Oxygen Treatment for Immature Infants beyond the Delivery Room: Lessons from Randomized Studies

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Without supplemental oxygen, extremely preterm infants often have low arterial oxygen tension (PaO_2) or arterial oxygen saturation (SaO_2) compared with older children. Until recently, oxygen was administered to these infants in the early weeks after birth, with little evidence to balance the risks and benefits. Five large randomized controlled trials of lower (85%-89%) vs higher (91%-95%) pulse oximeter saturation (SpO_2) targets with masking of group allocation now provide high quality evidence to guide practice and serve as a baseline for future research. It remains the case that restriction of supplemental oxygen in pursuit of reduced morbidities in this patient group carries a mortality risk that outweighs any other benefit. The evidence reiterates the need for caution against creeping change in practice. This review will summarize the evidence base for present approaches to titrating supplemental oxygen for preterm infants, provide deeper insights into the interpretation of the evidence from the recent trials, and identify some future challenges in improving care in this area.

Background

When oxygen therapy was introduced into neonatal care, oxygen tensions could not be measured and administration was guided by clinical judgement. High concentrations were often administered for prolonged periods. Trial evidence that several weeks of exposure to high concentrations of oxygen increased the risk of severe retinopathy of prematurity (ROP) prompted more restricted administration, and in the subsequent period, there was an increase in neonatal mortality and cerebral palsy. It has been estimated that oxygen restriction may have resulted in the death of 16 infants for each case of blindness that was prevented,[1] although other factors probably also contributed to the association.[2]

The development of blood gas analyzers, transcutaneous oxygen tension ($TcPO_2$) monitors, and pulse oximeter saturation (SpO_2) monitors allowed controlled oxygen therapy, with titration of oxygen to target values, but trials were not done to establish the optimal targets or monitoring technology. Clinical guidelines were developed from observational data and recommended that PaO_2 should be maintained between 50 and 80 mm Hg (6.7-10.7 kPa),[3] and later that SpO_2 should be targeted to 85%-95%.[4] PaO_2 and SpO_2 are not linearly related, and these ranges cannot be considered equivalent. The PaO_2 range associated with the SpO_2 range 85%-95% in oxygen dependent preterm infants in the first 2 weeks after birth is 28.5-67 mm Hg (3.8-8.9 kPa).[5] This indicates that the switch from $TcPO_2$ monitoring targeting a PaO_2 range of 50-80 mm Hg to SpO_2 monitoring targeting a saturation range 85%-95% ushered in a second era of unrecognized oxygen restriction, unsupported by trial evidence. Because these changes in practice occurred gradually and in parallel with reductions in mortality associated with increased implementation of antenatal steroid therapy and refinements to surfactant administration, any effect on mortality from changes in practice regarding oxygen supplementation during this period is unlikely to be identifiable in retrospect.

In the 1980s, it was increasingly recognized that oxidative stress is not only related to oxygenation. A number of other factors such as activities of antioxyenzymes,[6] free radical systems,[7] free iron,[8] and inflammation[9] all contribute to increased oxidative stress in the newborn. This created new interest concerning the optimal oxygen levels of the newborn and increased recognition that the optimal oxygen levels for premature infants may be different to those for older children and adults.

With wider use of SpO_2 monitoring, observational data suggested that targeting lower SpO_2 might reduce the risk of ROP without affecting the risk of mortality or cerebral palsy.[10-12] In the absence of evidence from controlled trials, Silverman argued that there had never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants.[13] At the turn of the century, the time was right for randomized controlled trials of oxygen targeting.

AAP	Academy of Pediatrics
BOOST	Benefits of Oxygen Saturation Targeting
BPD	Bronchopulmonary dysplasia
COT	Canadian Oxygen Trial
NEC	Necrotizing enterocolitis
NeOProM	Neonatal Oxygen Prospective Meta-Analysis
PaO_2	Arterial oxygen tension
ROP	Retinopathy of prematurity
SaO_2	Arterial oxygen saturation
SUPPORT	Surfactant Positive Pressure and Oxygenation Randomized Trial
$TcPO_2$	Transcutaneous oxygen tension
UK	United Kingdom

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STOP ROP and the First BOOST Trial

Two trials randomized convalescent preterm infants to higher vs lower SpO_2 targets. The Supplemental Therapeutic Oxygen for Pre-threshold Retinopathy of Prematurity (STOP ROP) trial[14] randomized preterm infants with prethreshold ROP at 35 weeks of gestation to lower (89%-94%) vs higher (96%-99%) SpO_2 targets. The hypothesis was that a higher oxygen tension at this later stage could retard the progression of established ROP. There was a small but clinically unimportant effect on ROP progression. The higher SpO_2 target was associated with more adverse pulmonary events and a greater number of infants still receiving oxygen or diuretics or still hospitalized at 3 months of corrected age.

