Supplemental Online Content

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

eTable 1. Baseline characteristics by gestation strata

		Gestation stratum 25-26 weeks		Gestation stratum 27-28 weeks	
		MIST group (N=90)	Control group (N=87)	MIST group (N=151)	Control group (N=157)
Gestation, weeks		26.0 (25.6–26.4)	26.1 (25.9–26.6)	28.0 (27.4–28.4)	27.9 (27.3–28.4)
Birth weight (g)		795 (161)	804 (146)	1009 (213)	997 (219)
Birth weight <10th centile		13 (14.4%)	12 (13.8%)	21 (13.9%)	22 (14.0%)
Female sex		45 (50.0%)	54 (62.1%)	71 (47.0%)	71 (45.2%)
Male sex		45 (50.0%)	33 (37.9%)	80 (53.0%)	86 (54.8%)
Plurality, birth order	**Singleton**	47 (52.2%)	57 (65.5%)	103 (68.2%)	112 (71.3%)
	First of multiples	16 (17.8%)	12 (13.8%)	25 (16.6%)	20 (12.7%)
	Second or subsequent multiple	27 (30.0%)	18 (20.7%)	23 (15.2%)	25 (15.9%)
Exposure to antenatal glucocorticoids	**2 or more doses prior to delivery**	54 (60.0%)	64 (73.6%)	102 (67.5%)	111 (70.7%)
	1 dose prior to delivery	31 (34.4%)	21 (24.1%)	32 (21.2%)	29 (18.5%)
	None	5 (5.6%)	2 (2.3%)	17 (11.3%)	17 (10.8%)
Delivery mode	**Vaginal delivery**	25 (27.8%)	22 (25.3%)	20 (13.2%)	30 (19.1%)
	Cesarean delivery with labour	40 (44.4%)	30 (34.5%)	56 (37.1%)	52 (33.1%)
	Cesarean delivery, no labour	25 (27.8%)	35 (40.2%)	75 (49.7%)	75 (47.8%)
Apgar score at 5 min		8 (7–8)	8 (7–9)	8 (7–9)	8 (7–9)
Age at randomization (hrs)		2.6 (1.4)	2.9 (1.4)	3.0 (1.5)	2.7 (1.5)
CPAP level at randomization (cm H_2O)		7 (6–8)	7 (6–8)	7 (6–8)	7 (6–8)
FiO_2 at randomization		0.35 (0.30–0.40)	0.35 (0.30–0.40)	0.35 (0.30–0.39)	0.35 (0.30–0.39)
FiO_2 ≤0.35		52 (57.8%)	54 (62.1%)	100 (66.2%)	96 (61.1%)

n (%), mean (SD) or median (interquartile range). Abbreviations: CPAP, continuous positive airway pressure; MIST, minimally invasive surfactant therapy. Denominators for all characteristics, and number of observations for continuous variables, are as per column headers.

eTable 2. Primary outcome and its components: extended generalized linear model

Outcome	MIST group	Control group	Adjusted risk difference (%) (95% CI)[a]	Adjusted relative risk (95% CI)[a]
Death or BPD[b]	105/241 (43.6%)	121/244 (49.6%)	-6.4 (-14.0 to 1.2)	0.87 (0.74–1.02)
Death prior to 36 weeks' PMA	24/241 (10.0%)	19/244 (7.8%)	1.8 (-4.1 to 7.7)	1.20 (0.58–2.46)
BPD[b] **in survivors to 36 weeks' PMA**	81/217 (37.3%)	102/225 (45.3%)	-7.9 (-14.0 to -1.9)	0.82 (0.71–0.95)

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy; PMA: postmenstrual age.
[a]Adjusted for gestation strata and other covariates known to influence the primary outcome (birth weight <10th percentile, sex, mode of delivery, plurality, antenatal glucocorticoid exposure, and 5-minute Apgar score).
[b]BPD: bronchopulmonary dysplasia (physiological definition) assessed at 36 weeks' postmenstrual age, and defined as: i) receiving mechanical respiratory support (mechanical ventilation / CPAP / nasal high flow ≥2 L/min); *or* ii) (if not receiving mechanical respiratory support): receiving oxygen with actual or effective FiO_2 ≥0.30; *or* iii) receiving oxygen with FiO_2 <0.30 and failed air trial; *or* iv) receiving oxygen with FiO_2 <0.30 and air trial not performed by physician request. See Methods for further details of physiological BPD assessment.

eTable 3. Primary outcome and its components: as treated and per protocol analyses

