

## Supplementary Appendix

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

Supplement to: Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009;361:1349-58.

## **Supplementary Appendix 1 (web appendix 1)**

### **Definitions of adverse events**

**Pulmonary airleak:** Any radiologically confirmed airleak serious enough to affect management (including pulmonary interstitial emphysema, pneumopericardium, pneumoperitoneum and pneumomediastinum).

**Pulmonary haemorrhage:** Copious bloody secretions with clinical deterioration requiring change(s) in ventilatory management.

**Persistent pulmonary hypertension:** Severe hypoxaemia disproportionate to the severity of lung disease and evidence of a right to left shunt.

**Major cerebral anomaly:** Evidence of parenchymal haemorrhage as determined by ultrasound, ventricular dilatation (defined as >97th centile for gestational age) or the presence of porencephalic cysts or cystic leukomalacia.

**Meconium aspiration syndrome:** The presence of meconium stained liquor at birth and severe respiratory distress with 1 hour of birth and compatible X ray changes.

**Necrotising enterocolitis:** Infants with abdominal distension, gastric aspirate and/or blood in stools together with abdominal X ray showing bowel oedema, pneumatosis or pneumoperitoneum, i.e. Bell's staging 2 or 3

**Late onset sepsis (>72 hours after birth) confirmed by blood or CSF culture:**

Any evidence of infection requiring antibiotic therapy which is confirmed on culture.

**Thrombocytopenia:** Platelet count less than  $150 \times 10^9/L$

**Abnormal coagulation:** Either a prothrombin time > 16 seconds, or an INR > 2.5 or an activated partial thromboplastin time > 49.5 seconds.

Supplementary Appendix 2 (web appendix)

Complete analysis of neurodevelopmental outcomes at 18 months

Outcome	Intensive care with cooling	Intensive care only	Comparative statistics - Risk ratio plus 95% CIs unless indicated
<b>COMPOSITE PRIMARY OUTCOME</b> – no. (%)	<b>163 (100%)</b>	<b>162 (100%)</b>	
Combined mortality and severe neurodevelopmental disability – no./total no. (%)	74/163 (45)	86/162 (53)	0.86 (0.68 – 1.07) P=0.17
<i>Not known</i> – no./total no. (%)	1/163 (0.6)	1/162 (0.6)	
Defined as <b>ONE</b> of :  1. Bayley MDI score <70 2. GMF impairment level 3-5 3. Bilateral cortical visual impairment			
<b>SECONDARY OUTCOMES</b>			
<b>Mortality</b>			
Deaths before discharge – no./total no. (%)	39/163 (24)	39/162 (24)	0.99 (0.67 – 1.46) P=0.98
Total deaths – no./total no. (%)	42/163 (26)	44/162 (27)	0.95 (0.66 – 1.36) P=0.78
Withdrawal of care – no./total no. (%)	34/39 (87)	29/39 (74)	N/A
<i>Not known</i> – no./total no. (%)	3/39 (8)	4/39 (10)	

Survival without neurological abnormality - no./total no. (%) Defined as MDI >84, PDI >84, no neuromotor impairment, normal vision, normal hearing.	71/163 (44)	45/162 (28)	1.57 (1.16-2.12)  P=0.003
<b>NEURODEVELOPMENTAL OUTCOMES IN SURVIVORS – no. (%)</b>	<b>120 (100%)</b>	<b>117 (100%)</b>	
Lost to follow-up - no.	1	1	
Severe neurodevelopmental disability - no./total no. (%)	32/120 (27)	42/117 (36)	0.74 (0.51 – 1.09)  P=0.13
Bayley MDI score <70 – no.  Includes <i>too disabled to test</i> – no.  < 55 – no.  Score unavailable – no. (%)  <i>Not known</i> – no.  <i>uncooperative/unreliable</i> – no.	28  22  4  5 (4)  3  2	38  31  2  7 (6)  3  4	28/115 (24%) vs.  38/110 (35%)  RR 0.70 (0.47 – 1.06)  P=0.09
Bayley MDI score categories  <70 - no. (%)  70-84 - no.(%)  ≥ 85 - no.(%)	  28 (24)  6 (5)  81 (70)	  38 (35)  12 (11)  60 (55)	Chi squared test  for linear trend on MDI levels vs. allocation P=0.03

