Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. Oxygen saturation and outcomes in preterm infants. N Engl J Med 2013. DOI: 10.1056/NEJMoa1302298

Supplementary Web Appendix

Contents

1. Members of the BOOST II UK, Australia and New Zealand Collaborative Groups

The members of the trial committees and local investigators are listed by trial. Figures in parentheses are the number of infants recruited in each center.

UK Trial

Investigator Group: P. Brocklehurst, P. Cairns, S. Deshpande, B.W. Fleck, H.L. Halliday, E. Hey (Deceased), N. Marlow, B. Stenson, W. Tin, S. Wardle

Trial Steering Committee: D. Azzopardi (Chair), P. Brocklehurst, J. Deeks, D. Field, B.W. Fleck, E. Hey (Deceased), D. Hull (Retired Chair), S. Kenyon, J. Pepperell, B. Stenson, J. Thomas, B. Weller, C. Williams

Data Monitoring Committee: D. Altman, I. Chalmers (Chair), R. Cooke, E. Juszczak (Trial statistician), H. McHaffie, N. Owens

Trial Statistician/Analyst: E. Juszczak, A. King

National Perinatal Epidemiology Unit Clinical Trials Co-ordinating Centre, University of Oxford: N. Armstrong, S. Ayers, U. Bowler, B. Boyle, P. Brocklehurst, A. Crowshaw, M. Gabriel, A. Gardiner, A. Garrett, E. Juszczak, A. Kennedy, S. Khenia, A. King, M. Laubeova, L. Merritt, P. Rushby, M. Slark, S. Wragg

Regional Research Nurses: B. Boyle, A. Dixon, K. Edwards, J. Findlay, S. Fritz, Y. Hooton, C. Macintyre-Beon, P. McGowan, S. Skinner, J. White

Trial Development and Implementation Group: U. Bowler, B. Boyle, P. Brocklehurst (Chair), P. Cairns, S. Deshpande, A. Dixon, K. Edwards, A. Fielder, J. Findlay, B.W. Fleck, Y. Freer, S. Fritz, M. Gabriel, A. Gardiner, A. Garrett, H.L. Halliday, E. Harling, E. Hey (Deceased), Y. Hooton, E. Juszczak, A. King, C. Macintyre-Beon, N. Marlow, P. McGowan, S. Skinner, B. Stenson, W. Tin, S. Wardle, J. White, C. Williams

Ophthalmology Trial Development and Implementation Group: U. Bowler, L. Butler, D. Clark, K. Cocker, A. Fielder, B. Fleck, A. Gardiner, A. Garrett, E. Juszczak, A. King, A. Laude, M. O'Keefe, B. Stenson, C. Williams, C. Wilson

Recruiting Center Staff:

Aberdeen Maternity Hospital (3) – M. Ezzat, J. Couper

Addenbrooke's Hospital, Cambridge (10) – A. Curley, M. Chewpreecha

Birmingham Heartlands Hospital (18) – M. Watkinson, T. Clohessy

Birmingham Women's Hospital (47) – A. Ewer, M. Thennatumadam

Bradford Royal Infirmary (33) – S. Oddie, A. O'Doherty

Derriford Hospital, Plymouth (14) – J. Madar, H. Kirby

Forth Park Hospital, Kirkcaldy (6) – S. Ainsworth, L. Brown

Hope Hospital, Manchester (16) – P. Settle, Z. Thomas

James Cook University Hospital, Middlesbrough (63) – W. Tin, S. Walker

Jessop Wing, Sheffield (48) – P. Bustani, J. Metherall

John Radcliffe Hospital, Oxford (9) – K. Ives, M. Clee

Leeds General Infirmary (23) – L. Miall, S. Burgess

Liverpool Women's Hospital (70) – N. Subhedar, P. McGowan

National Maternity Hospital, Dublin (37) – A. Twomey, B. Coronella

New Cross Hospital, Wolverhampton (22) – B. Kumararatne, M. Doodson

Ninewells Hospital, Dundee (15) – P. Fowlie, J. Reilly

Nottingham City Hospital (34) – D. Jayasinghe, C. Ward

Princess Anne Hospital, Southampton (1) – M. Hall, J. Armand

Princess Royal Maternity Hospital, Glasgow (4) – C. Lilley, J. O'Brien

Queen Alexandra Hospital, Portsmouth (40) – T. Scorrer, K. Edwards

Queen's Medical Centre, Nottingham (8) – S. Wardle, L. Fairbrother

Royal Infirmary of Edinburgh (29) – B. Stenson, A. Young

Royal Maternity Hospital, Belfast (52) – D. Sweet, M. Fitzsimons

Royal Shrewsbury Hospital (19) – S. Deshpande, M. Taplin

Royal Victoria Infirmary, Newcastle (61) – N. Embleton, L. Shah

Russells Hall Hospital, Dudley (10) – A. Mohite, A. Griffin

Singleton Hospital, Swansea (27) – J. Matthes, D. Owen

Southmead Hospital, Bristol (67) – D. Evans, D. Stubbs

St James's University Hospital, Leeds (28) – L. Miall, D. Thethy

St Michael's Hospital, Bristol (27) – P. Cairns, A. Bond

Sunderland Royal Hospital (40) – M. Abu-Harb, E.Cornell

University Hospital of North Tees (59) – S. Gupta, D. Carr

University Hospital, Coventry (26) – K. Blake, H. Wood

Wishaw General Hospital (7) – S. Ibhanesebhor, C. O'Hear

Australian Trial

Trial management committee: W. Tarnow-Mordi, C. Morley, L. Doyle, P. Davis, C. Cole, J. Simes, W. Hague, B.A. Darlow, V. Gebski, K. Simmer

Data and Safety Monitoring Committee: A. Berry (Chair), C. D’Este, F. Cockburn, I. Marschner

NHMRC Clinical Trials Centre; University of Sydney, Australia.

W. Tarnow-Mordi*, W. Hague, A. Ghadge*, I. Kolodziej, N. Muljadi

*(WINNER Centre for Newborn Research)

Trial Statisticians: A. Kirby, M. Donoghue

Recruiting Center Staff:

Canberra Hospital (41) – G. Reynolds, Z. Kecskes, M. Broom

Royal Prince Alfred Hospital (32) – N. Evans, G. Malcolm, S. Reid

Royal North Shore Hospital (63) – M. Kluckow, M. Jeffery, S. Sedgley, J. Knowles

Westmead Hospital (70) – B. Twible, M. Luig

John Hunter Hospital (140) – I. Wright, J. Buchan

Liverpool Hospital (32) – J. Stack, N. Pullbrook

Monash Medical Centre (26) – K. Tan, E. Yeomans, K. Elsayed, M. Hayes

Royal Women's Hospital (134) – B. Argus, B. Mills, K. Callanan

Royal Brisbane and Women's Hospital (52) – P. Colditz, M. Pritchard

Mater Mother's Hospital (145) – P. Gray, A. Shearman, L. Poulson

Flinders Medical Centre (55) – S. Morris, K. Cornthwaite

Women's & Children's Hospital (89) – B. Headley, R. Lontis, L. Goodchild

King Edward Memorial Hospital (222) – Y. Kok

Royal Hobart Hospital (30) – A. Cornelius, P. Dargaville, K. Butterley

National Taiwan University Hospital (4) – W-S Hsieh

New Zealand Trial

Trial Management Committee: B.A. Darlow, C. Kuschel, M. Meyer, M. Hewson, R. Broadbent, M. Elder, C. Cole

Trial Co-ordinating Centre: B.A. Darlow, M. Elder, J. Gardner, P. Graham, N. McNeill, A. Blackler, A. Ghadge

Data and Safety Monitoring Committee (as per BOOST II Australia)

Trial Statisticians: A. Kirby, M. Donoghue

Recruiting Center Staff:

Christchurch Women's Hospital (69) – B.A. Darlow, P. Graham, N. McNeill, M. Elder

Middlemore Hospital (56) – M. Meyer, T. Bushell

Auckland City Hospital (101) – C. Kuschel, M. Battin, S. Huth

Wellington Women's Hospital (76) – M. Hewson, F. Trist

Dunedin Hospital (38) – R. Broadbent, F. McCaffrey

2. Achieved SpO_2 distributions

Clinical staff were asked to adjust inspired oxygen to maintain the infants within the displayed SpO_2 range 88–92%. In each trial, the displayed SpO_2 values for each infant were recorded on the trial oximeters throughout the intervention and downloaded as part of the patient dataset. Sampling frequency was every 10 seconds and the averaging time was 8 seconds. Clinicians also filled in an oxygen log which recorded whether or not the infant was receiving supplemental oxygen. This was charted every 20 minutes in the UK trial and every hour in the Australian and New Zealand trials. We evaluated compliance with protocol by examining achieved SpO_2 distributions for each infant. Recorded values were converted back to actual values. The distribution of measured values that were outside the range 85–95% and were affected by the transitioning back of offset values to the normally displayed values was estimated by quadratic interpolation.

