Review Article

The International Network for Evaluating Outcomes (iNeo) of neonates: evolution, progress and opportunities

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Abstract: Neonates born very preterm (before 32 weeks' gestational age), are a significant public health concern because of their high-risk of mortality and life-long disability. In addition, caring for very preterm neonates can be expensive, both during their initial hospitalization and their long-term cost of permanent impairments. To address these issues, national and regional neonatal networks around the world collect and analyse data from their constituents to identify trends in outcomes, and conduct benchmarking, audit and research. Improving neonatal outcomes and reducing health care costs is a global problem that can be addressed using collaborative approaches to assess practice variation between countries, conduct research and implement evidence-based practices. The International Network for Evaluating Outcomes (iNeo) of neonates was established in 2013 with the goal of improving outcomes for very preterm neonates through international collaboration and comparisons. To date, 10 national or regional population-based neonatal networks/datasets participate in iNeo collaboration. The initiative now includes data on >200,000 very preterm neonates and has conducted important epidemiological studies evaluating outcomes, variations and trends. The collaboration has also surveyed >320 neonatal units worldwide to learn about variations in practices, healthcare service delivery, and physical, environmental and manpower related factors and support services for parents. The iNeo collaboration serves as a strong international platform for Neonatal-Perinatal health services research that facilitates international data sharing, capacity building, and global efforts to improve very preterm neonate care.

ǂ, a full list of the International Network for Evaluating Outcomes (iNeo) of Neonates investigators is provided in the Appendix 1.

Keywords: Preterm infants; outcomes research; neonatal intensive care

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Introduction

The International Network for Evaluating Outcomes (iNeo) in neonates is an international collaboration of nearly population-based national neonatal networks/datasets including 10 networks from 11 countries: Australia, New Zealand, Canada, Finland, Israel, Japan, Spain, Sweden, Switzerland, Tuscany region of Italy and the UK. The network has been, and continues to be, a powerful platform for applied health services and policy research that is aiming to improve patient-oriented outcomes for very preterm (VPT, born before 32 weeks of gestational age) neonates both in the member countries and globally. Only 1% of all births and 14–20% of all preterm births are VPT neonates; however, the rate of VPT birth is important to public health because of these neonates are at high-risk for mortality and childhood morbidities including cerebral palsy, cognitive delay, blindness and deafness (1,2). In addition, the cost of caring for VPT neonates is high both during initial hospitalization (3) and the lifetime cost of permanent impairments.

Various national and international networks/datasets, such as the Vermont Oxford Network in the USA (4), Canadian Neonatal Network (CNN) (5,6), Neonatal Data Analyses Unit in the UK (7) and Swedish Neonatal Quality Register (SNQ) (8,9) analyse data from their local populations to identify trends in outcomes of VPT neonates and benchmark the performance of centres within each network (2,3,10-15). Although most networks initially reported improvements in the rates of morbidity and mortality, recently CNN and other networks observed stagnant progress or worsening of outcomes (16-19). Even when continued outcome improvement was reported, there remained significant variation in the performance of units within neonatal networks. For example, Draper *et al.* reported the VPT survival rate varied from 74.8% to 93.2% between units in 10 European regions (20). In addition, the risk-adjusted mortality rate for VPT neonates in an Australia NICU was revealed to be lower than a Scottish NICU (21). However, generalizing results from a few NICUs to the population level risks introducing selection bias that can lead to inaccurate conclusions.

Ten years ago, based on individual reports of outcomes, collaborations between the CNN, the Neonatal Research Network of Japan (NRNJ), the Australian and New Zealand Neonatal Network (ANZNN) and the Swedish Neonatal Quality (SNQ) register (9) were initiated. In the first population-based retrospective comparison, we identified that the composite outcome of mortality or any major morbidity [nosocomial infection (NI), necrotizing enterocolitis (NEC), severe neurological injury, retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD)] was lower in NRNJ than Canada in very low birth weight (VLBW) neonates. In-depth analyses revealed that the CNN had higher rates of NI, NEC, and severe neurological injury whereas NRNJ had higher rates of ROP and BPD (22). While the VPT neonate mortality rate was similar between Canada and Australia/New Zealand, rates of NEC, severe neurological injuries, ROP and BPD were significantly lower in Australia/New Zealand than Canada, while the rates of early-onset sepsis and air leaks were higher and the average length of stay was longer than Canada (23,24).

While the variability in neonatal outcomes between Canada and other countries was clear, the factors contributing to the outcome variability were uncertain. Distinct population characteristics, differences in neonate severity of illness, diverse processes of care or delivery of health care could all contribute to outcome variability. For example, Australia/New Zealand has a significantly lower number of outborn VPT neonates than Canada (23); respiratory therapists play a prominent role in North American institutions, but are rarely present in European countries; and in Canada junior doctors are less likely to do shift work than in Europe and Australia.

Given the myriad of factors that could contribute to outcome variability in between countries, it was important to first characterize these factors then identify specific methods to improve neonatal care in each country. The initial care of VPT neonates is highly complex and is typically delivered in specialized units (60–80% of VPT neonates are initially admitted to tertiary NICUs). When VPT neonates no longer need complex care, they are

transferred to Level 2 units for the remainder of their hospitalization. Both the day-to-day cost of caring for each neonate in the NICU and the cumulative lifetime cost of care consume an enormous amount of resources. Collaborative sharing and learning between countries to assess practice variations, provide evidence for evidence-based practices, and monitor practice implementation had the potential to help improve outcomes and reduce health care costs globally. However, enabling rigorous comparisons between countries/networks required an understanding of the context for comparison in each country and a way to standardize data.

