Supplemental Material:

Table s1: Definition of moderate and severe neurodevelopmental impairment in the OC trial; a child was considered moderately impaired with a Bayley III cognitive score of 70-84 plus one of the other categories, whereas severe neurodevelopmental delay was diagnosed if any of the listed criteria were met; GMFCS = Gross Motor Function Classification System

	Moderate	**Severe**
Bayley III Cognitive Score	70-84	<70
	AND	**OR**
GMFCS Level	2	3-5
	OR	**OR**
Vision	NA	Blindness
	OR	**OR**
Hearing	Hearing deficit requiring amplification to understand commands	Hearing loss as defined as inability to understand commands despite amplification
	OR	**OR**
Seizure Disorder	Present	NA

Table s2. Epoch-specific adjusted mattress temperature difference by primary outcome. Infants with an unfavorable primary outcome (death/NDI) had significantly higher adjusted average mattress temperatures (MT) across all epochs (first line within each epoch in the table, in bold). All models were adjusted for severity of encephalopathy at enrollment, length of therapeutic hypothermia treatment, documented seizures, exposure to phenobarbital, morphine, or inotropes, and degree of organ dysfunction. Coefficients for all variables in each model are provided. NDI = Neurodevelopmental Impairment

Epoch	Predictor	Adjusted Temperature Difference (°C, 95% CI)	P-value
0-6h	**Death/NDI vs No NDI Group**	+3.4 (+1.5, +5.3)	0.0004
	120h Cooling vs 72h	-1.9 (-3.8, +0.03)	0.054
	Severe Encephalopathy	-1.0 (-3.3, +1.3)	0.39
	Phenobarbital Exposure	+1.7 (-1.0, +4.5)	0.22
	Documented Seizures	+0.2 (-2.7, +3.1)	0.88
	Morphine Exposure	-1.5 (-3.4, +0.4)	0.13
	Inotrope Exposure	+2.2 (-0.0, +4.4)	0.051
	Organ Dysfunction (per Organ)	+0.2 (-0.4, +0.8)	0.54
6-24h	**Death/NDI vs No NDI Group**	+1.5 (+0.2, +2.7)	0.024
	120h Cooling vs 72h	-0.8 (-2.4, 0.9)	0.35
	Severe Encephalopathy	+0.1 (-1.6, +1.8)	0.90
	Phenobarbital Exposure	+0.6 (-1.5, +2.6)	0.60
	Documented Seizures	+0.1 (-2.1, +2.3)	0.93
	Morphine Exposure	-0.0 (-1.4, +1.3)	0.95
	Inotrope Exposure	+2.7 (+1.2, 4.1)	0.0003
	Organ Dysfunction (per Organ)	+0.3 (-0.3, +0.8)	0.29
24-48h	**Death/NDI vs No NDI Group**	+2.1 (+0.9, +3.2)	0.0005
	120h Cooling vs 72h	-1.8 (-3.0, -0.6)	0.003
	Severe Encephalopathy	+0.4 (-0.8, +1.7)	0.50
	Phenobarbital Exposure	+1.0 (-0.3, +2.3)	0.14
	Documented Seizures	+0.3 (-1.0, +1.7)	0.64
	Morphine Exposure	-0.4 (-1.6, +0.8)	0.49
	Inotrope Exposure	+1.7 (+0.5, +2.9)	0.007

	Organ Dysfunction (per Organ)	0.0 (-0.4, +0.4)	0.94
48-72h	**Death/NDI vs No NDI Group**	+1.5 (+0.3, +2.7)	0.011
	120h Cooling vs 72h	-1.3 (-2.4, -0.1)	0.035
	Severe Encephalopathy	-0.4 (-1.7, +0.9)	0.55
	Phenobarbital Exposure	+0.4 (-0.9, +1.8)	0.53
	Documented Seizures	-0.9 (-2.3, +0.6)	0.24
	Morphine Exposure	-0.4 (-1.4, +0.7)	0.51
	Inotrope Exposure	+1.3 (-0.0, +2.6)	0.058
	Organ Dysfunction (per Organ)	+0.4 (-0.1, +0.8)	0.097

