Supplementary Appendix

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

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SUPPLEMENTARY APPENDIX

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SUPPLEMENTARY METHODS

Inclusion and Exclusion Criteria

Inclusion Criteria (must all be yes)

1. Did the subject suffer a cardiac arrest requiring chest compressions for at least two minutes (120 seconds) with return of spontaneous circulation/return of circulation (ROSC/ROC) for at least 20 minutes?
2. Is the subject greater than 48 hours (with a corrected gestational age of at least 38 weeks) and less than 18 years of age?
3. Does the subject require continuous mechanical ventilation?

Exclusion Criteria (must all be no)

1. Is the parent or legal guardian unable to speak English or Spanish?
2. Is randomization impossible within 6 hours of ROSC/ROC?
3. Does the patient have a Glasgow Coma Scale motor response of 5 or 6 prior to randomization?
4. Did the subject receive continuous infusion of epinephrine or norepinephrine at very high doses (≥ 2 μg/kg/minute) immediately prior to randomization?
5. Does the subject have a history of a prior cardiac arrest with chest compressions for at least 2 minutes during the current hospitalization but outside the 6 hour window for randomization?
6. Does the subject have a pre-existing terminal illness with life expectancy < 12 months?
7. Is there a lack of commitment to aggressive intensive care therapies including “do not resuscitate” orders or other limitations to care?
8. Was the cardiac arrest associated with severe brain, thoracic, or abdominal trauma?
9. Was there active and refractory severe bleeding prior to randomization?
10. Did the subject experience near drowning in ice water with a core temperature ≤ 32 °C on presentation?

11. Is the subject pregnant?
12. Is the patient participating in a concurrent interventional trial whose protocol, in the judgment of the THAPCA investigators, prevents effective application of one or both THAPCA therapeutic treatment arms, or otherwise significantly interferes with carrying out the THAPCA protocol?
13. Is the subject a newborn (< 48 hours of age) with a history of acute birth asphyxia?
14. Was the subject cared for in a neonatal intensive care unit (NICU) after arrest (i.e., would not be admitted to PICU)?
15. Is the subject known to have sickle cell anemia?
16. Is the subject known to have pre-existing cryoglobulinemia?
17. Does the subject have a central nervous system tumor with ongoing chemotherapy or radiation therapy?
18. Does the subject have chronic hypothermia secondary to hypovolemic, pituitary, or related condition for which body temperature is consistently below 37˚C?
19. Does the subject have progressive degenerative encephalopathy?
20. Does the subject have any condition in which direct skin surface cooling would be contraindicated, such as large burns, decubitus ulcers, cellulitis, or other conditions with disrupted skin integrity? (NOTE: subjects with open chest CPR should be included but placement of cooling mattresses will be modified as needed).
21. Has the subject been previously enrolled in the THAPCA Trials?

Site Training

A three day study training meeting was conducted prior to the start of the THAPCA Trials. This meeting was repeated annually as a mandatory three day retraining during the conduct of the trial. Additionally, the site neuropsychologists and neurologists received webinar training about the onsite evaluation procedures prior to the first examinations at each site or when there was a change in the site neuropsychologist or neurologist. Training was provided between meetings by one-on-one education sessions with the DCC, webinars and through the use of an online learning management system.

Outcome Training

Baseline Assessment

Caregivers were asked to complete the Parent/Caregiver Rating Form of the VABS-II which is a caregiver questionnaire. Caregivers were asked to base responses on the child's functioning prior to arrest. A site clinical research coordinator or other study staff sat with the family and obtained this information as soon as possible after randomization. If the family was unable to complete the VABS-II within the first 12 hours of admission, the study team tried to obtain the VABS-II every 6 hours until it was completed. Every effort was made to ensure that the VABS-II was completed within 12 hours of randomization. In addition, caregivers provided demographic information, ratings of family functioning, indicators of severity of functioning prior to arrest (e.g., does the child have a tracheostomy tube, ventilator, and/or feeding tube), rating of the child's global functioning, and perceived family burden. At the baseline assessment, information about pre-existing medical conditions and developmental disability was collected and the PCPC/POPC were rated by the study staff based on medical record review.

