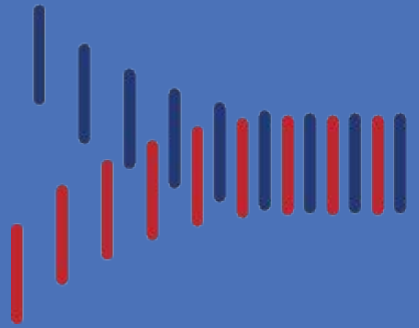
Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients

Investigator Meeting
Thursday, May 5

P-ICECAP



NIH SIREN
Emergency
Trials
Network

Good Morning!

Agenda

Time	Topic	Speaker
7:15 AM	**Breakfast**	
7:45 AM	State of the science	Dr. Alexis Topjian, MD
8:15 AM	Screening and enrollment for P-ICECAP	Moni Weber, RN, BSN, CCRP
8:45 AM	Protocol: Cooling Basics, Clinical Considerations, and Phases of Care	Dr. Frank Moler, MD
9:45:00 AM	**Break**	
9:55 AM	Clinical Standardization	Dr. Alexis Topjian, MD
10:55 AM	Consenting lessons from THAPCA	Dr. Alexis Topjian, MD, & Moni Weber, RN, BSN, CCRP
11:25 AM	WebDCU for Everyone	Sara Butler
12:10 PM	**Lunch**	

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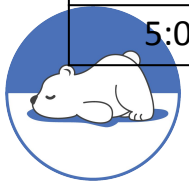
Agenda Cont.

Time	Topic	Speaker
12:10 PM	**Lunch**	
1:10 PM	Protocol and Standardization Game - Kahoot!	Dr. William Meurer, MD, & Moni Weber, RN, BSN, CCRP
2:10 PM	Adverse Event Reporting	Dr. Robert Silbergleit, MD
2:50 PM	Baseline & Central-Measured Outcome	Dr. Beth Slomine, PhD
3:35 PM	**Break**	
3:45 PM	Neurological Outcomes	Dr. Faye Silverstein, MD
4:00 PM	Central IRB and E-Consent	Dr. Robert Silbergleit, MD
4:15 PM	Adaptive Design	Dr. John VanBuren, PhD
5:00 PM	Adjourn Day 2	



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State of the Science

Dr. Alexis Topjian

Objectives

- Review TTM literature
  - Adult
  - Neonatal
  - Pediatric

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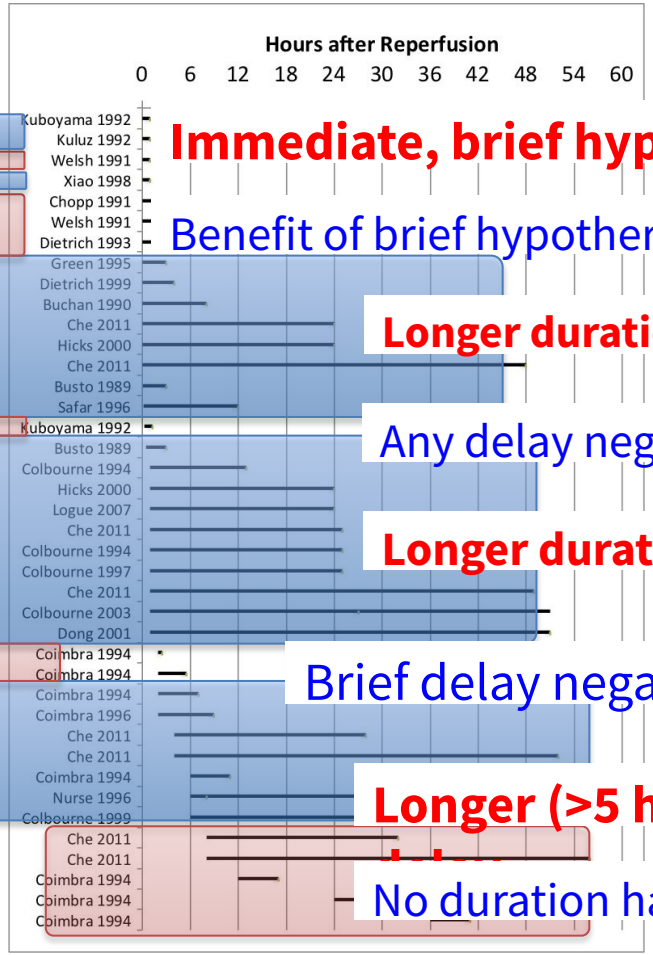
Animal studies of mild-moderate hypothermia (32-34°C).



Immediate, brief hypothermia has benefit

Benefit of brief hypothermia not long-lasting

Longer duration has lasting benefit

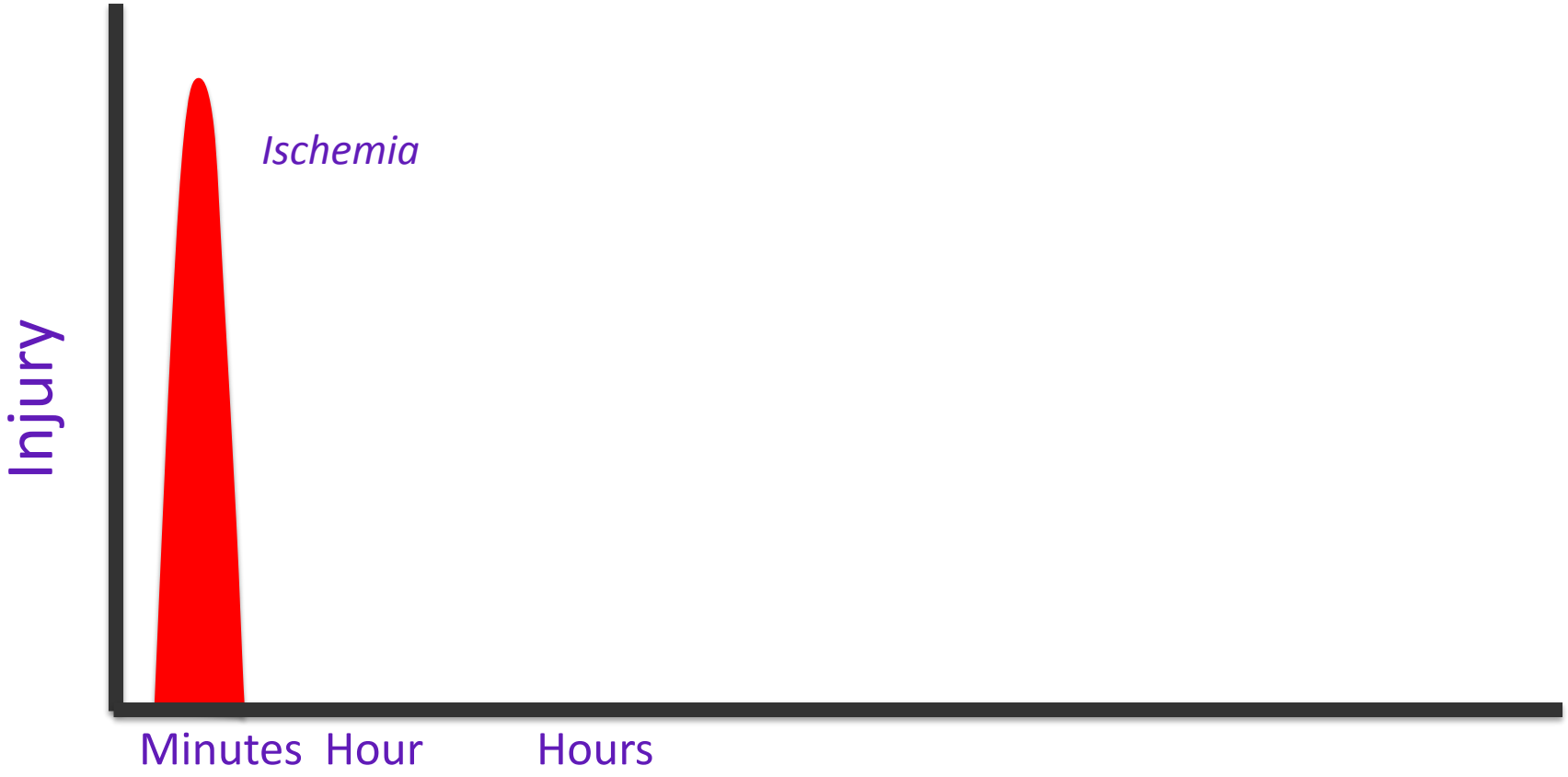
Any delay negates benefit of brief hypothermia

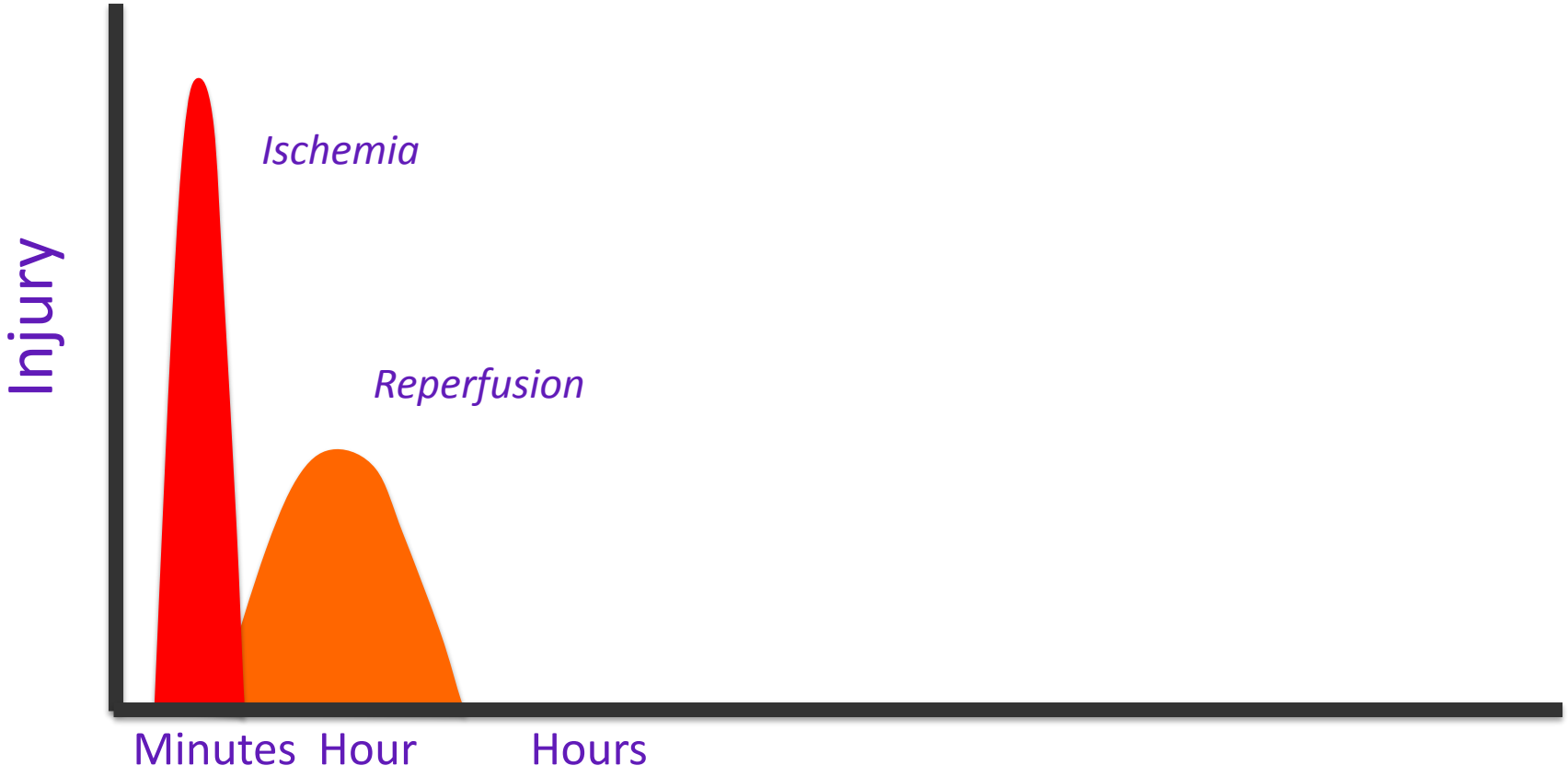
Longer duration has benefit after delay

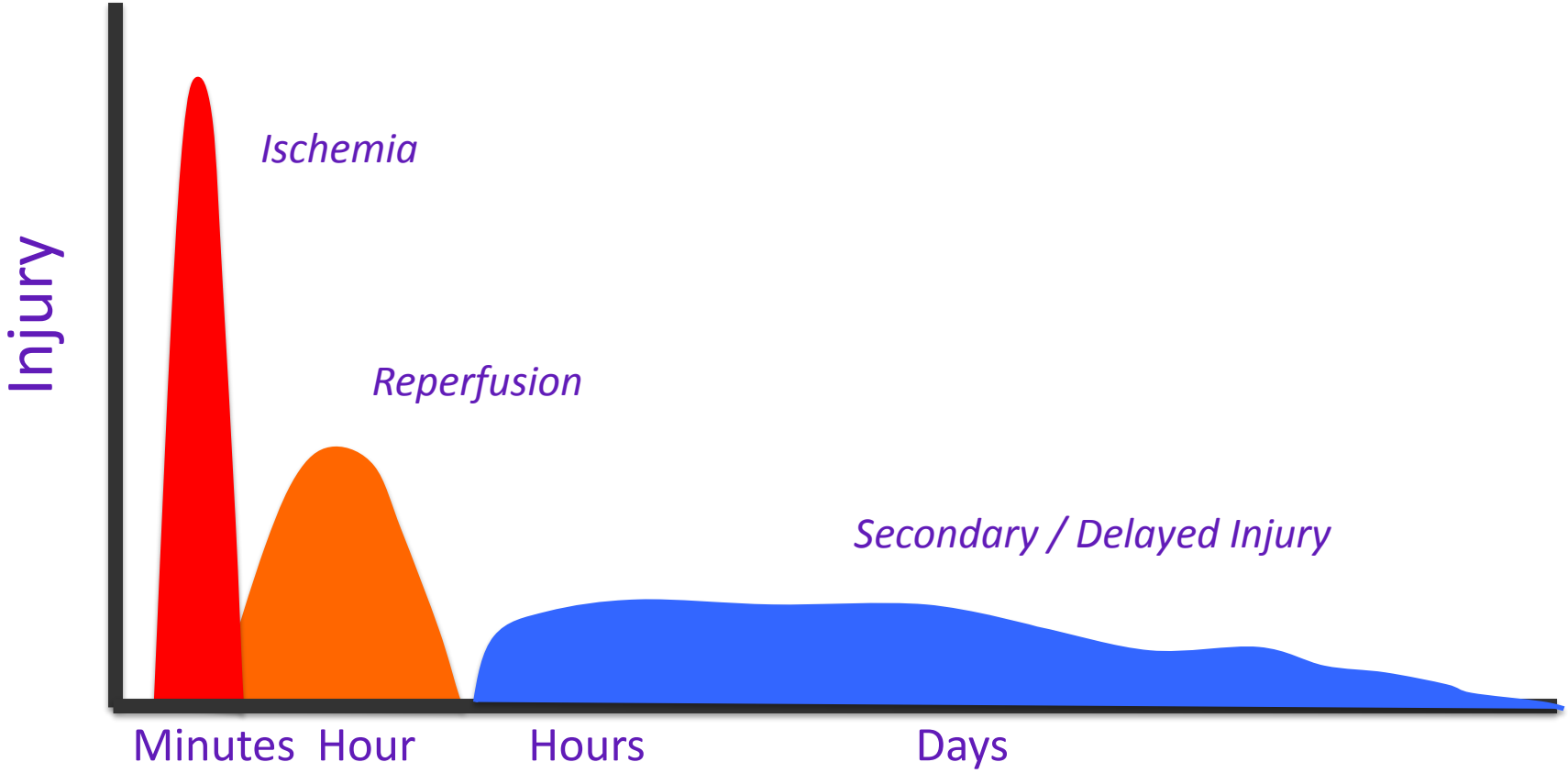
Brief delay negates benefit of brief or 3-hour hypothermia