Form of analysis	Outcome	MIST group	Control group	Adjusted relative risk (95% CI)[a]
As treated[b] *MIST N=243 Control N=240*	**Death or BPD**[c]	106/243 (43.6%)	118/240 (49.2%)	0.88 (0.74–1.04)
	Death prior to 36 weeks' PMA	24/243 (9.9%)	19/240 (7.9%)	1.23 (0.60–2.53)
	BPD[c] **in survivors to 36 weeks' PMA**	82/219 (37.4%)	99/221 (44.8%)	0.84 (0.70–0.99)
Per protocol[d] *MIST N=234 Control N=235*	**Death or BPD**[c]	103/234 (44.0%)	117/235 (49.8%)	0.88 (0.74–1.04)
	Death prior to 36 weeks' PMA	24/234 (10.3%)	19/235 (8.1%)	1.26 (0.62–2.56)
	BPD[c] **in survivors to 36 weeks' PMA**	79/210 (37.6%)	98/216 (45.4%)	0.83 (0.70–0.99)

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy; PMA, postmenstrual age.
[a]Adjusted for gestation strata.
[b]As treated: analyzed by treatment received (see Figure 1 for details of inclusions and exclusions).
[c]BPD: bronchopulmonary dysplasia (physiological definition) assessed as per eTable 2.
[d]Per protocol: analysis of data from infants i) eligible for study entry based on review of Case Report Form data, ii) randomized according to the prescribed method, iii) receiving the intervention they were allocated to in the randomization, and iv) have primary outcome data available. Exclusions from per protocol analysis in the MIST group (n=8): allocated treatment not received, required immediate intubation (n=2); received treatment as per the control group (n=2); later found to be outborn and hence ineligible (n=2); allocated to MIST group but from incorrect randomization envelope (n=1); withdrawn and data not made available (n=1). Exclusions in the control group (n=9): received treatment as per the MIST group (n=6); later found to be >28 weeks gestation at birth and hence ineligible (n=1); allocated to control group but from incorrect randomization envelope (n=2).

eTable 4. Primary outcome and its components: gestation strata

Outcome	Gestation stratum	MIST group	Control group	Adjusted relative risk (95% CI)[a]	*P* value for interaction[b]	RR (95% CI) adjusted for gestation and covariates[c]
Death or BPD[d]	**25-26 weeks**	50/90 (55.6%)	53/87 (60.9%)	0.91 (0.71–1.16)	0.78	0.89 (0.71–1.13)
	27-28 weeks	55/151 (36.4%)	68/157 (43.3%)	0.86 (0.60–1.23)		0.84 (0.61–1.16)
Death prior to 36 weeks' PMA	**25-26 weeks**	14/90 (15.6%)	6/87 (6.90%)	2.23 (0.90–5.52)	0.01	1.95 (0.90–4.23)
	27-28 weeks	10/151 (6.6%)	13/157 (8.3%)	0.79 (0.40–1.57)		0.79 (0.40–1.56)
BPD[d] in survivors to 36 weeks' PMA	**25-26 weeks**	36/76 (47.4%)	47/81 (58.0%)	0.81 (0.59–1.12)	0.95	0.80 (0.59–1.09)
	27-28 weeks	45/141 (31.9%)	55/144 (38.2%)	0.87 (0.57–1.32)		0.82 (0.56–1.19)

n/N (%). Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; MIST, minimally invasive surfactant therapy; PMA, postmenstrual age; RR, relative risk.
[a]Adjusted for gestation.
[b]Interaction of gestation stratum with treatment allocation in the statistical model.
[c]Adjusted for gestation and covariates known to influence the primary outcome (see eTable 2).
[d]BPD: bronchopulmonary dysplasia (physiological definition) assessed as per eTable 2.

eTable 5. Key clinical and safety outcomes: gestation strata

Outcome	Gestation stratum	MIST group	Control group	Adjusted relative risk[a] (95% CI)	*P* value for interaction[b]
Air leak requiring drainage	**25-26 weeks**	6/90 (6.7%)	13/87 (14.9%)	0.44 (0.19–1.00)	0.96
	27-28 weeks	5/151 (3.3%)	12/157 (7.6%)	0.44 (0.18–1.07)	
Need for intubation <72 h	**25-26 weeks**	44/90 (48.9%)	63/87 (72.4%)	0.67 (0.52–0.86)	0.013
	27-28 weeks	44/151 (29.1%)	113/157 (72.0%)	0.41 (0.29–0.58)	
Severe IVH – grade III or IV	**25-26 weeks**	6/90 (6.7%)	14/87 (16.1%)	0.41 (0.15–1.09)	0.083
	27-28 weeks	12/151 (7.9%)	10/157 (6.4%)	1.27 (0.74–2.17)	
Death or major morbidity[c]	**25-26 weeks**	53/90 (58.9%)	61/87 (70.1%)	0.84 (0.67–1.04)	0.88
	27-28 weeks	63/151 (41.7%)	75/157 (47.8%)	0.89 (0.61–1.30)	
Death during first hospitalization (all causes)	**25-26 weeks**	16/90 (17.8%)	7/87 (8.0%)	2.18 (0.97–4.88)	0.047
	27-28 weeks	12/151 (7.9%)	13/157 (8.3%)	0.95 (0.50–1.81)	
Major morbidity[c] in survivors	**25-26 weeks**	37/74 (50.0%)	54/80 (67.5%)	0.74 (0.56–0.97)	0.68
	27-28 weeks	51/139 (36.7%)	62/144 (43.1%)	0.88 (0.56–1.37)	

