Oxygen Use in the DR and NICU
Where are we now??

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Neonatal Resuscitation – Role of Oxygen

- The practice of mouth to mouth resuscitation was the first natural experiment using hypoxic gas mixtures for resuscitation. While supplemental oxygen is now the standard during neonatal resuscitation, this practice had never been validated in prospective controlled trials.

Oxygen of Room Air??

- It remains unclear whether supplemental oxygen facilitates this process or contributes to potential hypoxia/reoxygenation injury, inhibition of breathing and possible aggravation of atelectasis by the attenuation of nitrogen splinting

Basis of PRESOX Trial

- The optimal oxygen concentration for the very preterm infant has not been studied in large prospective multicenter trials powered to evaluate significant short and longer term outcomes including survival without neurodevelopmental impairment.

Previous Studies of Room Air vs Oxygen
Saugstad et al Biology of the Neonate. 2005; 87(1):27-34

- A systematic review of 6 randomized trials that compared the use of room air (RA) and 100% oxygen reported that RA was associated with a significant lowering of mortality from 13% to 8% p=0.0021, with a typical odds ratio of 0.57 (95% CI 0.42, 0.78); however no difference was observed for infants with a 1 minute of Apgar < 4 [Typical OR 0.81 (95%CI 0.54 - 1.21)]

Resuscitation with RA vs Oxygen
Ramji & Saugstad NeoReviews 2005;6 (#4) e172

- Analyses of existing trials demonstrated that the results were similar for non-third world environments (Valencia Spain, Vento et al)
- Mortality fell from 3.5% to 0.5%

RA vs Oxygen – Mortality for Term Infants Tan et al Cochrane Database of Systematic Reviews 2005

- In term infants neonatal mortality was 5.9% in the RA group and 9.8% in the 100% O2 group, Typical OR 0.59, (95% CI 0.40 - 0.870).

RA vs Oxygen – Mortality for Preterm Infants Ramji & Saugstad, OD. NeoReviews 2005;6 (#4) Saugstad et al Neonatology 2008; 94:174-82.

- Sub-group analysis confined to preterm infants revealed a greater reduction in mortality in the RA group from 35% in the 100% O2 group to 21% in the RA group [Typical OR 0.51 (95%CI 0.28 - 0.90, p<0.02)].
- The use of RA as the initial gas resulted in earlier initiation and maintenance of spontaneous breathing, and reduced mortality without any increase in neurodevelopmental disability

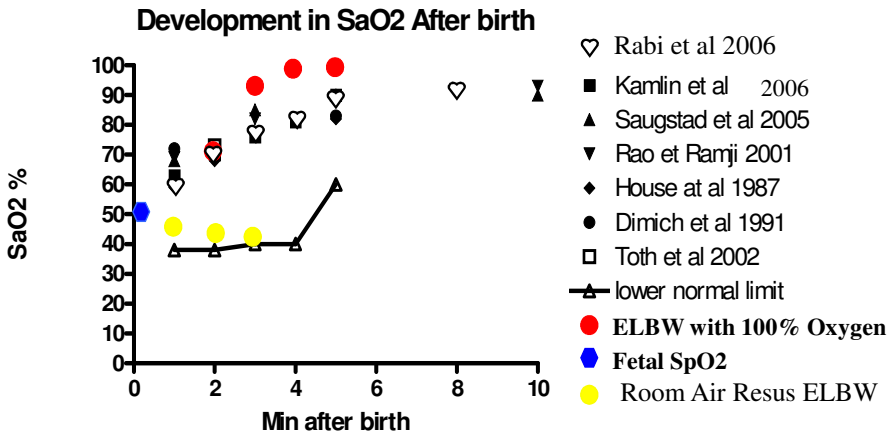
SpO2 Following Delivery

- Fetal SpO2 is between 45% to 55% with a Standard Deviation of about 9%
- A number of studies have noted the actual SpO2 values for normal term and near term infants during the first 5 minutes
- The increase in SpO2 from fetal levels occurs at about 5% per minute beginning at about 60% at 1 minute, and reaching 85% at 5 minutes
- This is slower for preterm infants

