, 1.08)	0.77 (0.65, 0.90)	0.76 (0.64, 0.89)
Mortality	0.85 (0.70, 1.02)	0.81 (0.64, 1.02)	0.79 (0.62, 1.00)
Sepsis	0.84 (0.71, 1.00)	0.80 (0.66, 0.98)	0.80 (0.66, 0.97)
Bronchopulmonary dysplasia	1.10 (0.95, 1.27)	0.72 (0.61, 0.86)	0.72 (0.61, 0.86)
Intraventricular hemorrhage/periventricular leukomalacia	1.14 (0.95, 1.37)	1.09 (0.88, 1.35)	1.08 (0.87, 1.34)
Retinopathy of prematurity treatment	0.81 (0.66, 0.99)	0.91 (0.71, 1.16)	0.90 (0.70, 1.15)
Length of stay, days	-7.5 (-10.7, -4.4)	-4.4 (-7.8, -1.1) <sup>§</sup>	-3.4 (-4.7, -3.1) <sup>§</sup>

<sup>†</sup>, adjusted for gestational age, birth weight z-score, multiple birth, sex, country. <sup>‡</sup>, Adjusted for gestational age, birth weight z-score, multiple birth, sex, country, and center volume. <sup>§</sup>, coefficient (95% CI) from general linear regression. CI, confidence interval; OR, odds ratio. Adapted with permission from Lehtonen L et al. *J Pediatr* 2020;226:112-7.

saturation target limits in the NICU. They identified that most neonatal units recently made changes to the upper and lower saturation target limits, which were now higher than previous limits. This change was reported by units in 8 out of 10 networks. They also identified that very few neonatal units set an upper target limit of >95% or a lower target limit of <85%. The concern with the changes in the oxygen saturation target was with regard to the rate of ROP. They also noted variations in criteria for retinopathy screening between neonatal units within networks, except for in Sweden, where all units followed a single guideline. Such variations could explain differences in the incidences of therapy for retinopathy between units within the network.

Isayama *et al.* (2021; submitted) recently evaluated whether treating pre-symptomatic patent ductus arteriosus (PDA) based on early routine echocardiography was associated with infant outcomes in a survey-linked retrospective cohort study of infants born at <29 weeks' gestation. There was wide variation among units within the networks regarding the proportions treating asymptomatic PDA (7–86%). Of the 246 units that responded to the survey, 126 units treated pre-symptomatic PDA. The primary outcome of early death or severe neurological injury was not significantly different between neonates in the units treating *vs.* not treating pre-symptomatic PDA, with an adjusted odds ratio of 1.00 (95% CI: 0.85–1.18). The practice of treating pre-symptomatic PDA was associated with an increase in retinopathy of prematurity.

Helenius *et al.* (26) evaluated survey responses from units regarding approaches to redirection of care—especially with reference to intracranial hemorrhage, which is a complication that is not uncommon but that shows wide variations. They

identified that certain units had lower rates of survivors with intracranial hemorrhage, which corresponded to higher rates of offering of redirection of care.

These variations in physical, human, and environmental unit practices and care philosophies have given us some insights into the causes of outcome variations. However, in a context where neonatal intensive care is constantly evolving (27), we need to identify additional mechanisms for collecting information on the changes and their associated effects on neonatal outcomes (5).

### *Studies utilizing an epidemiological underpinning*

A large data set allowed us to evaluate certain controversies in the neonatal-perinatal field regarding exposure assessment and outcomes evaluation. There is an ongoing debate with regards to classification of a fetus or neonate prior to birth or at the time of birth as small for gestational age or appropriate for gestational age. Martin *et al.* (28) evaluated country-specific birth weight references, common birth weight references, country-specific estimated fetal weight references, and common estimated fetal weight references to classify neonates in our international cohort, and then compared their neonatal outcomes. We noted that an association of being small for gestational age with the composite outcome was similar irrespective of the classification used. We noted that small-for-gestational-age neonates had higher odds of mortality and morbidity and, although the number of infants classified as small for gestational age differed based on the references used, the risk of the composite outcome was comparable between references. Koller-Smith *et al.* (29) evaluated this concept

further by creating two cohorts from three countries in iNeo network: very low gestational age and very low birth weight. The very low birth weight cohort had a higher number of small for gestational age infants (20% vs. 9%) and was also associated with higher rates of a composite adverse outcome compared to the very low gestational age cohort. However, the predictive powers of two models based on very low gestational age or very low birth weight for mortality and a composite outcome were similar, with areas under the curve of between 0.81 and 0.85. This allowed us to conclude that either population base is suitable for international benchmarking.

