Supplementary Appendix

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

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Methodology for limited ventilator strategy

CPAP Arm:
NICU management: CPAP infants could be intubated if they met any of the following criteria: an FiO2 >.50 required to maintain an indicated SpO2 > 88% for one hour, an arterial PaCO2 > 65 torr documented on a single blood gas within 1 hour prior to intubation, or hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. If intubated within the first 48 hours of life, infants were to receive surfactant. Following NICU admission, each unit utilized its standard method for CPAP delivery, which included the use of a ventilator, purpose built flow driver, or bubble CPAP circuit. Extubation for CPAP infants was to be attempted within 24 hours if all of the following criteria were met: a $PaCO_2$ < 65 torr with a pH > 7.20, an SpO_2 > 88% with an FiO_2 < 50%, a mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV), and hemodynamically stable, and without a clinically significant patent ductus arteriosus. Re-intubation criteria were the same as those for intubation. After 3 intubations, CPAP infants were treated using NICU standard practice.

Surfactant Arm: All infants were to be extubated within 24 hours of meeting all of the following criteria: $PaCO_2$ < 50 torr and pH > 7.30, $FiO_2 \leq .35$ with a SpO_2 >88%, a MAP < 8 cm H_2O, ventilator rate < 20 bpm, an amplitude < 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA. Once extubated, Surfactant infants were treated using NICU standard practice.
These criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery. [1]

Methodology for oximeter blinding strategy

4.1.1 Randomization and Masking, Storing and Assigning Oximeters
Two sets of envelopes will be used; one for the gestational age group 24 -25 6/7 weeks and one for the26 - 27 6/7 week gestational age group…. Inside the sealed envelope will be a white card which will contain the randomization number and treatment assignments. The card will indicate which of the Early CPAP/Early Surfactant treatments is selected and will indicate a color code for the High/Low SpO2 arm of the study. They will be specified as one of the following:

• **Treatment Group** (EARLY CPAP and permissive ventilation management) with an **Oximeter code** of either **Blue or Orange OR • Control Group** (Early SURFACTANT and conventional ventilator management) with an **Oximeter code** of either **Blue or Orange.**

The **Blue/Orange codes** will designate an assignment to either the **Low (85% - 89%)** or **High (91% -95%)** SpO2 group. The oximeters will be shipped directly to the clinical sites from Masimo. The Data Center will supply the

sites with the **Blue and Orange** labels and these color coded labels will correspond to the serial numbers on the oximeter(s). The serial number(s) will need to be recorded on the appropriate data form (**SUPP04 Form)**.

Note: The oximeters should be stored in such a manner that the individual who will be obtaining them and returning them to their original location can easily identify which oximeters belong to which color-coded randomization group. It is not recommended that the oximeters be identified with the blue or orange colored labels. A system whereby the serial numbers for each color group are identified at the storage sight, along with a list of which infants have been placed on which serial numbers, makes it possible to track oximeters without using the color coded labels on the devices themselves.

The person opening the envelope should announce to the team the assignment of the Early CPAP/Early Surfactant arm of the study. Someone should then take the opened envelope to the secure area where the oximeters are stored and select the oximeter (s) whose color code is specified in the randomization envelope. **Once the envelope is opened, it should be stored in a secure location only accessible to staff with "a need to know".** Randomization should be done only if sufficient numbers of oximeters of both types (i.e. high and low SpO2) are available to accommodate the delivery. Once the use of an oximeter has been completed, it should be returned to the color coded location for storing the inventory of oximeters (e.g., a color coded shelf) checking to be sure that the serial numbers match. A log should be maintained to record the date and time the particular oximeter is returned to this location.[2]