n/N (%). Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; MIST, minimally invasive surfactant therapy.
[a]Adjusted for gestation.
[b]Interaction of gestation stratum with treatment allocation in the statistical model.

[c]Death during first hospitalization, or major morbidity defined as any of: IVH grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity >stage II (assessed throughout hospitalization), physiological bronchopulmonary dysplasia (at 36 weeks PMA).[1]

eTable 6. Secondary outcomes: gestation strata

	Gestation stratum 25-26 weeks			Gestation stratum 27-28 weeks		
BINARY OUTCOMES	**MIST group (N=90)**	**Control group (N=87)**	**Adjusted relative risk (95% CI)[a]**	**MIST group (N=151)**	**Control group (N=157)**	**Adjusted relative risk (95% CI)[a]**
Respiratory						
Intubation at any time	65 (72.2%)	74 (85.1%)	0.85 (0.75–0.95)	67 (44.4%)	124 (79.0%)	0.57 (0.40–0.80)
Requirement for surfactant via endotracheal tube	35 (38.9%)	57 (65.5%)	0.59 (0.43–0.81)	44 (29.1%)	110 (70.1%)	0.42 (0.30–0.59)
Pulmonary hemorrhage	10 (11.1%)	7 (8.0%)	1.37 (0.61–3.05)	7 (4.6%)	8 (5.1%)	0.95 (0.41–2.20)
Oxygen therapy at day 28 (in survivors to day 28)	75/78 (96.2%)	76/81 (93.8%)	1.02 (0.95–1.10)	97/143 (67.8%)	107/146 (73.3%)	0.94 (0.81–1.10)
BPD (clinical definition)[b], in survivors to 36 weeks' PMA	40/76 (52.6%)	48/81 (59.3%)	0.89 (0.66–1.18)	54/141 (38.3%)	59/144 (41.0%)	0.96 (0.67–1.39)
Mechanical respiratory support at 36 weeks' PMA (in survivors)	26/76 (34.2%)	26/81 (32.1%)	1.06 (0.69–1.64)	27/141 (19.1%)	41/144 (28.5%)	0.70 (0.43–1.15)
Oxygen therapy at home[c]	11/72 (15.3%)	25/80 (31.3%)	0.49 (0.30–0.79)	20/139 (14.4%)	24/144 (16.7%)	0.92 (0.60–1.42)
Non-respiratory						
PDA requiring medical therapy	40 (44.4%)	53 (60.9%)	0.73 (0.58–0.91)	45 (29.8%)	58 (36.9%)	0.82 (0.55–1.23)
Late onset sepsis	27 (30.0%)	28 (32.2%)	0.93 (0.62–1.38)	28 (18.5%)	35 (22.3%)	0.83 (0.43–1.64)
IVH any grade	44 (48.9%)	48 (55.2%)	0.88 (0.63–1.24)	41 (27.2%)	43 (27.4%)	0.99 (0.66–1.48)
Cystic periventricular leukomalacia	1 (1.1%)	7 (8.0%)	0.14 (0.02–0.92)	5 (3.3%)	9 (5.7%)	0.59 (0.23–1.48)
NEC (modified Bell stage 2 or greater)	5 (5.6%)	5 (5.7%)	0.96 (0.32–2.86)	7 (4.6%)	12 (7.6%)	0.60 (0.22–1.64)
NEC requiring surgery	3 (3.3%)	3 (3.4%)	0.95 (0.26–3.50)	1 (0.7%)	2 (1.3%)	0.50 (0.05–5.53)
Spontaneous intestinal perforation	3 (3.3%)	6 (6.9%)	0.47 (0.10–2.18)	1 (0.7%)	0 (0%)	Not estimable