Because some infants with minimal lung disease can achieve high SpO_2 breathing air, not all high SpO_2 values represent poor clinical targeting. High SpO_2 in infants breathing air is unlikely to be associated with high arterial partial pressure of oxygen (PaO_2) and is not modifiable by the clinical staff. We therefore analyzed SpO_2 distributions during periods when we knew that the infants were receiving supplemental oxygen. In the UK trial this was evaluated for all blocks of 20 minutes or more when the infant was breathing supplemental oxygen. In the Australian trial, all whole hours of oxygen supplementation were analyzed and in the New Zealand trial all whole days of oxygen supplementation were analyzed. Because low SpO_2 values could be achieved by infants whether or not they were breathing supplemental oxygen and, in either case, low SpO_2 values would be likely to be associated with low PaO_2, we also analyzed SpO_2 values for the entire intervention period in each trial, whether or not the infants were receiving supplemental oxygen.

Supplementary Tables S1.1 and S1.2 show the percentage of time that the infants spent in different SpO_2 ranges when they were breathing supplemental oxygen throughout the intervention period (from randomization until 36 weeks' gestation or death or discharge from hospital). Percentages were calculated by pooling all readings obtained for each randomization group. Summary data are given separately for the two randomization groups and separate tables are provided for the two different oximeter calibration algorithms. For each individual infant the mean and median SpO_2 were determined and the tabulated values are the mean and median of these values for each group.

Supplementary Tables S1.3 and S1.4 show the percentage of time that the infants spent in different SpO_2 ranges for all of the time that they were on the study oximeter. Percentages were calculated by pooling all readings obtained for each randomization group. Summary data are given separately for the two randomization groups and separate tables are provided for the two different oximeter calibration algorithms. For each individual infant the mean and median SpO_2 were determined and the tabulated values are the mean and median of these values for each group.

We plotted pooled SpO_2 distribution histograms as cumulative percentages of time that the infants in each randomization group spent at each SpO_2 value because this gives an overview of their exposure to the whole range of SpO_2 values. These are presented as Figure 1 in the paper and are separated by trial and by oximeter calibration algorithm. It is apparent from Figure 1 in the paper and from the above tabulated data that after the change in oximeter calibration algorithms there was clearer separation in the distribution of SpO_2 between the randomization groups and infants in the low SpO_2 target group spent more time in their intended SpO_2 target range.

In the SUPPORT trial paper describing outcomes to hospital discharge [1] each infant's median SpO_2 value for the time that they were breathing supplemental oxygen was determined and cumulative frequencies of these medians were plotted for the two randomization groups. In order to facilitate comparison between trials we have used the same approach for the infants in the three BOOST II trials. Supplementary Figure S1 shows pooled cumulative frequencies for median SpO_2 whilst breathing supplemental oxygen. Separate histograms are provided for infants treated using the original and revised oximeter calibration algorithms. In the SUPPORT trial the peaks of the curves for the low and high SpO_2 target groups were at around 91% and 94%. It can be seen in Figure S1 that the peaks for the BOOST II trials when the original oximeters were in use were at around 89% and 92%. Different SpO_2 distributions were being achieved between trials even though the same oximeters and SpO_2 target ranges were in use. The peak for the low target group in this figure has to be estimated because the curve is flattened between 87–90% by the artefact in the original oximeter calibration.

3. Causes of death

Clinicians in the Australian and New Zealand trials were asked to report the causes of death, as entered onto the death certificate, in a pick list in the study data entry form. In the UK trial clinicians recorded causes of death using a pick list but the list items differed slightly from the list used in the Australian and New Zealand trials. For the UK trial, causes of death that were recorded on the death certificate were also obtained centrally. Blind to trial group allocation the UK causes of death were re-classified using the same classification system as that used in the Australian and New Zealand trials so that data from the three trials could be pooled. Individual infants could have more than one contributing cause recorded. Supplementary Tables S2.1 and S2.2 show the causes of death for infants in each trial and pooled between trials for infants managed with each oximeter calibration algorithm.

4. Adverse events

Adverse events are listed in table S.4.There were few adverse events reported in either randomization group in the BOOST II UK trial. There were no adverse events reported in the Australian and New Zealand trials. The recognised complications of prematurity were included as study outcome measures. This may explain the low frequency of separately reported adverse events.