Gagliardi *et al.* (30) studied the “male disadvantage” that has been reported for neonatal-perinatal outcomes of EPT neonates using a large twin-pair cohort dataset from iNeo. Of the 20,924 twins in the network, approximately one third were from male-male pairs, one third were from female-female pairs, and another one third were sex discordant. The females with a male co-twin had lower odds of mortality, severe neurological injury, and a composite outcome compared to female-female pairs. Males with a female co-twin also had lower odds of mortality. Males in male-male pairs had the highest odds of BPD and composite outcomes. We concluded that sex disparity in neonatal outcomes exists in EPT twins, with females having lower risk than males and opposite-sex pairs having lower risk than same-sex pairs.

A major controversy in the neonatal field is related to the treatment of PDA. Due to the wide variety of reported outcomes with PDA, several units have adopted a practice of not treating at all, whereas other units have actively looked for PDA within the first 24 hours and aggressively managed it. Isayama *et al.* (31) reviewed 39,096 neonates born at 24 weeks to 28 weeks' gestation from 139 neonatal units and assessed rates of PDA treatment at individual unit level (Figure 4). The relationship identified a nadir at a ratio of 1.13 with a significant quadratic effect, indicating that both low and high treatment rates were associated with death or severe neurological injury. Thus, having access to such large cohort allowed us to test some associations which are impossible or difficult to evaluate with randomized studies; however, the results are only amenable to epidemiological scrutiny if they can be tested in a large sample.

### **Training and mentoring**

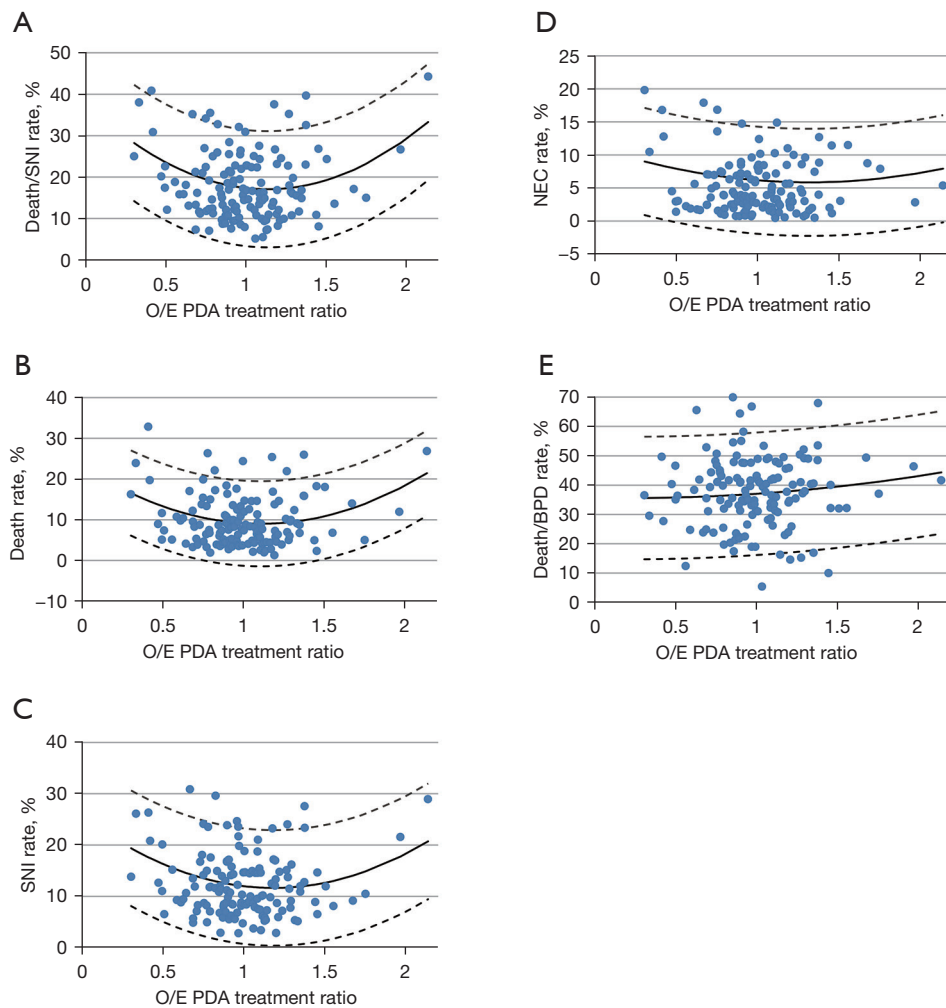
The iNeo collaboration has been successful in mentoring a graduate student, 3 post-doc fellows, and 3 post-MD

fellows, and has contributed to 2 PhD thesis chapters. The next goal is to engage in succession planning, as junior leaders from many networks are being supported to develop their skills in leading the individual networks.

### **Funding support: sources and return on investments**

The day-to-day management of the iNeo collaboration is overseen by the iNeo Director, while a Steering Committee comprising one or two members from each country assesses the overall progress of iNeo, evaluates the scientific merits of proposed projects, reviews results, identifies and articulates strengths and limitations of analyses, and recruits and trains junior researchers interested in international neonatal health. The iNeo Coordinating Centre is housed at the Maternal-infant Care Research Centre (MiCare) within the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital, Sinai Health System, Toronto. Each national network coordinating centre prepares local data for processing, extraction, and transfer, and disseminates findings to its respective sites.