Bayley MDI score [n; Median (IQR)]	89; 96 (89, 105)	77; 93 (85.5, 102.5)	Difference in median plus 95% CI; P-value from Wilcoxon rank-sum test 4 (0 to 8) P=0.04
Bayley PDI score <70 - no.	27	37	27 /114 (24%) vs. 37/109 (34%) RR 0.70 (0.46 – 1.06) P=0.09
Includes <i>too disabled to test</i> – no.	22	31	
< 55 – no.	4	4	
Score unavailable – no. (%)	6 (5)	8 (7)	
Not known – no.	5	6	
uncooperative/unreliable - no.	1	2	
Bayley PDI score categories			Chi squared test for linear trend on PDI levels vs. allocation P=0.03
<70 – no. (%)	27 (24)	37 (34)	
70-84 – no. (%)	9 (8)	14 (13)	
≥ 85 – no. (%)	78 (68)	58 (53)	
Bayley PDI [n; Median (IQR)]	88; 102 (90, 110)	74; 98 (86, 105)	Difference in median plus 95% CI; P-value from Wilcoxon rank-sum test 5 (1 to 9) P=0.02

Gross Motor Function neuromotor impairment levels 3 to 5 – no./total no. (%)	24/120 (20)	36/117 (31)	0.65 (0.41 – 1.02) P=0.06
Bilateral cortical visual impairment (No useful vision or light or gross movement only) - no.  <i>Not known – no. (%)</i>	8  1 (1)	12  3 (3)	8/119 (7%) vs. 12/114 (11%) RR 0.64 (0.27 – 1.50) P=0.30
No useful hearing – no. (%)  <i>Not known – no. (%)</i>	0 (0)  6 (5)	1 (1)  9 (8)	unestimable
Epilepsy –no. (Seizures requiring anticonvulsant therapy at the time of assessment}  <i>Not known – no. (%)</i>	12  4 (3)	16  1 (1)	12/116 (10%) vs. 16/116 (14%) RR 0.75 (0.37 – 1.51) P=0.42
Multiple neurodevelopmental disability – no. (%)  <i>Not known – no. (%)</i>  (Defined as the presence of <b>any two</b> of the following in an infant; neuromotor disability (Level 3-5 on GMF classification), mental delay (Bayley MDI score <70), epilepsy, cortical visual impairment, no useful hearing)	21 (18)  2 (2)	33 (20)  2 (2)	21/112 (19%) vs. 33/110 (30%) RR 0.63 (0.39 – 1.01) P=0.05

<b>Outcome</b>	<b>Intensive care with cooling – no. 120</b>	<b>Intensive care only – no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
<b>Hand preference</b> (majority on both attempts)			
Majority left – no. (%)	11 (9)	8 (7)	
Majority right – no. (%)	80 (67)	68 (58)	
Equal left and right – no. (%)	6 (5)	10 (9)	
Not attempted – no. (%)	23 (19)	31 (26)	
<b>Axis - head &amp; neck</b>			
Normal head control – no. (%)	94 (78)	80 (68)	1.15 (0.98 – 1.34) P=0.08
Abnormal head control – no. (%)	7 (6)	13 (11)	
Poor head control – no. (%)	14 (12)	15 (13)	
No obvious head control - no. (%)	5 (4)	9 (8)	
<b>Trunk</b>			
No apparent problem – no. (%)	91 (76)	75 (64)	1.18 (1.00 – 1.40) P=0.05
Can sit unsupported (less secure than normal child of same age) – no. (%)	6 (5)	8 (7)	

<b>Outcome</b>	<b>Intensive care with cooling – no. 120</b>	<b>Intensive care only – no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
Cannot be left sitting unless supported – no. (%)	10 (8)	17 (15)	
Very severe impairment (difficult to place in a sitting position) – no. (%)	13 (11)	17 (15)	
<b>Lower limb function - gait</b>			
Walks fluently – no. (%)	79 (66)	59 (50)	79/117 (68%) vs. 59/115 (51%) RR 1.32 (1.06 – 1.64) P=0.01
Gait functional but non-fluent – no. (%)	8 (7)	12 (10)	
Reduced mobility restricting life-style – no. (%)	0 (0)	1 (1)	
No independent walking– no. (%)	30 (25)	43 (37)	
<i>Not known (all appear to be walking)</i> – no. (%)	3 (3)	2 (2)	
<b>Upper limb function</b>			
No apparent problem – no. (%)	89 (74)	71 (61)	1.22 (1.02 – 1.46) P=0.03

