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Variations in Oxygen Saturation Targeting, and Retinopathy of Prematurity Screening and Treatment Criteria in Neonatal Intensive Care Units: An International Survey

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Keywords

Very preterm infants · Retinopathy of prematurity · Oxygen saturation targeting · Neonatal intensive care · Neonatal networks · Comparative analysis · Erythropoietin

The complete list of iNEO Investigators can be found in the online Supplementary Information.

Abstract

Background: Rates of retinopathy of prematurity (ROP) and ROP treatment vary between neonatal intensive care units (NICUs). Neonatal care practices, including oxygen saturation (SpO_2) targets and criteria for the screening and treatment of ROP, are potential contributing factors to the variations. ***Objectives:*** To survey variations in SpO_2 targets in 2015 (and whether there had been recent changes) and cri-

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teria for ROP screening and treatment across the networks of the International Network for Evaluating Outcomes in Neonates (iNeo). ***Methods:*** Online prepiloted questionnaires on treatment practices for preterm infants were sent to the directors of 390 NICUs in 10 collaborating iNeo networks. Nine questions were asked and the results were summarized and compared. ***Results:*** Overall, 329/390 (84%) NICUs responded, and a majority (60%) recently made changes in upper and lower SpO_2 target limits, with the median set higher than previously by 2–3% in 8 of 10 networks. After the changes, fewer NICUs (15 vs. 28%) set an upper SpO_2 target limit >95% and fewer (3 vs. 5%) a lower limit <85%. There were variations in ROP screening criteria, and only in the Swedish network did all NICUs follow a single guideline. The initial retinal examination was carried out by an ophthalmologist in all but 6 NICUs, and retinal photography was used in 20% but most commonly as an adjunct to indirect ophthalmoscopy. ***Conclusions:*** There is considerable variation in SpO_2 targets and ROP screening and treatment criteria, both within networks and between countries.

Introduction

The incidence of retinopathy of prematurity (ROP) varies considerably among centers, both within [1, 2] and between countries [3]. We recently reported that, for infants born between 24^0 to 27^6 weeks' gestation, the rates of ROP treatment varied from 4.4 to 30.4% across 10 neonatal networks contributing to the International Network for Evaluating Outcomes in Neonates (iNeo) [4]. Differing care practices and treatment criteria are amongst the possible factors contributing to the observed variations.

ROP is recognized as having a multifactorial etiology, but the most consistent associations are lower gestational age (GA), smaller size for gestation, and some measure of oxygen exposure [5]. Both hyperoxia and hypoxia, and fluctuations in oxygenation, are implicated in animal models of oxygen-induced retinopathy and clinical observational studies [5]. Being noninvasive and simple to use, monitoring supplementary oxygen by means of a pulse oximeter measuring oxygen saturation (SpO_2) has become routine since the 1990s [6]. Uncertainties about the optimal SpO_2 target range in preterm infants contribute to variations in practice between neonatal intensive care units (NICUs) [7], whilst recent trials of SpO_2 targeting in preterm infants [8] have resulted in many NICUs reappraising and changing their targets.

To identify possible contributors to the observed variation in rates of severe and treated ROP, we surveyed NICUs included in the iNeo dataset. We specifically sought information on each NICU's current SpO_2 target limits as well as any recent change, the criteria for screening for ROP, the personnel conducting initial retinal examinations, the use of digital photographs, and treatment criteria.

Methods

Online, prepiloted, anonymous questionnaires on treatment practices relating to extremely preterm infants under 29 weeks' gestation (68 questions taking 30 min to complete) were sent to the neonatologist directors of 390 tertiary NICUs in 10 collaborating population-based networks: Australia/New Zealand ($n = 28$), Canada ($n = 30$), Finland ($n = 5$), Israel ($n = 26$), Japan ($n = 204$), Spain ($n = 57$), Sweden ($n = 6$), Switzerland ($n = 12$), Illinois, the USA ($n = 18$), and the region of Tuscany, Italy ($n = 4$). All NICUs are level 3 or mixed level 2 and 3 and provide specialized care for infants born at <29 weeks' gestation. In Japan, 15 of 99 tertiary units do not participate in the iNeo, but the survey was sent to the 84 which do, plus 188 mixed level 2 and 3 units. The neonatologist respondents were instructed to provide answers reflecting their unit practice/protocols, based on their 2015 standards, and not personal preferences. No questions were mandatory, and the response rate was monitored weekly. A reminder questionnaire was sent twice to nonresponding units. The survey commenced in August 2016 and closed in December 2016. The responses were summarized and compared between the networks. The 9 questions relevant to ROP comprised 4 domains: SpO_2 (3 questions), erythropoietin use (1 question), ROP screening criteria and personnel conducting the examination (3 questions), and ROP treatment criteria and mode of treatment (2 questions) (Table 1). Survey questions regarding frequency included the choices: routine (90–100%), often (50–90%), sometimes (10–49%), and rarely/never (0–10%).