SpO2 Following Delivery

- During resuscitation of infants with significant asphyxia ie HR < 80 and/or apnea
- The SpO2 increased slower!! in infants receiving 100% oxygen compared with room air
- Thus for infants with 1 min Apgar < 4, the SpO2 at 1 min was 65% vs 58%, at 3 min 82% vs 78% and at 5 min 87% vs 86% for infants receiving Room air vs 100% Oxygen

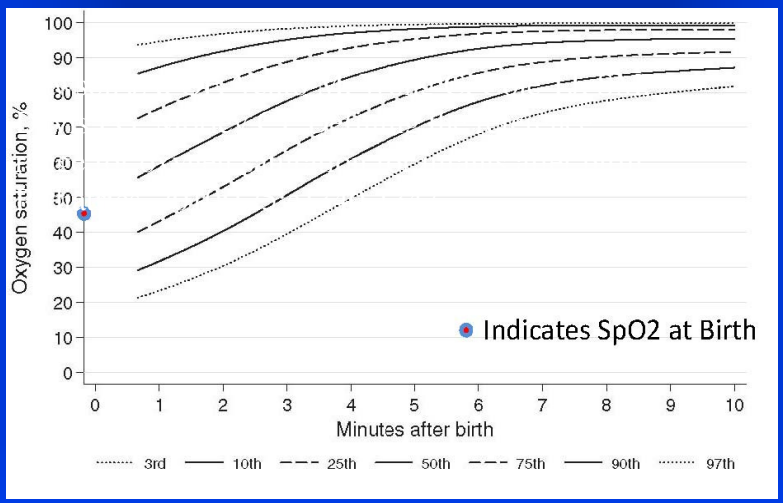
The SpO2 values for the first 5 minutes of life From available studies



Adapted from Saugstad J Peds 2006

Dawson et al. Reference range for oxygen saturation for infants after birth. Pediatrics. 2010;125;e1340

Infants 32- 36 weeks without Resuscitation



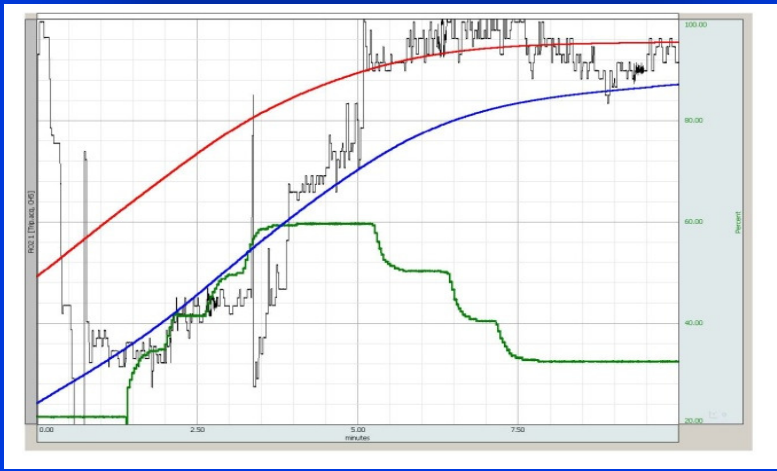
Targeted Oxygen Strategy Using SpO2 in DR for VLBW infants

- Try to increase SpO2 slowly over the first 8 to 10 minutes of life
- At birth SpO2 approximately 45% to 55%
- *Increase approximately 5% per minute for next 6-7 minutes*
- We use target of 65% to 70% at 3 minutes
- By 6 to 7 minutes target 80% to 85%
- Maintain SpO2 between 85% to 92% after that time

Room Air vs 100% Oxygen for the VLBW Infant Wang et al, Pediatrics 2008;121:1083-9

- Compared Room air with 100% oxygen during initial resuscitation in 41 patients
- 23 O2 and 18 RA, GA - 27.6 weeks (range 24-31) for O2 group and 28 weeks in the RA group (25-31).
- Mean birth weight was 1013g (range 495-2309) in the O2 group and 1091g (555-1840) in the RA group.
- O2 was increased in 25% increments if SpO2 was <70% at 3 minutes of life or <80 at 5 minutes of life.