<b>Outcome</b>	<b>Intensive care with cooling – no. 120</b>	<b>Intensive care only – no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
Some difficulty using hands together, feeds self – no. (%)	5 (4)	13 (11)	
Unable to feed self with either hand – no. (%)	26 (22)	33 (28)	
<b>Contractures</b>			
Present – no. (%)	13 (11)	11 (9)	
<i>Not known</i> – no. (%)	2 (2)	1 (1)	
<b>Convulsions</b>			
Currently on anticonvulsant medication – no. (%)	12 (10)	16 (14)	12/116 (10%) vs. 16/116 (14%) RR 0.75 (0.37 – 1.51) P=0.42
<i>Not known</i> – no. (%)	4 (3)	1 (1)	
No convulsions, no treatment – no. (%)	95 (79)	98 (84)	
<i>Not known</i> – no. (%)	4 (3)	1 (1)	
Convulsion in last 12 months – no. (%)	21 (18)	17 (15)	

<b>Outcome</b>	<b>Intensive care with cooling – no. 120</b>	<b>Intensive care only – no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
<i>Not known</i> – no. (%)	0 (0)	1 (1)	
Convulsion in last month – no. (%)	9 (8)	11 (9)	
<b>Visual or eye problem</b>			
Wears glasses – no. (%)	1 (1)	2 (2)	
<i>Not known</i> – no. (%)	1 (1)	2 (2)	
Squint present – no. (%)	8 (7)	19 (16)	8/118 (7%) vs. 19/114 (17%) RR 0.41 (0.19 – 0.89) P=0.02
<i>Not known</i> – no. (%)	2 (2)	3 (3)	
Normal or near normal vision – no. (%)	108 (90)	96 (82)	108/119 (91%) vs. 96/114 (84%) RR 1.08 (0.98 – 1.19) P=0.13
Impaired but appears to have useful vision – no. (%)	3 (3)	6 (5)	

<b>Outcome</b>	<b>Intensive care with cooling – no. 120</b>	<b>Intensive care only – no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
Light or gross movement only – no. (%)	7 (6)	8 (7)	
No useful vision (blind) – no. (%)	1 (1)	4 (3)	
<i>Not known</i> – no. (%)	1 (1)	3 (3)	
<b>Hearing problem</b>			
Normal or near normal – no. (%)	110 (92)	97 (83)	110/114 (96%) vs. 97/108 (90%) RR 1.07 (1.00 – 1.16) P=0.05
Hearing loss corrected with aids – no. (%)	0 (0)	4 (3)	
Some hearing loss not corrected by aids – no. (%)	4 (3)	6 (5)	
No useful hearing even with aids – no. (%)	0 (0)	1 (1)	
<i>Not known</i> – no. (%)	6 (5)	9 (8)	

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
<b>Mouth</b>			
Problem with articulation of speech			
No – no. (%)	86 (72)	72 (62)	86/97 (89%) vs. 72/81
Yes – no. (%)	11 (9)	9 (8)	(89%)
<i>Not known</i> – no. (%)	8 (7)	4 (3)	RR 1.00 (0.90 – 1.11)
<i>Not applicable</i> – no. (%)	15 (13)	32 (27)	P=0.96
Excessive drooling or dribbling during waking hours			
No – no. (%)	88 (73)	79 (67)	88/118 (75%) vs.
Yes – no. (%)	30 (25)	35 (30)	79/114 (69%) RR
<i>Not known</i> – no. (%)	2 (2)	3 (3)	1.08 (0.92 – 1.26)
			P=0.37
<b>Usual form of communication</b>			
Speech – no. (%)	91 (76)	74 (63)	91/119 (76%) vs. 74/117 (63%) RR 1.21 (1.02 – 1.43) P=0.03
Speech + formal systemised methods (e.g. signing) – no. (%)	4 (3)	6 (5)	
Formal systemised method only –	4 (3)	6 (5)	

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value)  Risk ratio plus 95% CIs unless indicated</b>
no. (%)			
Not communicating by speech or other method – no. (%)	20 (17)	31 (26)	
<i>Not known</i> – no. (%)	1 (1)	0 (0)	
<b>Feeding</b>			
Feeding difficulties present?			
No – no. (%)	82 (68)	76 (65)	
Yes – no. (%)	38 (32)	41 (35)	0.90 (0.63 – 1.30) P=0.58
Does or has the child require(d) tube feeding?			
No – no. (%)	101 (84)	93 (79)	
Yes – no. (%)	19 (16)	23 (20)	19/120 (16%) vs.
<i>Not known</i> – no. (%)	0 (0)	1 (1)	23/116 (20%) RR 0.80 (0.46 – 1.39) P=0.42
If <b>yes</b> , does the child have:			
a stoma? – no. (%)	0 (0)	1 (1)	
a gastrostomy? – no. (%)	10 (8)	10 (9)	
<b>GMFCS</b>			