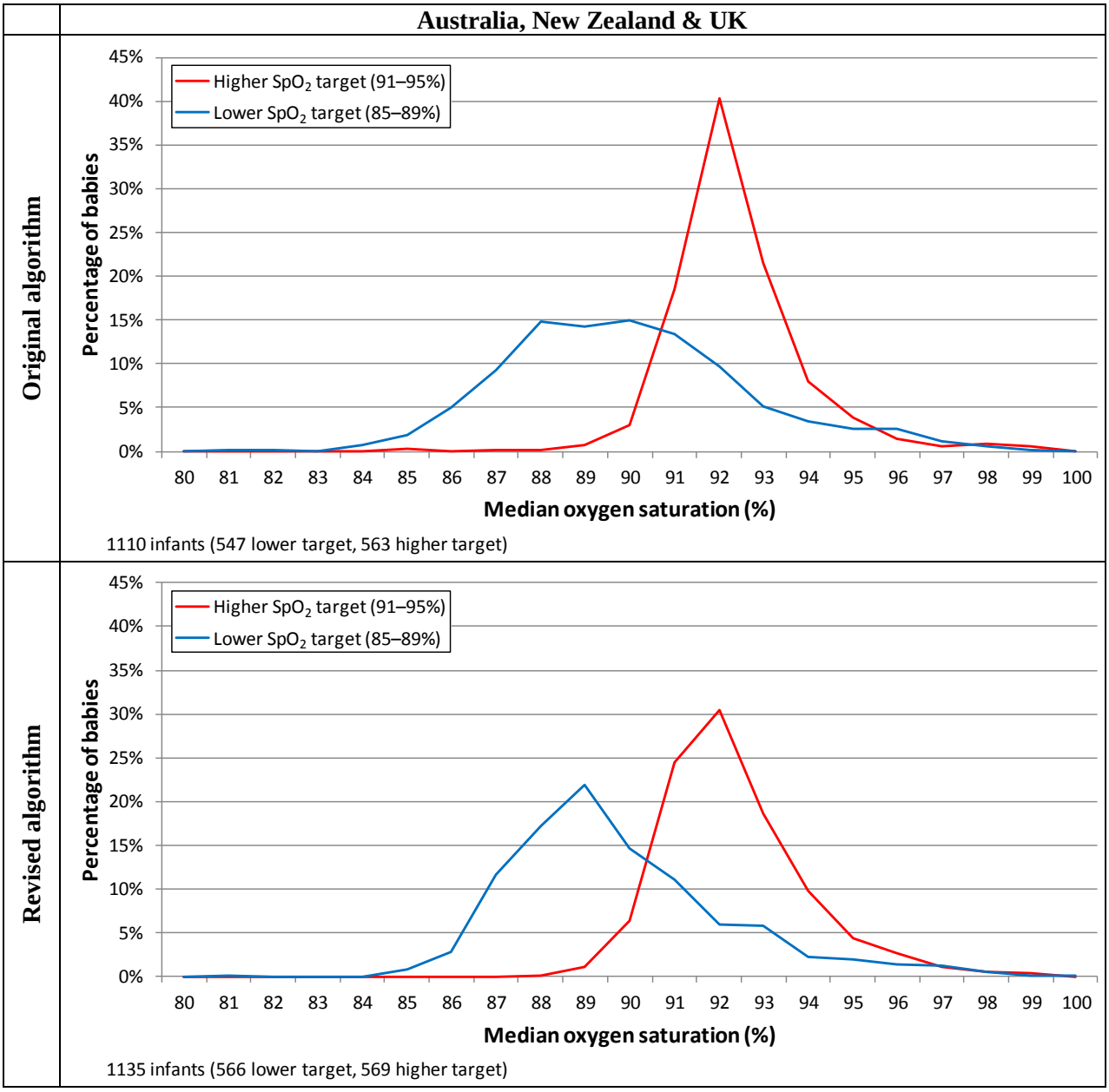
5. Reference

1. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sánchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010 May 7;362(21):1959–69.

6. Supplementary Figure S1

Supplementary Figure S1: Cumulative frequencies for median saturation for the BOOST II trials. Original and revised oximeter calibration algorithms.

Median saturation distribution graphs



7. Supplementary Tables S1.1–4

Supplementary Table S1.1: Summary of pooled actual SpO_2 values by treatment group, proportion of time in five SpO_2 ranges for time when the infant was receiving oxygen – original algorithm

Treatment	N	< 85%	85–89%	90%	91–95%	> 95%	Median	Mean
UK trial Low target	108	25.7%	20.0%	4.7%	33.5%	16.1%	91%	89.1%
UK trial High target	114	15.0%	15.2%	4.5%	46.6%	18.7%	92%	91.1%
Australian trial Low target	312	27.4%	23.2%	5.3%	33.1%	11.1%	90%	88.9%
Australian trial High target	327	13.5%	14.5%	4.4%	49.4%	18.6%	93%	91.7%
New Zealand trial Low target	127	21.1%	20.9%	5.2%	37.4%	15.5%	91%	90.2%
New Zealand trial High target	122	10.8%	12.7%	4.1%	50.3%	22.2%	93%	92.3%

Supplementary Table S1.2: Summary of pooled actual SpO_2 values by treatment group, proportion of time in five SpO_2 ranges for time when the infant was receiving oxygen – revised algorithm