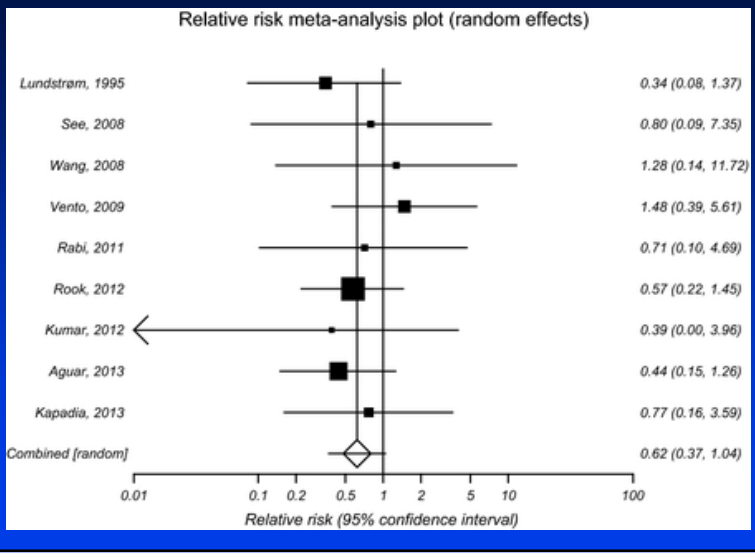
TOTS System
Showing FiO2 Changes as a record of Resuscitation



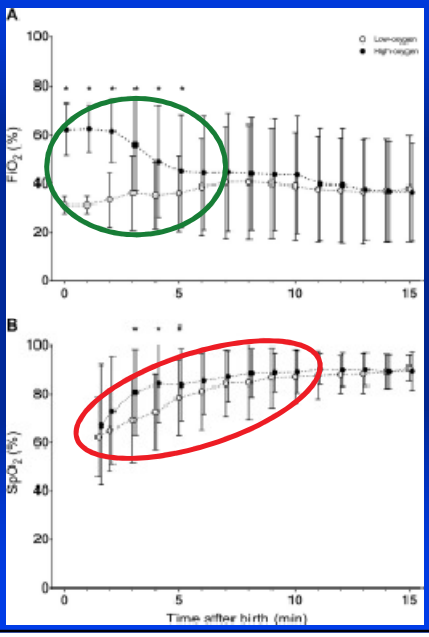
Room Air vs 100% Oxygen for the VLBW Infant
Wang et al, Pediatrics 2008;121:1083-9

- Every patient in the RA group met rescue criteria and required an increase in FiO2 by 3 minutes of life, six patients directly to 100% and 12 with incremental increases.
- SpO2 was significantly lower in the RA group from 2 to 10 minutes p=0.01 (SpO2 at 3 minutes, RA = 55% vs. 87% for O2 group).

Systematic review and meta-analysis of oxygen levels in the delivery room at ≤32 weeks – Mortality
Saugstad et al Acta Paediatrica 2014;103:744



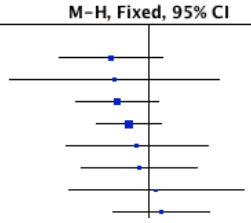
Rook et al J Pediatrics 2014 30% vs 65%, N=199



Most Recent Meta Analysis
Low vs Higher Oxygen in DR - Mortality

Study or Subgroup	Low Oxygen Events	Low Oxygen Total	High Oxygen Events	High Oxygen Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Armanian	0	14	0	13		Not estimable
Lundstrom 1995	2	34	6	35	15.5%	0.30 [0.06, 1.62]
Kumar	0	5	1	6	3.5%	0.33 [0.01, 10.11]
Aguar	4	34	7	26	19.5%	0.36 [0.09, 1.40]
Rook 2014	6	99	10	94	26.9%	0.54 [0.19, 1.56]
Rabi 2010	1	34	3	72	5.2%	0.70 [0.07, 6.96]
Kapadia 2013	2	26	3	30	7.2%	0.75 [0.12, 4.87]
Wang 2008	1	18	1	23	2.3%	1.29 [0.08, 22.22]
Vento 2008	4	37	3	41	7.1%	1.54 [0.32, 7.36]