	Gestation stratum 25-26 weeks			Gestation stratum 27-28 weeks		
BINARY OUTCOMES	**MIST group (N=90)**	**Control group (N=87)**	**Adjusted relative risk (95% CI)[a]**	**MIST group (N=151)**	**Control group (N=157)**	**Adjusted relative risk (95% CI)[a]**
Retinopathy of prematurity (stage 3 or greater)	13 (14.4%)	16 (18.4%)	0.78 (0.40–1.49)	6 (4.0%)	8 (5.1%)	0.85 (0.27–2.75)
Total number of surfactant doses[e]	1 (1–2)	1 (0–1)	N/A	1 (1–2)	1 (0–1)	N/A
Days of mechanical ventilation via endotracheal tube[f,g]	4 (0–20)	7 (2–23)	-4.37 (-8.68 to -0.07)	0 (0–4)	2 (0–8)	-1.25 (-2.17 to -0.33)
Days of CPAP[f,g]	25 (10–40)	31 (19–44)	-6.25 (-13.28 to 0.78)	13 (6–29)	17 (6–30)	-2.92 (-7.13 to 1.30)
Days of mechanical ventilation +CPAP[f,g]	38 (20–56)	44 (32–60)	-9.50 (-15.53 to -3.47)	14 (7–36)	23 (9–39)	-5.25 (-11.48 to 0.98)
Days of all mechanical respiratory support[f,g]	53 (31–71)	58 (40–74)	-5.04 (-14.39 to 4.31)	34 (12–50)	40 (16–56)	-7.08 (-14.73 to 0.57)
Days to regain birth weight[h,i]	9.9 (4.6)	11.1 (5.5)	-1.20 (-2.25 to -0.16)	10.2 (4.0)	10.4 (4.8)	-0.19 (-1.01 to 0.63)
Days of hospitalization[f,j]	92 (57)	96 (39)	-4.86 (-19.77 to 10.06)	73 (39)	76 (36)	-2.20 (-9.72 to 5.32)

n (%), n/N (%), mean (standard deviation) or median (interquartile range). Denominators for all outcomes, and number of observations for continuous variables, are as per column headers unless otherwise indicated. Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; IVH, intraventricular hemorrhage; MIST, minimally invasive surfactant therapy; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PMA, postmenstrual age.

[a]Adjusted for gestation.

[b]Need for oxygen and/or mechanical respiratory support (mechanical ventilation / CPAP / nasal high flow ≥2 L/min) at 36 weeks' postmenstrual age.

[c]Missing data for two infants in the 25-26 weeks' gestation stratum of the MIST group.

[d]Mean difference or difference in medians for severely skewed continuous outcomes, adjusted for gestation.

[e]Including dose, if given, during the trial intervention.

[f]25-26 weeks' gestation: N=89 for MIST group, N=87 for control group. [g]27-28 weeks' gestation: N=151 for MIST group, N=157 for control group.

[h]25-26 weeks' gestation: N=82 for MIST group, N=84 for control group. [i]27-28 weeks' gestation: N=149 for MIST group, N=152 for control group.

[j]27-28 weeks' gestation: N=149 for MIST group, N=156 for control group.

eTable 7. Primary outcome and its components: subgroup analysis by FiO_2 at randomization

Outcome	Subgroups based on FiO_2 at randomization[a]	MIST group	Control group	Adjusted relative risk[b] (95% CI)	*P* value for interaction[c]
Death or BPD[d]	**FiO_2 0.30-0.35**	58/152 (38.2%)	69/150 (46.0%)	0.84 (0.64–1.10)	0.59
	FiO_2 >0.35	47/89 (52.8%)	52/94 (55.3%)	0.94 (0.76–1.17)	
Death prior to 36 weeks' PMA	**FiO_2 0.30-0.35**	14/152 (9.2%)	10/150 (6.7%)	1.39 (0.68–2.83)	0.59
	FiO_2 >0.35	10/89 (11.2%)	9/94 (9.6%)	1.12 (0.47–2.68)	
BPD[d] in survivors to 36 weeks' PMA	**FiO_2 0.30-0.35**	44/138 (31.9%)	59/140 (42.1%)	0.78 (0.58–1.06)	0.50
	FiO_2 >0.35	37/79 (46.8%)	43/85 (50.6%)	0.92 (0.71–1.17)	

n/N (%). Abbreviations: CI, confidence interval; MIST, minimally invasive surfactant therapy; PMA, postmenstrual age.
[a]Age at randomization for subgroup with FiO_2 0.30-0.35: MIST group: mean 3.0 h (standard deviation 1.5 h); control group 2.9 (1.6) h. Age at randomization for subgroup with FiO_2 >0.35: MIST group: 2.6 (1.3) h; control group 2.6 (1.3) h.
[b]Adjusted for gestation strata.
[c]Interaction of FiO_2 subgroup with treatment allocation in the statistical model.
[d]BPD: bronchopulmonary dysplasia (physiological definition) assessed as per eTable 2.