Treatment	N	< 85%	85–89%	90%	91–95%	> 95%	Median	Mean
UK trial Low target	363	22.1%	26.3%	6.9%	30.9%	13.9%	90%	89.2%
UK trial High target	363	12.3%	17.8%	6.1%	43.4%	20.4%	93%	91.4%
Australian trial Low target	203	24.1%	31.1%	7.6%	29.2%	8.1%	89%	88.5%
Australian trial High target	206	10.8%	17.7%	6.5%	48.7%	16.4%	92%	91.4%

Supplementary Table S1.3: Summary of pooled actual SpO_2 values by treatment group, proportion of time in five SpO_2 ranges for all time when the infant was on a study oximeter – original algorithm

Treatment	N	< 85%	85–89%	90%	91–95%	> 95%	Median	Mean
UK trial Low target	113	19.5%	16.5%	4.1%	34.3%	25.6%	92	90.2
UK trial High target	115	12.3%	12.8%	3.8%	43.1%	28.0%	93	91.7
Australian trial Low target	344	13.5%	13.3%	3.5%	32.3%	37.5%	94	91.9
Australian trial High target	345	7.9%	8.9%	2.9%	37.6%	42.7%	95	93.4
New Zealand trial Low target	169	11.6%	12.9%	3.5%	34.6%	37.4%	94	92.6
New Zealand trial High target	167	6.6%	7.9%	2.6%	37.9%	45.0%	95	93.9

Supplementary Table S1.4: Summary of pooled actual SpO_2 values by treatment group, proportion of time in five SpO_2 ranges for all time when the infant was on a study oximeter – revised algorithm

Treatment	N	< 85%	85–89%	90%	91–95%	> 95%	Median	Mean
UK trial Low target	372	16.5%	21.1%	5.9%	32.6%	23.9%	91	90.3
UK trial High target	368	9.7%	14.4%	5.0%	40.0%	30.9%	93	92.1
Australian trial Low target	219	12.9%	18.5%	5.3%	32.6%	30.6%	92	91.2
Australian trial High target	220	7.2%	12.3%	4.7%	41.3%	34.4%	94	92.9

8. Supplementary Tables S2.1–2

Supplementary Table S2.1: Clinical outcomes at hospital discharge, by trial and by randomization group

	Australia				New Zealand				United Kingdom				All				
	Oxygen saturation		Relative risk		Oxygen saturation		Relative risk		Oxygen saturation		Relative risk		Oxygen saturation		Relative risk*		Int
	Low	High	Effect (95% CI)	P	Low	High	Effect (95% CI)	P	Low	High	Effect (95% CI)	P	Low	High	Effect (95% CI)	P	P†
Death at discharge	99/567 (17.5%)	83/567 (14.6%)	1.19 (0.91–1.56)	0.196	21/170 (12.4%)	24/170 (14.1%)	0.88 (0.51–1.51)	0.631	115/484 (23.8%)	96/483 (19.9%)	1.20 (0.94–1.52)	0.144	235/1221 (19.2%)	203/1220 (16.6%)	1.16 (0.98–1.37)	0.088	0.568
Death at 36 weeks' pma	91/567 (16.0%)	73/567 (12.9%)	1.25 (0.94–1.66)	0.129	17/170 (10.0%)	22/170 (12.9%)	0.77 (0.43–1.40)	0.395	108/484 (22.3%)	85/483 (17.6%)	1.27 (0.98–1.64)	0.067	216/1221 (17.7%)	180/1220 (14.8%)	1.20 (1.00–1.44)	0.045	0.306
Treated for ROP	32/482 (6.6%)	43/493 (8.7%)	0.76 (0.49–1.18)	0.222	11/158 (7.0%)	12/148 (8.1%)	0.86 (0.39–1.89)	0.704	67/395 (17.0%)	86/403 (21.3%)	0.79 (0.60–1.06)	0.116	110/1035 (10.6%)	141/1044 (13.5%)	0.79 (0.63–1.00)	0.045	0.965
NEC requiring surgery or leading to death	41/567 (7.2%)	33/567 (5.8%)	1.24 (0.80–1.94)	0.336	15/170 (8.8%)	12/170 (7.1%)	1.25 (0.60–2.59)	0.547	71/484 (14.7%)	52/480 (10.8%)	1.35 (0.97–1.89)	0.074	127/1221 (10.4%)	97/1217 (8.0%)	1.31 (1.02–1.68)	0.037	0.948
Severe IVH (≥ grade 3)	58/565 (10.3%)	56/566 (9.9%)	1.04 (0.73–1.47)	0.836	13/170 (7.6%)	12/169 (7.1%)	1.08 (0.51–2.29)	0.847	69/468 (14.7%)	58/476 (12.2%)	1.21 (0.87–1.67)	0.249	140/1203 (11.6%)	126/1211 (10.4%)	1.12 (0.89–1.41)	0.319	0.813
Other brain injury	37/506 (7.3%)	49/512 (9.6%)	0.76 (0.51–1.15)	0.195	21/161 (13.0%)	15/160 (9.4%)	1.39 (0.74–2.60)	0.298	56/412 (13.6%)	49/410 (12.0%)	1.14 (0.79–1.63)	0.481	114/1079 (10.6%)	113/1082 (10.4%)	1.01 (0.79–1.30)	0.910	0.196
PDA (req. medical or surgical treatment)	279/567 (49.2%)	277/566 (48.9%)	1.01 (0.89–1.13)	0.929	104/170 (61.2%)	90/170 (52.9%)	1.16 (0.96–1.39)	0.125	198/482 (41.1%)	186/483 (38.5%)	1.07 (0.91–1.25)	0.415	581/1219 (47.7%)	553/1219 (45.4%)	1.05 (0.97–1.15)	0.229	0.454
O_2 dependency at 36 weeks' pma	161/473 (34.0%)	191/492 (38.8%)	0.88 (0.74–1.04)	0.123	40/153 (26.1%)	58/147 (39.5%)	0.66 (0.47–0.92)	0.014	193/372 (51.9%)	212/392 (54.1%)	0.96 (0.84–1.10)	0.543	394/998 (39.5%)	461/1031 (44.7%)	0.90 (0.81–0.99)	0.034	0.116
BPD (physiological)									160/353 (45.3%)	172/376 (45.7%)	0.99 (0.85–1.16)	0.910	160/353 (45.3%)	172/376 (45.7%)	0.99 (0.85–1.16)	0.910	