The aim of the first Benefits of Oxygen Saturation Targeting (BOOST) Trial[15] was to determine whether maintaining SpO_2 at a higher level in extremely preterm infants with a long-term dependence on supplemental oxygen improved their growth and neurodevelopmental outcomes. Infants who were born before 30 weeks of gestation and who remained dependent on supplemental oxygen at 32 weeks of gestation were randomized to lower (91%-94%) vs higher (95%-98%) SpO_2 targets. There were no advantages in terms of growth and development in the higher target range, and it prolonged the duration of oxygen supplementation and increased resource usage. The BOOST trial masked the caregivers to the SpO_2 target range allocation of the infants by using offset oximeters that were adjusted to read 2% higher or lower than the underlying measured value.

Neonatal Oxygen Prospective Meta-Analysis

The 2 studies described above did not randomize infants to different oxygen saturation targets until several weeks after birth. It, therefore, became important to study the effects of different oxygenation from soon after birth. For this reason, the Neonatal Oxygen Prospective Meta-analysis (NeOProM) collaboration was launched.[16]

Five trials randomized preterm infants born before 28 weeks of gestation from the day of their birth to lower (85%-89%) vs higher (91%-95%) SpO_2 target ranges until the infants reached 36 weeks of postmenstrual age. Close to 5000 patients were enrolled. Outcome data up to at least 18-22 months have now been published from all of the trials.[17-22] The trials were prospectively designed to be very similar to permit meta-analysis. Two meta-analyses of the results, including the follow up outcomes have been performed.[23,24] The NeOProM individual participant data meta-analysis of the trials adds value in addition to the Cochrane review because of the enhanced ability to consider sub-group effects provided by the availability of individual participant data for the analyses.[24] There was not significant heterogeneity between trials for key outcomes (**Table I**).

The primary outcome of the meta-analyses—a composite of death or disability (blindness, deafness, cognitive impairment, or cerebral palsy) was not significantly different between groups. However, infants randomized to the lower (85%-89%) SpO_2 target range had significantly increased risk of mortality (risk difference 2.8%) and increased risk of necrotizing enterocolitis (NEC) (risk difference 2.2%). Infants randomized to higher (91%-95%) SpO_2 targets had a higher risk of ROP requiring treatment (risk difference 4.2%). Although these differences are modest, the lack of heterogeneity between trials and statistical significance, with large patient numbers make them likely to be reliable. There was no difference between groups in the risk of blindness, cerebral palsy, or deafness.

Assessing the effect of the intervention on bronchopulmonary dysplasia (BPD) is difficult. Because the protocols required one group to achieve higher SpO_2 readings than the other until 36 weeks, it is not surprising that significantly more infants randomized to higher SpO_2 targets required supplemental oxygen at 36 weeks of postmenstrual age (risk difference 5.9%). This estimate is biased by the protocols. To overcome this limitation, physiological tests were used in the Surfactant Positive Pressure and Oxygenation Randomized Trial (SUPPORT)[17] and BOOST-II United Kingdom (UK)[20] trials to determine the number of infants in each group who required supplemental oxygen at 36 weeks of gestation to achieve a SpO_2 of 90%.[25,26] If analysis is restricted to these 2 trials, the difference between groups in risk of BPD is smaller and not statistically significant (risk difference 2.4%, $P = .29$, **Table II**). Severe BPD (a requirement for positive pressure support or more than 30% oxygen at 36 weeks of postmenstrual age after receiving supplemental oxygen for at least 28 days) was reported in the Canadian Oxygen Trial (COT). This measure of more severe BPD was biased by protocol for the same reasons. It was observed in 31.8% of low SpO_2 target group infants and 33.1% of high SpO_2 target infants in the COT and was also not significantly different between groups (risk difference 1.3%, $P = .64$).