Odds Ratio M-H, Fixed, 95% CI



TO_2RPIDO – Targeted Oxygenation in the Resuscitation of Preterm Infants and their Developmental Outcomes
Methodology - RA Group

- Resuscitation is commenced with room air (21% O_2). After oximetry readings are established, FiO_2 is *increased by aliquots of 0.1 every minute (i.e to fiO_2 of 0.3 in the first step) from time 0* if pre-ductal SaO_2 continue to be:
- <65% before 5 minutes
- < 80% between 5 to 10 minutes
- <85% after 10 minutes
- FiO_2 will need to be *decreased* by 0.1 every 30 to 60 seconds if SaO_2 is $\geq$92% *at any time*

Torpido 1 Trial

- Study stopped for poor enrollment
- Thought that there was less interest in using 100% Oxygen
- Analyses performed – Currently the largest Trial evaluating lower vs higher FiO2 in Preterm Infants

Relative risk of neonatal (<28 day) mortality for air versus 100% FiO_2

	21% FiO_2	100%	(RR)[95% CI]	P
All infants	75/ 145 (51.7%)	85/ 144 (59.0%)	0.88 [0.71 – 1.08]	0.13
<28 wk gest	12/75 (16.0%)	5/85 (5.9%)	2.7 (1.1-10.0)	*0.04*

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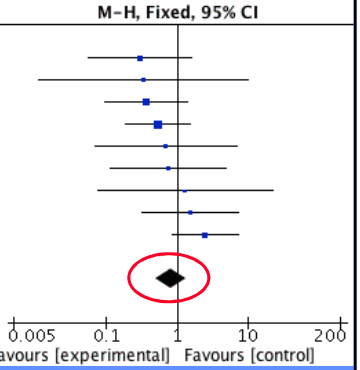
Torpido 2014	12	144	5	143	12.8%	2.51 [0.86, 7.32]
Total (95% CI)		**445**		**483**	**100.0%**	**0.83 [0.51, 1.34]**
Total events	32		39			

Heterogeneity: $Chi^2 = 8.56$, $df = 8$ ($P = 0.38$); $I^2 = 7\%$
Test for overall effect: $Z = 0.78$ ($P = 0.44$)



Review from Canadian Network
Rabi et al, Resuscitation 2015:Sept 7

- In 2006 most NICUs in Canada introduced room air resuscitation for babies at term and changed their practice for preterm babies – previously 100% O2, to either starting in 21% or at some intermediate concentration ie 40%.
- Reviewed CNN database for babies between 23 and 27 wks gestation,
- Evaluated occurrence of death or a severe brain injury (grade 3 or 4 IVH or PVL), for the 2 years up to their change in practice, and for 2 years after

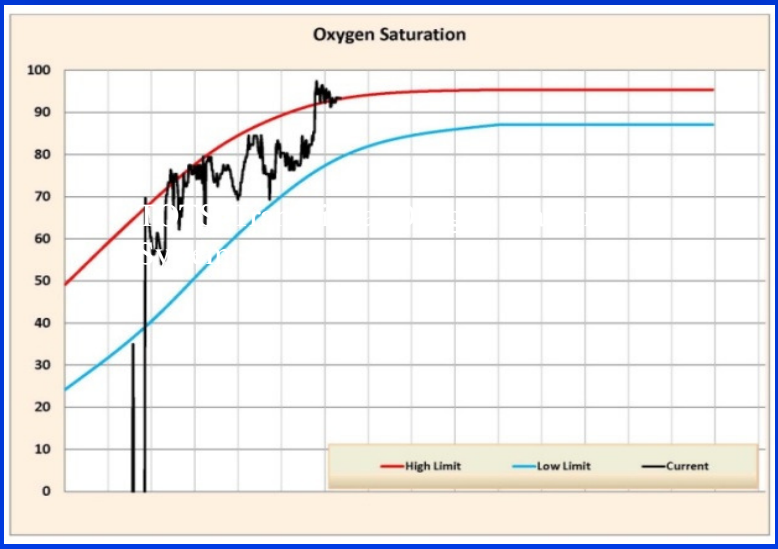
Review from Canadian Network
Rabi et al, Resuscitation 2015:Sept 7