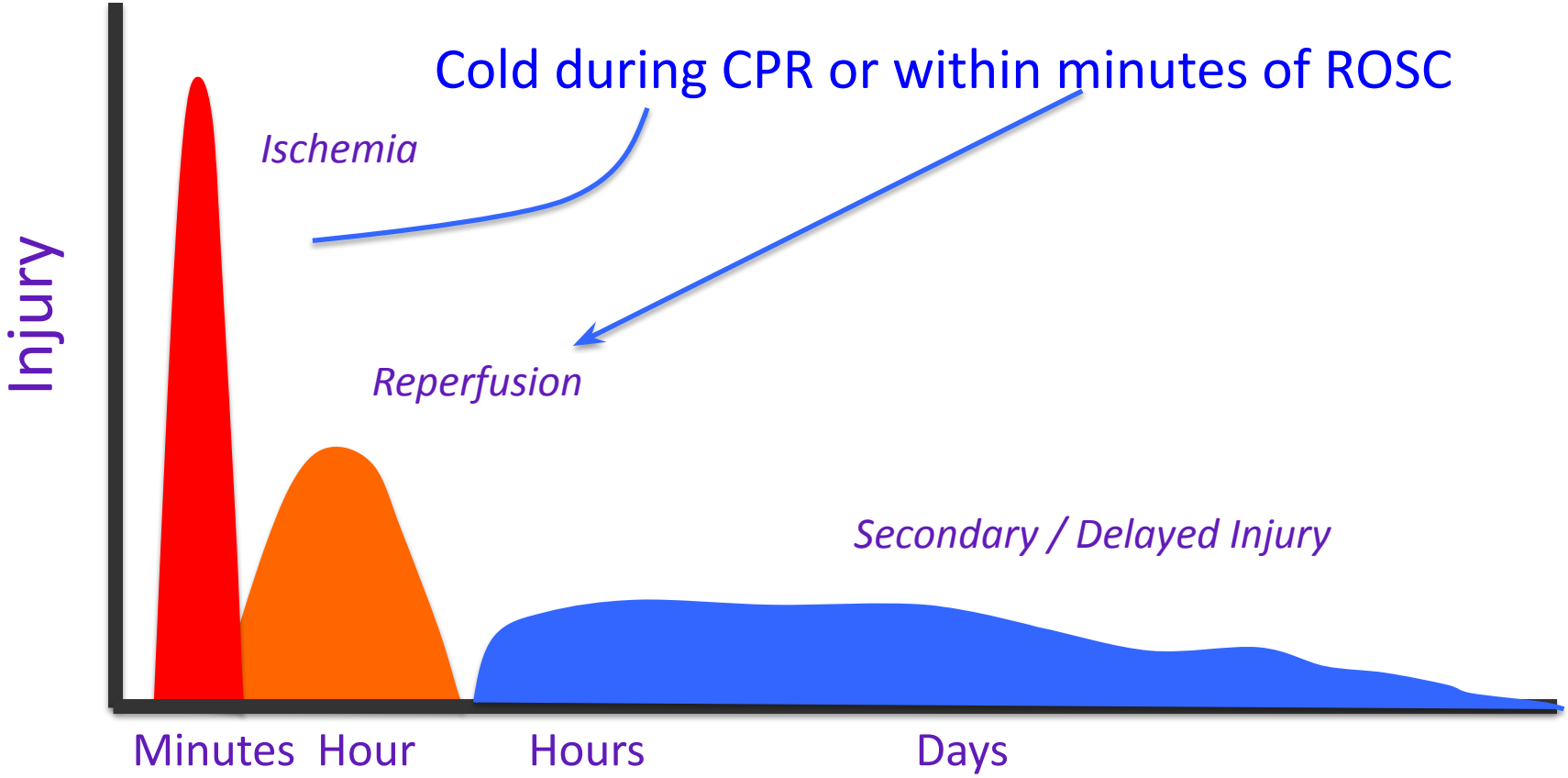
Longer (>5 hr) duration has benefit after 6-8 hour delay

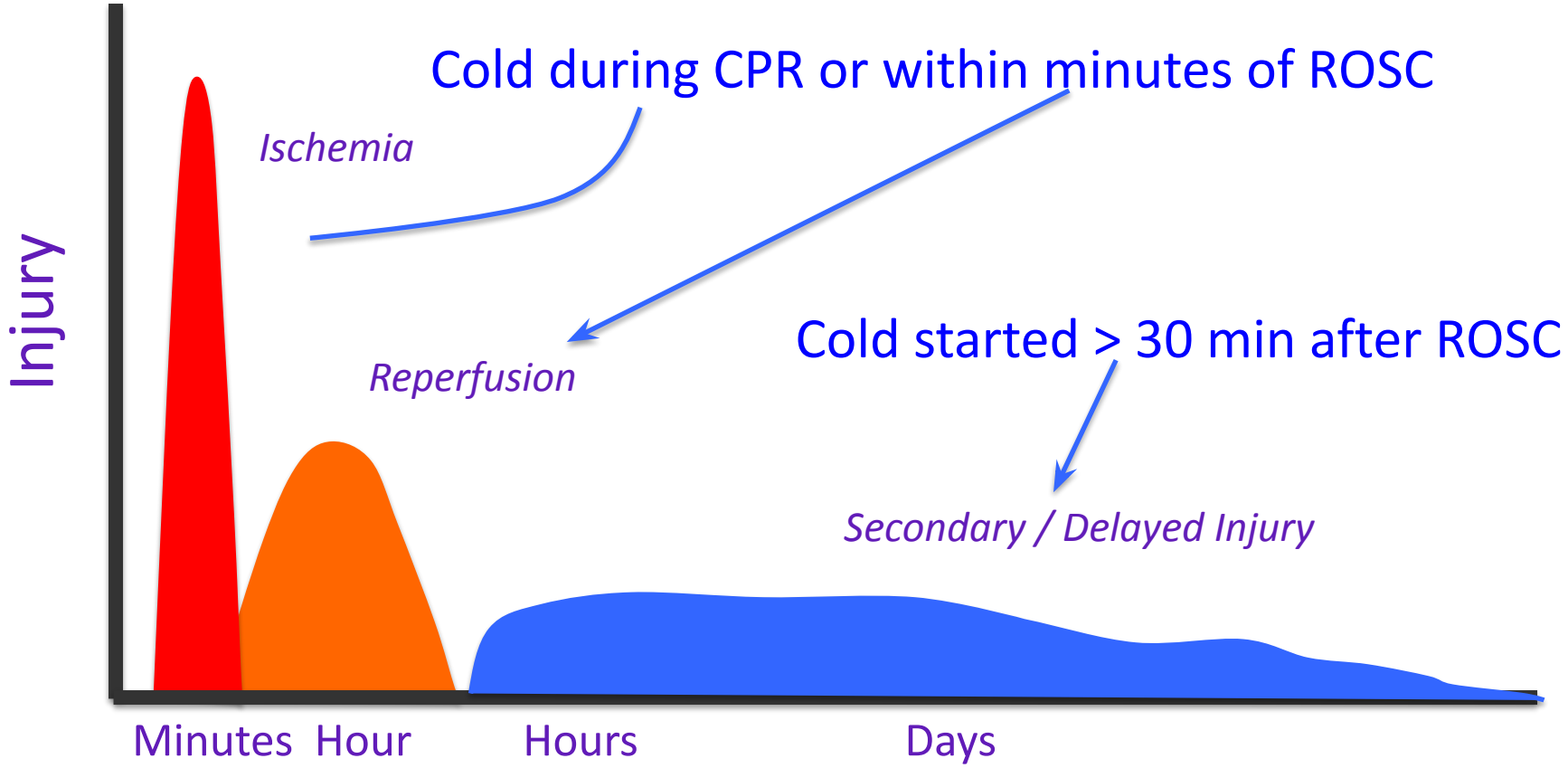
No duration has benefit after 8-12 hour delay


Injury
Ischemia
Minutes
Hour
Hours

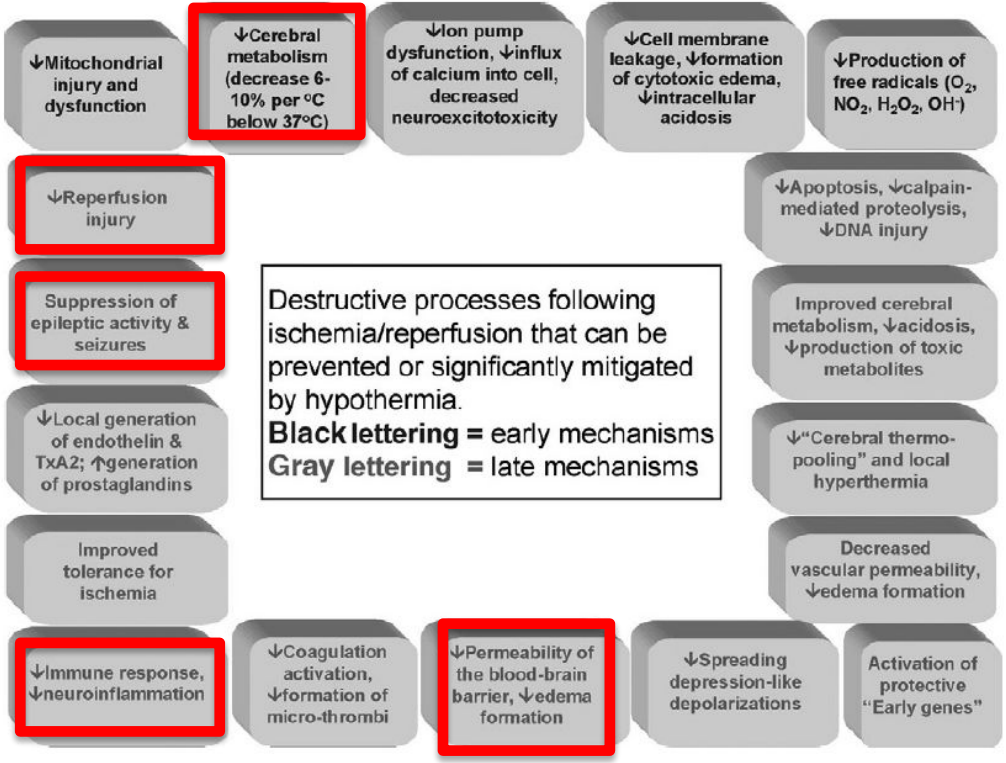

Injury
Ischemia
Reperfusion
Minutes
Hour
Hours


Injury
Ischemia
Reperfusion
Secondary / Delayed Injury
Minutes
Hour
Hours
Days


Cold during CPR or within minutes of ROSC
Ischemia
Reperfusion
Secondary / Delayed Injury
Injury
Minutes
Hour
Hours
Days


Cold during CPR or within minutes of ROSC
Ischemia
Injury
Reperfusion
Cold started > 30 min after ROSC
Secondary / Delayed Injury
Minutes
Hour
Hours
Days

Why Hypothermia?



Does Hypothermia Work in Humans?