Early Follow Up

PCPC/POPC ratings were also obtained by the study staff at each site at PICU and hospital discharge.

Three and Twelve Month Follow Up

All 3 and 12 month telephone interviews were conducted centrally by staff at the Kennedy Krieger Institute to assure uniform performance of administration of the semi-structured interview used to collect ratings on the VABS-II. Attempts were made to conduct interviews within one month of the designated follow up time (3 months $\pm$ 2 weeks or 12 months $\pm$ 2 weeks). Two to four weeks prior to the telephone interview, site CRCs contacted families to obtain the status of the child and verify current contact information.

In order to assess inter-rater reliability of the VABS-II telephone interviews, a subset of interviews (every 10^{th} interview) was recorded. Recorded interviews were reviewed and rescored by B.S. (neuropsychologist). Discrepant scores were adjudicated through discussion between B.S. and the interviewer. Overall inter-rater reliability was high (> 80% agreement).

During the three and twelve month telephone interview in addition to completing the VABS-II, information about the patient's global functioning, perceived family burden, the patient's medical conditions, as well as school performance (for children 5 years and older) was also obtained. PCPC/POPC ratings were obtained through consensus by J.C. and B.S. (rehabilitation physician and neuropsychologist) based on caregiver responses during the interview.

Twelve Month Onsite Evaluation

After the 12 month VABS-II was completed, onsite neuropsychological and neurological evaluations were completed. All survivors were eligible to participate in the neurological

evaluation and all children less than 5 years, 9 months were eligible for participation in the neuropsychological evaluation. Due to limitations in the age range of the tests, children who were 5 years, 9 months through 5 years, 11 months at the time of follow up were tested after their 6th birthday. Children 6 years of age and older who did not have a consistent means of functional communication (based on caregiver responses during the 12 month VABS-II) were not scheduled to participate in the neuropsychological evaluation and were assigned the lowest possible score for purposes of rank order analyses.

As part of the neuropsychological evaluation, a global cognitive score was obtained. For children less than 5 years, 9 months, this score was based on performance on the Mullen Scales of Early Learning (18). In children 6 years of age or older, who were deemed eligible for neuropsychological testing based on the results of the VABS-II, the two subtest version of the Wechsler Abbreviated Scale of Intelligence (19) was used to assess global cognitive functioning.

Data Management and Site Monitoring

Data were recorded on worksheets and entered into a secure Internet-based electronic data capture system (OpenClinica, OpenClinica Inc.) maintained at the DCC (University of Utah, Salt Lake, Utah). Initial VABS-II assessments were faxed to the DCC and centrally scored. Site monitors visited all enrolling sites to assess protocol adherence, regulatory compliance, and verify sources of selected data elements. This was supplemented by remote monitoring for which sites submitted documentation on selected data elements to the DCC and ongoing automated queries sent to sites for discrepant data.

SUPPLEMENTARY RESULTS

Temperature Intervention.

All temperature recordings up to 120 hours were independently reviewed by two individuals (FM and JMD); 89% of therapeutic hypothermia cases and 95% of therapeutic normothermia cases were assessed as Good or Adequate; the remainder were assessed as Poor or Incomplete/Not Evaluable recordings. Median with interquartile range (IQR) times from intervention initiation to reach goal temperature ranges of 33.0 ± 1.0°C or 36.75 ± 0.75°C for at least 1 hour, which defined the end of the induction phases and beginning of the maintenance phase of the temperature intervention, were 2.1 (IQR 1.5, 3.5) hours for hypothermia and 2.0 (IQR 1.1, 3.1) hours for normothermia. The time to the goal temperature range was 1 hour less or 1.1 and 1.0 hours, respectively. The median time from ROC until reaching the goal temperature range was 6.4 hours for hypothermia and 5.7 hours for normothermia groups. For hypothermia cases, the total duration of temperature in the 33.0 ± 1.0°C range was 48.0 (IQR 48.0, 48.0) hours, duration of rewarming 17.5 (IQR 15.1, 18.5) hours and normothermia after rewarming was 52.0 hours (IQR 50.0, 54.5). For normothermia cases, the duration was 120 hours (IQR 120.0, 120.0).