Table s3. Full model outputs for aOR (95% CI) of death/NDI by mattress temperature cut-off within each epoch. Epoch-specific dichotomous cut-offs for mattress temperature and odds of death/NDI. Adjusted odds ratio (aOR) with 95% CI is shown for each variable within each model, as well as the associated p-value. All models were adjusted for severity of encephalopathy at enrollment, length of therapeutic hypothermia treatment, documented seizures, exposure to phenobarbital, morphine, or inotropes, and degree of organ dysfunction. Coefficients for all variables in each model are provided. NDI = Neurodevelopmental Impairment

Model/Predictor	aOR for Death/NDI (95% CI)	P-value
0-6h		
≥33.0 cut-off	**17.0 (4.3-67.4)**	**<0.0001**
120h Cooling	2.0 (0.9-4.8)	0.11
Severe Encephalopathy	**5.3 (1.9015.1)**	**0.002**
Phenobarbital Exposure	1.3 (0.5-3.6)	0.62
Documented Seizures	2.7 (0.9-7.6)	0.070
Morphine Exposure	**3.6 (1.5-8.6)**	**0.004**
Inotrope Exposure	0.4 (0.2-1.0)	0.055
Organ Dysfunction (per Organ)	**1.5 (1.1-2.1)**	**0.011**
6-24h		
≥≥31.0 cut-off	3.3 (0.9-12.3)	0.075
120h Cooling	1.2 (0.5-2.8)	0.10
Severe Encephalopathy	1.8 (0.7-5.1)	0.25
Phenobarbital Exposure	2.9 (0.8-9.7)	0.09
Documented Seizures	1.6 (0.5-5.3)	0.47
Morphine Exposure	1.9 (0.8-4.3)	0.13
Inotrope Exposure	0.8 (0.3-2.1)	0.61
Organ Dysfunction (per Organ)	**1.4 (1.0-1.95)**	**0.037**
24-48h		
≥31.0 cut-off	**3.1 (1.3-7.5)**	**0.011**
120h Cooling	1.3 (0.6-2.8)	0.55

Severe Encephalopathy	**3.0 (1.2-7.9)**	**0.025**
Phenobarbital Exposure	1.5 (0.5-4.0)	0.44
Documented Seizures	2.2 (0.8-6.0)	0.14
Morphine Exposure	**3.0 (1.4 (6.4)**	**0.006**
Inotrope Exposure	0.7 (0.3-1.7)	0.43
Organ Dysfunction (per Organ)	**1.5 (1.1-2.0)**	**0.009**
48-72h		
≥ 32.0 cut-off	**3.3 (1.3-8.4)**	**0.012**
120h Cooling	1.5 (0.6-3.4)	0.38
Severe Encephalopathy	**3.0 (1.2-7.7)**	**0.022**
Phenobarbital Exposure	1.5 (0.6-4.2)	0.41
Documented Seizures	**2.9 (1.1-4.2)**	**0.039**
Morphine Exposure	**3.1 (1.4-7.1)**	**0.007**
Inotrope Exposure	0.7 (0.2-1.7)	0.39
Organ Dysfunction (per Organ)	**1.4 (1.0-1.9)**	**0.027**

Table s4. Full model outputs for aOR (95% CI) of death/NDI by mattress temperature trajectory group.

Infants were classified into four groups: 1) those that were below the cut-off at all three time points, 2) below

the cut-off at 0-6h but above one or both the 24-48h and 48-72h epochs, 3) above the 0-6h cut-off but below at least one of the 24-48h or 48-72h cut-offs, and 4) above all three cut-offs. Group 4 (above all three cut-offs) was used as the reference group for trajectory grouping, moderate encephalopathy was the reference group for severity of encephalopathy, and 72h of cooling was the reference group for duration of cooling. Adjusted odds ratio (aOR) with 95% CI is shown for each variable within each model, as well as the associated p-value. The first four models correspond to Figures 3B-E, and the last model corresponds to Supplemental Figure s1.