- 17 of 27 units participated
- Data collection for the OX100 (n = 1082
- 222 infants) and OXtitrate (n = 1244 infants) groups spanned 2004 to 2007 and 2006 to 2009
- 12 NICUs used RA, 5 intermediate level

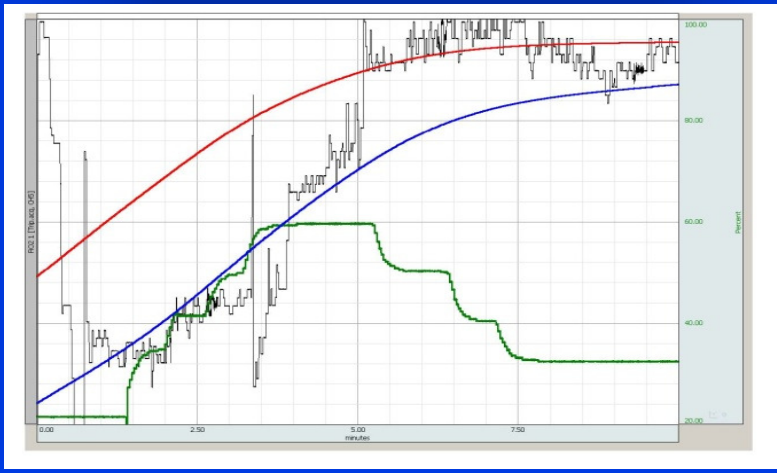
CNN Retrospective Review

- The adjusted odds ratio (AOR) of severe neurologic injury or death was significantly higher in the OXtitrate group compared with the OX100 (AOR 1.36; 95% CI 1.11, 1.66)
- The rate of each individual component of our composite primary outcome were also increased in the OXtitrate group and for the 2 Oxy titrate groups
- Overall - 13.3% increase in severe neurologic injury (AOR 1.33; 95% CI 1.07, 1.66) and a 16.9% increase in death before discharge (AOR 1.32; 95% CI 1.04, 1.67).

TOTS, Transitional Oxygen Tracking System



TOTS System
Showing FiO2 Changes as a record of Resuscitation



TOTS – Evaluation

Gandhi et al, E-PAS2012:2855.6

- ✓ Compared 20 VLBW infants TOTS vs No TOTS
- ✓ TOTS group 29wk ± 19d vs control 29wk ± 22d (p = 0.66). BW =1182 ± 524gm vs. 1142 ± 524gm
- ✓ Total resuscitation time in each group was 462 ± 105s in the TOTS group vs 462 ± 86 s in the control group (p = 0.846).
- ✓ TOTS group spent 243 ± 104 s (52% of time) within the 10th and 50th percentile range compared to the control group that spent 160 ± 89s (38% of time) in range (p = 0.034).

PRESOX Trial

- Planned for about 4 years or more
- Have begun enrolling- SLOW!!
- Plan is to combine with Torpido2 – now funded from Australian NHMRC

Discussion now:

- Blinding – probably not
- Use of targets – single SpO2 at 3-5 min vs range
- There was decreasing enthusiasm because of lack of interest in higher FiO2 – even .6 considered too high
- Results of Torpido and SUPPORT – led to reconsideration

Evidence prior to SUPPORT Trial

- There was no previous prospective data using oximetry, which had become the standard of care, that any range of oximetry limits and alarms would either increase or reduce Death or ROP
- ✓ In fact the publications which had reviewed cohorts before the start of SUPPORT suggested that selecting a lower range would reduce both ROP and Death