Modified Intention-to-treat

While a modified intention-to-treat based on pre arrest VABS-II ≥ 70 score was the primary analysis approach, alternative approaches (modified ITT removing patients not receiving assigned treatment, randomized over 6 hours post ROSC/ROC, and/or otherwise technically not meeting protocol criteria) did not markedly affect significance of study findings or estimated treatment effect. For example, among the 252 evaluable patients receiving their assigned treatment, the p-value for significance of treatment effect was 0.46, and the relative risk for a favorable one-year primary outcome for patients treated with hypothermia versus normothermia was 0.89 with 95% CI (0.64, 1.22). Among the 245 evaluable patients randomized within 6

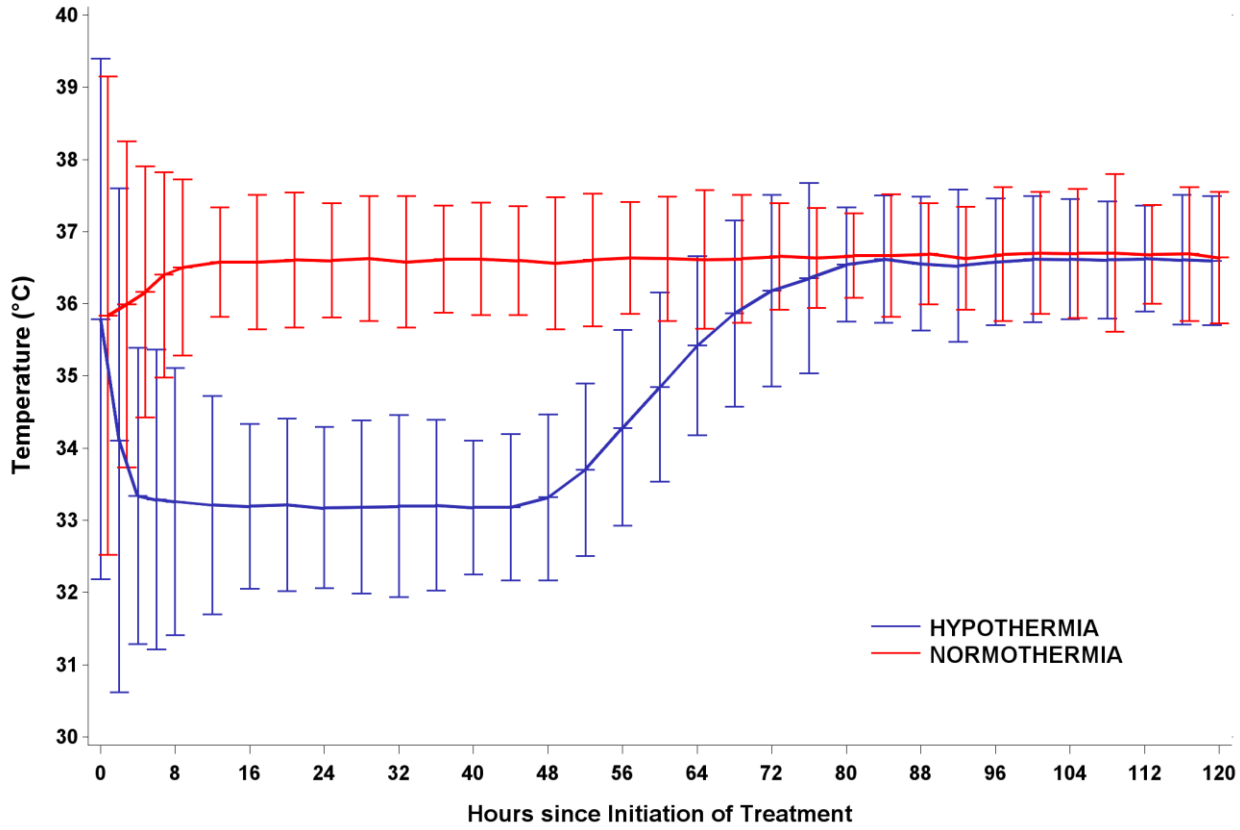
hours of ROSC/ROC and receiving their assigned treatment, the p-value for significance of treatment effect was 0.45, and the relative risk for a favorable one-year primary outcome for patients treated with hypothermia versus normothermia was 0.88 with 95% CI (0.64, 1.22).

