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Lessons Learnt from the Recent Trials of Oxygen Saturation Targeting in Extremely Preterm Infants

Objectives

- Review the results of the Canadian Oxygen Trial (COT)
- Compare the COT results with those of SUPPORT and the 3 BOOST II trials and identify the similarities, differences and limitations of these 5 trials
- Explain the trade-off between higher versus lower oximeter alarm settings

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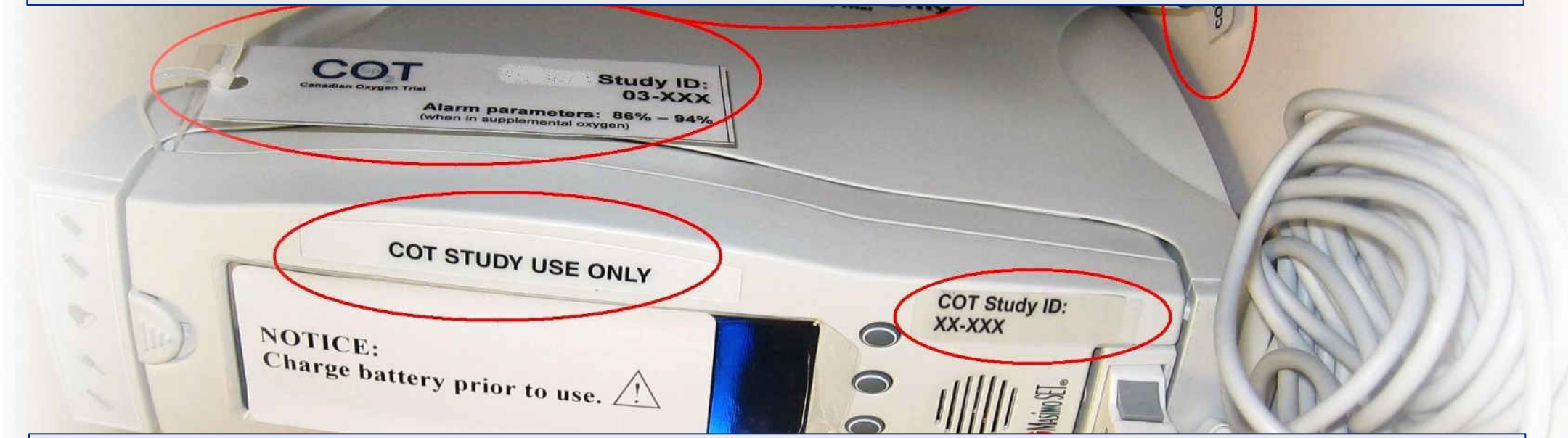
Main COT Study Question

P	In infants born at 23 0/7 to 27 6/7 wk,
I	does a target saturation of 85-89%
C	compared with 91-95%
O	increase or decrease the risk of death or neurosensory disability
T	at a corrected age of 18 months?

Target range for displayed saturations on off-set pulse oximeters: 88-92%



Low target range for true saturations: 85-89%
High target range for true saturations: 91-95%

Death or Disability at 18 Months

85-89%	91-95%
298 of 578	283 of 569
51.6%	49.7%

OR = 1.08 95% CI 0.85-1.37 p = .52

Components of Primary Outcome

	85-89%	91-95%	OR (95%CI)
Death	16.6%	15.3%	1.1 (0.8-1.5)
GMFCS ≥2	6.1%	6.4%	1.0 (0.6-1.7)
Bayley III < 85	40%	40%	1.0 (0.8-1.3)
Deafness	3.7%	2.5%	1.5 (0.7-3.2)
Blindness	1.0%	0.6%	1.7 (0.4-7.1)

Secondary Outcomes

	85-89%	91-95%	P-value
Severe ROP	12.8%	13.1%	.80
NEC	12.3%	9.3%	.10

Targeting lower saturations reduced the PMA at last use of oxygen therapy by 0.8 weeks; 95% CI -1.5 to -0.1; P=.03

COT Conclusions

Targeting oxygen saturations of 85-89% as compared with 91-95% had no significant effect on rates of

- death or disability at 18 months
- death before 18 months
- necrotizing enterocolitis
- severe retinopathy of prematurity