Table S1: Demographic and Clinical Characteristics of the Follow-up Cohorts

	CPAP	Surfactant	Lower Saturation	Higher Saturation
	N=511	N=479	N=479	N=511
Birth weight (grams) $^{\delta}$	849±186	852±193	858±186	844±192
Gestational age (weeks) $^{\delta}$	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1
	n/total(%)	n/total(%)	n/total(%)	n/total(%)
SGA (birthweight < 10th%)$^{€}$	23/511 (4.5)	32/479 (6.7)	17/479 (3.5)**	38/511(7.4)**
Male$^{€}$	256/511(50.1)	266/479(55.5)	240/479(50.1)	282/511(55.2)
Non-Hispanic White$^{€}$	196/511(38.4)	200/479(41.8)	178/479(37.2)	218/511(42.7)
Non-Hispanic Black$^{€}$	200/511(39.1)	177/479(37)	201/479(42)	176/511(34.4)
Hispanic$^{€}$	98/511(19.2)	85/479(17.7)	86/479(18)	97/511(19)
Other or unknown$^{€}$	17/511(3.3)	17/479(3.5)	14/479(2.9)	20/511(3.9)
Multiple gestation$^{€}$	138/511(27)	114/479(23.8)	124/479(25.9)	128/511(25)
Antenatal steroids, any$^{€}$	493/511(96.5)	456/479(95.2)	462/479(96.5)	487/511(95.3)
Cesarean section$^{€}$	352/511(68.9)	315/479(65.8)	332/479(69.3)	335/511(65.6)
Public insurance only$^{€}$	262/511(51.3)	257/479(53.7)	253/479(52.8)	266/511(52.1)
Mother married$^{€}$	244/511(47.7)	221/479(46.1)	222/479(46.3)	243/511(47.6)
Living with both biological parents$^{€}$	348/510(68.2)	329/479(68.7)	332/478(69.5)	345/511(67.5)
Maternal education< high school	128/506(25.3)	116/469(24.7)	115/471(24.4)	129/504(25.6)

degree[€]				
Income < $30,000/year[€]	260/493(52.7)	251/461(54.4)	239/456(52.4)	272/498(54.6)
English as primary language [€]	426/510(83.5)	403/478(84.3)	402/477(84.3)	427/511(83.6)
Severe ROP[€]	62/479(12.9)	58/434(13.4)	38/442(8.6)***	82/471(17.4)***
BPD[¶ €]	193/511(37.8)	187/479(39)	177/479(37)	203/511(39.7)
IVH grade 3-4/PVL[€]	70/510(13.7)	46/478(9.6)	56/478(11.7)	60/510(11.8)
NEC [€]	56/511(11)*	30/479(6.3)*	42/479(8.8)	44/511(8.6)
Late onset sepsis/meningitis[€]	167/511(32.7)	154/479(32.2)	155/479(32.4)	166/511(32.5)
Postnatal steroids[€]	34/508(6.7)*	55/476(11.6)*	41/477(8.6)	48/507(9.5)
Corrected age at follow up (months) [δ]	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

[δ] Mean ± SD

[€] no./total no.(%)

¶ At 36 weeks postmenstrual age

*p<0.05, ** p<0.01, ***p<0.001 (Comparison for groups within each intervention arm)

Comparisons of neonatal outcomes adjusted for stratification by center and gestational age and for familial clustering

Table S2: Outcomes for treatment groups by gestational age strata: CPAP vs. SURFACTANT

24 0/7-25 6/7 weeks	CPAP*	Surfactant*	ARR**	p
Death or NDI	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

26 0/7-27 6/7 weeks	CPAP*	Surfactant*	ARR**	p
Death or NDI	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31

Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S3: Outcomes for treatment groups by gestational age strata: LOWER VS. HIGHER OXYGEN SATURATION TARGETS