* Adjusted for country
† Country x treatment interaction

Footnote for Table S2.1:

P-values from tests for interaction of trial country and treatment group are included in the final column headed Int.

"Other brain injury" included porencephaly, ventriculomegaly, post-hemorrhagic hydrocephalus requiring a shunt or reservoir, periventricular leukomalacia or cerebral atrophy. BPD in the UK trial was defined as requiring supplemental oxygen to maintain actual SpO_2 at 90% or more.

Supplementary Table S2.2: Clinical outcomes at hospital discharge, by study and oximeter algorithm.

	ANZ					UK					All					
	Oxygen saturation		Relative risk		Trt x Soft int	Oxygen saturation		Relative risk		Trt x Soft int	Oxygen saturation		Relative risk*		Trt x Soft int	Trt x trial int
	Low	High	Effect (95% CI)	P	P	Low	High	Effect (95% CI)	P	P	Low	High	Effect (95% CI)	P	P	P
Original algorithm																
Death at discharge	78/516 (15.1%)	80/516 (15.5%)	0.98 (0.73–1.30)	0.863	0.082	20/113 (17.7%)	29/114 (25.4%)	0.70 (0.42–1.15)	0.156	0.015	98/629 (15.6%)	109/630 (17.3%)	0.90 (0.70–1.15)	0.390	0.006	0.253
Death at 36 weeks' pma	67/516 (13.0%)	72/516 (14.0%)	0.93 (0.68–1.27)	0.648	0.023	18/113 (15.9%)	26/114 (22.8%)	0.70 (0.41–1.20)	0.190	0.013	85/629 (13.5%)	98/630 (15.6%)	0.87 (0.66–1.13)	0.292	0.001	0.365
Treated for ROP	34/459 (7.4%)	34/445 (7.6%)	0.97 (0.61–1.53)	0.894	0.093	18/97 (18.6%)	27/90 (30.0%)	0.62 (0.37–1.04)	0.067	0.278	52/556 (9.4%)	61/535 (11.4%)	0.79 (0.56–1.12)	0.187	0.910	0.202
NEC requiring surgery or leading to death	38/516 (7.4%)	28/516 (5.4%)	1.36 (0.85–2.18)	0.203	0.539	17/113 (15.0%)	11/114 (9.6%)	1.56 (0.76–3.18)	0.216	0.657	55/629 (8.7%)	39/630 (6.2%)	1.42 (0.96–2.10)	0.083	0.591	0.750
Severe IVH (≥ grade 3)	48/516 (9.3%)	42/514 (8.2%)	1.14 (0.77–1.69)	0.520	0.470	18/108 (16.7%)	12/111 (10.8%)	1.54 (0.78–3.05)	0.208	0.421	66/624 (10.6%)	54/625 (8.6%)	1.23 (0.88–1.73)	0.233	0.481	0.448
Other brain injury	36/470 (7.7%)	42/469 (9.0%)	0.86 (0.56–1.31)	0.472	0.603	12/94 (12.8%)	12/93 (12.9%)	0.99 (0.47–2.09)	0.978	0.677	48/564 (8.5%)	54/562 (9.6%)	0.89 (0.61–1.28)	0.523	0.338	0.740
PDA (req. medical or surgical treatment)	269/516 (52.1%)	256/515 (49.7%)	1.05 (0.93–1.18)	0.436	0.851	46/113 (40.7%)	47/114 (41.2%)	0.99 (0.72–1.35)	0.936	0.578	315/629 (50.1%)	303/629 (48.2%)	1.04 (0.93–1.16)	0.485	0.826	0.724
O_2 dependency at 36 weeks' pma	137/447 (30.6%)	168/442 (38.0%)	0.81 (0.67–0.97)	0.021	0.641	56/95 (58.9%)	48/88 (54.5%)	1.08 (0.84–1.39)	0.548	0.280	193/542 (35.6%)	216/530 (40.8%)	0.89 (0.77–1.03)	0.128	0.826	0.066