Effects of Targeting Lower Saturations

Trial	Death at DC or Follow-up	Severe ROP
SUPPORT	↑	↓↓
BOOST NZ	No Diff	No Diff
BOOST AU	No Diff	No Diff
BOOST UK	No Diff	No Diff
Pooled BOOST II	No Diff	↓
COT	No Diff	No Diff

Meta-Analysis and GRADE Summary

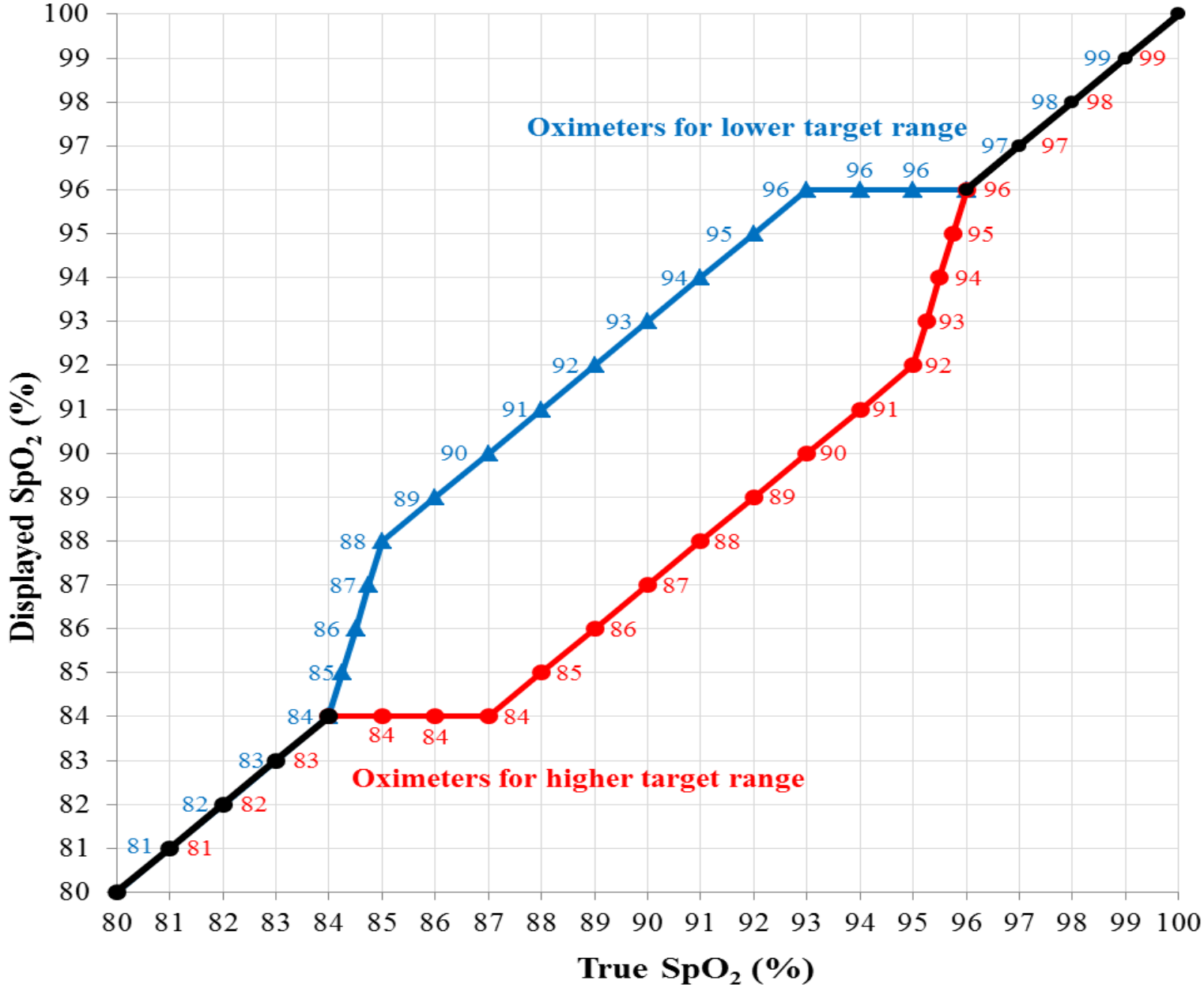
Outcome	RR (95% CI)	Quality
Death or Disability	1.02 (0.94-1.14)	Moderate
Death < 24 mo	1.16 (0.98-1.37)	Moderate
Death < Discharge	1.18 (1.03-1.36)	Low
Disability	1.03 (0.73-1.45)	Moderate
NEC	1.24 (1.05-1.47)	Moderate
ROP	0.72 (0.50-1.04)	Low