24 0/7-25 6/7 weeks	Lower*	Higher*	ARR**	p
Death or NDI	115/261(44.1)	112/276(40.6)	1.09(0.89,1.32)	0.42
Death before 18-22 mo CA	91/267(34.1)	79/283(27.9)	1.23(0.95,1.59)	0.12
Death/NDI determined	261/276(94.6)	276/289(95.5)	0.99(0.96,1.03)	0.69
NDI	24/170(14.1)	33/197(16.8)	0.8(0.49,1.3)	0.37
BSID-III cognitive score < 70	17/169(10.1)	22/196(11.2)	0.86(0.47,1.56)	0.62
Gross motor function level ≥ 2	13/173(7.5)	13/200(6.5)	1.07(0.53,2.17)	0.86
Moderate/severe cerebral palsy	10/173(5.8)	12/200(6.0)	0.86(0.39,1.88)	0.70
Blindness, bilateral	1/173(0.6)	3/200(1.5)	0.39(0.04,3.69)	0.41
Blindness, in at least one eye	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)	0.41
Hearing impairment	4/173(2.3)	10/200(5.0)	0.5(0.16,1.53)	0.22

26 0/7-27 6/7 weeks	Lower*	Higher*	ARR**	p
Death or NDI	70/351(19.9)	59/346(17.1)	1.17(0.85,1.6)	0.33
Death before 18-22 mo CA	49/366(13.4)	39/365(10.7)	1.28(0.86,1.89)	0.22

Death/NDI determined	351/378(92.9)	346/373(92.8)	1(0.96,1.04)	0.97
NDI	21/302(7.0)	20/307(6.5)	0.99(0.54,1.84)	0.98
BSID-III cognitive score < 70	17/302(5.6)	16/307(5.2)	0.98(0.49,1.97)	0.95
Gross motor function level ≥ 2	13/306(4.2)	10/311(3.2)	1.32(0.57,3.01)	0.52
Moderate/severe cerebral pal	10/306(3.3)	8/311(2.6)	1.22(0.47,3.2)	0.68
Blindness, bilateral	4/306(1.3)	3/311(1.0)	1.38(0.31,6.05)	0.67
Blindness, in at least one eye	4/306 (1.3)	5/311 (1.6)	0.83(0.23,3.03)	0.78
Hearing impairment	8/306(2.6)	2/311(0.6)	4.18(0.88,19.87)	0.07

*no./total no. (%)

** Adjusted Relative Risk (95% CI)

Relative risk and p values adjusted for stratification factors (study center and interaction between treatment and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table S4: Comparison of Cognitive outcomes for SUPPORT treatment arms

CPAP vs. Surfactant	CPAP	SURF	ARR*	p
BSID-III cognitive composite score**	91.3 ± 0.7	90.4 ± 0.8		0.33
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	111/502(22.1)	126/472(26.7)	0.82(0.66,1.02)	0.08
BSID-III cognitive composite score < 80¶	65/502(12.9)	81/472(17.2)	0.74(0.55,1)	0.05

Lower vs. Higher Oxygen Saturation Targets	LOWER	HIGHER	ARR*	p
BSID-III cognitive composite score **	91.2 ± 0.8	90.5 ± 0.7		0.48
BSID-III cognitive composite score ***	90(85,100)	90(80,100)		
BSID-III cognitive composite score < 85¶	105/471(22.3)	132/503(26.2)	0.85(0.68,1.07)	0.16
BSID-III cognitive composite score < 80¶	68/471(14.4%)	78/503(15.5%)	0.91(0.67,1.22)	0.53

*ARR (Adjusted relative risk)

** (adjusted mean ± standard error)

***(median, interquartile range)

¶ [no./total no.(%)]

Means, relative risks and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

Table S5: Reasons for Eye surgery Lower vs. Higher Oxygen Saturation Target Groups

Reason for Eye surgery	**Lower** **N=31**	**Higher** **N=67**	**Total** **N=98**
Retinopathy of Prematurity	26 (84%)	59 (88%)	85 (87%)
Strabismus	1 (3%)	4 (6%)	5 (5%)
Cataract	1 (3%)	0	1 (1%)
Other	3 (10%)	4 (6%)	7 (7%)

References

1. Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010;362:1970-9.

2. SUPPORT Manual of Operations, January 4, 2005, Revised March 10, 2005