Oxygen Saturation Monitoring
Chow et al, Pediatr 2003; 111:339-45

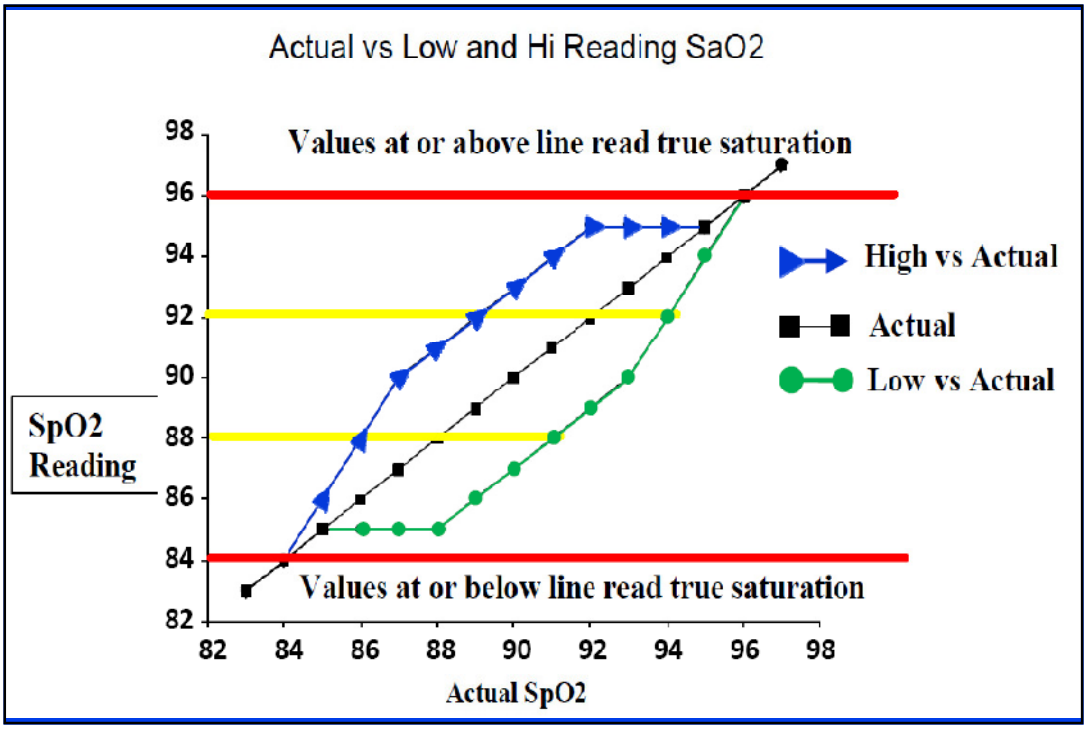
- ✓ Chow et al at Cedars in LA adopted an approach which involved a number of interventions including less oxygen during resuscitation, and a subsequent SpO2 range of 85% to 93% for infants < 32, and 83% - 93% for "smallest and highest risk infants"
- ✓ They reported a significant decrease in ROP Grades 3 to 4 from 12.5% in 1997 to 2.5% in 2001 and ROP laser treatment from 4.5% in 1997 to 0% in the last 3 years of this intervention and increased survival!

Chow et al, Pediatr 2003 111:339-345
Began April 1998

	1997		1998		1999		2000		2001		Total	
Birth Weight (g)	*n*	% Surviv	*n*	% Surviv	*n*	% Surviv	*n*	% Surviv	*n*	% Surviv	*n*	% Surviv
500–749	14	**48**	15	40	18	73	15	87	12	**75**	74	58
750–999	25	**74**	27	78	18	78	21	82	17	**81**	108	83
1000–1249	24	**88**	20	100	26	96	28	100	21	**94**	119	95
1250–1500	29	**97**	27	100	26	100	28	100	36	**97**	146	99
Total	92	**81**	89	83	88	85	92	93	86	**90**	447	86

Methods

- Oxygen saturation targeting ***was initiated within the first two hours after birth*** and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/CPAP for >72 hours, whichever occurred first
- Adjustments in supplemental oxygen to maintain the displayed saturation within the target range of 88 to 92% were performed by the clinical staff, not the researchers



Results – Patient Population – Oximetry Study*

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birth weight	836±193 grams	825±193 grams
Gestational age	26±1 weeks	26±1 weeks
Race, White/Black/Hispanic	37/39/20%	42/35/19%
Antenatal corticosteroids	96.8%	95.6%
Multiple births	24.6%	26.6%

* [illegible]

Results – Primary Outcome – Oximetry Study

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)	
Severe ROP/death	28.3%	32.1%	0.90 (0.76, 1.06)	
Severe ROP	**8.6%**	**17.9%**	**0.52 (0.37, 0.73)**	**NNT=11**
Death	**19.9%**	**16.2%**	**1.27 (1.01, 1.60)**	**NNH=27**