These concepts, along with enthusiasm of participating networks/data custodians, led to the establishment of an iNeo collaboration in 2013 with funding support from the Institute of Human Development, Child and Youth Health at the Canadian Institutes of Health Research (25). The underlying premise of iNeo was to collect information from population-based networks/datasets on the outcomes, characteristics, practices and culture of the member sites; evaluate the impact of such variations on outcomes and to identify the best models of health service delivery (incorporating medical and non-medical variations); report back to the units the results of analyses; empower units to embrace implementation of data-linked and evidence-based practice changes and ultimately improve outcomes for VPT neonates both within the iNeo countries and globally. In the sections below, we highlight the aims of iNeo and their fulfilment to date and identify opportunities to both expand this initiative to other countries and improve trajectories of growth and development of VPT neonates.

Development and evolution of iNeo

The initial iNeo collaboration comprised 7 datasets from 8 countries, which included Australia and New Zealand (as one network), Canada, Israel, Japan, Spain, Sweden, and the UK Neonatal Collaborative (26). The directors/custodians of these networks/datasets got together at a face-to-face meeting in 2012 to explore the feasibility of the collaboration and how to operationalize the idea. Conceptualizing iNeo was a smooth process; however, we noted many operationalization challenges. After much discussion, the protocol for this initiative was developed and published (27). Subsequently, we added Finland, Switzerland and the Tuscany region of Italy as full members of iNeo bringing the current total to 10 networks/datasets from 11 countries. There have been 3 full-team face-to-face meetings where the development of a minimum dataset, modification of the dataset, analytical plans and results were discussed. Our initial goal was to combine VPT and VLBW neonates (birthweight <1,500 grams) as our base population because of the variability of population criteria used by the networks. However, following our discussions, iNeo now only includes VPT neonates in order to avoid severely growth restricted neonates of high gestational age (GA) in the dataset. The central coordination center for iNeo houses all data and is located in Toronto, Ontario, Canada. Further exploration is needed to determine whether a concept like distributed-data analyses can be applied to allow other countries to have data access.

Aims and achievements of iNeo

The collaboration was built with several aims, which we highlight here while describing what iNeo has achieved and what is planned for the future.

Aim 1: compare national neonatal outcomes and health service organization for VPT neonates

National comparisons of neonatal outcomes and health service organizations have been the primary aim of the iNeo from the outset. The strategy stemmed from a group of studies that each reported comparisons between network outcomes of two countries (22-24,27,28) and culminated in the first ever comparison of outcomes from 9 countries (26). Our key finding was that there are marked variations in adverse outcome rates between countries and none of the participating countries has the best outcomes for all morbidities. A composite outcome of neonatal mortality or morbidities varied from 26% to 42% across countries; however, when confounders were adjusted, two countries had higher standardized rates, two countries had no difference in standardized rates and four countries had lower standardized rates than the other countries (26). We speculated that these differences could be a result of population characteristics, data collection mechanisms, societal factors, healthcare organization factors, cultural factors and practice differences. Untangling composite outcome factors further, we assessed differences in mortality among neonates born at 24–30 weeks' GA and reported that the survival rate at specific GAs varied between countries; in particular, at 24 weeks' GA survival varied from ~35% to 84% between countries (29). Similar to mortality, the rates of any ROP varied markedly between networks, especially

the rates of treated ROP varied between 4% to 30% between countries (30). Further evaluation of the variation in rates of sepsis (31), NEC (32), and severe brain injury (33) between countries/datasets are underway.

The iNeo database contains information on >200,000 VPT infants, a population size that has allowed us to evaluate the association between exposure to risk factors and neonatal outcomes with a very high precision and especially study rare exposures such as severe congenital heart defects (34). For example, we identified that maternal diabetes was not associated with composite adverse outcome of mortality or major morbidities in VPT neonates (35), and that triplets of <29 weeks' GA had similar outcomes to singletons of <29 weeks' GA (36). In contrast, preterm neonates of <29 weeks GA born to mothers with hypertensive disorder were associated with lower odds of mortality, severe brain injury and treated ROP and higher odds of BPD than preterm neonates of <29 weeks GA born to normotensive mothers (37). These associations were, however, highly variable between countries suggesting that we need large datasets to improve the precision of our estimates and the need for network collaborations to generate such large datasets.

Aim 2: identify differences in site-level physical, human, and environmental characteristics, as well as care practices that underlie variations in outcomes

Outcome differences between countries could be a result of variability in care practices as many others have explored; however, the iNeo collaboration hypothesized that the outcome differences could also be a result of site-level physical, human-power, and environmental factors. To identify such variations, a carefully designed, pre-piloted survey with 67 questions (needing 35–45 minutes to complete) was circulated to 390 institutions participating in iNeo. The survey asked about clinical care practices as well as unit-level physical, human, and environmental characteristics as they were in the year 2015. The respondents were also instructed to reply based on unit-level practices and not personal preference. The survey was circulated in 2016 and closed after 3 rounds of reminders. None of the questions were mandatory. A total of 329 (84%) units responded to the survey making this a very high-response survey. We identified marked variations in how perinatal-neonatal services are organized between countries participating in iNeo (38), despite the fact that most of the countries have a publicly-funded healthcare system.