Model/Predictor	aOR for Death/NDI (95% CI)	P-value
All Infants		
Trajectory Group 1	**0.0 (0.0-0.0)**	**<0.0001**
Trajectory Group 2	**0.06 (0.01-0.38)**	**0.002**
Trajectory Group 3	0.45 (0.18-1.15)	0.096
120h Cooling	2.10 (0.84-5.26)	0.11
Phenobarbital Exposure	1.50 (0.54-4.16)	0.44
Documented Seizures	**3.11 (1.07-9.07)**	**0.037**
Morphine Exposure	**3.87 (1.59-9.39)**	**0.003**
Inotrope Exposure	**0.34 (0.13-0.88)**	**0.027**
Organ Dysfunction (per organ)	**1.43 (1.04-1.97)**	**0.030**
Severe Encephalopathy	**4.85 (1.56-15.0)**	**0.006**
Infants Surviving to Discharge		
Trajectory Group 1	**0.0 (0.0-0.0)**	**<0.0001**
Trajectory Group 2	**0.02 (0.00-0.20)**	**0.007**
Trajectory Group 3	0.37 (0.12-1.18)	0.093
120h Cooling	1.33 (0.45-3.92)	0.60
Phenobarbital Exposure	1.11 (0.29-4.17)	0.88
Documented Seizures	**6.01 (1.56-23.2)**	**0.009**
Morphine Exposure	**5.37 (2.06-14.0)**	**0.0006**
Inotrope Exposure	**0.25 (0.07-0.84)**	**0.025**
Organ Dysfunction (per organ)	1.31 (0.90-1.90)	0.15
Severe Encephalopathy	3.30 (0.85-12.8)	0.08

Moderate Encephalopathy		
Trajectory Group 1	**0.0 (0.0-0.0)**	**<0.0001**
Trajectory Group 2	**0.09 (0.01-0.09)**	**0.041**
Trajectory Group 3	0.42 (0.13-1.38)	0.15
120h Cooling	2.34 (0.83-6.61)	0.11
Phenobarbital Exposure	1.46 (0.44-4.80)	0.53
Documented Seizures	**3.63 (1.01-13.0)**	**0.048**
Morphine Exposure	**4.51 (1.57-13.0)**	**0.005**
Inotrope Exposure	**0.26 (0.08-0.92)**	**0.036**
Organ Dysfunction (per organ)	**1.66 (1.10-2.51)**	**0.016**
Severe Encephalopathy		
Trajectory Group 1	**0.0 (0.0-0.0)**	**<0.0001**
Trajectory Group 2	**0.01 (0.00-0.28)**	**0.007**
Trajectory Group 3	0.83 (0.04-17.6)	0.90
120h Cooling	1.33 (0.06-30.3)	0.86
Phenobarbital Exposure	2.27 (0.07-70.2)	0.64
Documented Seizures	5.34 (0.04-671)	0.50
Morphine Exposure	1.27 (0.13-12.4)	0.84
Inotrope Exposure	0.18 (0.01-3.32)	0.25
Organ Dysfunction (per organ)	0.86 (0.46-1.62)	0.65
Full 33.5 Intention to treat (sensitivity)		
Trajectory Group 1	**0.0 (0.0-0.0)**	**<0.0001**
Trajectory Group 2	**0.08 (0.01-0.44)**	**0.004**
Trajectory Group 3	0.44 (0.17-1.13)	0.088
120h Cooling	2.49 (0.98-6.35)	0.055
Phenobarbital Exposure	1.39 (0.47-4.14)	0.55
Documented Seizures	**3.14 (1.02-9.69)**	**0.046**
Morphine Exposure	**4.49 (1.84-11.0)**	**0.001**
Inotrope Exposure	**0.30 (0.11-0.81)**	**0.018**
Organ Dysfunction (per organ)	**1.42 (1.03-1.95)**	**0.031**
Severe Encephalopathy	**8.51 (2.62-27.6)**	**0.0004**

Supplemental Figure s1. Sensitivity analysis of outcome by mattress temperature (MT) trajectory group in all 191 infants treated at 33.5°C for whom outcome data were available (n=169). Using Group 4 as the reference group, Groups 1 and 2 both had significantly reduced odds for death/NDI and 100% and 90% NDI-free survival, with a nonsignificant ~35% decrease in odds in Group 3. Percentages indicate those with NDI-free survival within each trajectory group. All models were adjusted for morphine, inotrope, and phenobarbital exposure, documented seizures, severity of encephalopathy as listed in the original trial documentation, therapeutic hypothermia treatment duration, and degree of end-organ involvement. All infants were included regardless of how many MT readings were available within each epoch.