Data Analysis

Data are reported using descriptive statistics. The *t* test was used to compare mean percentage differences between the upper and lower SpO_2 target limits for each network and the iNeo collaboration overall.

Ethics Approval

All participating networks obtained ethics/regulatory approval or the equivalent from their local granting agencies as part of the protocol for collaborative comparisons of international health services and practices for quality improvement in neonatal care [9]. Specific approval for this project was obtained from the Research Ethics Board at Mount Sinai Hospital, Toronto where the project was coordinated. The responders were asked to complete the survey only if they provided consent for data assimilation and anonymous reporting.

Table 1. iNeo Web survey questions on treatment practices related to ROP

1	What is the current SpO_2 target range after NICU admission for preterm infants (<29 weeks' GA) in your institution?	Lower limit	Upper limit	Comments
2	Did you change the SpO_2 target range for preterm infants (<29 weeks' GA) after NICU admission recently, based on recent RCTs (SUPPORT, BOOST, COT)?	Yes	No	
3	If yes, what was the prior SpO_2 target range after NICU admission?	Lower limit	Upper limit	Comments
4	Do you generally use erythropoietin for very preterm infants?	<26 weeks'	26–28 weeks	
5	What are the criteria for routine mandatory ROP screening in your unit?	BW-based criteria	GA-based criteria	Other
6	Who generally conducts the initial eye examination for ROP screening in your unit?	An ophthalmologist	A nonophthalmologist	
7	What method is used for the initial eye examination for ROP screening in your unit?	Indirect ophthalmoscopy only	Retinal photography only	Both
8	What are the criteria for ROP treatment (laser ablation/intravitreal anti-VEGF) for your infants (your institution or where you refer them to)?	Type 1 ROP#	Threshold ROP*	Other
9	Do you use anti-VEGF injections for the treatment of ROP?	Yes	No	

iNeo, International Network for Evaluating Outcomes of Neonates; SpO2, pulse oximeter-measured oxygen saturation; NICU, neonatal intensive care unit; GA, gestational age; RCTs, randomized controlled trials (SUPPORT, Surfactant, Positive Pressure and Oxygenation Randomized Trial [13]; BOOST, Benefits of Oxygen Saturation Targeting Trials [14]; COT, Canadian Oxygen Trial [18]); ROP, retinopathy of prematurity; BW, birth weight; VEGF, vascular endothelial growth factor.

Definition according to ET-ROP criteria [10]: Zone I, any stage ROP with disease; Zone I, stage 3 ROP with or without disease; Zone II, stage 2 or 3 ROP with disease.

* Definition according to CRYO-ROP criteria [11]: at least 5 contiguous or 8 cumulative clock hours of stage 3 ROP in the presence of disease.

Results

Overall, 329 of 390 (84%) NICUs responded to some or all of the ROP-related questions, with the response rate varying between 76 and 100% of the participating units in individual networks (median 96%).

SpO_2 Targeting

Of the NICUs that responded, 194 (60%) had recently changed their SpO_2 targets. In 7 networks, a majority of NICUs made changes, in 2 networks 50% of the units made changes, and in Japan, a minority of units (36%) made changes (Fig. 1; online suppl. Fig.; for all online suppl. material, see www.karger.com/doi/10.1159/000490372).

The most common upper SpO_2 target limit prior to change was 92% (range 90–98%), adopted by 25% of NICUs overall and 43% of NICUs making a change, excluding Japan (where only 6 of 151 NICUs adopted this target). After the change, the upper SpO_2 target limit was 94 or 95% (range 90–98%) in 68% of the NICUs. The most common lower SpO_2 target limits prior to change were 88% (in 20% of NICUs) and 85% (in 11% of NICUs). After change, the lower SpO_2 limit was 90% (34% overall and 43% of NICUs making a change). In all networks, the median upper SpO_2 target increased after change, except for Japan where it remained at 95%. Canada and Japan were the only networks where the median lower SpO_2 target did not increase after change, remaining 88% in Canada and falling from 90 to 88% in Japan.