eTable 8. Key clinical and safety outcomes: subgroup analysis by FiO_2 at randomization

Outcome	Subgroups based on FiO_2 at randomization[a]	MIST group	Control group	Adjusted relative risk[b] (95% CI)	*P* value for interaction[c]
Air leak requiring drainage	**FiO_2 0.30-0.35**	4/152 (2.6%)	14/150 (9.3%)	0.29 (0.11–0.79)	0.20
	FiO_2 >0.35	7/89 (7.9%)	11/94 (11.7%)	0.67 (0.32–1.40)	
Need for intubation <72 h	**FiO_2 0.30-0.35**	47/152 (30.9%)	93/150 (62.0%)	0.50 (0.37–0.68)	0.86
	FiO_2 >0.35	41/89 (46.1%)	83/94 (88.3%)	41/89 (46.1%)	
Severe IVH - grade III or IV	**FiO_2 0.30-0.35**	12/152 (7.9%)	14/150 (9.3%)	12/152 (7.9%)	0.52
	FiO_2 >0.35	6/89 (6.7%)	10/94 (10.6%)	0.60 (0.27–1.32)	
Death or major morbidity[d]	**FiO_2 0.30-0.35**	69/152 (45.4%)	81/150 (54.0%)	0.85 (0.64–1.13)	0.83
	FiO_2 >0.35	47/89 (52.8%)	55/94 (58.5%)	0.89 (0.72–1.10)	
Death during first hospitalization (all causes)	**FiO_2 0.30-0.35**	17/152 (11.2%)	11/150 (7.3%)	1.53 (0.84–2.81)	0.56
	FiO_2 >0.35	11/89 (12.4%)	9/94 (9.6%)	1.23 (0.51–2.96)	
Major morbidity in survivors	**FiO_2 0.30-0.35**	52/135 (38.5%)	70/139 (50.4%)	0.78 (0.56–1.10)	0.75
	FiO_2 >0.35	36/78 (46.2%)	46/85 (54.1%)	0.84 (0.66–1.07)	

n/N (%). Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; MIST, minimally invasive surfactant therapy.
[a]See eTable 7 footnote for time of randomization of these subgroups.
[b]Adjusted for gestation strata.
[c]Interaction of FiO_2 subgroup with treatment allocation in the statistical model.
[d]Death or major morbidity defined as per eTable 5.

eTable 9. MIST intervention – procedural details and safety outcomes

		25-26 weeks gestation (N=92)	27-28 weeks gestation (N=151)	All gestations (N=243)
Surfactant successfully administered[a]		92/92 (100%)	151/151 (100%)	243/243 (100%)
Premedication used	**None**	33/81 (40.7%)	64/144 (44.4%)	97/225 (43.1%)
	Atropine	4/81 (4.9%)	3/144 (2.1%)	7/225 (3.1%)
	Sucrose	42/81 (51.9%)	75/144 (52.1%)	117/225 (52.0%)
	Other	2/81 (2.5%)	2/144 (1.4%)	4/225 (1.8%)
Number of catheterization attempts	**1**	65/88 (73.9%)	117/151 (77.5%)	182/239 (76.2%)
	2	17/88 (19.3%)	28/151 (18.5%)	45/239 (18.8%)
	3	5/88 (5.7%)	5/151 (3.3%)	10/239 (4.2%)
	4	1/88 (1.1%)	1/151 (0.7%)	2/239 (0.8%)
Surfactant dose administered (mg/kg)		200 (198–203)	201 (199–203)	200 (198–203)
Surfactant reflux observed		33/92 (35.9%)	60/149 (40.3%)	93/241 (38.6%)[b]
Undue discomfort[c]		5/91 (5.5%)	19/147 (12.9%)	24/238 (10.1%)
Bradycardia (heart rate <100 bpm)		55/90 (61.1%)	57/151 (37.7%)	112/241 (46.5%)
Bradycardia >10 s		36/90 (40.0%)	40/151 (26.5%)	76/241 (31.5%)
Hypoxemia (SpO_2 <80%)		64/91 (70.3%)	103/150 (68.7%)	167/241 (69.3%)
Hypoxemia >30 s		37/91 (40.7%)	65/150 (43.3%)	102/241 (42.3%)
Positive pressure inflations required		15/88 (17.0%)	19/151 (12.6%)	34/239 (14.2%)
Duration positive pressure inflations (s)[d]		30 (20–60)	30 (20–60)	30 (20–60)
Procedure duration (min)		5.0 (4.0–8.0)	5.0 (4.0–7.0)	5.0 (4.0–8.0)
Emergent intubation		1/92 (1.1%)	0/151 (0%)	1/243 (0.4%)
Intubation within 1 h		3/92 (3.3%)	1/151 (0.7%)	4/243 (1.6%)
ΔFiO_2[e]		-0.13 (-0.18 to -0.09)	-0.10 (-0.15 to -0.08)	-0.10 (-0.17 to -0.08)
Treatment ineffective[f]		10/91 (11.0%)	19/150 (12.7%)	29/241 (12.0%)
ΔCO_2 (mm Hg)[g]		-6.0 (-12.0 to 2.0)	-7.0 (-12.5 to -0.5)	-6.5 (-12.0 to 0.0)