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
No neurological abnormality – no. (%)	85 (71)	63 (54)	Survivors assessed: 1.32 (1.07 – 1.61) P=0.007 Intention-to-treat population: 85/163 (52%) vs. 63/162 (39%) RR 1.34 (1.05 – 1.71) P=0.02
Level 1-2	11 (9)	18 (15)	
Level 3-5	24 (20)	36 (31)	
			Chi squared test on linear trend of GMFCS levels vs. allocation P=0.01
<b>Neurological examination scores</b>			

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
Total raw score median, (IQR) no. <i>Not known – no. (%)</i>	74 (61.25-75) 108 12 (10)	72 (43.25-75) 106 11 (9)	Difference in median plus 95% CI; P-value from Wilcoxon rank- sum test 0 (0 to 2) P=0.10
> 73 (%) – no. (%)	84 (70)	75 (64)	
65 - 73 (%) – no. (%)	2 (2)	2 (2)	
< 65 (%) – no. (%)	22 (18)	29 (25)	
<i>Not known – no. (%)</i>	12 (10)	11 (9)	
<b>Neurological abnormality</b>			
No abnormality – no. (%)	87 (73)	69 (59)	Survivors assessed: 1.23 (1.02 – 1.48) P=0.03 Intention-to-treat population: 87/163 (53%) vs. 69/162 (43%) RR 1.25 (1.00 – 1.58) P=0.05
Spastic bilateral 2 limb involvement – no. (%)	1 (1)	2 (2)	

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value)  Risk ratio plus 95% CIs unless indicated</b>
+left sided hemiplegia – no. (%)	1 (1)	0 (0)	
Spastic bilateral 3 limb involvement – no. (%)	0 (0)	1 (1)	
+right sided hemiplegia – no. (%)	0 (0)	1 (1)	
Spastic bilateral 4 limb involvement – no. (%)	23 (19)	29 (25)	
+ choreoathetoid movement disorder – no. (%)	1 (1)	1 (1)	
+ dystonic movement disorder – no. (%)	0 (0)	1 (1)	
+ right sided hemiplegia – no. (%)	1 (1)	0 (0)	
Right sided hemiplegia – no. (%)	0 (0)	0 (0)	
Left sided hemiplegia – no. (%)	0 (0)	1 (1)	
Movement disorder (dyskinetic) – no. (%)	2 (2)	3 (3)	
Choreoathetoid – no. (%)	1 (1)	3 (3)	
Non-classifiable – no. (%)	3 (3)	5 (4)	
<b>Distribution of involvement</b>			
L/R asymmetry of tone or function – no. (%)	17 (14)	16 (14)	
<i>Not known</i> – no. (%)	0 (0)	2 (1)	

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value)  Risk ratio plus 95% CIs unless indicated</b>
<b>If <i>yes</i>, which is worse?</b>			
R – no. (%)	9 (8)	6 (5)	
L – no. (%)	8 (7)	10 (9)	
<b>Upper/Lower equally affected?</b>			
No – no. (%)	20 (17)	16 (14)	
Yes – no. (%)	76 (63)	74 (63)	
<i>Not known</i> – no. (%)	7 (6)	15 (13)	
<b>If <i>not equally</i>,</b>			
Upper – no. (%)	8 (7)	8 (7)	
Lower – no. (%)	11 (9)	8 (7)	
<i>Not known</i> – no. (%)	1 (1)	0 (0)	
<b>Head growth</b>			
Head circumference – age/sex standardised (SDS)			Difference in mean adjusted for baseline value (analysis of covariance)
Baseline mean (SD)	-0.023 (1.17)	0.22 (1.13)	
Not known – no	41	44	
Follow-up mean (SD)	-0.97 (1.84)	-1.04 (2.06)	0.26 (-0.28 to 0.81)
Not known – no.	6	5	P=0.34

<b>Outcome</b>	<b>Intensive care with cooling - no. 120</b>	<b>Intensive care only -no. 117</b>	<b>Comparative statistics (P value) Risk ratio plus 95% CIs unless indicated</b>
Head circumference at follow-up more than 2SD below the mean  – no.  Not known – no.	24 (21)  6	28 (25)  5	0.84 (0.52-1.36)  P=0.48