Sensitivity Analysis

Sensitivity analyses were conducted to examine the potential effect of missing primary outcome data on the analysis results. Twelve patients eligible for the primary analysis (two assigned to therapeutic hypothermia and ten to therapeutic normothermia) had missing outcomes. When all possible realizations of missing outcomes were imputed, no scenarios yielding significant p-values for treatment effect in the primary analysis occurred. Point estimates of the relative risk for a favorable one-year outcome for patients treated with hypothermia versus normothermia ranged from 1.03 under the imputed scenario most favorable to hypothermia (i.e., assuming that both hypothermia-arm patients with missing data had a favorable one-year outcome, and that all ten patients in the normothermia arm with missing data had unfavorable one-year outcome) to 0.82 under the imputed scenario most favorable to normothermia.

SUPPLEMENTARY FIGURES AND TABLES

Figure S1. Temperature of Patients during 120 Hours of Targeted Temperature Management, According to Treatment Group.



The temperature curves show the means of all primary temperature readings within each time interval (for example, all primary temperature readings from 22 to 26 hours after the initiation of treatment are counted in the category “24 hours since initiation of treatment”). The mean temperatures shown at the horizontal axis time point of 0 hours since initiation of treatment include only temperatures recorded at the time of initiation of treatment. During the first 8 hours after initiation of treatment, 2-hour time intervals are used, with 4-hour time intervals used for the 12 hour time point and beyond. The I bars indicate ±2 SD from the mean temperature within each time interval. Time points for normothermia are slightly shifted to prevent overlap. Temperatures recorded after early termination of treatment are not included in this analysis.

Table S1. Medical History and Primary Cause of the Cardiac Arrest.*

Characteristic	Hypothermia Group (N = 166)	Normothermia Group (N = 163)
Medical history – no. (%)		
No pre-existing medical condition	13 (8)	17 (10)
Pre-existing non-cardiac medical condition		
Lung or airway disease	54 (33)	55 (34)
Neurologic condition	57 (34)	48 (29)
Gastrointestinal disorder	50 (30)	50 (31)
Prenatal condition	44 (27)	42 (26)
Immunocompromised condition or taking immunosuppressive medication	20 (12)	26 (16)
Renal condition	18 (11)	26 (16)
Failure to thrive	16 (10)	18 (11)
Endocrine condition	11 (7)	10 (6)
Transplant	8 (5)	12 (7)
Other	42 (25)	27 (17)
Pre-existing cardiac medical condition		
Acquired heart disease	28 (17)	25 (15)
Arrhythmia	38 (23)	30 (18)
Congenital acyanotic heart disease	77 (46)	68 (42)
Congenital cyanotic heart disease	20 (12)	23 (14)
Pre-existing pulmonary hypertension		
Associated with congenital heart disease	7 (4)	7 (4)
Not associated with congenital heart disease	3 (2)	3 (2)
Primary cause of the cardiac arrest – no. (%)		
Cardiovascular event	89 (54)	74 (45)
Respiratory event	45 (27)	55 (34)
Congenital heart disease	24 (14)	27 (17)
Neurological event	3 (2)	1 (1)
Multiple organ system failure	0 (0)	2 (1)
Drug overdose	2 (1)	0 (0)
Electrolyte imbalance	0 (0)	1 (1)
Unknown	3 (2)	3 (2)

* P>0.05 for all comparisons between the two groups.