The differences identified in various surveys can explain some of differences in outcomes; however, some of the variability merely reflects different ways of providing care. There was variations identified in the respiratory management of neonates of 23–29 weeks' GA who were on continuous positive airway pressure support and receiving 30–39% oxygen with some units tolerate high oxygen need and continue CPAP, whereas some units utilize practice of intubate, administer surfactant and extubate (39). It is conceivable that this could explain the variations in the BPD rate between countries (40). In order to understand variations in BPD and ROP, the iNeo survey asked about oxygen saturation limits and determined that >60% of units recently increased their oxygen saturation targets (41) based on recent trial results. The survey also evaluated other practice variations including probiotic use, feeding practices and other risk factors of NEC (42); approach to redirecting care of critically-ill neonates (43); delivery-room deaths across countries (44); screening and treatment criteria for ROP (41); and preventative measures for severe brain injury (45). Finally, we surveyed the physical layout, facilities available, visiting policies (46), and staffing available (47) and identified significant variations between units and countries.

Our next phase of understanding the reasons for differences in outcomes is by linking the survey responses to actual practices and outcomes from individual units and to understand whether any of the practice differences are associated with outcomes or not. These analyses are ongoing and preliminary results are hypothesis generating. We identified that there is marked variations in implementation of proposed NEC prevention practices; however, there was no relationship of implementation of these practices with unit rates of surgical NEC (48). More work is needed to continue evaluating changes in practices and factors associated with improvement in outcomes.

Aim 3: identify clinical and organizational practice improvements relevant to each network

Prior to our multi-country outcomes comparison, individual countries had no idea as to how their outcomes compared with other countries. The results of our first multi-country comparison generated a lot of interest among the participants, which led to several teleconferences and face-to-face meetings to exchange ideas, practices and unit organization and identify potential improvements for local implementation. Several teams of iNeo investigators have visited other collaborating countries to learn and share their knowledge.

More recently, we investigated changes in outcome trends between 2007 and 2015 in iNeo countries to identify areas for improvement. Consistent outcome improvement was observed in a few countries, a static trend in some countries and worsening outcomes in others (49). The differences in outcome trends were hypothesized to be the result of similar factors as described above; however, this challenged us to think beyond those factors as trend evaluation within a country implies those factors being constant.

Aim 4: implement and continually evaluate the impact of data-informed and evidence-linked clinical and organizational practice changes in NICUs within participating networks

Identification of outcomes trends in iNeo countries enabled us to focus first on identifying harmonized definitions for commonly used terminologies in neonates. In collaborations with the International Neonatal Consortium and e-Newborn initiative, a white paper has been produced identifying the need for harmonized definitions. We are also engaged in further work for standardization of terminology (50). A second step will be to develop a data-informed method of identifying clinical and organizational practices that may be associated with improved efficiency and outcomes. This work has only just begun in a few countries; however, discussions are ongoing.

Aim 5: train and mentor junior researchers in the conduct of Neonatal-Perinatal health services research

Training and mentoring junior researchers have been key objectives of iNeo collaboration. Since the inception of iNeo, we have trained 2 post-doctoral fellows, 3 doctoral candidates, 1 master's level researcher, 2 master's candidates, 3 post-MD fellows and 1 pre-medical student who all have been successful in completing one project each and publishing it in reputable journals. The training has been open to international trainees and more trainees will be accommodated as we continue to accrue more data.

iNeo research methods in brief

Participation

The following neonatal networks are currently participating in the iNeo collaboration: Australian and New Zealand Neonatal Network (ANZNN, 29 units), Canadian Neonatal Network (CNN, 30 units), Finnish Medical Birth Register (FinMBR, 5 units), Israeli Neonatal Network (INN, 27 units), Neonatal Research Network of Japan (NRNJ, 73 units), Spanish Neonatal Network (SEN1500, 46 units), Swedish Neonatal Quality register (SNQ, 37 units), Swiss Neonatal Network (SNN, 9 NICU), Tuscany region of Italy (TIN Toscane on-line, 4 units) and the UK Neonatal Collaborative (UKNC, 131 units) (*Table 1*, Appendix 1). All the participating networks collect, analyze, and benchmark the performance and outcomes of their units. Furthermore, to obtain robust population-based estimates, we carefully avoided networks that only included highly specialized units.

Development of a minimum dataset

A minimum dataset was created at the iNeo planning meeting in July, 2012 after a detailed review of all the data items collected the eight original participating networks—the elements common to all networks (e.g., gestational age, birth weight, sex, etc.) were selected for the minimum dataset (Appendix 2). 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) (51) and Systematized Nomenclature of Medicine (SNOMED) (52) dictionaries. To ensure consistency and facilitate comparisons over time, some networks redefined their original data formats as part of an ongoing process, while other networks extract data from their databases following the iNeo definitions. Currently, all networks/countries have provided data from 2007–2016 to the coordinating center. The collection items were increased recently to reflect changes in care provision to VPT neonates. New data will only include data from 2017.