JAMA Pediatr 2015;169: 332-40

Similarities Between Trials

- Target populations (apart from SUPPORT)
- Oximeters incl. masking algorithm
- Saturation target ranges
- Sample sizes (apart from NZ)
- Long-term primary outcome of death or disability (apart from SUPPORT)

Masking Algorithm of Study Oximeters in SUPPORT, BOOST II and COT



Differences Between Trials

- Oximeter alarm settings:
  - Prescription and audits
- Calibration software versions
- Enrollment of target sample size:
  - Early stopping of enrollment in BOOST II in UK and Australia
- Rates of adverse outcomes

Target Ranges Versus Alarms

Do busy NICU nurses respond to mental saturation target ranges?

Or do they respond to alarms?

Protocol-Prescribed Alarm Settings

Trial	Lower Alarm	Upper Alarm
SUPPORT	84%	96%
BOOST NZ	87%	93%
BOOST AU	86% (80-85%)	94%
BOOST UK	---	95%
COT	86%	94%

COT Audits of Adherence to Alarms

During the COT enrollment phase:

- Monthly analysis of downloaded saturations of all active patients at the Data Coordinating Center
- Monthly confidential feedback to research teams in all clinical sites
- Monthly distribution of “league tables”

COT Sp2 Canadian Oxygen Trial

Newsletter

ISSUE 26 MARCH 2009

Oxygen Saturations - "On-target" Performance

Here we recognize/reward the top 3 centres for their adherence to the oxygen target saturations, based on the monthly saturation reports for the first 3 days of life. To qualify for an award, your centre will need to have at least 3 babies included in any given report.

February Winners

"On-target" Performance:

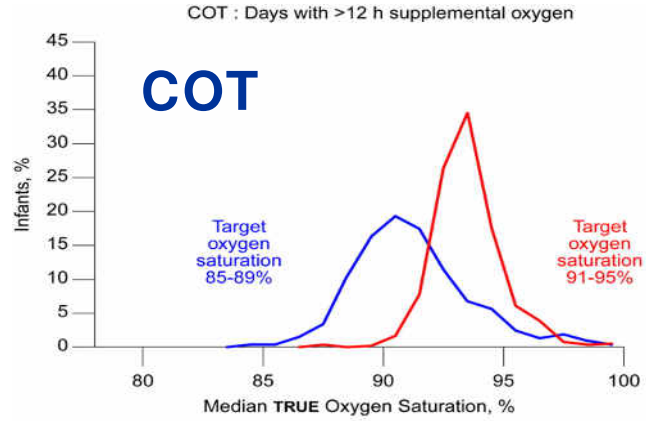
1. IWK Health Centre (Halifax, NS)
2. Hospital of the University of Pennsylvania (Philadelphia, PA)
3. B.C. Children's Hospital (Vancouver, BC)

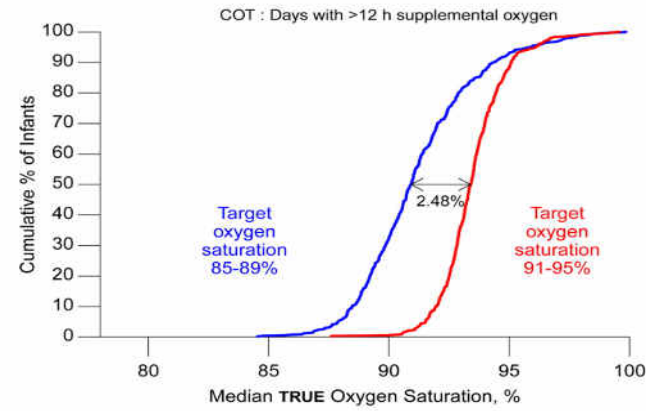
Congratulations to you and your teams!