Table I. Meta-analysis of the NeOProM trials[23]

Outcomes	SpO_2 85%-89%	SpO_2 91%-95%	Risk ratio	95% CI	*P*	I^2	Risk difference
Death or major disability	1218/2380	1170/2374	1.04	0.98-1.10	0.18	27%	1.9%
Death	484/2433	418/2440	1.16	1.03-1.31	.012	0%	2.8%
Major disability	734/1903	752/1964	1.01	0.93-1.09	0.80	22%	0.2%
Severe ROP	214/2022	305/2067	0.72	0.61-0.85	<.001	69%	4.2%
NEC	277/2464	223/2465	1.24	1.05-1.47	.011	0%	2.2%
Blindness	25/1910	23/1965	1.13	0.65-1.97	0.66	0%	0.1%
Cerebral palsy	106/1910	107/1967	1.02	0.79-1.32	0.88	20%	0.1%
Deafness	65/1905	66/1964	1.02	0.73-1.43	0.91	0%	0%

BSID-III, The Bayley Scales of Infant and Toddler Development–Third Edition.
Major disability was any of cerebral palsy with Gross Motor Functioning Classification System level 2 or higher, BSID-III composite cognitive or language score <85, blindness, or deafness. Severe ROP was disease >stage 3 or requiring treatment by laser photocoagulation, cryotherapy, or bevacizumab treatment. Definition of NEC was defined differently between trials.

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Table II. Requirement for supplemental oxygen at 36 weeks of postmenstrual age (all 5 trials) and BPD defined using a physiological test of oxygen dependency at 36 weeks of postmenstrual age (2 trials)

	SpO_2 85%-89%	SpO_2 91%-95%	Risk ratio	95% CI	*P*	I^2	Risk difference
O_2 at 36wk	788/2057	936/2118	0.87	0.81-0.94	<.001	44%	5.9%
BPD	365/893	409/944	0.94	0.85-1.05	0.29	0%	2.4%

The Significance of a Change in the Oximeters Midway through the Trials

An additional complexity comes from the identification after the trials commenced recruitment of an issue with the calibration of the Masimo Radical oximeters (Masimo, Irvine, California) used in all 5 trials.[27] This was a feature of Masimo oximeters in general at the time and was not limited solely to the trial oximeters. The oximeter returned fewer SpO_2 values than expected in the 87%-90% range and shifted displayed SpO_2 values above 87% upward by 1%-2%. This narrowed the lower SpO_2 target range because readings above 87% that would otherwise have been in the low target range of 85%-89% were inflated to higher values that were above the target range. It also pushed the groups together and lowered the SpO_2 range under study because SpO_2 values in the high target range of 91%-95% were being falsely elevated by up to 2% when they were in fact lower. The manufacturers provided revised calibration software that eliminated the issue.[27] Revised oximeters were introduced into the UK and Australian BOOST-II trials[20] and the COT.[19] These 3 trials, therefore, have subpopulations of infants treated with the original and the revised oximeters. After the revised oximeters were introduced, there was clearer separation between groups in histograms of SpO_2 distribution in the UK and Australian BOOST-II trials and the infants allocated to lower SpO_2 spent more time in their intended target range.[20] An analysis of the median SpO_2 values in the BOOST-II trials before and after the revision of the oximeters has suggested that the oximeter revision had less effect on the median SpO_2 values,[28] but the aim of the trials was to determine the relative risks and benefits of higher and lower SpO_2 values, not central values. Analysis of the medians excludes the time the infants spent with high or low SpO_2.

The oximeter revision changed the intervention and meant that the revised study oximeters returned saturation distributions more like those obtained with other oximeters.[27] Consequently, the data gathered using the revised oximeters are worth considering separately. Recruitment was completed to the planned sample size in the COT. The BOOST-II UK and BOOST-II Australia trials were stopped early when an interim safety analysis performed by the data monitoring committees showed a highly significant difference in mortality between groups in infants treated with the revised oximeters.[20] In the 1716 infants treated with revised oximeters in BOOST-II UK, BOOST-II Australia, and the COT trial, the difference in mortality between infants randomized to lower vs higher SpO_2 targets was 6.1% (risk ratio 1.38, 95% CI 1.13-1.68, $P = .001$, number needed to treat 17).[23] A test for interaction showed a significant difference between mortality results obtained with the original and revised oximeters ($P = .03$).