After any SpO_2 target change, fewer NICUs adopted an upper SpO_2 target >95% (15 vs. 28% before any change) and all but 4 of the 50 NICUs with an upper SpO_2 target >95% after any change were in Japan. After change, 10

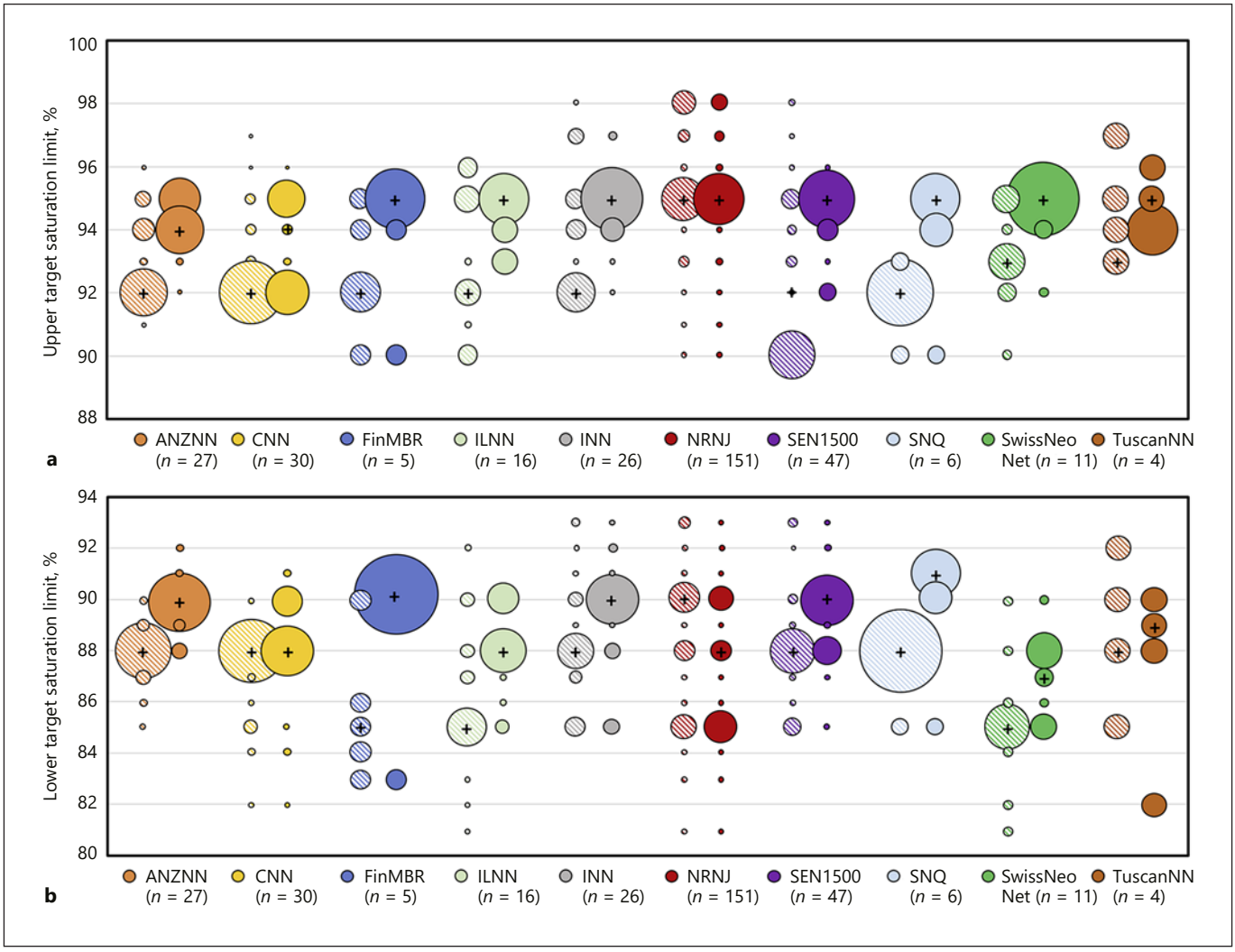

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Fig. 1. Upper (**a**) and lower (**b**) oxygen saturation (SpO_2) target limits before (left) and after (right) any changes in response to published SpO_2 targeting trials [13, 14]: all iNeo NICUs responding to the survey. The size of the circle corresponds to the percentage of units within the network, i.e., a larger circle denotes a higher percentage. The median value for each network is indicated with "+"; *n*, number of NICUs. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane Online.