Which Ones?
Neonates
Children
Adults

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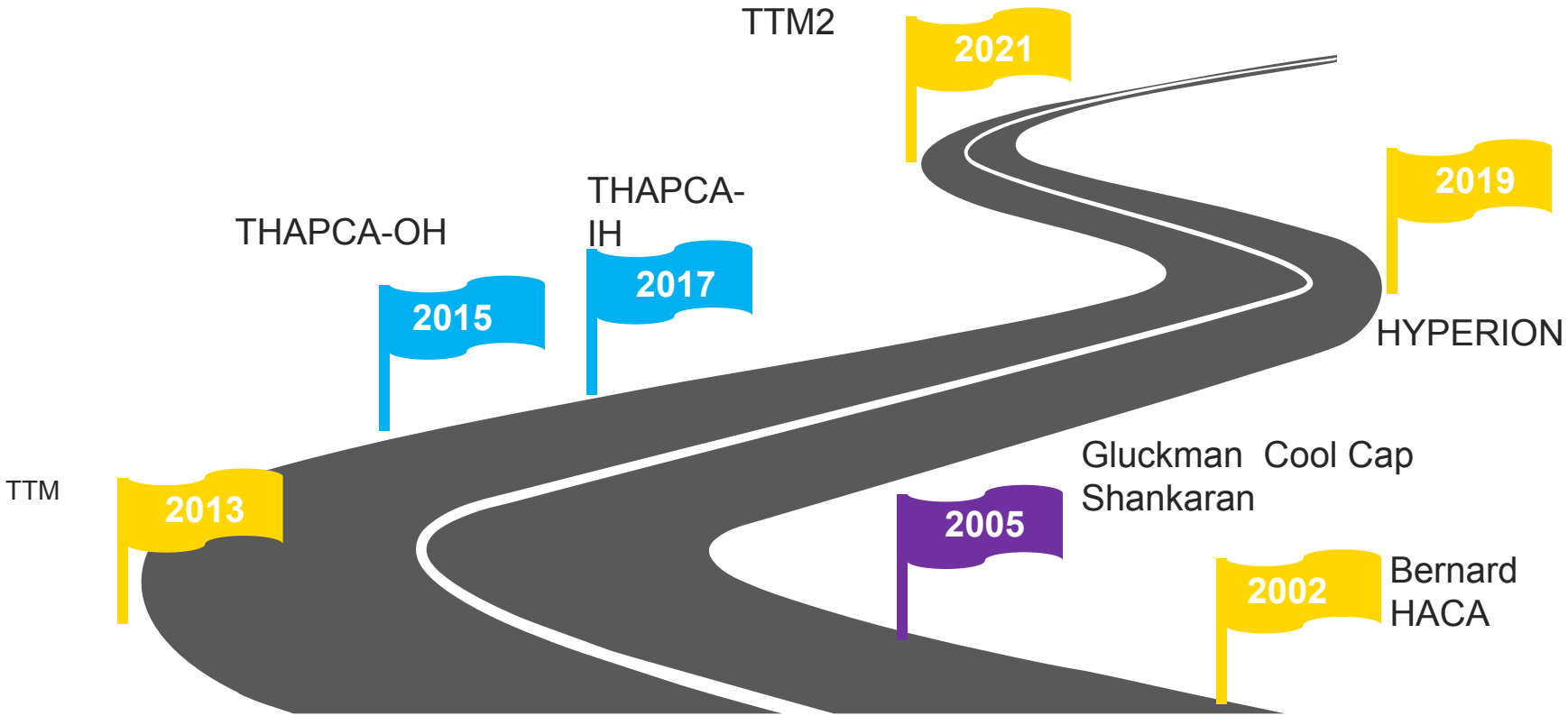
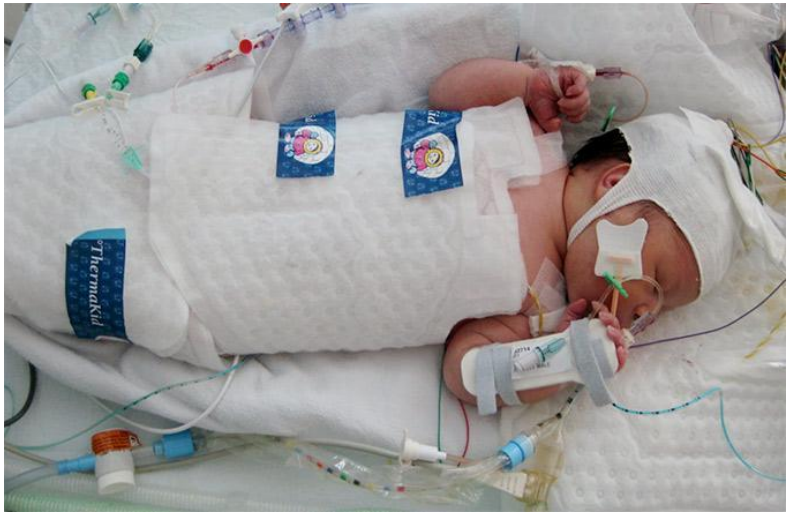
The Road to Pediatric TTM





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Cochrane Hypothermia for Perinatal Asphyxia

11 randomised controlled trials 105 term and late preterm infants with moderate/ severe encephalopathy and evidence of intrapartum asphyxia.

Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in

- mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75 (95% CI 0.68 to 0.83)
- mortality (typical RR 0.75 (95% CI 0.64 to 0.88),
- neurodevelopmental disability (typical RR 0.77 (95% CI 0.63 to 0.94)

Some adverse effects of hypothermia included an increase sinus bradycardia and a significant increase in thrombocytopenia.

Jacobs, Cochrane Review, 2013

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Neonates: >8 RCTs

	Intervention	Number
Azzopardi (2009)	33-34°C vs. 36.8-37.2 x 72 hrs	325
Bharadwaj (2012)	33-34°C vs. 36.5°C x 72 hrs	130
Gane (2013)	33-34°C vs. 36.5°C x 72 hrs	122
Jacobs (2011)	33-34°C vs. 36.8°C x 72 hrs	221
Joy (2013)	33-34°C vs. 36.5°C x 72 hrs	160
Li (2009)	33-34°C vs. 36.5-37°C x 72 hrs	93
Shankaran (2005)	34.5°C vs. 36.5-37°C x 72 hrs	208
Simbruner (2010)	33-34°C vs. 36.5-37.5°C x 72 hrs	129

Quality of Evidence: High
Total number of term neonates in trials: 1388
Ongoing studies: combining treatments, selective head cooling

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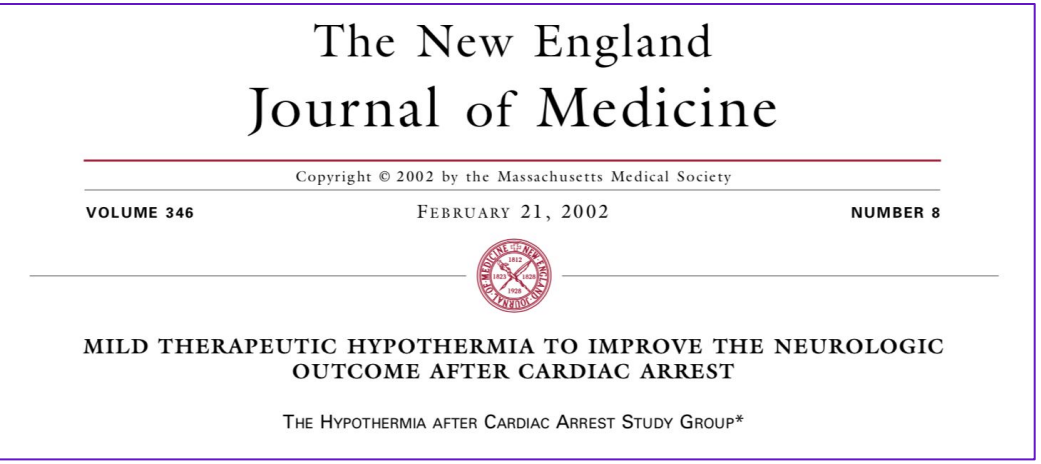


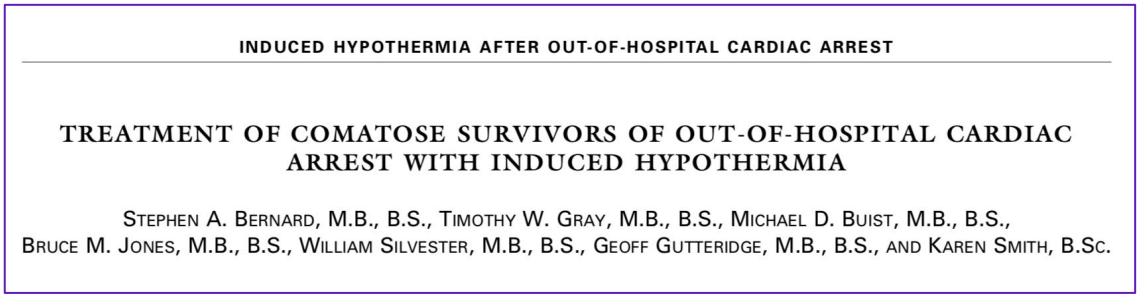
The New England
Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

24 hrs x 32-34°C vs. No temperature control



INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S., BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

12 hrs x 33° vs. No temperature control

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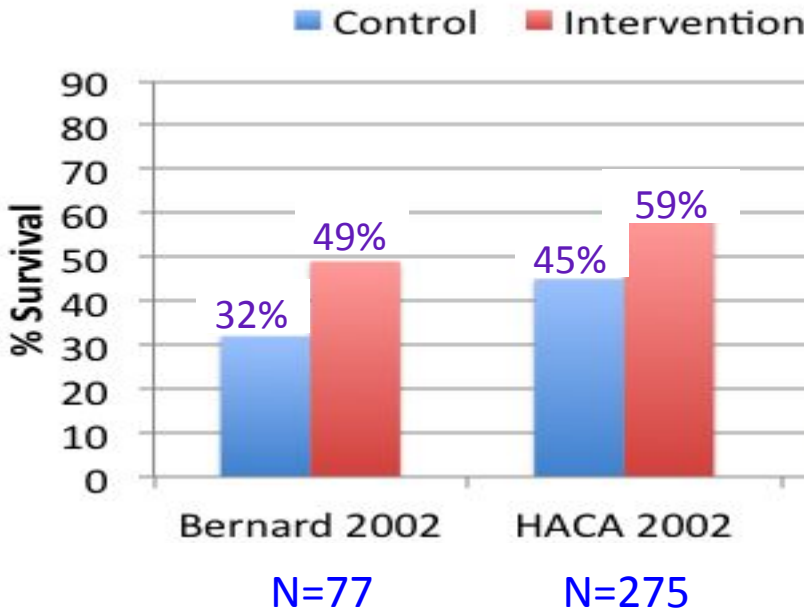
The Early Studies

Control of temperature at 33°C or 32-34°C results in more survival (49-59%) than no temperature control (32-45%).



Hypothermia after Cardiac Arrest Study Group 2002; NEJM 346: 549; Bernard 2002; NEJM 346: 557

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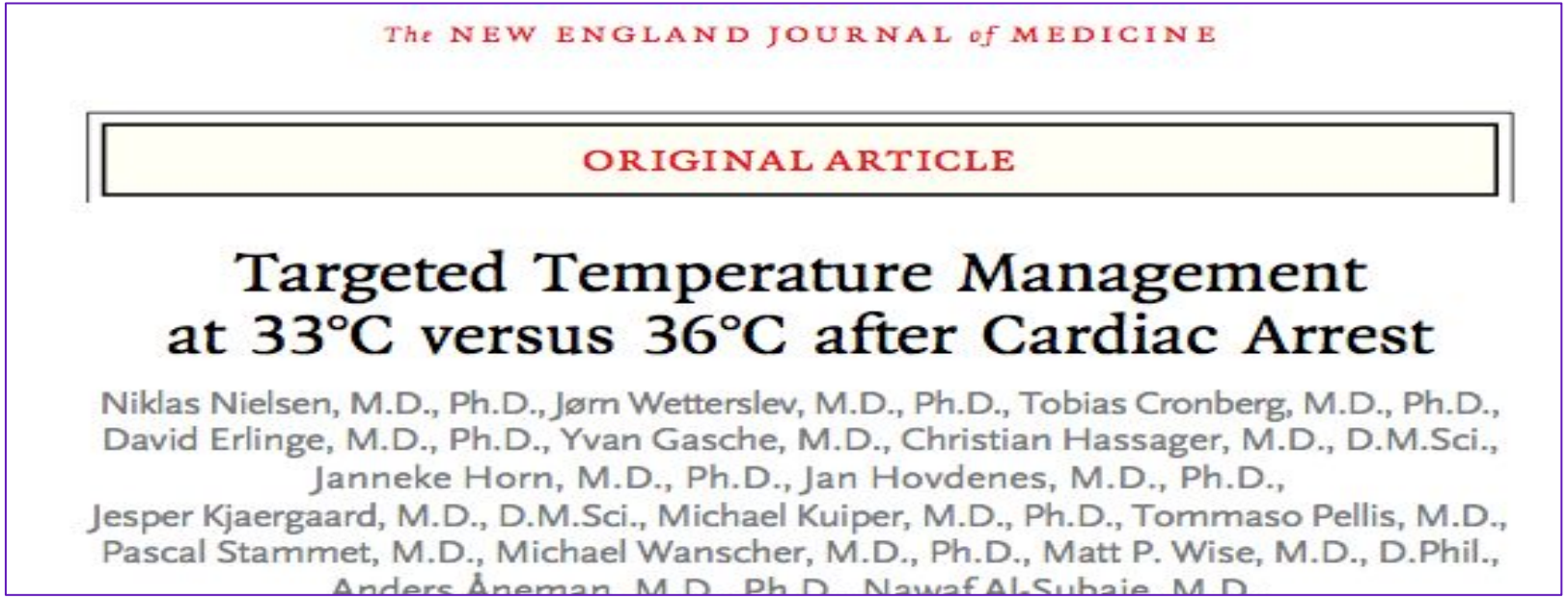

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D.

- 939 subjects
- Shockable rhythms/witness non-shockable
- Regimented post-arrest care and prognostication

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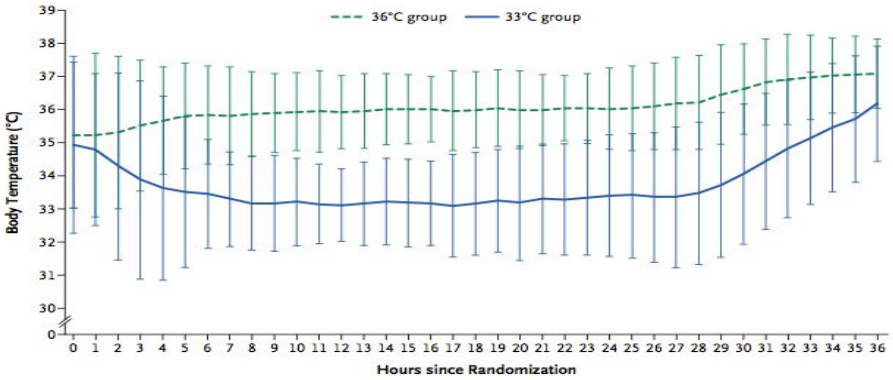
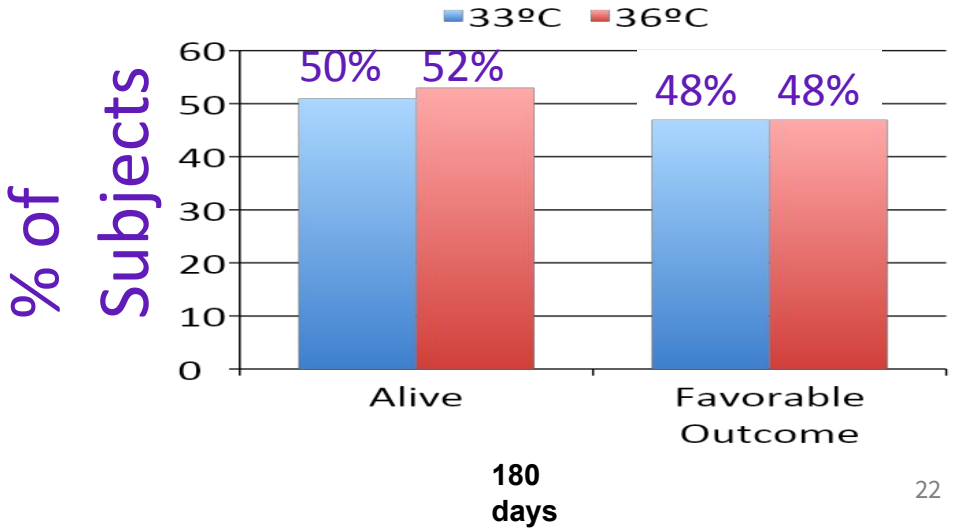
Nielsen 2013 - TTM Trial