Table S2. Location within Hospital at Time of Cardiac Arrest.

	Hypothermia N = 166	Normothermia N = 163	Overall N = 329
Intensive care unit (includes intermediate care)	96 (58%)	106 (65%)	202 (61%)
Emergency department	26 (16%)	17 (10%)	43 (13%)
Inpatient ward	20 (12%)	14 (9%)	34 (10%)
Operating room	14 (8%)	13 (8%)	27 (8%)
Other clinical location (radiology, laboratory, etc.)	9 (5%)	11 (7%)	20 (6%)
Non-clinical location (cafeteria, waiting room, etc.)	1 (1%)	2 (1%)	3 (1%)

Table S3. Clinical Characteristics Prior to Intervention for Study Population.

Clinical characteristics prior to intervention – median (IQR)	**HYPOTHERMIA (N=166)**	**NORMOTHERMIA (N=163)**
First measured body temperature (°C) (n=321)	35.7 (34.4, 37.0)	36.0 (34.7, 37.0)
pH (n=290)	7.36 (7.27, 7.44)	7.32 (7.24, 7.42)
PaCO2 (mmHg) (n=290)	38.5 (31.5, 47.0)	40.5 (34.0, 47.0)
PaO2 (mmHg) (n=289)	132.5 (67.5, 287.5)	161.0 (72.0, 284.0)
Saturation (%) (n=279)	98.0 (91.0, 100.0)	99.0 (92.0, 100.0)
HCO3/Bicarbonate (mmol/L) (n=290)	22.0 (17.0, 27.0)	22.0 (18.0, 26.0)
Lactate (mmol/liter) (n=289)	5.7 (2.5, 11.9)	7.2 (3.5, 12.2)
Sodium (mmol/L) (n=314)	144 (140, 149)	144 (140, 149)
Potassium (mmol/L) (n=313)	3.9 (3.2, 4.6)	3.8 (3.2, 4.5)
Bicarbonate (mmol/L) (n=285)	21.0 (16.0, 27.0)	21.0 (17.0, 24.0)
Chloride (mmol/L) (n=292)	105 (100, 109)	105 (100, 109)
BUN (mg/dL) (n=291)	15.0 (9.0, 22.5)	15.0 (10.0, 24.0)
Creatinine (mg/dL) (n=291)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)
Glucose (mg/dL) (n=299)	178 (116, 269)	188 (119, 281)
Magnesium (mg/dL) (n=258)	2.1 (1.8, 2.6)	2.1 (1.8, 2.4)
Ionized calcium (mmol/L) (n=283)	1.2 (1.1, 1.4)	1.2 (1.1, 1.3)
Total calcium (mg/dL) (n=257)	9.2 (8.2, 10.2)	8.9 (8.1, 10.2)
Phosphate (mg/dL) (n=218)	5.8 (4.3, 8.7)	6.2 (4.9, 8.3)
ALT/SGPT (U/L) (n=270) *	61 (29, 200)	39 (22, 111)
AST/SGOT (U/L) (n=258) *	148 (49, 355)	81 (47, 203)
Total bilirubin (mg/dL) (n=260)	0.7 (0.4, 1.3)	0.8 (0.4, 1.4)
PT (seconds) (n=267)	19.4 (16.3, 26.8)	19.5 (15.8, 26.0)
PTT (seconds) (n=272)	68.0 (37.0, 150.0)	99.6 (39.5, 165.0)
INR (n=272)	1.7 (1.4, 2.3)	1.8 (1.4, 2.4)
Amylase (U/L) (n=156)	30.0 (16.0, 67.0)	30.0 (13.0, 44.0)
Lipase (U/L) (n=148)	51.5 (21.0, 106.0)	44.0 (21.0, 81.5)
Hemoglobin (g/dL) (n=304) *	12.3 (10.6, 13.7)	11.6 (10.0, 13.4)
Platelet count (10^3/microL) (n=303)	142 (94, 251)	124 (65, 252)
White blood cell (10^3/microL) (n=301)	11.7 (7.1, 17.6)	9.6 (6.0, 16.6)

* P<0.05 for comparison.