NICUs adopted a lower target <85% compared with 15 NICUs before change.

Table 2 shows the mean difference between the upper and lower SpO_2 targets limits in 2015 and prior to any change, for either all NICUs in each network or only NICUs that changed SpO_2 targets. In the Australian and New Zealand Neonatal Network (ANZNN) and Finland, the SpO_2 target range was significantly narrower after change, both for the network overall and for those NICUs making a change. However, in Canada, the SpO_2 target range was significantly narrower only in the 50% of the NICUs making a change. In contrast, in Japan, the target range was significantly wider in the 43% of NICUs making a change. There were no other significant differences in SpO_2 targets limits, in either individual networks or the iNeo overall.

ROP Screening Criteria

A majority of NICUs used screening criteria based on a GA and/or birth weight (BW) cut-off (only 1 was re-

Table 2. Mean percentage difference between upper and lower SpO_2 target limits in 2015 and prior to any change for each network overall or NICUs that changed the SpO_2 target

Network	2015 targets		Prior targets		*p*
	n	mean	*n*	mean	
ANZNN					
All units	26	4.4	27	5.2	0.007
Change units	25	4.4	25	5.2	0.007
CNN					
All units	30	5.27	30	5.83	0.17
Change units	15	4.73	15	5.87	0.04
FinMBR					
All units	5	5.2	5	6.6	0.04
Change units	3	4.67	3	7.0	0.01
ILNN					
All units	16	6.19	16	6.88	0.18
Change units	14	6.21	14	7.0	0.17
INN					
All units	26	5.58	26	5.7	0.41
Change units	19	5.47	19	5.68	0.35
NRNJ					
All units	151	8.26	151	7.3	0.08
Change units	66	7.82	66	7.11	0.02
SEN1500					
All units	47	4.98	47	5.32	0.15
Change units	37	5.19	37	5.62	0.12
SNQ					
All units	6	4.17	6	4.33	0.27
Change units	5	4.0	5	4.2	0.17
SwissNeoNet					
All units	11	7.55	11	8.0	0.33
Change units	8	7.12	8	7.75	0.31
TuscanNN					
All units	4	7.5	4	6.0	0.21
Change units	2	9.5	2	6.5	0.21
iNeo Total					
All units	**323**	**6.7**	**323**	**6.5**	**0.28**
Change units	**194**	**6.12**	**194**	**6.23**	**0.31**

SpO_2, pulse oximeter-measured oxygen saturation; NICU, neonatal intensive care unit; ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane Online; iNeo, International Network for Evaluating Outcomes of Neonates.

quired) (Fig. 2), but there remained considerable variation, and only Sweden had a single guideline for all NICUs (<31 weeks' GA with no BW cut-off). The most common screening criterion was GA <31 weeks' or BW <1,250 g. However, some NICUs used a GA cut-off of <30 weeks' and some a BW cut-off of <1,000 g.

In all networks, an ophthalmologist usually completed the initial eye examination. In 6 NICUs (4 in the ANZNN and 2 in Japan), the initial examination was undertaken by a nonophthalmologist. Whilst most NICUs in all networks used indirect ophthalmoscopy for this examination, retinal photography was used in some NICUs in each network, most frequently together with ophthalmoscopy (15% all NICUs). Fourteen NICUs (5%) spread over 6 networks used retinal photography alone for the initial eye examination.

ROP Treatment Criteria

There was variation in treatment criteria both within and between networks (Fig. 3), with most NICUs (65%) using early treatment (ET)-ROP type 1 disease criteria [10], 29% CRYO-ROP threshold criteria [11], and a few (6%) other criteria. Anti-VEGF (vascular endothelial growth factor) therapy was used in 43% of NICUs and in all 10 networks (range 23–81% of NICUs).

Erythropoietin Use

Erythropoietin was not used in Canada, Finland, or Sweden, and rarely in other networks (4–23% of NICUs), except for Spain (42% of NICUs) and Japan (93% of NICUs). These results did not differ for infants <26 weeks' and 26–28 weeks' GA.