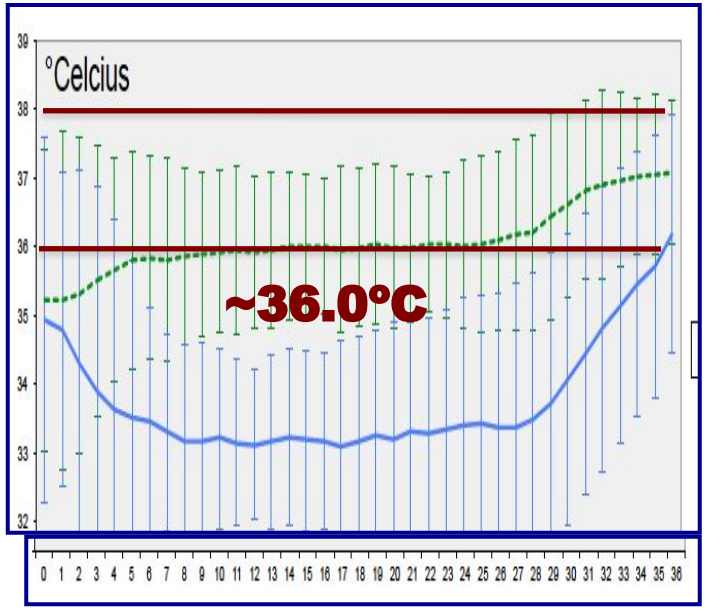
- This trial enrolled more patients than all prior trials combined (N=939)
- Treatment was successfully delivered
- No difference in primary or secondary outcomes



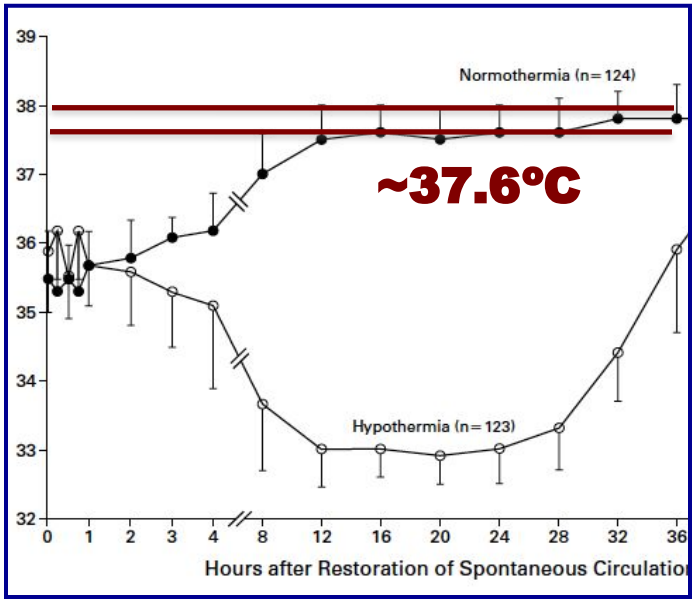


Marked differences in “control” group

Nielsen et al



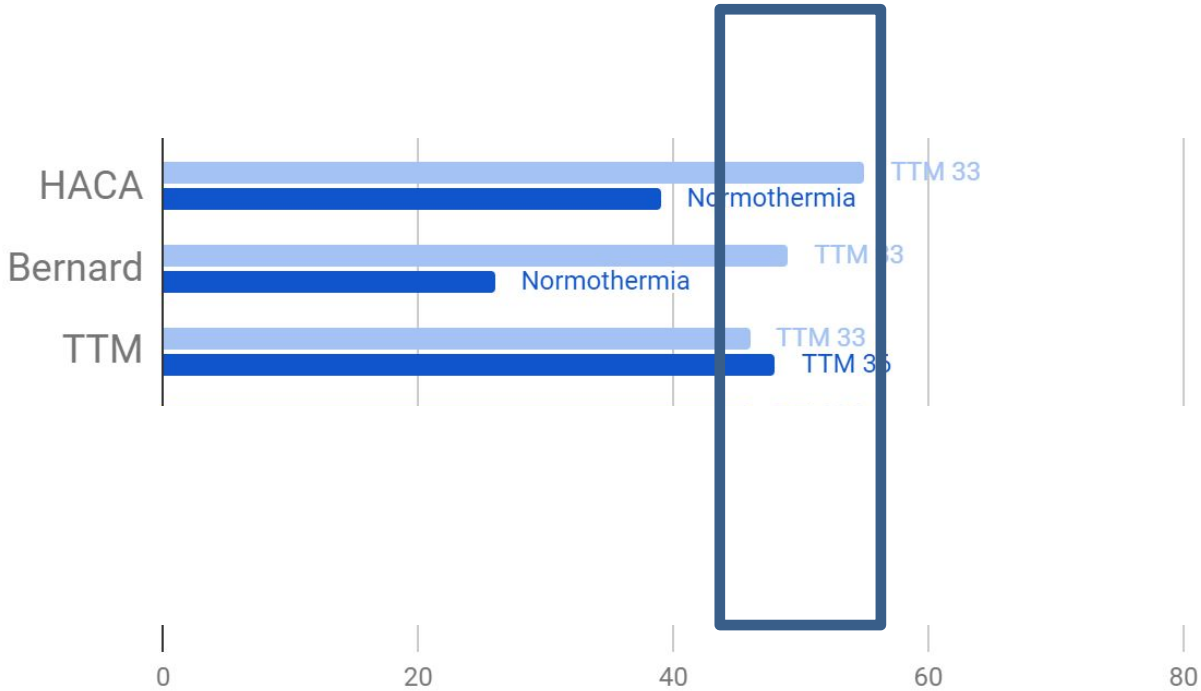
HACA study



Bernard et al: ~37.3°C

Large difference in maintenance temperatures

The Early adult studies.. Cooling outcomes



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Hyperion Trial

- 33°C vs 37°C for 24 hours non-shockable rhythm
- IHCA or OHCA, GCS 8
- Excluded no flow > 10 min, CPR > 60 min
- CPC at 90 days
- Approximately 284 in each treatment arm

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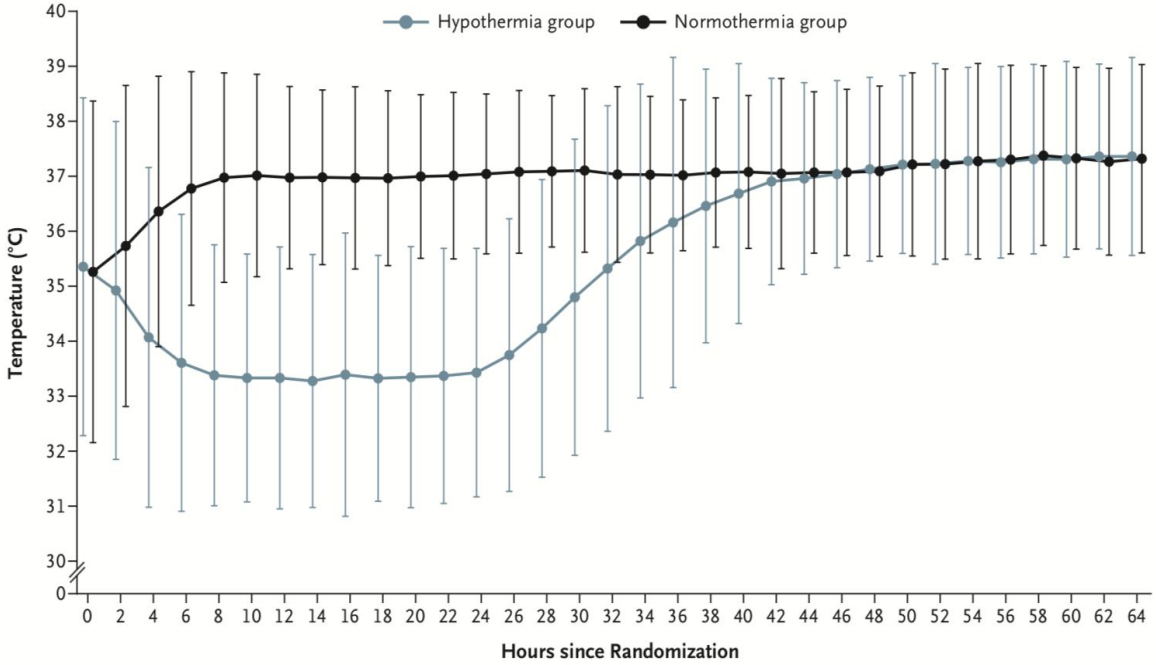
HYPERION Trial



No. at Risk																															
Hypothermia group	253	256	267	264	263	266	265	251	254	248	246	244	244	240	243	236	242	232	233	231	224	224	214	218	211	205	205	201	205	198	194	190	184
Normothermia group	271	274	269	273	273	268	265	266	262	262	256	250	256	252	249	242	241	241	231	231	230	227	215	216	209	200	203	186	194	183	185	185	187

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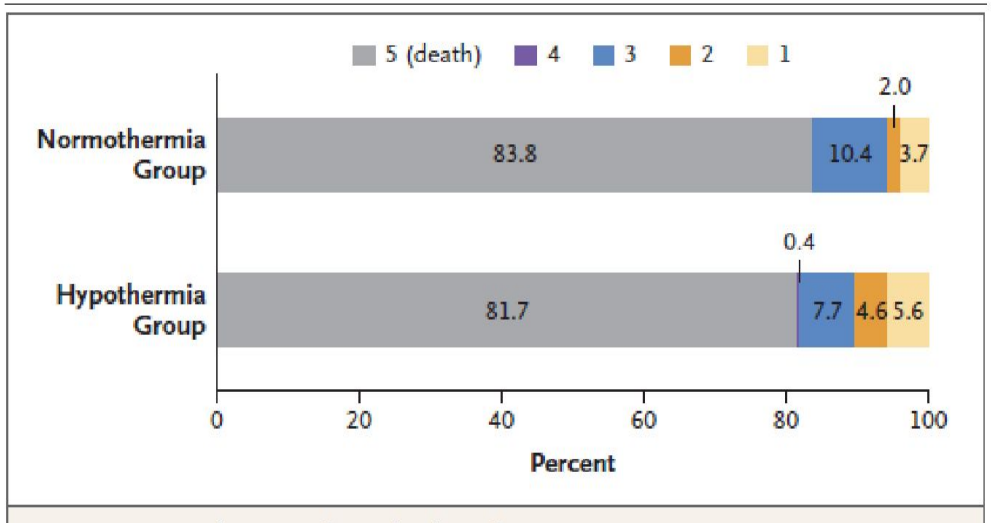
HYPERION - Outcomes

- Improved neurologic outcome
- No difference in mortality
- No difference in adverse events



5.7 %

P=0.04

10.2 %

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2021

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Population

Inclusion

- Age ≥ 18 years
- OHCA of presumed cardiac cause
- Sustained ROSC >20 min.
- Unconscious
  - Defined by the FOUR score motor response <4
  - Not able to obey verbal command
- No limitations in care
- < 3 hours after ROSC

Exclusion

- Unwitnessed cardiac arrest with initial rhythm asystole
- Temperature on admission <30°C
- On ECMO prior to ROSC
- Suspected pregnancy
- Intracranial bleed
- Severe COPD long-term O2

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Children's Hospital of Philadelphia

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After randomization

Hypothermia 33°C

40 h
Sedation
Ventilation

Normothermia with early treatment of fever < 37.8°C

72 h of fever treatment
96 h to neuroprognostication
Full organ support until discharge or WLST

Outcomes
Primary: death at 6 months
Secondary: modified Rankin at 6 months

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Children's Hospital of Philadelphia

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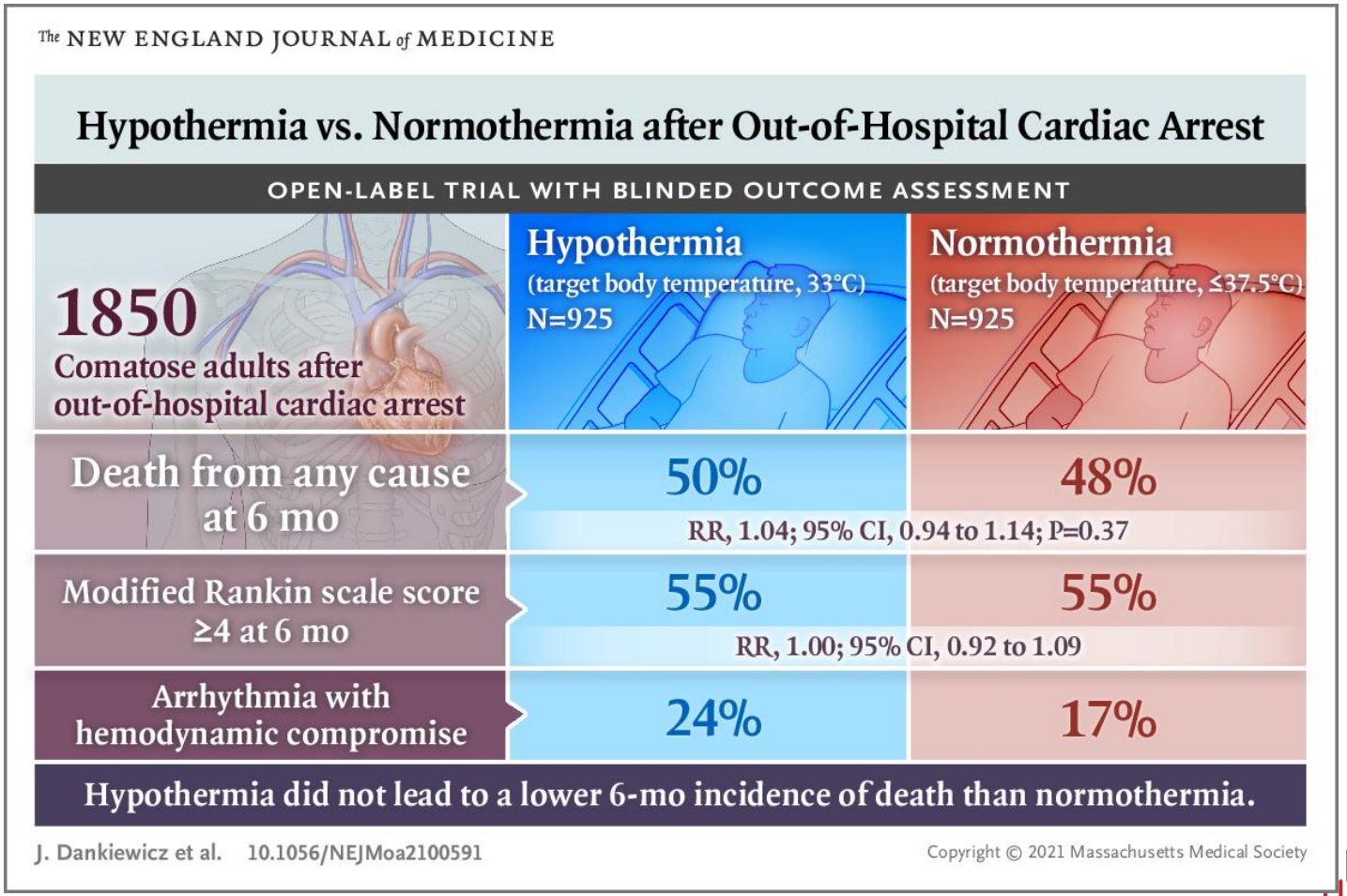