BPD (physiological)						47/91 (51.6%)	41/84 (48.8%)	1.06 (0.79–1.42)	0.707	0.591	47/91 (51.6%)	41/84 (48.8%)	1.06 (0.79–1.42)	0.707	0.591	
Revised algorithm																
Death at discharge	42/221 (19.0%)	27/221 (12.2%)	1.56 (1.00–2.43)	0.049		95/371 (25.6%)	67/369 (18.2%)	1.41 (1.07–1.86)	0.014		137/592 (23.1%)	94/590 (15.9%)	1.45 (1.15–1.84)	0.002		0.714
Death at 36 weeks' pma	41/221 (18.6%)	23/221 (10.4%)	1.78 (1.11–2.87)	0.015		90/371 (24.3%)	59/369 (16.0%)	1.52 (1.13–2.04)	0.005		131/592 (22.1%)	82/590 (13.9%)	1.59 (1.24–2.04)	<.001		0.571
Treated for ROP	9/181 (5.0%)	21/196 (10.7%)	0.46 (0.22–0.99)	0.040		49/298 (16.4%)	59/313 (18.8%)	0.87 (0.62–1.23)	0.436		58/479 (12.1%)	80/509 (15.7%)	0.77 (0.57–1.06)	0.108		0.125
NEC requiring surgery or leading to death	18/221 (8.1%)	17/221 (7.7%)	1.06 (0.56–2.00)	0.860		54/371 (14.6%)	41/366 (11.2%)	1.30 (0.89–1.90)	0.174		72/592 (12.2%)	58/587 (9.9%)	1.23 (0.89–1.71)	0.209		0.588
Severe IVH (≥ grade 3)	23/219 (10.5%)	26/221 (11.8%)	0.89 (0.53–1.52)	0.674		51/360 (14.2%)	46/365 (12.6%)	1.12 (0.78–1.63)	0.536		74/579 (12.8%)	72/586 (12.3%)	1.04 (0.77–1.41)	0.791		0.484

	ANZ					UK					All					
	Oxygen saturation		Relative risk		Trt x Soft int	Oxygen saturation		Relative risk		Trt x Soft int	Oxygen saturation		Relative risk*		Trt x Soft int	Trt x trial int
	Low	High	Effect (95% CI)	P	P	Low	High	Effect (95% CI)	P	P	Low	High	Effect (95% CI)	P	P	P
Other brain injury	22/197 (11.2%)	22/203 (10.8%)	1.03 (0.59–1.80)	0.916		44/318 (13.8%)	37/317 (11.7%)	1.19 (0.79–1.78)	0.414		66/515 (12.8%)	59/520 (11.3%)	1.13 (0.81–1.57)	0.470		0.691
PDA (req. medical or surgical treatment)	114/221 (51.6%)	111/221 (50.2%)	1.03 (0.86–1.23)	0.775		152/369 (41.2%)	139/369 (37.7%)	1.09 (0.91–1.31)	0.327		266/590 (45.1%)	250/590 (42.4%)	1.06 (0.93–1.21)	0.368		0.631
O_2 dependency at 36 weeks' pma	64/179 (35.8%)	81/197 (41.1%)	0.87 (0.67–1.13)	0.286		137/277 (49.5%)	164/304 (53.9%)	0.92 (0.78–1.07)	0.279		201/456 (44.1%)	245/501 (48.9%)	0.90 (0.79–1.03)	0.140		0.732
BPD (physiological)						113/262 (43.1%)	131/292 (44.9%)	0.96 (0.80–1.16)	0.682		113/262 (43.1%)	131/292 (44.9%)	0.96 (0.80–1.16)	0.682		

* Adjusted for country

P-values from tests of interaction between SpO_2 target group and oximeter calibration algorithm, for each study and for all studies combined (Trt x Soft int) and between target SpO_2 group and trial country (Trt x trial int) are provided.