Discussion

In this large international survey, we identified considerable variation in SpO_2 target limits for very preterm infants across 329 contributing NICUs from 10 networks and 11 countries. A majority (60%) of NICUs made changes, such that the median lower and upper SpO_2 target limits were set 2–3% higher than previously in 8 of the 10 networks. ROP screening criteria varied considerably amongst NICUs, with Sweden being the only network with a single guideline followed by all NICUs. The initial retinal examination was carried out by an ophthalmologist in all but 6 NICUs. Retinal photography was used in 20% of the NICUs, with 75% of these using it at the same time as indirect ophthalmoscopy. Treatment criteria varied less than screening criteria, with all but 6% of the NICUs following 1/2 criteria; however, only 65% NICUs treated ET-ROP type 1 disease [10]. In 8 networks, erythropoietin was never or rarely used, but it was used in 43% of NICUs in Spain and 93% in Japan.

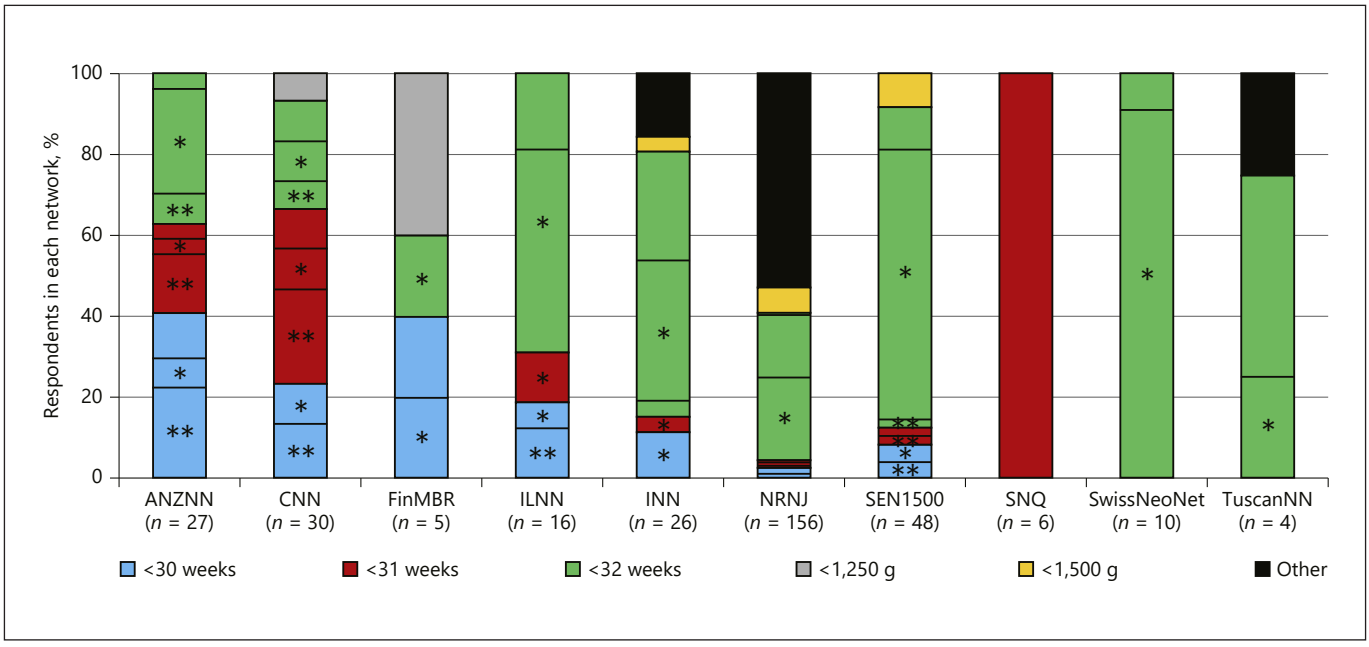

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Fig. 2. Retinopathy of prematurity (ROP) screening criteria. All numbers are the percentage of units within each network. * Indicates that the screening criteria is a combination of the specified gestational age (GA) or a birth weight (BW) <1,500 g; ** indicates that the screening criteria is a combination of the specified GA or a BW <1,250 g. The category "Other" included GA <29 weeks in combination with different BWs, and BW <1,000 g with different combinations of GA. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane Online.