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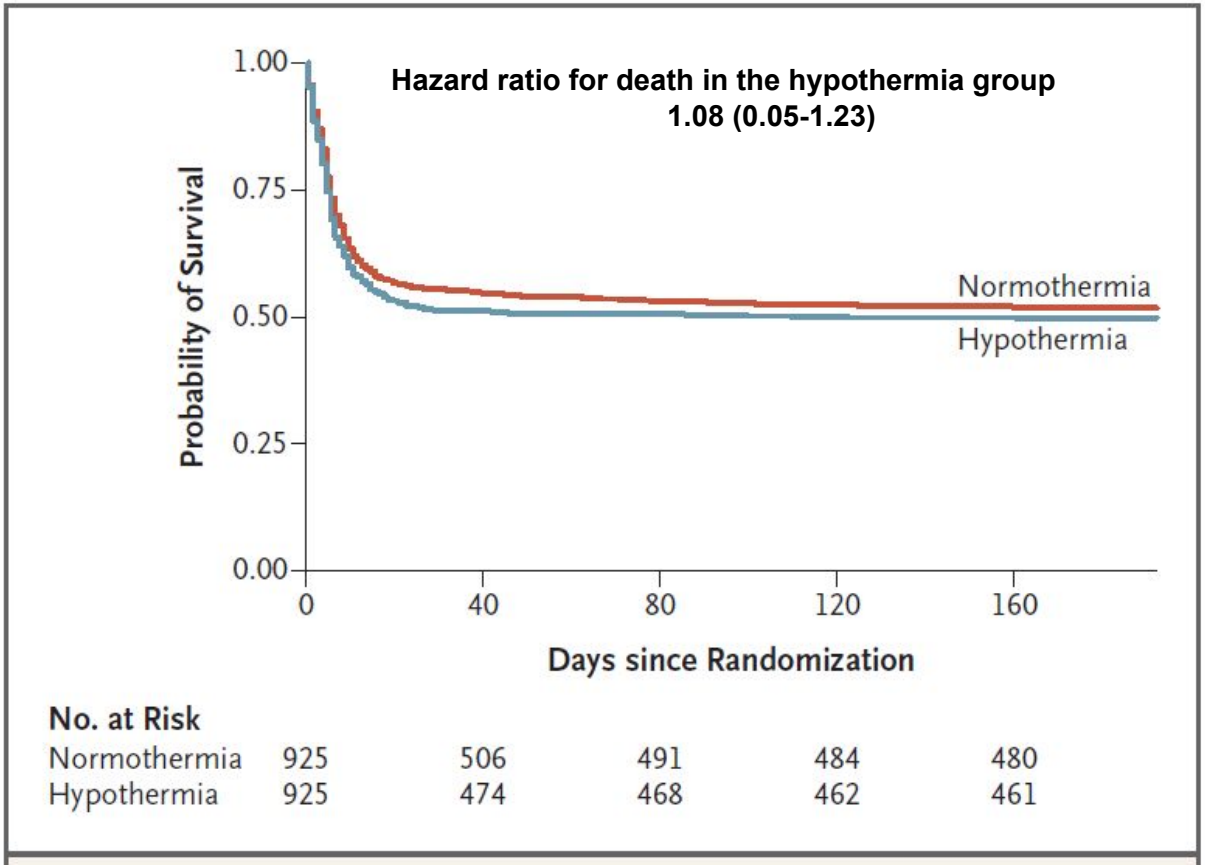

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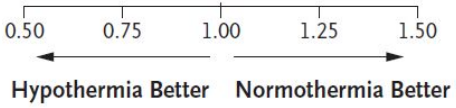
No mortality beneficial effect of hypothermia in any of the pre-specified subgroups

A Death at 6 Months

Subgroup	Hypothermia	Normothermia	Relative Risk of Death (95% CI)
	no. of patients		
All patients	925	925	1.04 (0.94–1.14)
Sex			
Male	738	729	1.03 (0.92–1.15)
Female	187	196	1.10 (0.94–1.29)
Age			
<65 yr	421	457	0.99 (0.83–1.18)
≥65 yr	504	468	1.04 (0.94–1.15)
Time to ROSC from cardiac arrest			
<25 min	419	416	1.09 (0.91–1.33)
≥25 min	506	509	1.02 (0.92–1.12)
Initial rhythm			
Nonshockable	259	231	1.04 (0.94–1.14)
Shockable	666	694	1.00 (0.87–1.15)
Shock on admission			
Not present	665	651	1.07 (0.95–1.23)
Present	260	274	1.01 (0.89–1.15)



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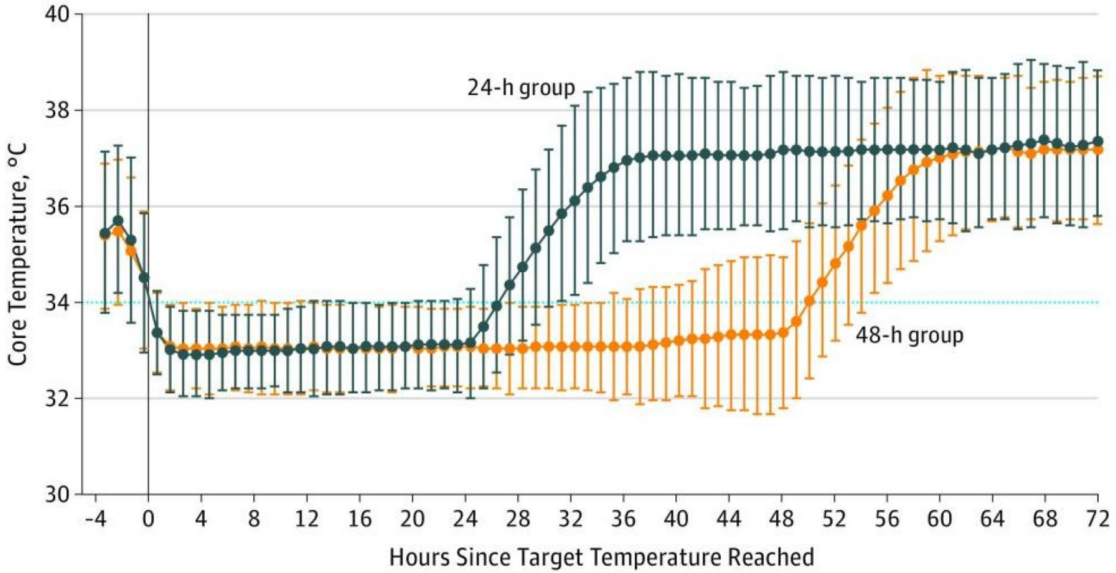
Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest

A Randomized Clinical Trial

Hans Kirkegaard, MD, PhD, DMSci, DEA
Urmet Arus, MD; Christian Storm, MD
Susanne Ilkjær, MD, PhD; Anni Nørgaa
Alf Inge Larsen, MD, PhD, FESC; Valdo
Timo Laitio, MD, PhD; Markus B. Skrif



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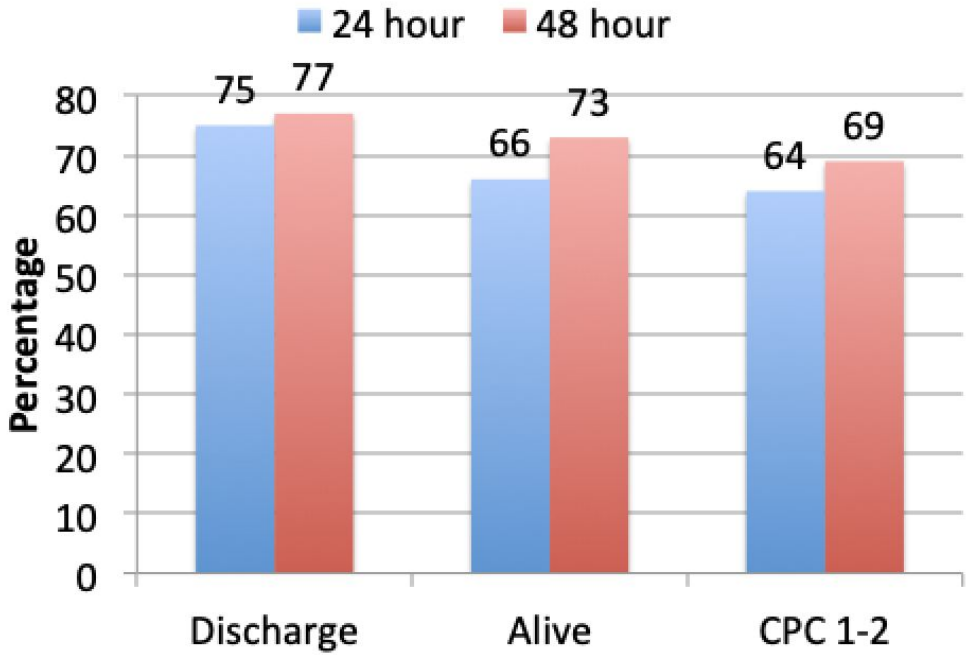
TTM for 48 vs. 24 Hours



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Kirkegaard 2017 JAMA 318: 341–350

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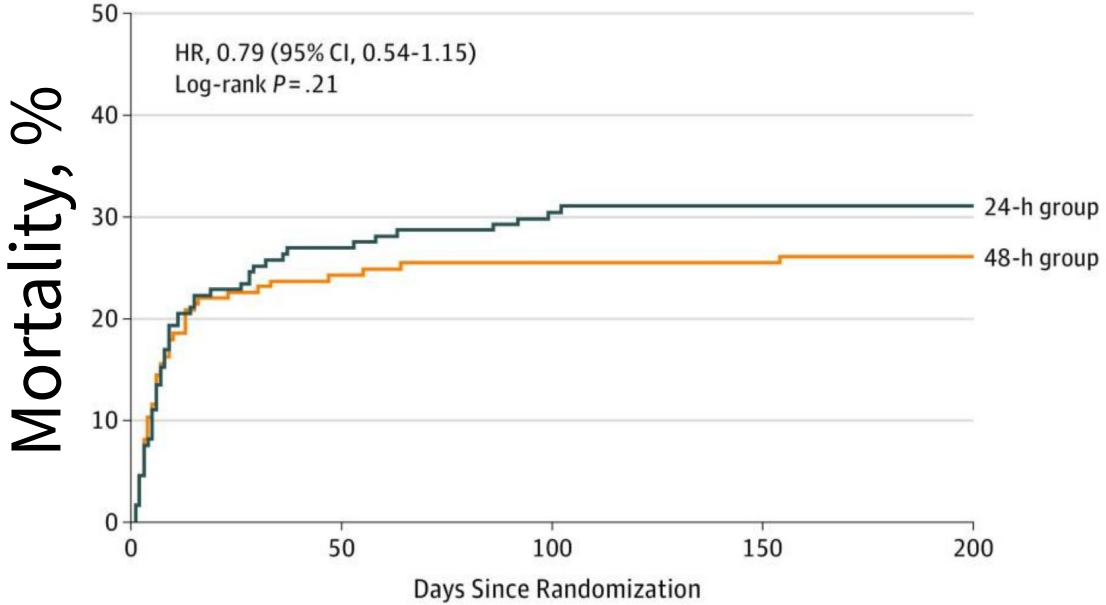
TTM for 48 vs. 24 Hours



Kirkegaard 2017 JAMA 318: 341–350

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

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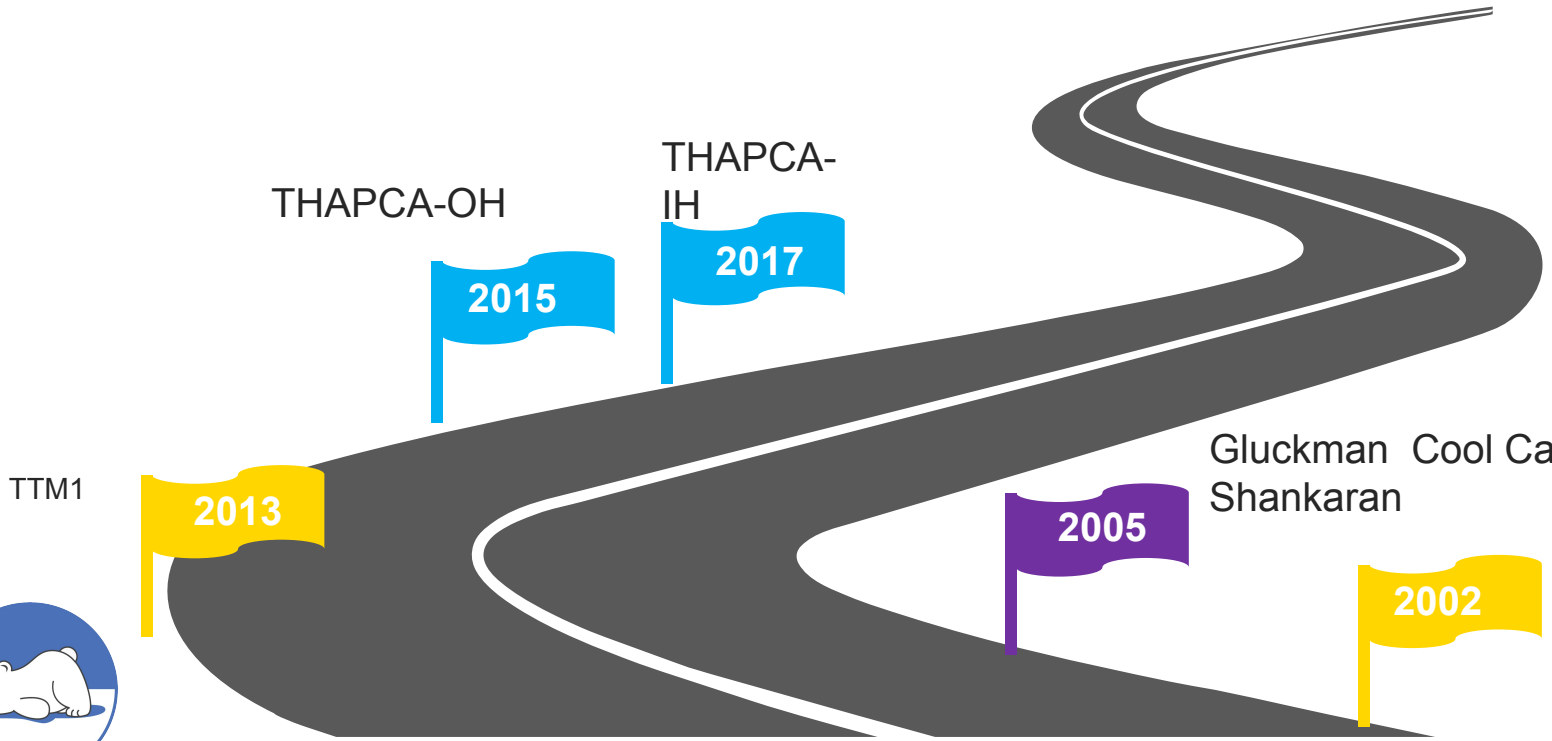
The Road to Pediatric TTM…