Outcomes

The main outcomes of interest for the iNeo collaboration are the following:

- Mortality: death prior to discharge from NICU;
- Severe neurological injury (53): defined as intraventricular hemorrhage with ventricular dilatation, or parenchymal injury [including periventricular leukomalacia (PVL) with or without intraventricular hemorrhage];
- Stage 2 or 3 NEC (54): based on modified Bell's criteria;
- Severe ROP (55): defined as stage 3 or 4 ROP, or need

Table 1 Characteristics of participating networks

Network name	Australia and New Zealand Neonatal Network (ANZNN)	Canadian Neonatal Network (CNN)	Finnish Medical Birth Register (FinMBR)	Israeli Neonatal Network (INN)	Neonatal Research Network Japan (NRNJ)	Spanish Neonatal Network (SEN 1500)	Swedish Neonatal Quality Register (SNQ)	Swiss Neonatal Network (SNN)	Tuscany Neonatal Network (ToscanNN)	UK Neonatal Collaborative (UKNC)
Number of inhabitants	Australia: 23 million; NZ: 4.4 million	34 million	5.5 million	7.9 million	126 million	47 million	10.5 million	8 million	3.7 million	52 million
Number of birth/years	Australia: 300,000; NZ: 60,000	380,863	50, 000	182,000	946,065	415,22	120,000	80,000	31,000	687,000
Level III NICUs in the country/ region	Australia: 23; New Zealand: 6	30	5	27	100	56	6	9	4	49
Level III NICUs in the network	29	30	5	27	73	46	6	9	4	49
Network contribution	National	National	National	National	National - partial	National	National	National	Regional	National-partial
Possible to link neonatal databases with other related neonatal databases	Australia New Zealand assisted conception database, Cerebral Palsy register	National Surveillance, follow-up	Register keeper	National birth and death register	Follow-up data, Prenatal database, Birth and Death Certificates	SEN1500 Follow-up database, VON, EuroNEoNet	Ophthalmological, prenatal, follow-up database, Medical birth/cause of death register, National Transport Register, National Surveillance Database	Follow-up	Regional birth register, follow-up data	All relevant

for laser surgery, or intraocular injections of anti-vascular endothelial growth factor agents;

- ❖ NI (56): defined as culture proven sepsis (blood or cerebrospinal fluid positive for pathogenic organism) after 2 days of postnatal age;
- ❖ BPD (57): defined as oxygen requirement at 36 weeks post-menstrual age.

These morbidities are associated with an increased risk of long-term severe neurodevelopmental impairment (odds ratios of 1.5 to 3.0) (58). Various studies have shown these morbidities to be predictors of long-term adverse outcomes (59). We are also interested in other outcomes such as patent ductus arteriosus requiring surgical ligation, receipt of delivery room cardiopulmonary resuscitation, air leak syndrome, and resource utilization (length of stay and length of respiratory support).

Analytical framework

(I) Descriptive analyses of baseline factors: the distribution of neonate characteristics and country-level broad organizational structural features are summarized as counts and percentages for categorical variables using the mean and standard deviation, or the median and interquartile range for continuous variables, and compared among all networks using the Chi-square test for categorical and ANOVA F-test or Mood's median test for continuous variables.

(II) Statistical comparisons of outcomes between networks: for the adverse outcomes analyses, initial crude rates and associated 95% and 99% confidence intervals are calculated and graphically displayed using 'caterpillar plots' to visually identify differences between networks. To adjust for multiple baseline characteristics, standardized mortality/morbidity ratios (SMRs) are computed using the 'indirect standardization' approach. Each network's observed rate is compared with the expected rate based on the total sample from all other networks to identify networks with rates significantly above or below average. For each outcome, the expected number of events is computed as the sum of predicted probabilities from a multivariable model (logistic regression or zero inflated negative binomial models based on data distribution) adjusted for confounders. Network SMR are graphically displayed using 'funnel' plots with 95% and 99% prediction intervals for comparison between networks. In addition, pair-wise comparisons between specific networks with high- and low-outcome rates are performed using multivariate models adjusted for confounders. Statistical models employ generalized estimating equations to adjust analyses for clustering of neonates within networks and for multiples. Statistical significance is evaluated by applying a Bonferroni correction to account for multiple pair-wise comparisons.

Program administration

The day-to-day management of the iNeo collaboration is overseen by the iNeo Director while a Steering Committee comprising of 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 Director is supported by the iNeo Program Coordinator and a dedicated statistician. The iNeo Coordinating Centre is housed at the Maternal-Infant Care Research Centre (MiCare) within the Samuel Lunenfeld Research Institute at Mount Sinai Hospital, Toronto. Each national data coordinating centre is responsible for local data processing, extraction, transfer, and dissemination of findings to their respective sites.

Financial support for the iNeo coordinating center is provided by an Applied Research Chair Grant from the IHDCYH, CIHR and the infrastructure of individual networks is supported by their own budgets (Appendix 3). The individual 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 countries and iNeo-affiliated investigators. The policies and procedures governing the transfer of data between national data centres are guided by specific data sharing agreements signed by all participants and their institutes (Appendix 4).