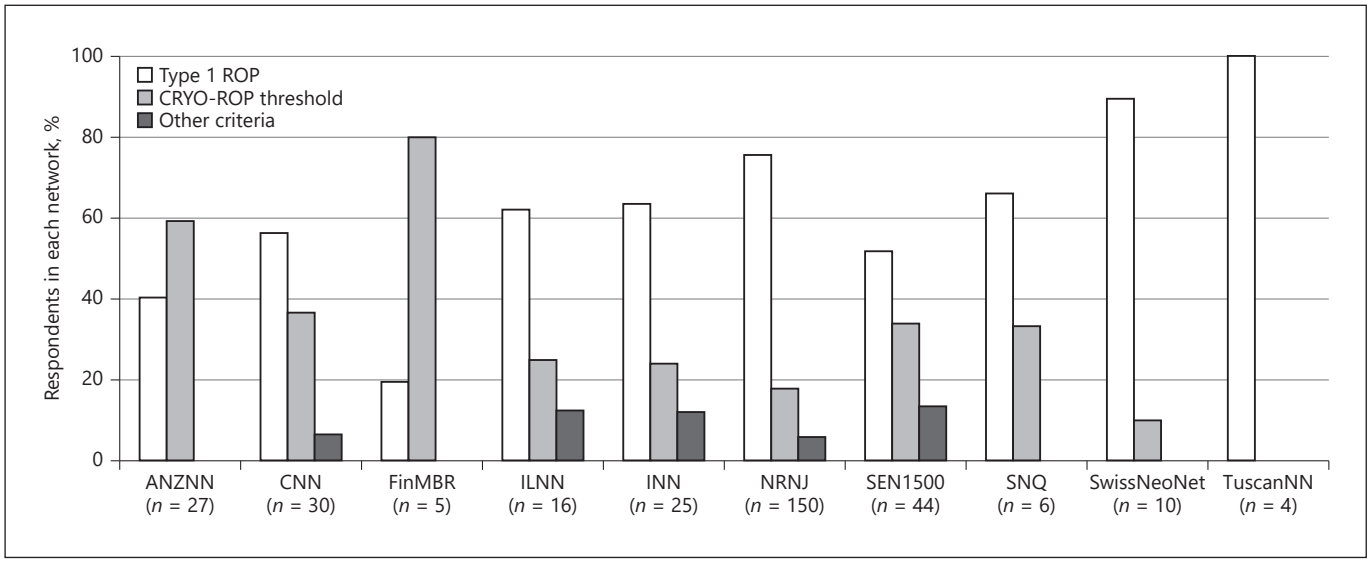

Fig. 3. Retinopathy of prematurity (ROP) treatment criteria. All numbers are a percentage of units within each network. # Type 1 ROP as defined by the Early Treatment for Retinopathy of Prematurity Cooperative Group 2003 [10]; * threshold ROP as defined by the Cryotherapy for Retinopathy of Prematurity Cooperative Group 2001 [11]. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; ILNN, Illinois Neonatal Network; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, TIN Toscane Online.

A recent survey of 200 European NICUs reported that 81% had changed their SpO_2 limits in the previous 10 years [12], with new limits typically 3–5% higher than previously, and 54% of NICUs citing strong or very strong scientific evidence in support of these changes. Although we did not survey the reasons for change, it is probable that the 60% of NICUs that changed their SpO_2 targets also did so in response to recent trial data and the resulting commentaries [13–16].

The 5 recent trials of lower (85–89%) or higher (91–95%) SpO_2 targeting in infants <28 weeks' gestation all found no differences in the primary outcome of death or neurodevelopmental impairment at 18–24 months of age [17–20]. However, 3 trials reported an increased risk of death at hospital discharge in infants randomized to the lower SpO_2 target [13, 14]. A Cochrane review of all 5 trials, comprising nearly 5,000 infants, confirmed an increased risk of death at 18–24 months (risk ratio [RR] 1.16; 95% confidence interval [CI] 1.03–1.31]) and severe necrotizing enterocolitis (RR 1.24; 95% CI 1.05–1.47) with the lower SpO_2 target, but a decreased risk of ROP requiring treatment (RR 0.72; 95% CI 0.61–0.85) [8]. It is likely that concerns about increasing the risk of ROP is one reason why not all NICUs have adopted higher SpO_2 targets [21–23]. However, our survey suggests that whilst many NICUs did change to higher SpO_2 targets, some with initial upper limits >95% changed to an upper limit of ≤95%, most notably in Japan. In our previous report, we found that Japan had the highest rate of both ROP and ROP treatment for infants 24^0 to 27^6 weeks' gestation [4]. It will be interesting to see if the altered SpO_2 targets impact the incidence of ROP in Japan and other countries over the coming years.