"Other brain injury" included porencephaly, ventriculomegaly, post-hemorrhagic hydrocephalus requiring a shunt or reservoir, periventricular leukomalacia or cerebral atrophy. BPD in the UK trial was defined as requiring supplemental oxygen to maintain actual SpO_2 at 90% or more.

9. Supplementary Tables S3.1–2

Supplementary Table S3.1: Cause of death by treatment allocation – original oximeters

Cause of death (can have > 1)	Australia Oxygen saturation target		New Zealand Oxygen saturation target		United Kingdom Oxygen saturation target		All Oxygen saturation target	
	Low (85–89%) (N=57)	High (91–95%) (N=56)	Low (85–89%) (N=21)	High (91–95%) (N=24)	Low (85–89%) (N=20)	High (91–95%) (N=29)	Low (85–89%) (N=98)	High (91–95%) (N=109)
Congenital abnormality	0	0	0	0	0	2	0	2
Pulmonary hypoplasia	0	0	0	1	0	0	0	1
Severe Respiratory Distress Syndrome (RDS)	21	20	7	7	1	6	29	33
Chronic lung disease	6	7	5	6	2	4	13	17
Pneumonia	1	0	0	0	0	0	1	0
Grade 3/4 intraventricular hemorrhage	23	22	6	4	5	5	34	31
Meningitis	0	3	1	1	0	1	1	5
Septicemia	10	9	4	6	7	9	21	24
Necrotizing enterocolitis	13	9	4	6	5	2	22	17
Sudden infant death syndrome (SIDS)	0	0	0	0	0	0	0	0
Other	42	28	14	10	6	12	62	50
Unknown	0	0	0	0	1	1	1	1
No information	0	0	0	0	1	1	0	0

Supplementary Table S3.2: Cause of death by treatment allocation – revised oximeters. No New Zealand infants were managed using the revised oximeters

Cause of death (can have > 1)	Australia Oxygen saturation target		United Kingdom Oxygen saturation target		All Oxygen saturation target	
	Low (85–89%) (N=42)	High (91–95%) (N=27)	Low (85–89%) (N=95)	High (91–95%) (N=67)	Low (85–89%) (N=137)	High (91–95%) (N=94)
Congenital abnormality	1	1	2	0	3	1
Pulmonary hypoplasia	0	2	0	0	0	2
Severe Respiratory Distress Syndrome (RDS)	16	9	7	15	23	24
Chronic lung disease	7	3	11	9	18	12
Pneumonia	0	0	5	2	5	2
Grade 3/4 intraventricular hemorrhage	13	8	13	13	26	21
Meningitis	0	0	1	1	1	1
Septicemia	6	3	22	12	28	15
Necrotizing enterocolitis	10	8	29	14	39	22
Sudden infant death syndrome (SIDS)	0	0	0	0	0	0
Other	31	15	31	16	62	31
Unknown	0	0	3	6	3	6

10. Supplementary table S.4

Supplementary Table S4: Adverse events reported in the BOOST II UK trial

ID	Group	Details of event	Severity reported	Level of causality reported	Was this a SUSAR?*	Outcome	Treatment required	Concomitant medication
1	Lower SpO2	Clinically unstable baby. Lower SpO2 displayed on monitor than clinical impression. Second monitor showed higher SpO2. Concern resolved rapidly.	Mild	Possibly related to the intervention	No	Recovered	None	Morphine
2	Higher SpO2	BOOST monitor shut down. Changed to new monitor	Mild	N/A	No	Recovered	None	None
3	Higher SpO2	Massive pulmonary haemorrhage.	Severe	Not related to the intervention	No	Death	Adrenalin Blood and fresh frozen plasma	Dobutamine Dopamine Morphine Penicillin Gentamycin
4	Lower SpO2	Bowel perforation	Severe	Not related to the intervention	No	Recovered	Metronidazole Vancomycin Cefotaxime	None
5	Higher SpO2	Deterioration with abdominal discolouration and increasing lactate. Treated for necrotizing enterocolitis	Severe	Not related to the intervention	No	Death	Cefotaxime Vancomycin Metronidazole	Dopamine Dobutamine
6	Higher SpO2	Acute collapse with grossly distended tense abdomen. X-ray consistent with NEC	Severe	Not related to the intervention	No	Death	Adrenaline Bicarbonate Calcium Magnesium Vecuronium	None
7	Lower SpO2	Hypopituitarism	Moderate	Not related to the intervention	No	Recovered	Thyroxine Hydrocotisone	Abidec Sytron

*Suspected Unexpected Serious Adverse Reaction