All networks/data custodians have obtained ethics/regulatory approval or its equivalent from their 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 the Mount Sinai Hospital, Toronto, Ontario Canada for the development, compilation, hosting and management of the iNeo dataset at the MiCare Research

Centre. Privacy and confidentiality are of utmost iNeo importance to the iNeo collaboration, and as such data is handled in accordance with the Privacy Commissioner's guidelines.

Manuscripts published as a result of projects arising from the iNeo collaboration follow the iNeo publication principles (Appendix 5), and all publications have "on behalf of iNeo" as the final author. The remaining publication principles govern data requests and approval, data transfer and analyses, and approval of manuscripts and publications.

Lessons learned

The evolution of iNeo has taught us all critical lessons about the establishment of international collaborations; similarities and differences in healthcare systems, resources, and operations; and variations in outcomes including the following:

(I) Working with the legal or contracts office at each data hosting institution is critical to overcome systems-associated challenges when establishing international collaborations;

(II) Privacy and confidentiality are of utmost importance when handling healthcare related data, and it is essential to follow all necessary steps to protect the information;

(III) Collaborative approaches involving all participating parties can lead to a very fruitful harmonization;

(IV) Everyone should be willing to accept their deficiencies, learn from others and teach others at the same time;

(V) Allowing data access to all participating countries has many administrative hurdles, including financial support; however, when the processes are incorporated into the collaborative model it facilitates the data sharing process;

(VI) Large collaborations require buy-in from local units; in particular, local units need to understand the contribution of their data to the greater good and the importance of access to large data pools for answering questions with a higher degree of certainty.

Future plans

Future plans for iNeo include the following:

(I) Expansion of network: the success of iNeo has sparked the interest of several other countries who would like to participate as well. Norway, Taiwan, South Korea, and California in the USA have all expressed interest discussions have begun to potentially add them to the collaboration. In addition, one large unit in Singapore and two in Hong Kong are currently submitting data to the Australian and New Zealand Neonatal Network (ANZNN). More Singapore and Hong Kong units are anticipated to contribute data from 2020. Given the global interest in iNeo, we are expecting that the collaboration will expand to include more countries over the next 2 years.

(II) Harmonization of data collection across networks: members of iNeo are collaborating with the International Neonatal Consortium (INC) to harmonize data collection of common neonatal conditions, demographic characteristics and diagnoses. The plan is to develop measurable and impactful criteria for use in benchmarking, quality improvement activities and research over the next 2 years. Participants of iNeo have published papers on the harmonization of definitions for both BPD (40) and NEC (60), and we aim to develop recommendations for other diagnoses related to VPT neonates over the next 2 years.

(III) Dissemination of data collection tools to networks in Low-Middle Income countries: one goal of iNeo is to help develop benchmarking capacity in Low-Middle Income Countries. For this reason, we have shared our minimal database with several NICU in India and China (where 60 units are collecting data using a similar format), which will allow them to benchmark and compare their outcomes among themselves and internationally.

(IV) International neonatal follow-up network: There is a growing interest among iNeo countries to compare 2–3 years neurodevelopmental outcome data for the extremely preterm (<28 weeks GA) neonates. However, networks and countries use different instruments to collect neurodevelopmental outcomes data. To address this problem, iNeo is in the beginning stages of creating a tool to measure the equivalency of outcomes assessed using different instruments. The tool may not result in perfect data harmonization; however, we hope to discover some patterns that can be investigated further.

(V) Development and execution of network-based clinical trials: to further improve VPT outcomes, high-quality, evidence-informed therapies are needed. However,

evidence for new therapies usually comes from large randomized trials, which are time consuming and expensive to conduct. Established networks can facilitate point-of-care trials (61) by linking trial data collection to routine network-level data collection and acting as a conduit for identifying eligible patients, both of which significantly reduce trial cost.

(VI) Collaborative quality improvement activities: the greatest impact any data collection project can have is when data are converted to information and action. For example, multiple networks have reported successful neonatal outcome improvement through data-driven quality improvement efforts (62-66). However, many of the iNeo countries do not have established national/regional quality improvement programs that use their network data. For these networks, the next goal is to learn from networks with established quality improvement programs and use the experience to establish a national/regional quality improvement program in their home countries.

Conclusions

The iNeo collaboration serves as a strong international platform for Neonatal-Perinatal health services research for VPT neonates. The data generated by iNeo continues to provide neonatal benchmarking standards for each country and unit, which will hopefully lead to detailed discussion on how to improve outcomes for VPT neonates globally. Simultaneous capacity building by training junior researchers continues be an added benefit.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1 iNeo networks and investigators