n/N (%) or median (interquartile range). As treated population (N=243). Abbreviations: MIST, minimally invasive surfactant therapy; SpO_2, oxygen saturation.

*Successful proceduralists were neonatologists (55 individuals, 170 procedures), senior neonatal trainees (29 individuals, 62 procedures), respiratory therapists (7 individuals, 8 procedures) and neonatal nurse practitioners (3 individuals, 3 procedures). Standard laryngoscopy and videolaryngoscopy were used in 97% and 3% of MIST procedures, respectively. A 16G Angiocath was the conduit for surfactant administration in 90% of cases, with a LISAcath used in the remainder.

[b]Suction was required because of surfactant reflux in 25/93 cases (26.9%).

[c]Subjective determination of whether the infant suffered undue discomfort, reported by the Treatment Team nurse/respiratory therapist.

[d]Duration reported for infants receiving positive pressure inflations.

[e]FiO_2 at 4 h post-intervention minus FiO_2 pre-intervention, determined for infants not intubated at 4 h post-intervention. Paired observations available for 80 and 139 infants in the 25-26 weeks' and 27-28 weeks' gestation strata, respectively.

[f]Defined as no improvement in FiO_2 at 4 h post-intervention (infant still supported with CPAP), or intubated <4 h post-intervention with FiO_2 above intubation threshold.

[g]PCO_2 at 4 h post-intervention minus PCO_2 pre-intervention, determined for infants not intubated at 4 h post-intervention. Paired observations available for 62 and 104 infants in the 25-26 weeks' and 27-28 weeks' gestation strata, respectively.

eTable 10. Serious adverse events and cause of death

		MIST group (N=241)	Control group (N=244)	Total (N=485)
Serious adverse events				
Infants experiencing an SAE		25 (10.3%)	27 (11.1%)	52 (10.7%)
Total number of serious adverse events		26	28	54
Unexpected death		7	6	13
Life-threatening deterioration		14	16	30
Medical occurrence that will prolong hospitalization		1	3	4
Medical occurrence that is likely to result in persistent and significant disability or incapacity		1	1	2
Medical occurrence that could have become serious if untreated		2	4	6
Relationship of the SAE to the infants enrolment in the study as determined by clinicians	**Unrelated**	24	28	52
	Possibly related	2	0	2
SAE occurring at the time of the study intervention		0	0	0
Cause of death[a]				
Severe RDS		2	1	3
Pulmonary hemorrhage		4	3	7
Intractable heart failure secondary to PDA		2	0	2
Chronic lung disease		2	0	2
Severe intraventricular hemorrhage		5	5	10
Septicemia		7	7	14
Pneumonia		1	0	1
Meningitis		1	0	1
NEC/SIP		3	2	5
Other		1[b]	2[c]	3