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children

Enrolled 2009 - 2012

ORIGINAL ARTICLE

Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children

Enrolled 2009 - 2015

Moler NEJM 2015

Moler NEJM 2017

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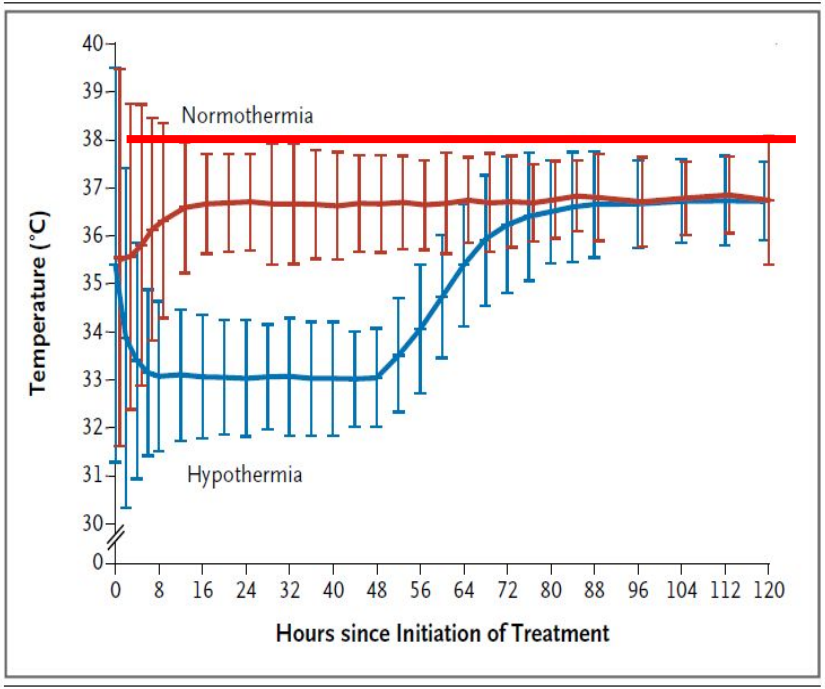
THAPCA Trials: IHCA and OHCA

- 2 days to 18 years old
- Motor GCS < 5
- CPR > 2 minutes
- Randomized within 6 h of ROC
- Intervention
  - 33°C or 36.8 °C for 48 h
  - Normothermia through 120h
- Primary Outcome
  - VABS > 70 at 1 year



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Moler, NEJM, 2015, 2017

THAPCA: In Hospital Cardiac Arrest

N = 329

RESULTS

Stopped for Futility

cause of futility after a review of interim efficacy analyses by the data and safety monitoring board.

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Moler NEJM 2017

Results

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Risk (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
Alive with VABS-II score ≥70 at 1 yr	48/133 (36)	48/124 (39)	−2.6 (−14.5 to 9.2)	0.92 (0.67 to 1.27)	0.63†
Detailed supportive analysis‡					0.85§
Death	65/133 (49)	67/124 (54)			
VABS-II score					
<45 or lowest possible	2/133 (2)	0/124			
45–69	18/133 (14)	9/124 (7)			
≥70	48/133 (36)	48/124 (39)			
Secondary outcomes					
Alive at 1 yr	81/166 (49)	74/161 (46)	2.8 (−8.0 to 13.7)	1.07 (0.85 to 1.34)	0.56†
Change in VABS-II score from baseline to 1 yr¶					0.70‖
Death	85/164 (52)	87/153 (57)			
Lowest possible VABS-II score	1/164 (1)	0/153			
Decrease in VABS-II score from baseline					
>30 points	12/164 (7)	8/153 (5)			
16–30 points	17/164 (10)	14/153 (9)			
≤15 points or improved	49/164 (30)	44/153 (29)			

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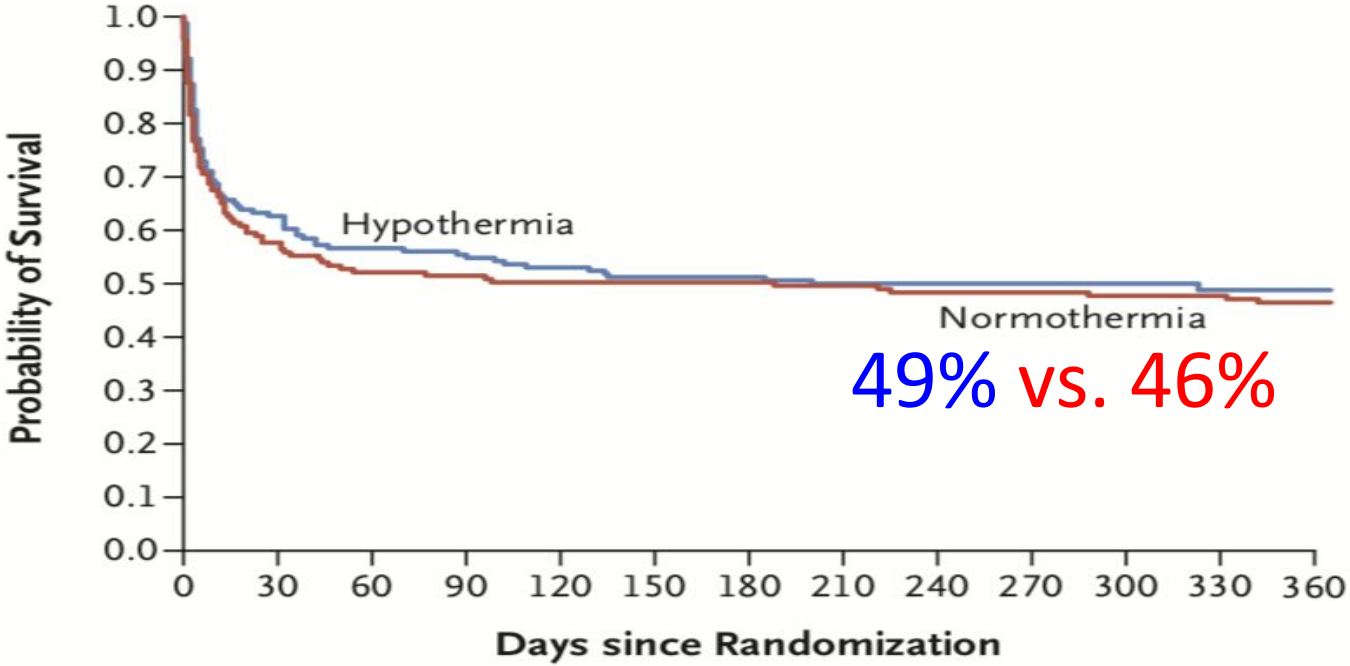
THAPCA- IHCA



No. at Risk

Hypothermia	166	104	94	92	88	85	85	83	83	83	83	81	81
Normothermia	163	94	84	82	80	80	80	79	77	77	76	76	74

THAPCA- OHCA

Table 1. Baseline Characteristics of the Patients before Randomization.*

Characteristic	Hypothermia Group (N=155)	Normothermia Group (N=140)
Demographic characteristics		
Age — yr		
Median	2.1	1.6
Interquartile range	0.6–10.1	0.4–7.0
Age category — no. (%)		
<2 yr	76 (49)	73 (52)
2 to <12 yr	48 (31)	45 (32)
≥12 yr	31 (20)	22 (16)
Male sex — no. (%)	102 (66)	94 (67)
Medical history — no. (%)		
No preexisting medical condition	81 (52)	71 (51)
Preexisting medical condition		
Lung or airway disease	33 (21)	34 (24)
Neurologic condition	30 (19)	19 (14)
Gastrointestinal disorder	19 (12)	22 (16)
Prenatal condition	15 (10)	22 (16)
Congenital heart disease	14 (9)	21 (15)
Other	34 (22)	37 (26)
Characteristics of the cardiac arrest		
Primary cause of the cardiac arrest — no. (%)		
Respiratory event	111 (72)	102 (73)
Cardiovascular event	14 (9)	18 (13)
Other	11 (7)	4 (3)
Unknown	19 (12)	16 (11)
Bystander witnessed cardiac arrest — no./total no. (%)	58/145 (40)	51/136 (38)
Bystander performed CPR — no./total no. (%)	101/149 (68)	85/134 (63)

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THAPCA- OHCA

Table 1. (Continued.)

Characteristic	Hypothermia Group (N=155)	Normothermia Group (N=140)
Initial rhythm noted by EMS or hospital — no. (%)		
Asystole	85 (55)	87 (62)
Bradycardia	9 (6)	10 (7)
Pulseless electrical activity	25 (16)	18 (13)
Ventricular fibrillation or tachycardia	14 (9)	9 (6)
Unknown	22 (14)	16 (11)
Time from cardiac arrest to CPR in 82 patients — min		
Median	3.0	2.0
Interquartile range	0.0–7.0	0.0–8.0
Duration of CPR in 186 patients — min		
Median	23.0	28.0
Interquartile range	15.0–35.0	19.0–45.0
First hospital patient arrived at was the study hospital — no. (%)	45 (29)	43 (31)
Chest compressions still required at time of arrival at first hospital — no./total no. (%)	97/152 (64)	100/137 (73)
No. of doses of epinephrine		
Administered by EMS in 270 patients†		
Median	2.0	1.0
Interquartile range	0.0–3.0	0.0–2.0
Administered at hospital in 289 patients†		
Median	1.0	2.0
Interquartile range	0.0–3.0	0.0–4.0
All doses administered by EMS and at hospital in 265 patients		
Median	3.0	3.0
Interquartile range	2.0–4.5	2.0–5.0

* CPR denotes cardiopulmonary resuscitation, and EMS emergency medical services.
† P<0.05 for the comparison between the two groups.

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THAPCA: Out Of Hospital Cardiac Arrest

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Likelihood (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
Alive with VABS-II score ≥70 at 1 yr	27/138 (20)	15/122 (12)	7.3 (−1.5 to 16.1)	1.54 (0.86 to 2.76)	0.14†
Detailed supportive analysis					0.14‡
Death	87/138 (63)	88/122 (72)			
Disability					
Profound§	16/138 (12)	11/122 (9)			
Moderate-to-severe¶	8/138 (6)	8/122 (7)			
Good functional status‖	27/138 (20)	15/122 (12)			
Secondary outcomes					
Alive at 1 yr	57/151 (38)	39/136 (29)	9.1 (−1.8 to 19.9)	1.29 (0.93 to 1.79)	0.13†
1-yr change in VABS-II score from baseline					0.13**
Death	94/151 (62)	97/134 (72)			
Lowest possible VABS-II score	6/151 (4)	1/134 (1)			
Decrease in VABS-II score					
>30 points	19/151 (13)	15/134 (11)			
16–30 points	11/151 (7)	4/134 (3)			
≤15 points or improved	21/151 (14)	17/134 (13)			

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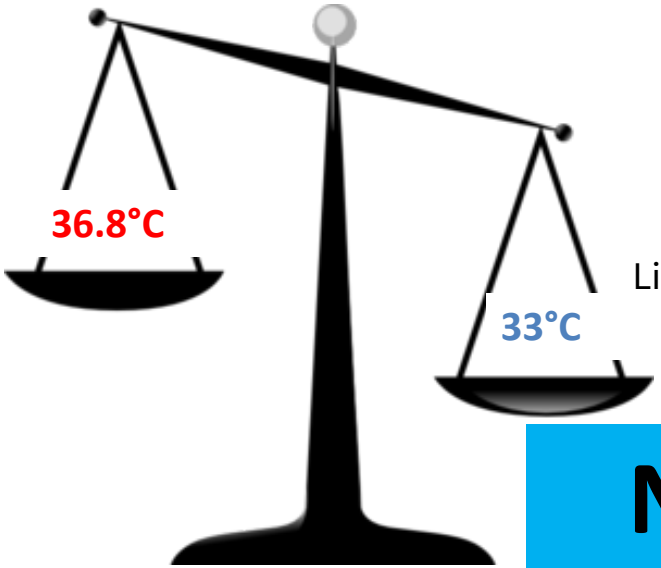
THAPCA: OHCA- Did it work?

Favorable Neuro (VABS >70) at 1 year (n=260)

Normothermia: 12%

Hypothermia: 20%

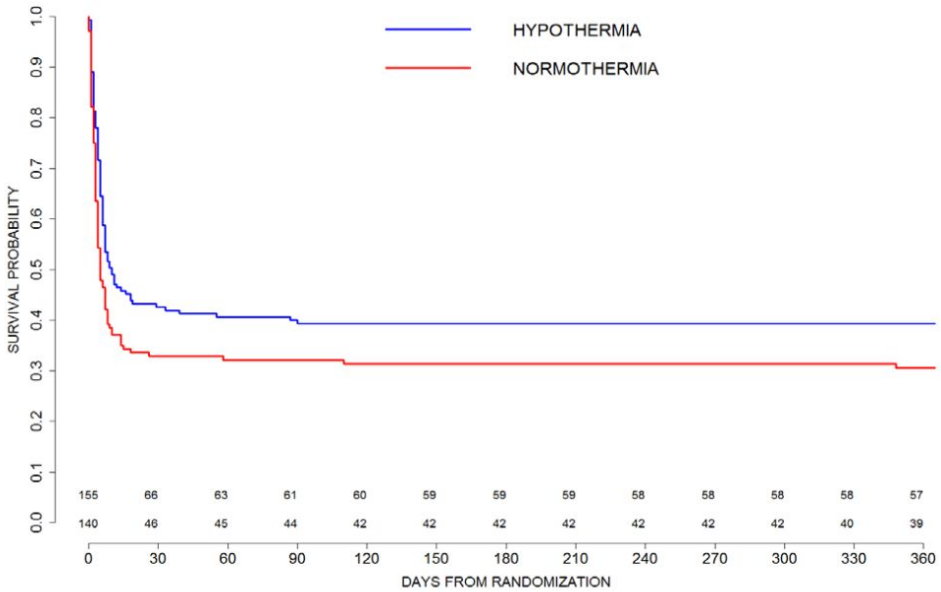


Likelihood Ratio 1.54 (0.9-2.8), **p=0.14**

No statistically significant difference in outcomes

THAPCA: OHCA- Survival Over Time

Significant Difference



Log-rank test, p=0.04

Moler FW, N Engl J Med 2015.