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Appendix 2 Minimal dataset

Variables	Characteristics
ID	Unique ID assigned by site or coordinating center
Country	Code for country (alphabetical list)
Center	Code number
Demographics	
Gestational age	Weeks and days
Birth weight	kg
Birth year info	Year
Birth quarter info	Quarter
Age at NICU admission	Hours:minutes
Sex	Male/Female/Ambiguous/Unknown
Maternal age	Years
Antenatal details	
Antenatal corticosteroid use	Yes/No/Unknown
	If YES, was it Complete/Incomplete/Unknown
Rupture of membranes duration	<24 hours/24 hours to 1 week/>1 week /unknown or missing
Maternal high blood pressure	All hypertensive disorders (pregnancy induced and otherwise)
	Yes/No/Unknown or Missing
Maternal diabetes	All glucose homeostasis disorders (pregnancy induced and otherwise)
	Yes/No/Unknown or Missing
Birth details	
Mode of delivery	Vaginal/Caesarean section/Unknown or missing
Presentation	At birth or closest to the time of birth
	Vertex/Breech/Other/Unknown or missing
Births this pregnancy	If one of the fetus dies in-utero, pregnancy defined as twin/triplet as appropriate and not singleton or twin based on live births
	Singleton/Twin/Triplet/Higher order
Birth order	First/Second/Third/Forth/Unknown or missing
Place of birth	Inborn applies to tertiary care hospital where NICU is located. Outborn includes those babies who needed to be transferred to NICU after birth for ongoing neonatal care from facility other than hospital in which they are cared for
Immediate postnatal care	
Need for intubation	Within first 30 minutes of birth
	Yes/No/Unknown or Missing
Need for CPAP	Within first 30 minutes of birth
	Yes/No/Unknown or Missing
Need for CPR during initial stabilization	CPR includes chest compression and/or epinephrine
	Within first 30 minutes of birth
	Yes/No/Unknown or Missing
Apgar at 1 minute	0 to 10, Unknown or Missing
Apgar at 5 minutes	0 to 10, Unknown or Missing
Admission status	
Re-admission	Yes/No/Unknown or Missing
Admission head circumference (cm)	Up to one decimal point
Admission length (cm)	Up to one decimal point
Admission temperature (¢J)	Up to one decimal point
Severity of illness score used	Whatever score is used by network
Neonatal course	
Duration of supplemental O_2	In days or hours (use midnight as cut-off)
Duration of CPAP	In days or hours (use midnight as cut off)
Duration of mechanical ventilation	In days or hours (use midnight as cut off)
Duration of TPN in days	In days/hours (use midnight as cutoff)
Surfactant	Yes/No/Unknown or Missing
Diagnoses/procedures	
PDA	Clinical or echocardiographic diagnosis. We will collect information on method commonly used in separate survey
	Yes/No/Unknown or Missing
Indomethacin or other NSAID for PDA treatment	Yes/No/Unknown or Missing
Surgical ligation	Yes/No/Unknown or Missing
RDS	Clinical and/or radiological criteria
	Yes/No/Unknown or Missing
Air leak	Includes Pneumothorax, Pneumomediastinum
	Yes/No/Unknown or Missing
Air Leak requiring drainage	Needle paracentesis or chest tube will be included
	Yes/No/Unknown or Missing
BPD at 28 days (need for supplemental oxygen)	X-ray is not mandatory
	Yes/No/Unknown or Missing
BPD at 36 weeks (need for supplemental oxygen)	X-ray is not mandatory
	Yes/No/Unknown or Missing
Postnatal steroid use for BPD	Only systemic use (not inhaled steroid use)
	Yes/No/Unknown or Missing
NEC (diagnosed using Bell's criteria)	Stage 2 or higher only
	Yes/No/Unknown or Missing
Surgery for NEC (laparotomy/drainage)	Yes/No/Unknown or Missing
IVH (most severe grade) prior to discharge	Classification could be SEH/GMH, IVH, VE, IPE
PVL or persistent parenchymal opacity	Persistent intraparenchymal echolucency or cysts identified on US or MRI
	Yes/No/Unknown or Missing
International ROP criteria	In either eye, record the worst stage
Treatment for ROP	Anti-VEGF or laser
	Yes/No/Unknown or Missing
Early onset sepsis	Infection within 72 hours (3 days) of birth—positive blood and/or CSF for pathogenic organism
	Yes/No/Unknown or missing
Early onset sepsis	If yes—organism
	E. Coli/GBS/Other Gram negative bacteria/Other Gram positive bacteria/Fungal/Viral/Other/Unknown
Late onset sepsis	Infection after 3 days (or 72 hours of age)—positive blood and/or CSF for pathogenic organism
LOS episode 1	Organism
	If multiple organisms are grown in culture consider most virulent: Virulence should be counted as: Fungal–Gram negative (including E coli), Gram positive (including GBS), viral, mycoplasma, other in that sequence.
LOS episode 1	Postnatal age in days
LOS episode 2	Organism
	If multiple organisms are grown in culture consider most virulent: Virulence should be counted as: Fungal–Gram negative (including E coli), Gram positive (including GBS), viral, mycoplasma, other in that sequence.
LOS episode 2	Postnatal age in days
LOS episode 3	Organism
	If multiple organisms are grown in culture consider most virulent: Virulence should be counted as: Fungal–Gram negative (including E coli), Gram positive (including GBS), viral, mycoplasma, other in that sequence.
LOS episode 3	Postnatal age in days
LOS episode 4	Postnatal age in days
LOS episode 5	Postnatal age in days
Congenital anomalies	Major congenital anomaly—defined as those life-threatening or likely to affect quality of way to a significant degree
	Yes/No/Unknown or missing
	If YES to above, please mention all congenital anomalies you have for a particular infant.
Discharge Information	
Age at discharge/death	Postnatal age in calendar days
Delivery room death	Yes/No
Death	Prior to discharge from NICU
	Yes/No
Cause of death if available	
Discharge destination	Home/Level 2 or HDU/SCBU/Pediatric ward/PICU/Out of area or country/Rehabilitation/palliative care/Unknown or missing/Other/Unknown
Breastfeeding/breast milk at discharge	Yes/No/Unknown or missing
Oxygen at discharge	Yes/No/Unknown or missing
Weight at discharge/death	Kg
Oxygen at discharge	Discharge information file
	This includes deaths if baby died before discharge, enter information from last available recording
	Yes/No/Unknown or missing
Weight at discharge	Kg
Data fields added from 2017	
$MgSO_4$ for neuroprotection	When given intrapartum
	Yes/No/Unknown or missing
Presence of labor	Prior to birth
	Yes/No/Unknown or missing
Deferred or delayed cord clamping for >30 seconds	Yes/No/Unknown or missing
Cord milking	Yes/No/Unknown or missing
Age at surfactant administration	Minutes
Inhaled nitric oxide	At any time during NICU stay
	Yes/No/Unknown or missing
Ever received mechanical ventilation	At any time during NICU stay
	Yes/No/Unknown or missing
Received INSURE	Intubated, surfactant given and extubated within 30 minutes
	Yes/No/Unknown or missing
LISA	Received surfactant via less invasive method
	Yes/No/Unknown or missing
Any postnatal steroid for BPD	Anytime during NICU stay
	Yes/No/Unknown or missing
Any respiratory support at 36 weeks	Includes CPAP, high flow, mechanical ventilation, nasal cannula,
	Yes/No/Unknown or missing
Spontaneous intestinal perforation	Yes/No/Unknown or missing
NEC treated with drain	Yes/No/Unknown or missing
ROP plus disease	Yes/No/Unknown or missing
Aggressive posterior ROP	Yes/No/Unknown or missing
Age of first culture proven infection	Days
Organism isolated in first infection	Name of organism
Number of culture proven infections	
Any episode of culture proven (blood or csf) for fungal infection	Yes/No/Unknown or missing
Number of packed red blood cell transfusion	
Death due to NEC	Yes/No/Unknown or missing