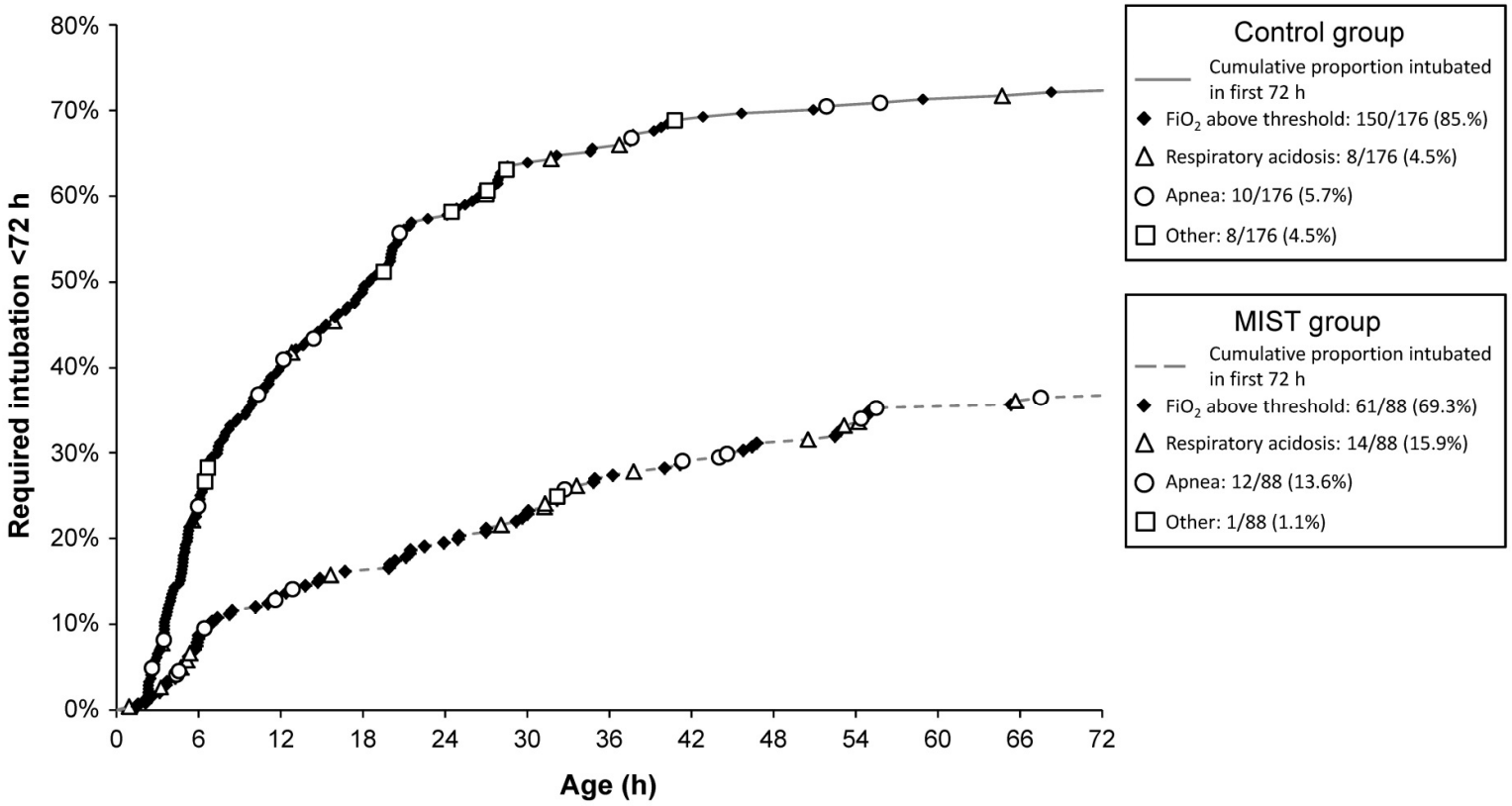
n or n (%). Abbreviations: MIST, minimally invasive surfactant therapy; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SAE, serious adverse event; SIP, spontaneous intestinal perforation.
[a]Age at death was 0-6 days: MIST 11, control 9, total 20; 7 days to 36 weeks' postmenstrual age: MIST 13, control 10, total 23; beyond 36 weeks' postmenstrual age: MIST 4, control 1, total 5.
[b]Chronic respiratory failure with suspected cystic fibrosis.
[c]Renal failure (n=2).

eTable 11. Clinical and procedural details by treatment group and survival to hospital discharge

	MIST group		Control group	
	Survived (N=215)	**Died (N=28)**	**Survived (N=221)**	**Died (N=20)**
CPAP level pre-intervention (cm H_2O)	7 (6–8)	6 (6–7)	7 (6–8)	6 (6–7)
FiO_2 pre-intervention	0.35 (0.31–0.40)	0.35 (0.33–0.40)	0.35 (0.33–0.40)	0.37 (0.32–0.42)
Trachea catheterized at first attempt	163/215 (75.8%)	19/24 (79.2%)	N/A	N/A
Bradycardia >10 s during intervention	68/214 (31.8%)	8/27 (29.6%)	N/A	N/A
Hypoxemia >30 s during intervention	93/214 (43.5%)	9/27 (33.3%)	N/A	N/A
Positive pressure inflations required	29/212 (13.7%)	5/27 (18.5%)	N/A	N/A
FiO_2 post-intervention	0.30 (0.25–0.36)	0.32 (0.28–0.38)	0.35 (0.30–0.40)	0.38 (0.30–0.42)
ΔFiO_2[a]	-0.11 (-0.17 to -0.09)	-0.09 (-0.11 to -0.05)	N/A	N/A
Treatment ineffective[b]	34/214 (15.9%)	2/27 (7.4%)	N/A	N/A
Intubated <4 h post-intervention	20/215 (9.3%)	2/28 (7.1%)	66/221 (29.9%)	8/20 (40.0%)
Intubated <24 h of age	41/215 (19.1%)	5/28 (17.9%)	126/221 (57.0%)	13/20 (65.0%)
Intubation <72 h of age	66/215 (30.7%)	20/28 (71.4%)	161/221 (72.9%)	16/20 (80.0%)