Table S4. Baseline VABS-II, PCPC, and POPC for THAPCA-IH population eligible for primary outcome.

	Hypothermia N = 135	Normothermia N = 134	Overall N = 269
Vineland Adaptive Behavior Scales-II (VABS-II)			
N (completed and scorable)	131	127	258
Min	70	70	70
Max	143	156	156
Mean	96.3	95.1	95.7
SD	15.3	16.2	15.7
Median	94	93	94
Pediatric Cerebral Performance Category (PCPC)			
Normal = 1	83 (61%)	87 (65%)	170 (63%)
Mild disability = 2	38 (28%)	33 (25%)	71 (26%)
Moderate disability = 3	12 (9%)	8 (6%)	20 (7%)
Severe disability = 4	2 (1%)	5 (4%)	7 (3%)
Coma or vegetative state = 5	0 (0%)	1 (1%)	1 (0%)
Pediatric Overall Performance Category (POPC)			
Good = 1	50 (37%)	52 (39%)	102 (38%)
Mild disability = 2	54 (40%)	51 (38%)	105 (39%)
Moderate disability = 3	24 (18%)	22 (16%)	46 (17%)
Severe disability = 4	7 (5%)	8 (6%)	15 (6%)
Coma or vegetative state = 5	0 (0%)	1 (1%)	1 (0%)

Note: 31 patients in the hypothermia arm and 29 patients in the normothermia arm had baseline VABS-II less than 70 or had no baseline VABS-II available and POPC or PCPC ≥ 3, and were excluded from the primary analysis.

Table S5. Cause of Death.

	Hypothermia N = 85	Normothermia N = 88
Cardiovascular failure / futility	26 (31%)	33 (38%)
Withdrawal for poor neurologic prognosis / brain death declared	33 (39%)	29 (33%)
Withdrawal for other system failure	12 (14%)	10 (11%)
Respiratory failure / futility	3 (4%)	7 (8%)
Other	9 (11%)	9 (10%)
Unknown	2 (2%)	0 (0%)

Table S6. 12 month functioning on the Mullen Scales of Early Learning (Mullen) and 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI)[1]

	Hypothermia	Normothermia	P-value
Mullen Early Learning Composite (age < 5 years 9 months) – no. (%)	n=53	n=35	0.13[4]
Lowest possible score	16 (30)	5 (14)	
49 – 69 (well below average)	17 (32)	10 (29)	
70 – 84 (below average)	7 (13)	11 (31)	
85 – 115 (average)	12 (23)	7 (20)	
> 115 (above average)	1 (2)	2 (6)	
WASI IQ (age ≥ 6 years) – no. (%)[2]	n=15	n=13	0.27[5]
Lowest possible score[3]	2 (13)	3 (23)	
55 – 69 (well below average)	1 (7)	1 (8)	
70 – 84 (below average)	2 (13)	3 (23)	
85 – 115 (average)	9 (60)	6 (46)	
> 115 (above average)	1 (7)	0 (0)	
Mullen Early Learning Composite or WASI IQ (all ages combined) – no. (%)	n=68	n=48	0.46[6]
Lowest possible score	18 (26)	8 (17)	
< 70 (well below average)	18 (26)	11 (23)	
70 – 84 (below average)	9 (13)	14 (29)	
85 – 115 (average)	21 (31)	13 (27)	
> 115 (above average)	2 (3)	2 (4)	

[1] Only children alive at one year are represented in table. Thirty-nine children, 13 in the Hypothermia group and 26 in the Normothermia group, were known to be alive at one year but are not represented because of missing neuropsychological data.