Financial support for the iNeo Coordinating Centre was provided by an Applied Research Chair Grant from the Institute of Human Development Child and Youth Health at the Canadian Institutes of Health Research, and the infrastructure of the individual member networks is supported by their own budgets (identified in funding opportunities). The member network coordinating centres also act as local training sites for trainees in health services research in neonatal-perinatal medicine. In order to foster a true international collaboration, the data collected and housed at the iNeo Coordinating Centre are available to all iNeo member networks and iNeo-affiliated investigators. We have obtained ethics/regulatory approval or its equivalent from the local granting agencies to allow for de-identified data to be collated and sent to the iNeo Coordinating Centre. Overall coordination of the project is also approved by the Research Ethics Board at Mount Sinai Hospital in Toronto, Ontario, Canada. The privacy and confidentiality of patient data is in accordance with the Privacy Commissioner's guidelines. The group meets every month via a video conferencing platform to discuss existing and new proposals, review the results of existing analyses, brainstorm ideas for future projects with respect to the changing landscape of neonatology, and plan their course of action. The collaboration also meets face-to-face each year during the Pediatric Academic Society's annual meeting to



**Figure 4** Relationships between observed/expected patent ductus arteriosus treatment ratio and outcomes. (A) Primary outcome: death or severe neurological injury; (B) Secondary outcome: death; (C) Secondary outcome: severe neurological injury; (D) Secondary outcome: necrotizing enterocolitis; (E) Secondary outcome: death or bronchopulmonary dysplasia. The O/E PDA treatment ratio was the ratio of observed PDA treatment rate divided by expected PDA treatment rate in an individual unit. The expected PDA treatment rate was estimated using a multivariable logistic regression model constructed using data from all other units in the study after adjusting for potential confounders. BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; O/E PDA treatment ratio, observed/expected patent ductus arteriosus treatment ratio; SNI, severe neurological injury. Adapted with permission from Isayama *et al.* *J Pediatr* 2020;220:34-9.

review overall data structure, quality, and governance issues.

### Future directions and plans

The next phase in this collaboration will evaluate how neonatal outcomes are associated with neurodevelopmental outcomes and whether variations persist. A recent review by Ding *et al.* (32) meta-analyzed estimates from different countries and reported that rates of moderate-to-severe

neurodevelopmental disability were 42% for infants born at 22 weeks' gestation, 41% at 23 weeks, 32% at 24 weeks, and 23% at 25 weeks' gestation. The Effective Perinatal Intensive Care in Europe (EPICE) collaboration has standardized outcome definitions and measures at 2 years corrected age in 15 European regions for infants born <28 weeks' gestation (33). Rates of neurodevelopmental impairment ranged from 10% to 26%; however, outcome ascertainment was done using parental questionnaires

with response rates as low as 47% in certain regions. We recently compared outcomes of EPT neonates in iNeo networks from Australia-New Zealand and Canada and the EPIPAGE cohort in France born during the year 2011. We identified that mortality was higher in the EPIPAGE cohort compared to Canadian cohort, and mortality or moderate-to-severe neurosensory impairment was higher in EPIPAGE compared to both Australia-New Zealand and Canada. There was no difference in neurosensory impairment among survivors. This increase persisted even after considering differences in baseline characteristics and neonatal complications, suggesting the possible contribution of unmeasured factors that could vary by country (e.g., maternal characteristics, health care organization) or diverging philosophies on end-of-life decisions. The most important lesson learned in this exercise was that there are variations in the ways children are assessed in different countries and jurisdictions, such that harmonization of criteria for classifying children with arbitrary cut-offs could be a challenge (34). However, detailed investigation of variations across settings with similar health care delivery systems is desperately needed to learn the reasons for the variations and identify which modifiable factors can be incorporated into future research on quality improvement and clinical practices.

We perceive a few areas of investigation that will serve as a springboard into the next phase of this incredibly successful collaborative: these include infection (predisposing factors and preventive factors), surgical/lethal necrotizing enterocolitis, infant growth trajectories and their influence on outcomes, comparison and harmonization of infant neurodevelopmental outcomes across countries or networks, and finally, outcomes of neonates with fairly common congenital anomalies.

### Challenges: current and future

The collaboration has accomplished neonatal data harmonization, except for our work on sepsis and necrotizing enterocolitis, which is ongoing. Data harmonization for neurodevelopmental outcomes could be a challenge and would require a different set of knowledge users and decision makers from each network. We have begun the initial work in this area, and we are confident we will be able to identify common grounds as we have done previously. Accomplishing this next phase of work will require additional funding for the next five years and the collaboration is currently exploring various ways to identify

and secure this support.

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