Infants treated with the revised oximeters were enrolled later than the infants treated with the original oximeters. An alternative explanation for the larger mortality difference observed with the revised oximeters would be that oxygen targeting became more successful over time as the trials progressed. If this hypothesis is correct then the possibility that greater success in achieving the study target saturations increased the difference in mortality would have a similar implication—that the result for mortality pooling all data from the 5 trials may underestimate the mortality risk of targeting lower SpO_2.

Implications for Patients

The trial groups chose to use a composite of death or disability as the primary outcome, and this was not statistically significantly different between groups. This requires careful interpretation. An individual patient could not have both elements of this composite. It would be incorrect for parents or clinicians to assume that the lack of a significant effect on the composite primary outcome means that the significant effect on mortality was in some way counterbalanced by an opposite effect on disability. This was not the case. The trials show without heterogeneity that targeting higher saturations increased the chances of an infant surviving by 2.8% (all data) to 6.1% (revised oximeters). Despite their greater numbers, the survivors who were randomized to the higher SpO_2 target range were not at greater risk of disability or blindness than the survivors who were randomized to the lower SpO_2 target range. One or more of the measures of disability was identified in 38.5% of low target group survivors and in 38.3% of high target group survivors. The percentage of survivors with the individual outcomes of blindness, deafness, or cerebral palsy was not higher in the high target group survivors. So for the management of the individual patient, this is in our opinion very clear. The higher saturation target range should be preferred.

The estimate of relative risk for the composite outcome of death or disability is dominated by the measures of disability because overall disability in survivors (38.4%) was more than twice as common as death (18.5%). With no significant difference in disability between groups, the significant effect on mortality was swamped in the composite outcome by the lack of a difference in disability.[29] It might be a lesson for future large-scale collaborations to be cautious in the choice of composite outcomes because of the complexity of their interpretation.

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Disability in these studies was defined by any of, or a combination of deafness, blindness, cerebral palsy, or cognitive impairment. These impairments vary in severity and should not in most cases be considered equivalent to or worse than death. Because there were more survivors in the high target group, for the percentage of survivors with disability to be the same between groups, the absolute number of surviving infants with a disability who were randomized to the higher target range is slightly greater.

The trials show unequivocally that treating patients with higher SpO_2 target ranges will result in more infants being treated for ROP. Fortunately, this treatment is usually effective and there was not an increase in the number of blind infants. There were in fact 2 more blind infants in the lower SpO_2 target groups than in the higher target groups despite there being a greater number of high-target group survivors. The historical observation that oxygen restriction may have caused 16 additional deaths for each case of blindness prevented[1] can, therefore, now be revised. In these trials, there were 66 additional deaths in the 2433 infants in the low-target groups without a single case of blindness being prevented. Nevertheless, an increase in infants requiring treatment for ROP is an undesirable outcome. The treatment is invasive and has permanent structural effects on the development of the eye. Hopefully future advances in prevention and treatment will diminish this concern. Retinopathy of prematurity has been associated with increased risk of other adverse outcomes of prematurity,[30] but in the NeOProM trials, the increased risk of ROP requiring treatment in infants randomized to higher SpO_2 was not accompanied by any increase in the risk of other adverse outcomes.

How do Lower SpO_2 Targets Increase the Risk of Mortality?

When these trials were planned, available observational data did not suggest that lower SpO_2 targets would be associated with increased risk of mortality.[10] The lower target range was within the range of values considered clinically appropriate,[4] and yet the lack of heterogeneity in the mortality findings shows that the NeOProM trials are remarkably consistent. This reinforces the importance of randomized trials over observational data. There was no single cause of mortality that explains the mortality difference in isolation, although NEC was an important contributor.

It will be important to analyze further the achieved saturation patterns in the trials and their relation to outcomes. This will require knowledge of the proportion of time infants spent at each saturation value over the entire range throughout the intervention. Analyses should not be restricted to the time when the infants were breathing supplemental oxygen. If time spent with lower SpO_2 is harmful, this is likely to be the case whether or not the infant was breathing supplemental oxygen and the infants in the lower target groups were intended by protocol to have lower SpO_2 readings even when breathing air. It should not be assumed that the explanatory factor is the time spent with markedly low SpO_2 because this is only a small proportion of total time. It may be equally important to consider what SpO_2 readings the infants with morbidity or mortality spent more of their time at.