[2] One participant was administered the Vocabulary and Matrix Reasoning subtests from the Wechsler Intelligence Scale for Children - Fourth Edition in place of the comparable WASI subtests.

[3] Children age 6 and over with lowest possible score were reported to have no consistent means of functional communication on the 12 month VABS-II assessment interview. These children did not participate in the onsite neuropsychological evaluation and were assigned the lowest possible score.

[4] P-value reflects the Mann-Whitney test based on the continuous Mullen Early Learning Composite score. Patients with a score < 49 are assigned a rank of -1000 (i.e., the lowest possible score).

[5] P-value reflects the Mann-Whitney test based on the continuous WASI IQ score. Patients considered ineligible for the evaluation due to the severity of their injury are assigned a rank of -1000 (i.e., the lowest possible score).

[6] P-value reflects the Mann-Whitney test based on the continuous Mullen Early Learning Composite or WASI IQ score.

Table S7. Adverse Events Reported During Intervention Period (120 hours) by Treatment Received.

	Hypothermia N = 161	Normothermia N = 160	P-value[1]
Hypokalemia[2]	42/161 (26%)	31/160 (19%)	0.15
Hyperkalemia[2]	2/161 (1%)	7/160 (4%)	0.10
Hypoglycemia[2]	7/161 (4%)	3/160 (2%)	0.22
Hyperglycemia[2]	20/161 (12%)	18/160 (11%)	0.75
Hypophosphatemia[2]	10/161 (6%)	6/160 (4%)	0.33
Neutropenia[2]	1/161 (1%)	1/160 (1%)	1.00
Thrombocytopenia[2]	12/161 (7%)	10/160 (6%)	0.68
Clinical or Electrographic Seizure[3]	34/161 (21%)	30/160 (19%)	0.60
Repeat Cardiac Arrest[3]	19/161 (12%)	25/160 (16%)	0.33
Received any form of Renal Replacement Therapy[3]	40/161 (25%)	37/160 (23%)	0.72

[1] P-values for all comparisons are 2-sided mid p-values, based on an exact likelihood ratio test.

[2] Medical Dictionary for Regulatory Activities (MedDRA) lower level term of adverse events reported in adverse events log.

[3] Patient experienced event or therapy as reported on daily data collection forms.

Table S8. Summary of Serious Adverse Events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class by Treatment Received[1]

	Hypothermia		Normothermia	
MedDRA System Organ Class	**Patients N=161**	**Events N=128**	**Patients N=160**	**Events N=128**
Blood and lymphatic system disorders	4 (2%)	4	1 (1%)	1
Cardiac disorders	30 (19%)	37	34 (21%)	38
Gastrointestinal disorders	2 (1%)	2	3 (2%)	3
General disorders and administration site conditions	8 (5%)	9	7 (4%)	7
Infections and infestations	9 (6%)	9	11 (7%)	12
Injury, poisoning and procedural complications	4 (2%)	4	6 (4%)	6
Investigations	3 (2%)	3	4 (3%)	4
Metabolism and nutrition disorders	1 (1%)	1	1 (1%)	1
Musculoskeletal and connective tissue disorders	1 (1%)	1	2 (1%)	2
Nervous system disorders	32 (20%)	33	29 (18%)	30
Renal and urinary disorders	1 (1%)	1	6 (4%)	6
Respiratory, thoracic and mediastinal disorders	13 (8%)	13	9 (6%)	11
Vascular disorders	11 (7%)	11	7 (4%)	7

* P>0.05 for all comparisons between the two groups.

[1] MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). MedDRA: MedDRA® trademark is owned by IFPMA on behalf of ICH.

Table S9. Primary Outcome by Subgroup Populations.