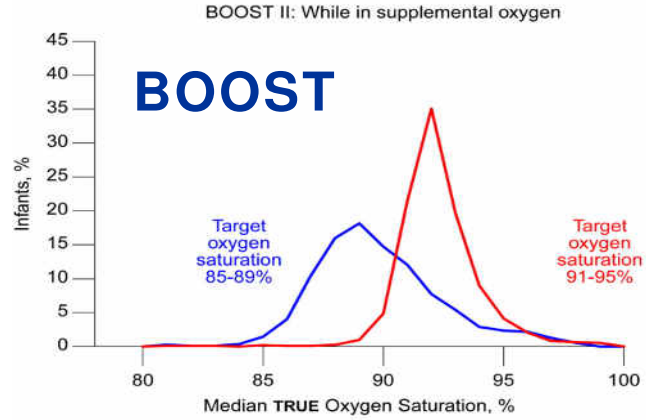
Goal of Oxygen SaturationTargeting

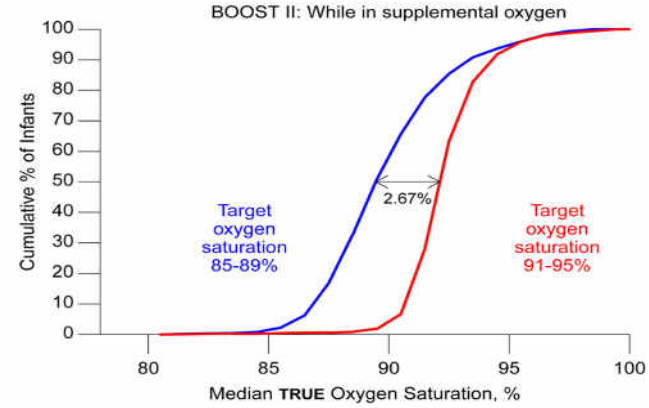
"Providers need to understand that cumulative oxygen saturations over time represent a bell shaped curve, and the role of the health care team is to minimize the tails in both directions".

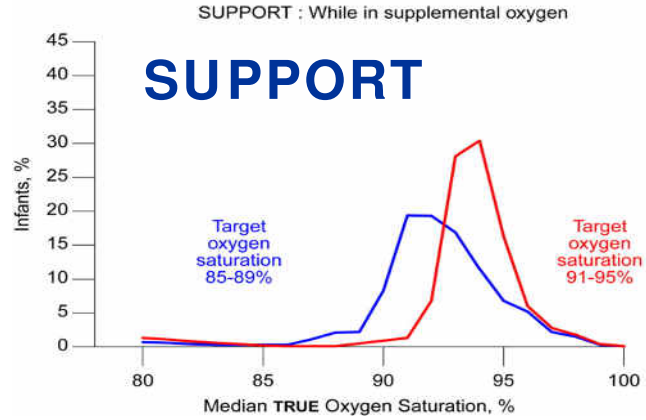
Greenspan and Goldsmith, Pediatrics 2006; 118:1741