Appendix 3 iNeo funding sources

Funding for iNeo has been provided by a Canadian Institutes of Health Research Chair in Reproductive and Child Health Services and Policy Research (APR-126340) held by PSS. The Australian and New Zealand Neonatal Network is predominantly funded by membership contributions from participating centers. The Canadian Neonatal Network is supported by a team grant from the Canadian Institutes of Health Research (CTP 87518), the Ontario Ministry of Health, and individual participating centers. The Finnish Medical Birth Register is governmentally funded and kept by the National Institute for Health and Welfare (THL). The Israel Neonatal Network very low birth weight infant database is partially funded by the Israel Center for Disease Control and the Ministry of Health. The Neonatal Research Network of Japan is partly funded by a Health Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan. SEN1500 is supported by funds from the Spanish Neonatal Society (SENeo). The Swedish Neonatal Quality Register is funded by the Swedish Government (Ministry of Health and Social Affairs) and the body of regional health care providers (County Councils). SwissNeoNet is partially funded by participating units in the form of membership fees. Tuscany Neonatal Network is funded by the Tuscany Region. The United Kingdom Neonatal Collaborative receives no core funding. MV acknowledges a research grant FIS17/0131 from the Instituto de Investigación Sanitaria Carlos III (Ministry of Science, Innovation and Universities; Kingdom of Spain) and RETICS funded by the PN 2018-2021 (Spain), ISCIII-Sub-Directorate General for Research Assessment and Promotion and the European Regional Development Fund (FEDER), reference RD16/0022.

Role of the Funders/Sponsors: The funding bodies played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix 4 Principles of iNeo data sharing

Background

The overarching goal of iNeo collaboration is to generate new knowledge, develop quality improvement initiatives and monitor changes in outcomes and practices of neonates. In order to effectively use the dataset the following guiding principles for data sharing are developed which are based on the policy by Medical Research Council, UK.[73] Results arising from the data collected and shared as a result of the iNeo collaboration are expected to meet the high standards of conducting database research including scientific quality and ethical requirements. A major impetus behind iNeo collaboration includes the provision that data arising from the iNeo collaboration will be available to the scientific community of participating networks with as few restrictions as possible so as to maximize the value of the data for research and for eventual patient and public benefit.

Currently, each network's dataset are held by the individual networks. Within the framework of the iNeo collaboration, agreed minimal dataset for eligible infants from each network will be transferred to the iNeo Coordinating Centre after proper data transfer agreements are in place. These data will be accessed by iNeo Coordinating Centre research staff with the understanding that they are confidential to the iNeo collaboration only. Preliminary analyses will be conducted at iNeo coordinating center in Toronto.

In order to foster a true international collaboration, the data collected and housed at the iNeo Coordinating Centre will also be available to all iNeo member networks and iNeo-affiliated investigators after the principal analyses of this research proposal are completed. Specific collaborators/contributors from individual networks may take responsibility for certain analyses under the supervision of respective network director (who is a member of the iNeo Governing Board). In the initial phase, it will be preferred to send data requests to iNeo Coordinating center where analyses will be conducted and results will be sent to primary investigator(s). In the later phase of collaboration (after first year), it will be possible to either send dataset with requested variables to investigators or develop an "e-portal" where iNeo dataset could be assessed.