SUPPORT Trial

Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959

- ✓ O_2 saturation targeting in the range of 85-89% did not affect severe ROP/death
- ✓ O_2 saturation targeting in the range of 85-89% resulted in a significant reduction in severe ROP (17.9 to 8.6%, NNT = 11)
- ☒ However, mortality was significantly increased in the 85-89% target group (19.9 versus 16.2%, NNH = 27)

Comparison of Trials

	SUPPORT	BOOST 2	COT
Number Recruited	1316	2448	1201
Gest Age weeks	24-27 6/7	< 28	23 0 - 27 6/7
Randomization Window Randomization Age	< 2hours	Up to 24 hours 17- 18 hrs IQR 11-22hrs	Up to 24 hours
Exclusion Criteria	Decision not to provide care	Not Viable, Anomalies, Not available for follow-up	BOOST 2 + PPHN

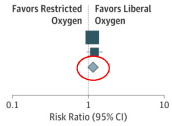
From: **Oxygen Saturation Target Range for Extremely Preterm Infants: A Systematic Review and Meta-analysis**

JAMA Pediatr. 2015;169(4):332-340. doi:10.1001/jamapediatrics.2014.3307

A Death to hospital discharge

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II trial,[15] 2013	235	1221	203	1220	65.0	1.16 (0.98-1.37)
SUPPORT II trial,[13] 2010	130	654	107	662	35.0	1.23 (0.98-1.55)
Total (95% CI)		**1875**		**1882**	**100.0**	**1.18 (1.03-1.36)**
Total events	365		310			

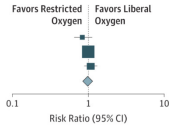
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.17$, $df = 1$ ($P = .68$); $I^2 = 0\%$
Test for overall effect: $z = 2.39$ ($P = .02$)



B Death or severe disability before 18-24 mo

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial,[29] 2014	65	167	76	168	15.7	0.86 (0.67-1.11)
COT,[12] 2013	298	578	283	569	54.9	1.04 (0.92-1.16)
SUPPORT,[28] 2012	185	612	171	622	29.4	1.10 (0.92-1.31)
Total (95% CI)		**1357**		**1359**	**100.0**	**1.02 (0.92-1.14)**
Total events	548		530			

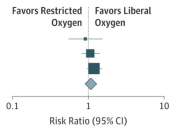
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.49$, $df = 2$ ($P = .29$); $I^2 = 20\%$
Test for overall effect: $z = 0.44$ ($P = .66$)



C Death before 18-24 mo

Study or Subgroup	Restricted Oxygen, No. Events	Restricted Oxygen, No. Total	Liberal Oxygen, No. Events	Liberal Oxygen, No. Total	Weight, %	Risk Ratio (95% CI)
BOOST II-New Zealand trial,[29] 2014	25	170	27	170	10.2	0.93 (0.56-1.53)
COT,[12] 2013	97	585	88	577	36.5	1.09 (0.83-1.42)
SUPPORT,[28] 2012	140	633	118	648	53.3	1.21 (0.98-1.51)
Total (95% CI)		**1388**		**1395**	**100.0**	**1.13 (0.97-1.33)**
Total events	262		233			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.10$, $df = 2$ ($P = .58$); $I^2 = 0\%$
Test for overall effect: $z = 1.55$ ($P = .12$)



Where does that Leave Us???

- Initial Meta Analysis - show increase death on Low SpO2 treated infants
- There will be a current detailed Cochrane Analysis from the NeoProm Group shortly and that will be followed by an individual patient meta-analysis
- We have no studies of other ranges – ie 88% to 92%
- At present most are choosing to use the high range –ie from 90% to 95% till more data available
- Are further studies needed/likely???

Conclusions

- These trials initially used identical masked oximeters, placed within the first 24 hrs of life in 4965 infants < 28 weeks gestational age in 4 Continents
- Each trial was rigorously run and monitored
- There was a pre-specified agreement to perform an individual patient meta analysis on the overall results and the NeoProm group has continued to meet and collaborate.