SAFETY

THAPCA OHCA Safety

Table 3. Safety Outcomes within 7 Days after Randomization and 28-Day Mortality.

Outcome	Hypothermia Group (N=153)	Normothermia Group (N=139)	P Value*
Blood-product use — no./total no. (%)			
Any	83/153 (54)	74/138 (54)	0.92
Type			
Cryoprecipitate	13/153 (8)	12/137 (9)	0.94
Fresh-frozen plasma	50/153 (33)	41/138 (30)	0.59
Packed red cells or whole blood	65/153 (42)	59/137 (43)	0.92
Platelets	19/153 (12)	12/137 (9)	0.32
Arrhythmias — no./total no. (%)			
Serious	17/153 (11)	13/137 (9)	0.66
Type			
Asystole	6/153 (4)	5/137 (4)	0.91
Atrial (supraventricular tachycardia, atrial flutter, junctional ectopic tachycardia)	4/153 (3)	2/137 (1)	0.53
Pulseless electrical activity	1/153 (1)	0/137	0.53
Ventricular (sustained ventricular tachycardia >30 sec, ventricular fibrillation, torsades)	5/153 (3)	5/137 (4)	0.86
Other	7/153 (5)	2/137 (1)	0.14
Culture-proven infections			
Any — no./total no. (%)	70/153 (46)	54/137 (39)	0.28
No. of infections	109	76	
No. of days at risk	978	765	
[illegible]	[illegible]	[illegible]	[illegible]
All-cause mortality 28 days — no./total no. (%)	87/153 (57)	93/139 (67)	0.08

THAPCA OHCA Safety

	Hypothermia N = 153	Normothermia N = 139	P-value[1]
Hypokalemia[2]	35/153 (23%)	19/139 (14%)	0.04
Hyperkalemia[2]	3/153 (2%)	7/139 (5%)	0.17
Hypoglycemia[2]	12/153 (8%)	12/139 (9%)	0.81
Hyperglycemia[2]	15/153 (10%)	16/139 (12%)	0.64
Hypophosphatemia[2]	7/153 (5%)	6/139 (4%)	0.92
Neutropenia[2]	4/153 (3%)	1/139 (1%)	0.26
Thrombocytopenia[2]	16/153 (10%)	2/139 (1%)	0.001
Clinical or Electrographic Seizure[3]	62/153 (41%)	49/139 (35%)	0.36
Repeat Cardiac Arrest[3]	10/153 (7%)	13/139 (9%)	0.38
Received any form of Renal Replacement Therapy[3]	3/153 (2%)	10/139 (7%)	0.03

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

[2] 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.

THAPCA IHCA Safety

Table 3. Safety Outcomes within 7 Days after Randomization and 28-Day Mortality.

Outcome	Hypothermia Group (N=161)	Normothermia Group (N=160)	P Value*
Blood-product use — no. (%)			
Any	139 (86)	140 (88)	0.76
Cryoprecipitate	53 (33)	67 (42)	0.10
Fresh-frozen plasma	96 (60)	92 (58)	0.70
Packed red cells or whole blood	129 (80)	133 (83)	0.49
Platelets	106 (66)	104 (65)	0.88
Arrhythmias — no. (%)			
Serious	25 (16)	23 (14)	0.78
Asystole	3 (2)	5 (3)	0.50
Atrial†	7 (4)	4 (2)	0.39
Pulseless electrical activity	3 (2)	5 (3)	0.50
Ventricular‡	8 (5)	7 (4)	0.81
Other	11 (7)	9 (6)	0.66
Culture-proven infections			
Any — no. (%)	44 (27)	46 (29)	0.78
No. of infections	55	52	
No. of days at risk	1107	1059	
No. of infections per 100 days (95% CI)§	5.0 (3.7–6.5)	4.9 (3.7–6.4)	1.00
All-cause mortality at 28 days — no. (%)	59 (37)	66 (41)	0.40

THAPCA IHCA Safety

Table S6: Serious adverse events

	Hypothermia group (n=284)	Normothermia group (n=297)	HR [95%CI]	*P* value
Renal replacement therapy between days 0 and 7, (%)	38 (13.4)	37 (12.4)	1.08 [0.69 ; 1.68]	0.74
Acute pulmonary edema secondary to left ventricular dysfunction between days 0 and 7, (%)	19 (6.7)	26 (8.7)	0.75 [0.42 ; 1.34]	0.33
Seizures between days 0 and 7, (%)	67 (23.6)	72 (24. 2)	0.95 [0.69 ; 1.30]	0.73
Severe cardiac arrhythmia between days 0 and 7, (%)	35 (12.3)	31 (10.4)	1.19 [0.74 ; 1.91]	0.48
Severe bleeding between days 0 and 7, (%)	16 (5.6)	17 (5.7)	0.99 [0.50 ; 1.94]	0.97
Bacteremia between days 0 and 28, (%)	12 (4.2)	11 (3.7)	1.14 [0.50 ; 2.57]	0.76
CVC infection between days 0 and 28, (%)	4 (1.4)	2 (0.6)	-	-
Urinary tract infection days 0 and 28, (%)	9 (3.2)	12 (4.1)	0.78 [0.33 ; 1.84]	0.57
Other nosocomial infections between days 0 and 28, (%)	5 (1.8)	5 (1.7)	-	-
Early-onset pneumonia[a], (%)	73 (25.7)	65 (21.9)	1.19 [0.87 ; 1.63]	0.28
VAP**, (%)	44 (15.5)	35 (11.8)	1.34 [0.86 ; 2.01]	0.19
Vasopressors between days 0 and 7, (%)	233 (82.0)	241 (81.1)	1.01 [0.92 ; 1.11]	0.81

THAPCA OHCA: Limitations

Selection Criteria

Coma and motor GCS <5

No stratification of injury severity

Underpowered

85% Power to detect a

20% improvement in 1 year Neurologic Outcome

Intervention

Was 48 hours the right duration

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Resuscitation 2018

Clinical paper

Therapeutic hypothermia after paediatric cardiac arrest: Pooled randomized controlled trials☆

Barnaby R. Scholefield[a,*], Faye S. Silverstein[b], Russell Telford[c], Richard Holubkov[c], Beth S. Slomine[d], Kathleen L. Meert[e], James R. Christensen[d], Vinay M. Nadkarni[f], J. Michael Dean[c], Frank W. Moler[b]

Table 2
Primary and Secondary Outcomes.*.

	Treatment Assigned				
	Hypothermia	Normothermia	Risk Difference	Relative Risk	P Value
Primary Outcome					
Survival at 12 months with VABS ≥ 70	75/271 (28%)	63/246 (26%)	2.1 (-5.6, 9.7)	1.08 (0.81, 1.42)	0.61†
One year status (detailed)					0.40‡
Death	152/271 (56%)	155/246 (63%)			
Profound disability (VABS < 45 or lowest possible)§	18/271 (7%)	11/246 (4%)			
Moderate to severe disability (VABS 45-69)¶	26/271 (10%)	17/246 (7%)			
Good functional status (VABS ≥ 70)‖	75/271 (28%)	63/246 (26%)			

2019: International Liaison Committee on Resuscitation

- For infants and children with OHCA, **TTM be used to target a central temp < 37.5° C**
- Inconclusive evidence to support or refute the use of **TTM 32°C to 34°C** compared to **TTM 36°C to 37.5 °C**
- The task force **preferred the used of TTM 32°C to 34°C** as opposed to TTM 36°C to 37.5 °C

Soar et al., Circulation, 2019

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

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AHA PALS Guidelines 2019: Temperature

For infants and children < 18 years of age who are comatose after **IHCA** or **OHCA** it is reasonable

5 days of normothermia (36°C to 37.5°C)

OR

2 days of hypothermia (32°C to 34°C)

followed by 3 days of continuous normothermia

There is insufficient evidence to support a recommendation regarding treatment duration

Duff et al., Circulation, 2019, Topjian Circulation 2020

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The NEW ENGLAND JOURNAL of MEDICINE

Hyperion

for

A bit more like kids

J.-B. Lascarrou, H. Merdji, A. Le Gouge, G. Colin, G. Grillet, P. Girardie, E. Coupez, P.-F. Dequin, A. Cariou, T. Boulain, N. Brule, J.-P. Frat, P. A. N. Pichon, M. Landais, G. Plantefeve, J.-P. Quenot, J.-C. Chakarian, M. S. S. Legriel, J. Letheulle, D. Thevenin, A. Desachy, A. Delahaye, V. Botoc, S. F. Martino, B. Giraudeau, and J. Reignier, for the CRICS-TRIGGERSEP G

Lascarrou JB, et al. NEJM 2019

TTM2

Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

J. Dankiewicz, T. Cronberg, G. Lilja, J.C. Jakobsen, H. Levin, S. Ullén, C. Rylander,

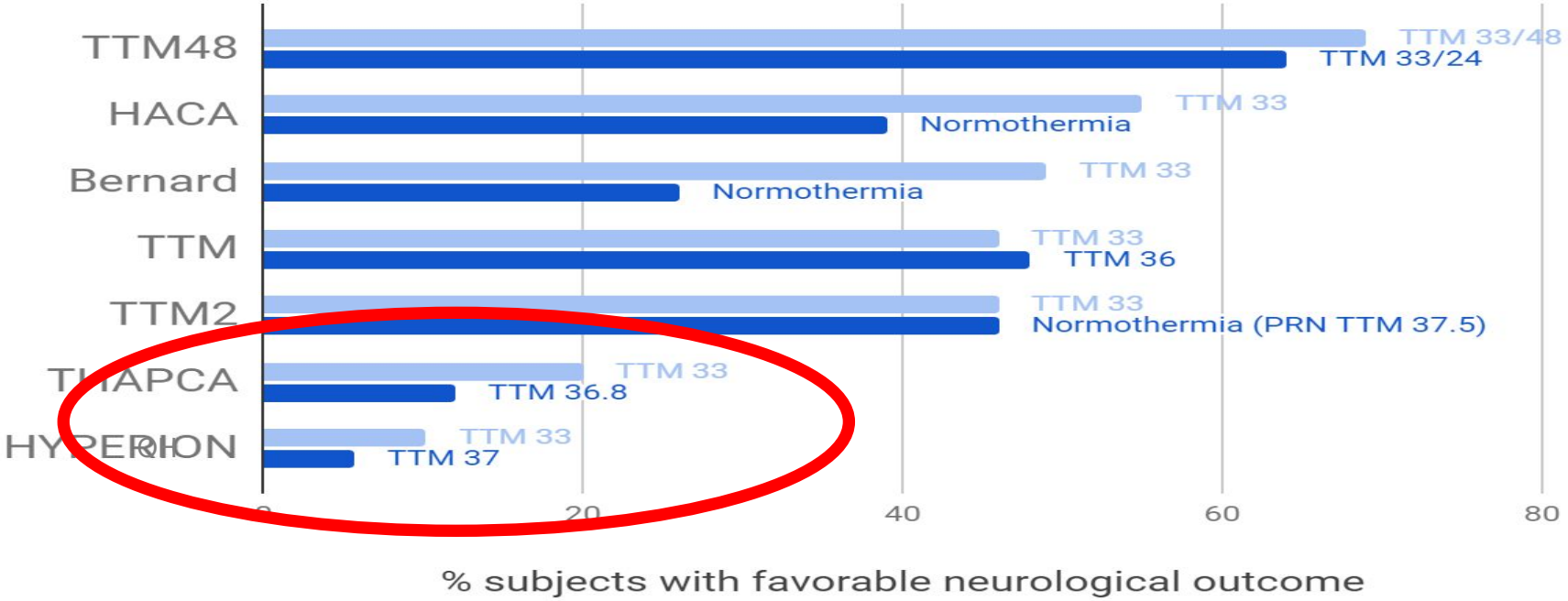
Not so much like kids

S. Christensen, M. Haenggi, A. Levis, A. Lundin, J. During, S. Schmidbauer, T.R. Keeble, G.V. Karamasis, C. Schrag, E. Faessler, O. Smid, M. Otáhal, M. Maggiorini, P.D. Wendel Garcia, P. Jaubert, J.M. Cole, M. Solar, O. Borgquist, C. Leithner, S. Abed-Maillard, L. Navarra, M. Annborn, J. Undén, I. Brunetti, A. Awad, P. McGuigan, R. Bjørkholt Olsen, T. Cassina, P. Vignon, H. Langeland, T. Lange, H. Friberg, and N. Nielsen, for the TTM2 Trial Investigators*

How do we compare to adults?

Characteristic	Hyperion	THAPCA-OH	TTM2
Age (years)	**67**	**2**	**64**
Male	**64%**	**66%**	**80%**
Witnessed	**93%**	**39%**	**91%**
Bystander CPR	**70%**	**65%**	**80%**
First Doc rhythm Shockable	**0%**	**7%**	**73%**
Non-shockable	**90%**	**85%**	**24%**
CPR duration (min)	**16 (10-26)**	**26 (15-45)**	**25 (16-40)**
Cause of Arrest respiratory	**55%**	**72%**	**n/a**

How do we put this all together?