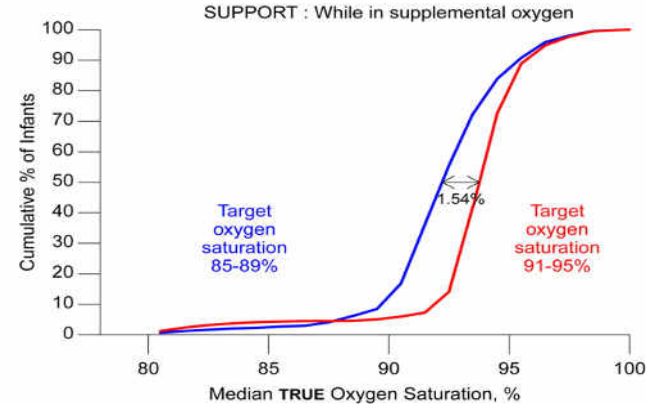






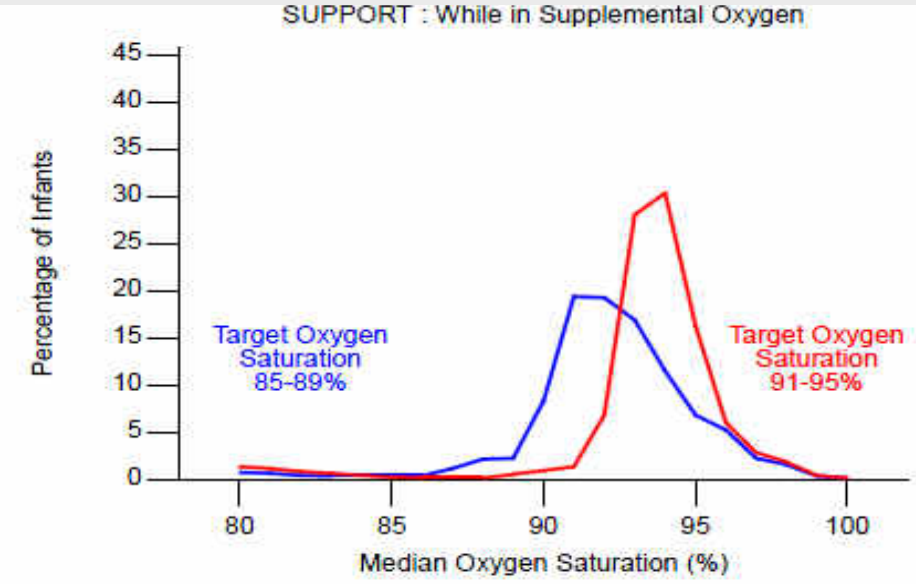


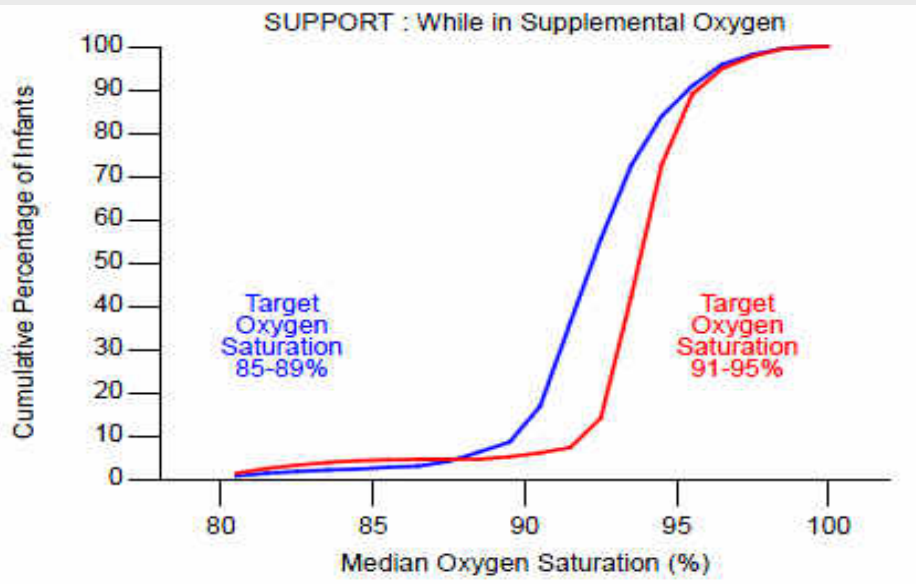


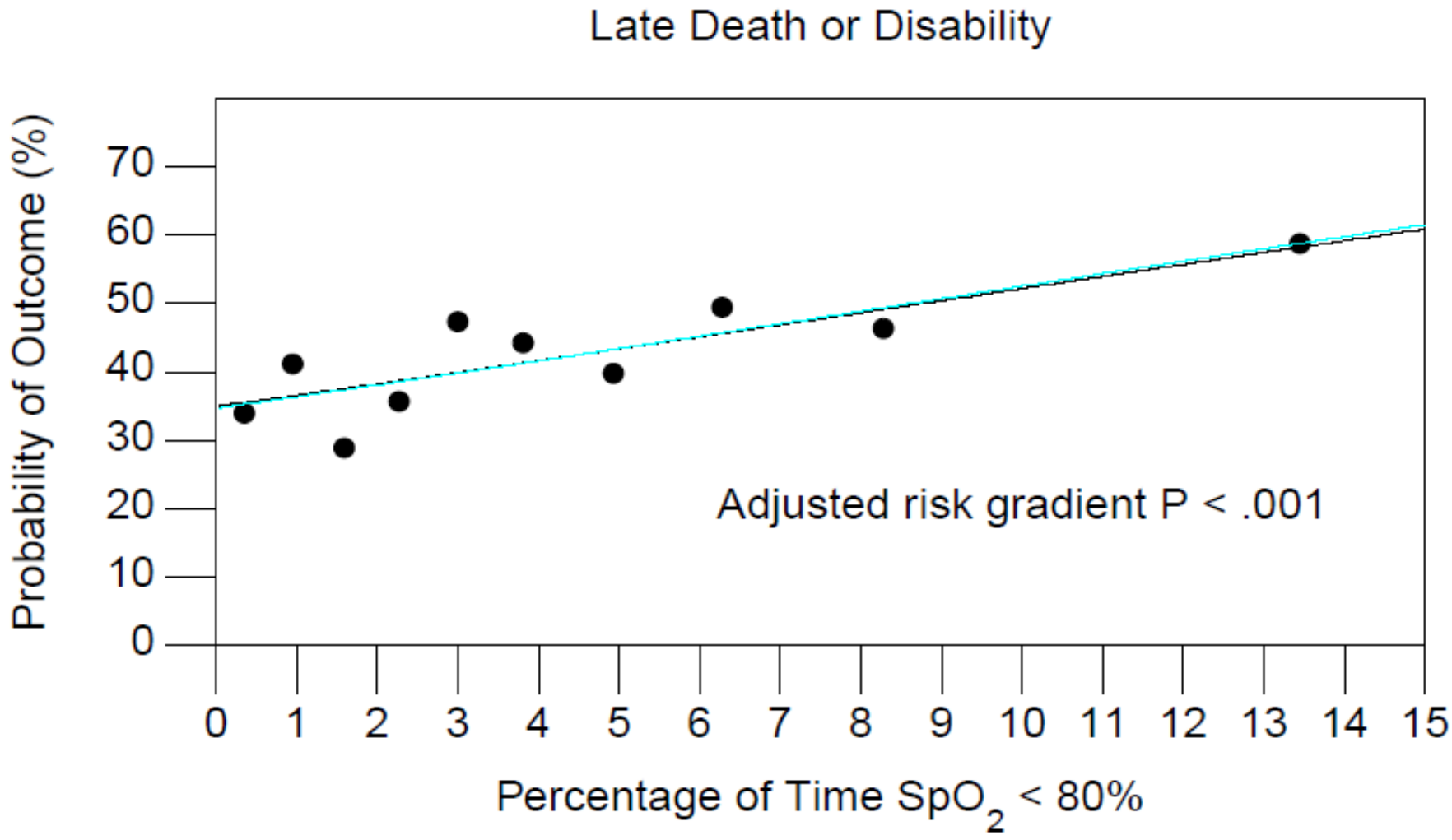


J Pediatr
2014; 165:666

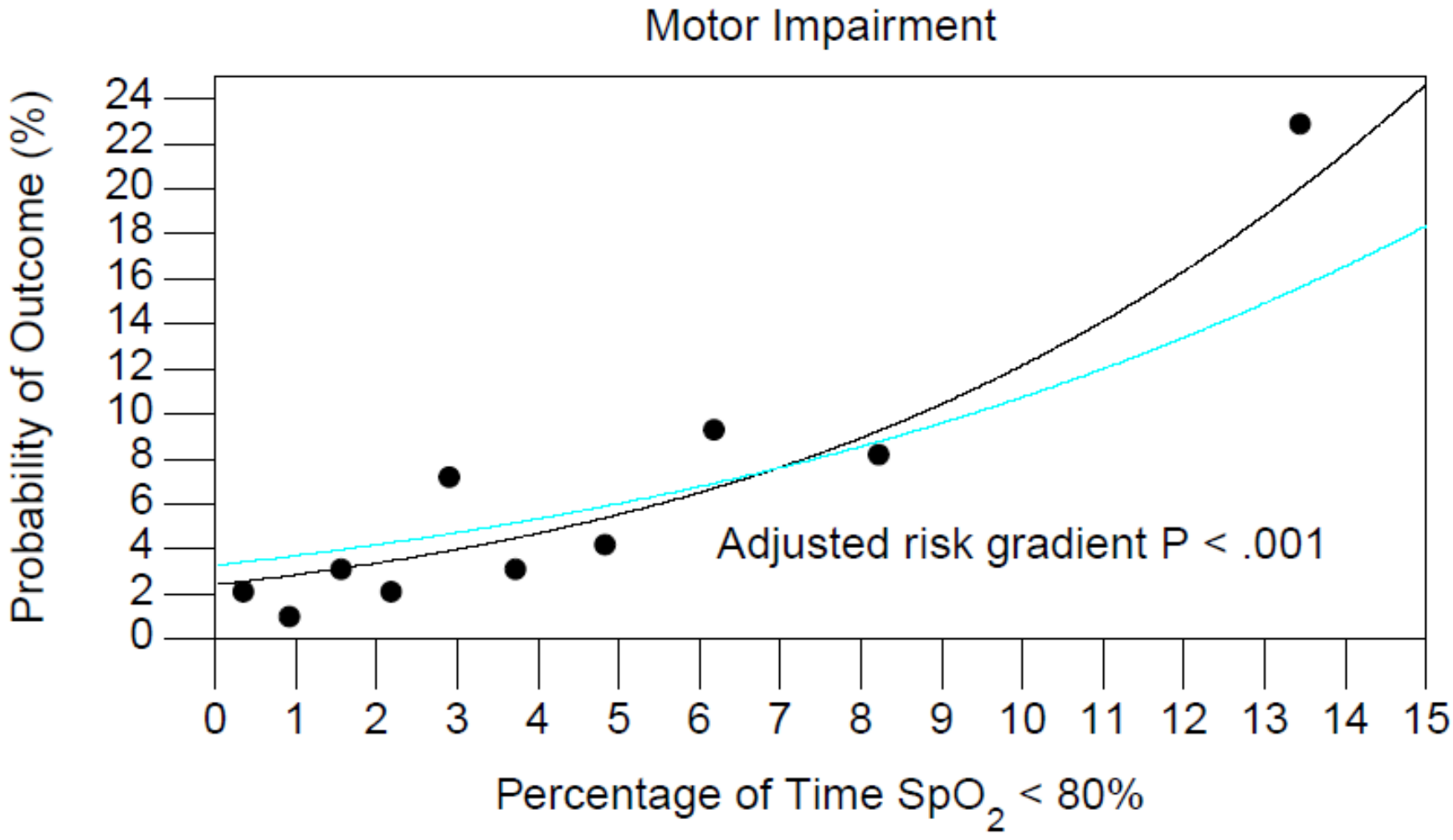
SUPPORT had the greatest overlap between saturations in the two target ranges, and the longest tails. SUPPORT also had the biggest treatment effects of all 5 trials.







JAMA 2015;314:595-603



JAMA 2015;314:595-603

Oximeter Calibration Software

"Both the original and revised calibration algorithms perform within the recommended standards for accuracy, but the revised algorithm is associated with improved SpO_2 targeting"

Stenson B et al: N Engl J Med 2011; 364:1680