An individual data request will first be discussed and approved by Scientific Advisory Board (made of 2 individuals from each network). Once approved, SAB will direct the Governing Board to instruct iNeo coordinating center to conduct relevant analyses and in the later phase to release dataset to investigators. We are currently exploring the possibility of developing an "e-portal" whereby, under the supervision of their network director, researchers from all networks will be able to gain access to pre-packaged, anonymised and de-identified data subsets to address their research question. In the meantime, researchers interested in using the iNeo data will be asked to come in person to work collaboratively with statistical support available at the iNeo Coordinating Centre or to submit a request to the iNeo Coordinating Centre to have their analyses performed by members of the iNeo Coordinating Centre staff.

In all scenarios/projects involving the analyses and/or transfer of data out of the iNeo Coordinating Centre, approval of project proposals will be the responsibility of the iNeo Scientific Advisory Committee. The Scientific Advisory Committee will be formed of two members from each network and will be responsible for assessing additional projects proposed by member networks/individuals, approving requests for data transfer and analyses, evaluating the results of the primary analyses, advising member sites on knowledge translation, and taking lead roles in addressing Aims 3 and 4 of the research program. In the event that the iNeo collaboration cease to operate, the data collected will be managed according to the decision of the governing board (destruction or return the custody of dataset). At all times the iNeo Director, co-investigators and iNeo staff will ensure that data are held securely and a list of ongoing/completed analyses are made available electronically via the iNeo website (www.ineonetwork.org).

Data sharing policy

Proposals for projects requiring data sharing and transfer will be considered by the iNeo Scientific Advisory Committee. In order to safeguard the scientific integrity and validity of the data, any new studies that request data to be shared to an individual network must receive approval from the Scientific Advisory Committee who will perform a peer review of the proposed project before granting such approval. This process will evaluate and confirm that the:

- Responsibilities and rights of all parties have been agreed at the outset;
- Proposed project has a clear scientific justification, anticipated output, and timeline;
- Appropriate regulatory permissions—ethical, legal and institutional—are in place before data can be shared;
- Funds required to support data extraction and transfer are in place; and

- ❖ Proposals do not overlap with analysis that has been performed or is still being performed.

Privacy and confidentiality will be strictly maintained during any data collection and transfer according to local rules and regulations. No directly identifiable data will be collected or transmitted and in all reports only aggregate data will be presented. The iNeo Director will be responsible for coordinating applications for the use of the data generated by the iNeo collaboration. This will ensure that the iNeo Director is aware of all planned analyses and publications in order to prevent duplication and to coordinate effective dissemination of information.

The collection, collation and transfer of all data will be governed by ethical/regulatory approval from the local granting agencies of each member site and network. Approval from the Research Ethics Board at Mount Sinai Hospital, Toronto for the development, compilation, hosting and management of the iNeo dataset at the MiCare Research Centre will be obtained and maintained as up to date by the iNeo Director.

Publication of approved studies

Researchers who use the iNeo data should send the penultimate draft of any publications to the iNeo Scientific Advisory Committee to ensure correct contextual interpretation of the dataset. A standard acknowledgement that needs to be included in any publication will be provided by the iNeo coordinator. This will include but not limited to the following: "The iNeo Scientific Advisory Committee approved the use of the data included in this publication. Data were extracted from the original dataset for this study by members of the iNeo Coordinating Centre."

Appendix 5 Publication policy

The following outlines the policy on publications based on all analysis of the iNeo dataset and any other related projects:

(I) No publications should precede (i) publication of iNeo protocol, and (ii) publication of the results of the primary network-level analyses, for which the iNeo Governing Board and Scientific Advisory Committee will be listed as authors;

(II) All publications should have "iNeo Collaboration" as final author;

(III) The principal primary analyses comparing outcomes between the eight networks will include the names of all participating units from all networks. This list should be referred back to in each subsequent publication;

(IV) Publications subsequent to the publication of the primary analyses should be authored by individuals who meet the criteria for authorship as laid out by ICJME. These names should be followed by "iNeo Collaboration" as final author;

(V) All data requests will be handled on a first-come first-served basis. Individual investigators will have 12 months to submit their work to journals for publication. After which they may lose right to the analyses and publish the results;

(VI) The names of the members of the iNeo Governing Board and Scientific Advisory Board should be listed in the Acknowledgements/at the end of each manuscript (subject to allowance by the journal);

(VII) Members of the iNeo Governing Board and Scientific Advisory Board could act as authors for individual projects depending upon their contribution to the project;

(VIII) For those publications arising from projects additional to the core research proposed here, a standard acknowledgement should be included in any publication: 'The iNeo Scientific Advisory Committee approved the use of the data included in this publication. Data were extracted from the original dataset for this study by members of the iNeo Coordinating Centre.';

(IX) Publications must conform to the rules of plagiarism and scientific accuracy at all times. This will be the responsibility of the authors of the publication;

(X) Prior to publication, all manuscripts should be submitted to the Scientific Advisory Board for their approval. The members of the Scientific Advisory Board will have 2 weeks to make a decision regarding approval and provide comments or suggestions. If no response is received, the project will be considered approved by the member of SAB;

(XI) Disagreement or disputes regarding authorship and publication should be brought to the attention of iNeo Governing Board. In such events, the decisions of the iNeo Governing Board will be binding to all parties involved.