The degree of separation between groups in SpO_2 distribution that was achieved in these trials is smaller than was intended by protocol, substantially because the lower target groups had higher than intended SpO_2. The higher target groups did not have lower than intended values.[20] Observational data suggest that compliance with targets is more readily achieved with higher SpO_2 upper limits.[31] Lower SpO_2 values are on the steeper part of the hemoglobin-oxygen dissociation curve, where small changes in alveolar oxygen tension will produce bigger swings in saturation and are, therefore, intrinsically more unstable.[32] With manual oxygen adjustment, time spent in range is greater when a higher range is targeted.[20,33]

The available data regarding achieved SpO_2 from the trials are limited because not all of the trials have published details of their achieved SpO_2 patterns. Comparisons so far are limited to achieve median SpO_2 while breathing supplemental oxygen. An individual infant's median SpO_2 value gives no information about how much time was spent with high or low SpO_2 or within the intended target range, and the randomization group distribution of these medians conveys limited information. Even with this limitation it is clear that the distributions of median SpO_2 values differed between trials.

A post-hoc analysis of data from the COT showed that observed mortality differences between randomized groups were not larger in centers that achieved greater separation between groups in median saturations whereas breathing supplemental oxygen for more than 12 hours per day,[34] so separation between groups in median saturations may not be a strong determinant of risk. However, this information is difficult to interpret in the absence of more detailed information about achieved SpO_2 and with the analysis restricted to time breathing supplemental oxygen. If there is an important threshold of SpO_2 to optimize survival, the influence of separation between groups in median SpO_2 may depend on where in the SpO_2 range that separation occurs.

An analysis from the SUPPORT trial suggested that the risk of mortality was significantly increased in infants with median SpO_2 during the first 3 days after birth in the lowest quartile of observed median values (less than or equal to 92%).[35] It should be noted that this value is well above the upper limit of 89% SpO_2 intended for infants randomized to the lower SpO_2 target range.

It has been suggested that the masking algorithm used to conceal treatment allocation distorted the displayed (masked) SpO_2 values in the COT and that this may have influenced nursing staff behaviors, reducing the separation between groups.[36] This analysis has not been reported for the underlying achieved SpO_2 readings.

Whatever the explanation, the lower target groups in the NeOProM trials achieved higher than intended SpO_2 and this should raise a caution that the mortality risk of achieving the lower SpO_2 target range may be underestimated.

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The trials were planned to take part in an individual participant data prospective meta-analysis and this enabled detailed sub-group analyses. The post-hoc sub-group analysis of the data from SUPPORT which generated a hypothesis that the effect of low SpO_2 targets on mortality might be observed mostly in growth restricted infants was not confirmed.[37] The pre-specified subgroup analysis of the full NeOProM dataset using a common definition of SGA and a further post-hoc analysis using the same definition used in the SUPPORT trial did not show a significant difference between small for gestational age and appropriate for gestational age infants in the effects of SpO_2 targets on risk of mortality at 18-24 months.[38,39] In further sub-group analyses of the NeOProM dataset there were not significant differences in the effect of the intervention on mortality related to gender or gestation at birth.[24]

If the trials influence practice and clinical teams pay more attention to oxygen target ranges and alarm settings, and particularly if the use of automated systems becomes more widespread, this may bring further opportunity to improve outcomes. If the higher SpO_2 range is implemented without appropriate education of nurses respiratory therapists and physicians, there is a risk that exposure to higher than intended SpO_2 values will be increased and that this may alter the balance of risks and benefits.