Japan and Canada were the only networks where the median lower SpO_2 target did not increase after any SpO_2 target change, although in the 50% of NICUs in Canada that changed SpO_2 targets, the median lower target increased from 88 to 90%. The relative stability of the lower SpO_2 target in Canada might be because many NICUs collaborated in the Canadian Oxygen Trial (COT), which did not find a difference in mortality between lower and higher SpO_2 targets [18]. No NICUs in Japan were involved in the recent trials, and only a minority made any change in SpO_2 targets.

The NeOProM trials investigated the effects SpO_2 target limits rather than alarm limit settings. In a preliminary study using the trial Masimo SpO_2 monitor, compliance with SpO_2 target limits was found to be only 50% on average [7]. Compliance was improved when the alarm limits were tighter at 1% above and 1–2% below the target limits, and also when the SpO_2 target was wider. In 8 of the 10 iNeo networks, the median SpO_2 target range was narrower after change, although this was only significant in the ANZNN and Finland. Interestingly, Switzerland and the ANZNN had the lowest rates of ROP treatment in our previous study, but here they had respectively relatively wide (7.6%) and narrow (4.4%) median target ranges [4]. How best to achieve compliance with target ranges remains controversial, but having set alarm limits and feedback on compliance are likely to be important [24, 25].

Japan was the only network where a majority of NICUs (93%) treated very preterm infants with erythropoietin. In a meta-analysis of erythropoietin treatment to prevent anemia of prematurity, receipt of erythropoietin was associated with a significantly increased risk of severe ROP (RR 1.48; 95% CI 1.02–2.13) [26]. Japan had both the lowest mortality and highest rate of ROP treatment in the iNeo [4], and any association with erythropoietin use would require further investigations.

The ROP screening criteria used varied within every network with the exception of Sweden, where a single recommendation was followed. Screening criteria, ideally, should be based on national or regional epidemiology, such as the ongoing active surveillance provided by SWEDROP [27]. It is possible that some variations in screening criteria reflect local epidemiology, but a review of national guidelines may also be warranted.

Digital retinal photography by trained nonopthalmologists has the advantage of decreasing the time burden on ophthalmologists and provides a permanent record of the retinal findings. There is some evidence that remote reading of digital images has good sensitivity for referral-warranted ROP, requiring an examination by an ophthalmologist [28], and it is likely that this approach will be more widely used in the future.

We identified that 29% of NICUs stated they were using CRYO-ROP criteria despite the benefits of earlier treatment [10]. A sub-sample of ANZNN NICUs was resurveyed on this question, and all respondents (90% of those surveyed) indicated that they used ET-ROP type 1 criteria, some acknowledging having previously misread the question. Even though the criteria were clearly defined in the original questionnaire, the term "threshold" (and variants such as pre-threshold) is used loosely in the literature and can be misleading. It is possible that responses to this question from other networks were similarly affected; therefore, it is hard to draw conclusions from this part of the survey without resurveying all NICUs, which was not practical. Anti-VEGF therapy was

used in some NICUs across all networks, but we did not survey specific indications for its use, or whether initial or rescue therapy was used.

The strengths of our survey include a large, multinational engagement with a high response rate. We captured contemporary practice and the changing nature of practice in response to new evidence. A limitation was that the survey was completed by a single individual at each site but we did seek NICU policies rather than opinions, so this should not be a source of bias. Ambiguity in questionnaires is always a concern. We trialled the survey questions amongst iNeo authors, and no problems were identified with the ROP treatment criteria question, but some of the actual survey respondents appeared to misunderstand the question. As part of a larger survey, we had to limit the number of questions related to ROP, and others, including SpO_2-monitor alarm settings, could be considered in future surveys. We did not link the survey results to actual outcomes, which will be the next research project for our iNeo collaboration. In addition, we envision that these data will inform quality improvement initiatives across each network.

In conclusion, we have identified considerable variation in SpO_2 targets, both within networks and between countries, despite recent changes by many NICUs to adopt higher SpO_2 targets, with the upper limit most frequently set at 94–95%, the lower limit at 90%, and a trend to narrower SpO_2 targets. In 2015, fewer NICUs than previously targeted SpO_2 limits >95% or <85%. Ongoing collaborative research is needed to identify and monitor the effects of changing neonatal practices and optimize outcomes for very preterm infants.

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Disclosure Statement

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