BOOST II Interim Subgroup Analysis in December 2010

- Initiated by investigators, not by the Data Safety Monitoring Board
- Ad-hoc (unscheduled)
- Led to early closure of enrollment in BOOST II Australia and UK

The Perils of Stopping Early
JAMA 2010; 303:1180

- "Stopped early" trials overestimate the treatment effect
- Clinicians, meta-analysts and policy makers should not rely on "stopped early" trials for accurate estimates of treatment effects

Conclusions I

Meta-analysis of oxygen saturation targeting trials to date suggests:

- increased in-hospital mortality and NEC rates with lower target range
- likely increased rate of severe ROP with higher target range
- no effect on the composite outcome of death or disability at 18 -24 months

Conclusions II

- Oximeter alarm settings differed between the 5 RCTs
- Monitoring of adherence to alarms differed between the RCTs
- The RCT with the longest tails in the distributions of saturations had the greatest treatment effects

Outcome Rates Differ Between Trials

Trial	Death before Discharge	Severe ROP
SUPPORT	18.0%	13.4%
BOOST NZ	13.2%	7.5%
BOOST AU	16.0%	7.7%
BOOST UK	21.8%	19.2%
COT	15.2%	12.9%

What Are Your Outcome Rates?

An example from a Canadian NICU:

- Our mortality rate in infants < 28 weeks is less than 6%.
- Our rate of severe ROP is average but could be improved.
- Our lower alarm has been set at 85% for many years.
- Why would we change it now?