n/N (%) or median (interquartile range). As treated population. Abbreviations: CPAP, continuous positive airway pressure; MIST, minimally invasive surfactant therapy.
[a]FiO_2 at 4 hrs post-intervention minus FiO_2 pre-intervention, determined for infants not intubated at 4 h post-intervention.
[b]Defined as no improvement in FiO_2 at 4 h post-intervention (infant still supported with CPAP), or intubated <4h post-intervention with FiO_2 above intubation threshold.

eFigure 1. Requirement for intubation <72 h

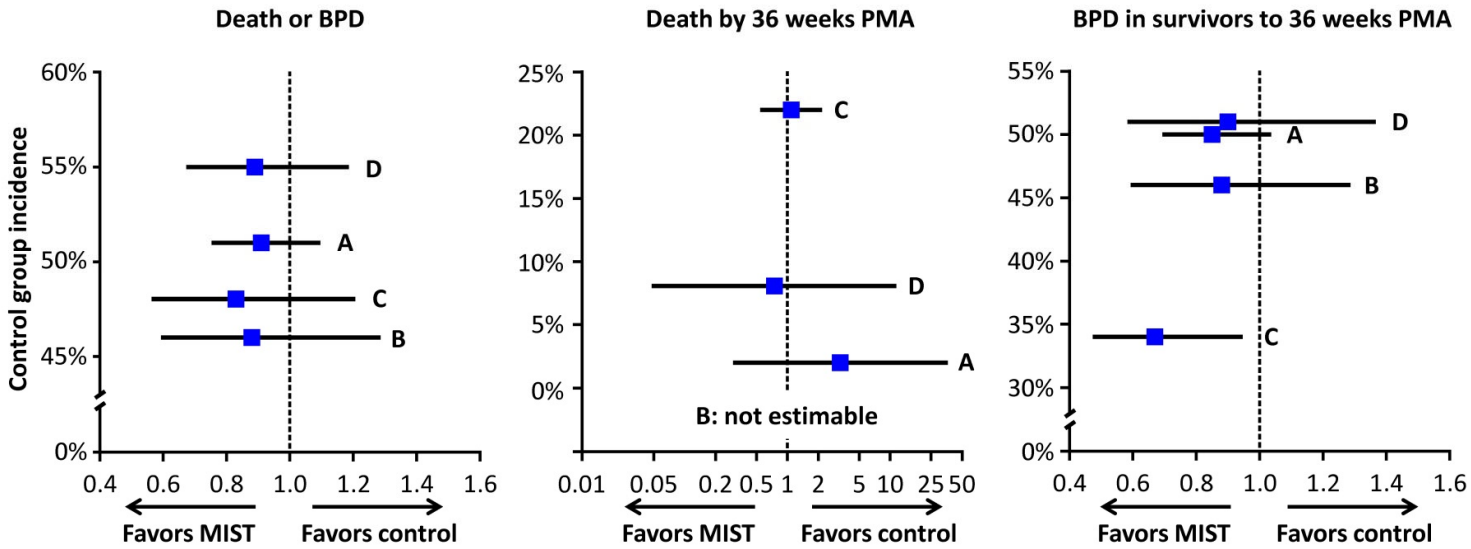


Number remaining unintubated

MIST	241	220	209	202	194	186	176	171	166	161	156	154	153
Control	244	186	146	124	104	89	84	76	74	72	70	69	68

Shows plots of cumulative proportion of infants requiring intubation over the course of the first 72 h. Abbreviation: MIST, minimally invasive surfactant therapy. Dashed line: MIST group; solid line: control group. Reason for intubation indicated in individual data points (see figure legends).

eFigure 2. Primary outcome treatment effects in regional subgroups



Relative risk and 95% confidence intervals for treatment effect (X-axis) plotted against outcome incidence in the control group (Y-axis) for de-identified study regions A-D. Abbreviations: BPD, bronchopulmonary dysplasia; MIST, minimally invasive surfactant therapy; PMA, postmenstrual age. Left panel: death or BPD; center panel: death by 36 weeks' PMA; right panel: BPD at 36 weeks' PMA. Relative risk of death not estimable in region B as there were no deaths in either study group by 36 weeks' PMA. $P > .05$ for all tests of interaction between region and treatment allocation in the statistical model.

eReference

1. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 2003;289(9):1124-1129.