Oximeter Alarm Limits in the NeOProM Trials

The study group allocation in the NeOProM trials was masked to the caregivers by the oximeters having an offset that caused the oximeter to display a value 3% higher or 3% lower than the actual value. Infants in both randomization groups were targeted to the same displayed SpO_2 range of 88%-92% to deliver the target actual SpO_2 ranges of 85%-89% and 91%-95%. The trial protocols advised upper and lower alarm settings (in the BOOST II-UK trial there was an advised high SpO_2 alarm value but not an advised low alarm value). These advised alarm limits took the offset into account. The underlying actual SpO_2 alarm settings that were advised can be determined and they were similar between the trials (**Table III**). In all of the NeoProM trials, for infants in the high target groups the advised alarm settings meant that the oximeters would sound an alarm at an actual SpO_2 of 96% (equivalent to an upper alarm setting on a nontrial oximeter of 95%). The advised lower alarm would sound at an actual SpO_2 of either 88% or 89% (equivalent to a lower alarm setting on a nontrial oximeter of 89% or 90%. For the low target groups, the advised alarm settings meant that the oximeters would sound an alarm at an actual SpO_2 of 84% (equivalent to a lower SpO_2 alarm limit of 85%). The upper alarm would sound at an actual SpO_2 of either 91% or 92% (equivalent to an upper alarm limit of 90% or 91%). There was not significant heterogeneity between the trials in the results for mortality or NEC. Achieved SpO_2 distributions were similar between the infants in BOOST-II UK and BOOST-II Australia in the absence of a protocol recommended low SpO_2 alarm setting in the UK trial. Clinicians wishing to implement the evidence by using the alarm settings used in the NeOPrOM trials for the high SpO_2 target groups might, therefore, consider using a high SpO_2 alarm setting of 95% and a low SpO_2 alarm setting of either 89% or 90% if they are using a device that alarms when the set limit is crossed.

International Guidelines

New clinical recommendations and guidelines have recently been published. The Committee on Fetus and Newborn of the American Academy of Pediatrics (AAP) released guidance on oxygen targeting in preterm infants[40] but stopped short of recommending a target range or a lower alarm limit. The report predated the most recent meta-analyses of the full outcomes from the trials. Given that the trials were explicitly designed with prospective individual participant data meta-analysis in mind, we recommend that the AAP review their conclusions and provide practical guidance in the light of the new

Table III. SpO_2 values that would trigger an oximeter alarm in the NeOProM trials

High target groups	Low alarm setting (Displayed SpO_2)	High alarm setting (Displayed SpO_2)	Actual SpO_2 for a low alarm	Actual SpO_2 for a high alarm
SUPPORT	86	94	88	96
COT	87	93	89	96
BOOST-II Aus	86	94	88	96
BOOST-II NZ	87	93	89	96
BOOST-II UK*	NA	94	NA	96
Low target groups	**Low alarm setting (Displayed SpO_2)**	**High alarm setting (Displayed SpO_2)**	**Actual SpO_2 for a low alarm**	**Actual SpO_2 for a high alarm**
SUPPORT	86	94	84	92
COT	87	93	84	91
BOOST-II Aus	86	94	84	92
BOOST-II NZ	87	93	84	91
BOOST-II UK*	NA	94	NA	92

AUS, Australia; *NA*, not applicable; *NZ*, New Zealand.
In the high target groups, the offset study oximeters displayed SpO_2 values that were 3% lower than the actual value. In the low target groups, the offset study oximeters displayed SpO_2 values that were 3% higher than the actual value.
*Low alarm limits were not specified for the BOOST-II UK trial.

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evidence from meta-analysis of the full trial results. The summary of the AAP report does not mention the evidence of increased mortality with lower SpO_2 target ranges or the lack of effect of these lower ranges in preventing blindness. New European guidelines recommend a SpO_2 target range of 90%-94% with alarm limits of 89 and 95%.[41]

Conclusions

There is now high quality evidence to inform oxygen saturation targeting in extremely preterm infants. It has been demonstrated that restricting oxygen supplementation in the hope of reducing morbidity has no important benefit and carries an unacceptable mortality risk. These findings emerged from large trials that were spread widely across the developed world and are likely to be generalizable in similar resource settings in terms of nurse staffing and timely availability of ROP screening and treatment. It is possible that further trials might yield additional survival advantage. The oxygen tensions associated with SpO_2 values of 90%-95% are still low relative to previously recommended PO_2 ranges. The fact that the mortality finding was unexpected even though highly consistent between studies demonstrates the crucial importance of participation in clinical trials.

These trials have shown that oxygen saturation target ranges are important, but they are unlikely to have produced the ideal approach. Although they should inform current practice, further trials will be needed to investigate alternative SpO_2 ranges and newer monitoring technologies that incorporate automated oxygen adjustment. The NeOProM individual participant data meta-analysis has not identified sub-groups of infants for whom the trial results differ. Further analysis of the achieved oxygen distributions may help to determine whether different target ranges should apply at different postnatal ages. SpO_2 target ranges should be evidence based and no longer determined by individual clinician preference. ■

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