	% Alive and VABS ≥ 70		
	Hypothermia N = 133	Normothermia N = 124	P value[2]
Age Group at Randomization			
<2 years	31/82 (38%)	31/79 (39%)	0.81
2-11 years	13/37 (35%)	12/28 (43%)	0.53
>= 12 years	4/14 (29%)	5/17 (29%)	0.85
Sex			
Male	25/79 (32%)	26/73 (36%)	0.55
Female	23/54 (43%)	22/51 (43%)	0.77
Ethnicity			
Hispanic or Latino	10/30 (33%)	8/21 (38%)	0.88
Not Hispanic or Latino	37/97 (38%)	38/96 (40%)	0.83
Stated as Unknown	1/6 (17%)	2/7 (29%)	
Race			
Asian	3/4 (75%)	1/3 (33%)	0.78
Black or African American	14/43 (33%)	12/30 (40%)	0.39
White	28/77 (36%)	25/75 (33%)	0.67
Other	0/4 (0%)	5/7 (71%)	0.11
Unknown	3/5 (60%)	5/9 (56%)	
Patient had congenital heart disease			
Yes	27/79 (34%)	29/70 (41%)	0.35
No	21/54 (39%)	19/54 (35%)	0.77
Patient was post-operative cardiac surgery			
Yes	16/41 (39%)	19/50 (38%)	0.91
No	32/92 (35%)	29/74 (39%)	0.57
ECMO used after cardiac arrest and prior to randomization			
Yes	20/77 (26%)	27/82 (33%)	0.34
No	28/56 (50%)	21/42 (50%)	0.92
ECMO used at time of treatment initiation			
Yes	19/75 (25%)	26/82 (32%)	0.34
No	29/58 (50%)	22/42 (52%)	0.76

[1] Denominators reported reflect those with known outcome status.
[2] P-values are mid p-values from an exact score test for treatment effect within subgroup in a logistic model controlling for age category (except for within age group comparisons).

Table S10. Primary Outcome by Subgroups of Descriptive Exploratory Interest[1]

	% Alive and VABS ≥ 70		
	Hypothermia N = 133	Normothermia N = 124	P value[2]
All Cases	48/133 (36%)	48/124 (39%)	0.65
Initial Arrest Rhythm[3]			
Asystole	2/12 (17%)	0/5 (0%)	0.70
Bradycardia	24/75 (32%)	24/68 (35%)	0.53
Pulseless electrical activity (PEA)	13/28 (46%)	12/30 (40%)	0.68
Ventricular fibrillation or tachycardia	8/14 (57%)	12/16 (75%)	0.57
Unknown	1/4 (25%)	0/5 (0%)	0.13
CPR Duration (minutes)[3]			
2-15	30/56 (54%)	21/47 (45%)	0.38
15-30	5/20 (25%)	6/17 (35%)	0.38
>30	13/57 (23%)	21/60 (35%)	0.13
Arrest Etiology[3]			
Cardiac	24/72 (33%)	26/56 (46%)	0.13
Respiratory	16/34 (47%)	13/40 (33%)	0.54
Congenital Heart Disease	6/21 (29%)	7/22 (32%)	0.88
Other	2/6 (33%)	2/6 (33%)	0.72

[1] Denominators reported reflect those with known outcome status.

[2] P-values shown are mid p-values from an exact score test for treatment effect within subgroup in a logistic model controlling for age category.

[3] The exploratory subgroup analyses of rhythm, arrest duration, and arrest etiology represent factors known associated with cardiac arrest outcome.

Table S11. Blood Product Use within 7 Days after Randomization by Treatment Received excluding ECMO cases.

Outcome	Hypothermia Group (N = 76)	Normothermia Group (N = 66)	P Value[1]
Blood-product use – no. (%)			
Any	54 (71)	46 (70)	0.86
Type			
Cryoprecipitate	11 (14)	14 (21)	0.30
Fresh-frozen plasma	26 (34)	21 (32)	0.77
Packed red blood cells or whole blood	46 (61)	41 (62)	0.85
Platelets	26 (34)	16 (24)	0.20

[1]P values for all comparisons are two-sided mid-P values, based on an exact likelihood-ratio test.