Hypothermia vs No Hypothermia

Pediatric Quality of Life HRQoL Measure	Unadjusted Mean (95% CI) HRQoL Measure			Adjusted Mean (95% CI) HRQoL Measure			
	Therapeutic Hypothermia	No Therapeutic Hypothermia	Mean Difference	Therapeutic Hypothermia	No Therapeutic Hypothermia	Mean Difference[a]	p

Comparison to Normative Data

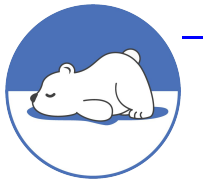
Domain	Normative Data[a] ($n = 1,455$)	No Therapeutic Hypothermia ($n = 78$)	Mean Difference[b] (95% CI)	p	Therapeutic Hypothermia ($n = 50$)	Mean Difference[c] (95% CI)	p
Physical Summary	84.5 (12.3)	65.9 (35.9)	18.6 (15.3–21.9)	< 0.001	78 (26.4)	6.5 (2.8–10.1)	< 0.001
Psychosocial Summary	77.1 (14.1)	67.5 (26.1)	9.6 (6.2–13)	< 0.001	77.9 (16.9)	−0.8 (−4.8 to 3.2)	0.70

Total Summary

Minimally Clinically Important Difference: physical 6.9 psychosocial 5.5

Summary

- TTM (32-36°C) x 24 hrs in adults (2 RCT)
  - 33°C not superior to 36°C for lightly injured (1 RCT)
  - 33°C is superior to 37°C for more severe (1 RCT)
  - Very early hypothermia – mostly neutral (5 RCT)
  - *TTM2 – results later this year (1 RCT)*
  - Signal for 48 hrs better than 24 hrs (1 RCT)
- Usual durations are 33°C x 48 hrs in pediatrics
  - For pediatric OHCA favors 33°C x 48 hrs (1 RCT)
  - For pediatric IHCA neutral for 33°C x 48 hrs (1 RCT)
- Usual durations are 33°C x 72 hrs in neonates
  - For HIE in neonates, favors 33°C x 72 hrs (8-10 RCT)



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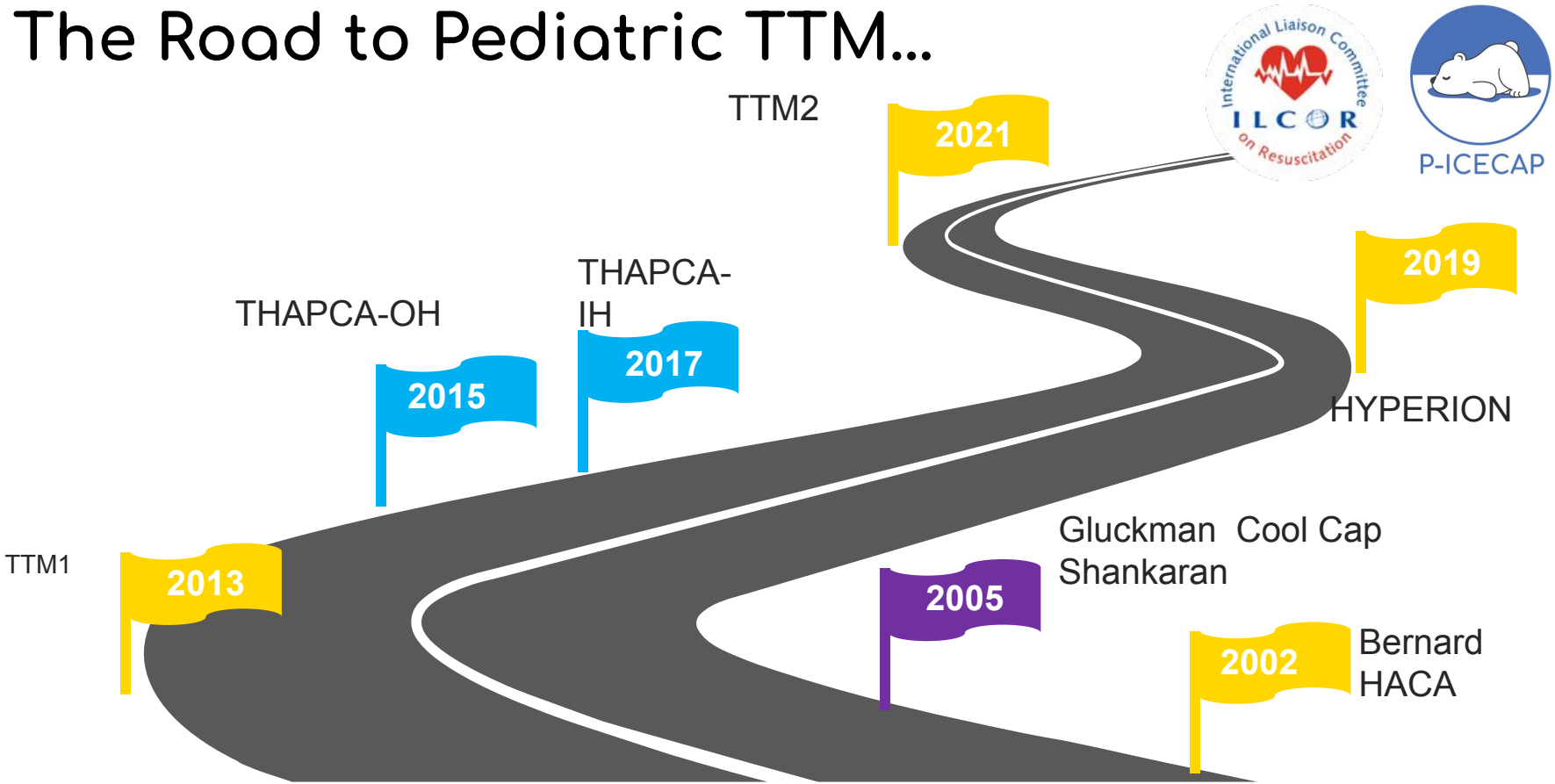
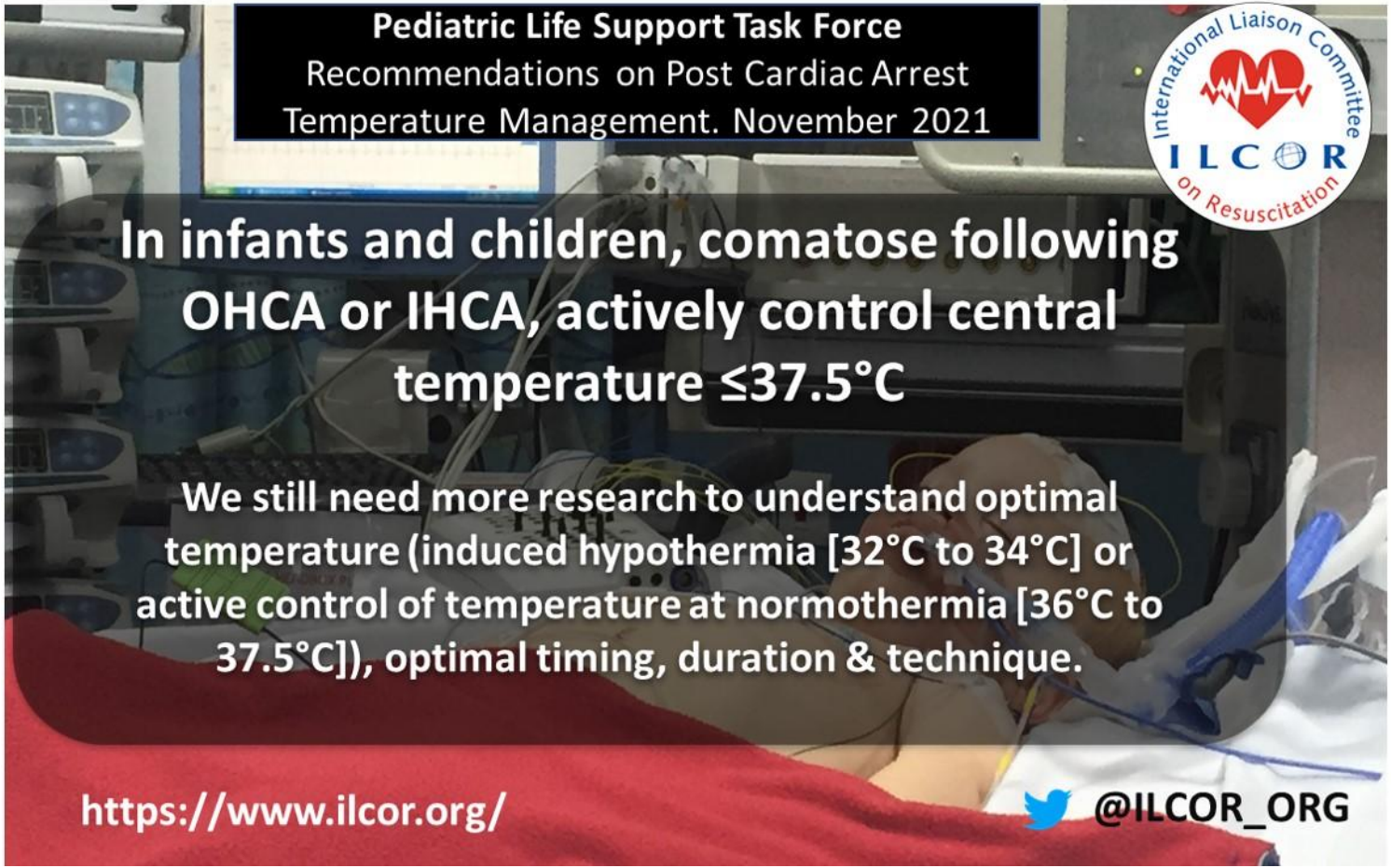
The Road to Pediatric TTM…




Pediatric Life Support Task Force
Recommendations on Post Cardiac Arrest Temperature Management. November 2021
International Liaison Committee on Resuscitation
ILCOR
In infants and children, comatose following OHCA or IHCA, actively control central temperature ≤37.5°C
We still need more research to understand optimal temperature (induced hypothermia [32°C to 34°C] or active control of temperature at normothermia [36°C to 37.5°C]), optimal timing, duration & technique.
https://www.ilcor.org/
@ILCOR_ORG

Questions and Discussion

Screening and Enrollment for P-ICECAP

Moni Weber

2 Truths and a Lie About Moni

P-ICECAP

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

SIREN

Inclusion Criteria

- Age 2 days (CGA≥ 38 weeks) to < 18 years
- Chest compressions for at least 2 minutes
- Coma or encephalopathy after resuscitation from OHCA
- Requires mechanical ventilation through endotracheal tube or tracheostomy
- Definitive temperature control device initiated
- Randomization within 6 hours of ROSC
- Informed consent from LAR including intent to maintain life support for 120 hours

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First Truth/Lie about Moni

I know how to juggle

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Exclusion Criteria

- Glasgow Coma Motor Score (GCMS) = 6
- LAR does not speak English or Spanish
- Duration of CPR > 60 minutes
- Severe hemodynamic instability requiring continuous infusion of epinephrine or norepinephrine of 2 µg/kg/minute or initiation of ECMO
- Pre-existing severe neurodevelopmental deficits with PCPC =5 or progressive degenerative encephalopathy
- Pre-existing terminal illness, unlikely to survive to one year

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Exclusion Criteria Cont.

- Cardiac arrest associated with brain, thoracic, or abdominal trauma
- Active and refractory severe bleeding prior to randomization
- Extensive burns or skin lesions incompatible with surface cooling
- Planned early withdrawal of life support before 120 hours
- Sickle cell anemia
- Pre-existing cryoglobulinemia
- Non-fatal drowning in ice covered water

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Exclusion Criteria Cont.

- Central nervous system tumor with ongoing chemotherapy
- Previous enrollment in P-ICECAP trial
- Prisoner
- Chronic hypothermia
- New post-cardiac arrest diabetes insipidus
- Known pregnancy

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Second Truth/Lie about Moni

My first research job included entering data as 0s and 1s

Screening for P-ICECAP

Screen ALL surviving out-of-hospital pediatric cardiac arrests

Screen in real time! (*Use Screen Failure Form for those not included in study*)

This means you will need to set up a system to be notified of all such patients as they arrive.

- U Mich: communicate with Survival flight to send out a group page going to all study team members
- Make connections in your ED and/ or your P-ICU
- Administrative sources
- Be creative for your hospital system

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Screen Failure Version 1 (23-Mar-2022) Page 1 of 3

Instructions:

Enter all patients who had an out-of-hospital cardiac arrest and were admitted alive to the PICU.

Patient Information:

A01		Screen failure ID *Assigned by WebDCU*	
A02		Site ID *Derived by WebDCU*	
A03		Site name *Derived by WebDCU*	
A04		Screening date	__ __-__ __ __
A05		Birth sex	○ Male
A06		Ethnicity	○ Hispanic or Latin ○ Not Hispanic or L ○ Unknown
A07		Race *Check all that apply.*	☐ American Indian ☐ Asian ☐ Black or African A ☐ Native Hawaiian ☐ White ☐ Unknown
A08		Age	_____
A08u		Age units	_____ (For
A09		Informed consent	○ Not approached ○ Declined ○ Obtained
A10	*If A09 is 'Not approached' or 'Declined'*	Reason not approached or declined	
A11	*If A09 is 'Obtained'*	Date of informed consent	__ __-__ __ __
A21		Screening completed within six hours of ROSC	○ No
B01		Reason patient was not randomized	○ A: Site operation ○ B: Patient eligibi ○ C: Both A and B ○ D: Other

If this is a source document, sign and date: _____ *Print name* _____ *Signature*

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Screen Failure Version 1 (23-Mar-2022) Page 2 of 3

Site operation issues

B02	*If B01 is A or C*	Brief explanation of site operation issues *Site operation issues include staffing issues or limitations*	

Inclusion criteria

Q11	*If B01 is B or C*	Age 2 days to less than 18 years *Age defined with corrected gestational age of at least 36 weeks.*	○ No	○
Q12		Chest compressions for at least 2 minutes	○ No	○
Q13		Coma or encephalopathy after resuscitation from OHCA	○ No	○
Q14		Requires mechanical ventilation *Airway must be stable via an endotracheal tube or a tracheostomy tube.*	○ No	○
Q15		Definitive temperature control device initiated	○ No	○
Q16		Possible to randomize within 6 hours from ROSC	○ No	○

Exclusion criteria

Q51	*If B01 is B or C*	Informed consent from LAR not obtained	○ No	○
Q52		Glasgow coma motor score equal to 6	○ No	○
Q53		LAR does not speak English or Spanish	○ No	○
Q54		Duration of OHCA CPR greater than 60 minutes	○ No	○
Q55		Severe hemodynamic instability *Instability that includes the requirement of continuous infusion of epinephrine or norepinephrine of 2 µg/kg/minute or initiation of ECMO.*	○ No	○
Q56		Pre-existing severe neurodevelopmental deficits *Severe neurodevelopment deficits include a PCPC score equal to 5 or progressive degenerative encephalopathy.*	○ No	○
Q57		Pre-existing terminal illness, unlikely to survive to one year	○ No	○
Q58		Cardiac arrest associated with brain, thoracic, or abdominal trauma	○ No	○
Q59		Active and refractory severe bleeding prior to randomization	○ No	○
Q60		Extensive burns or skin lesions incompatible with surface cooling	○ No	○

If this is a source document, sign and date: _____ *Print name* _____ *Signature* __-__-__

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Screen Failure Version 1 (23-Mar-2022) Page 3 of 3

Q61	*If B01 is B or C*	Planned early withdrawal of life support before 120 hours	○ No	○ Yes
Q62		Sickle cell anemia	○ No	○ Yes
Q63		Pre-existing cryoglobulinemia	○ No	○ Yes
Q64		Non-fatal drowning in ice covered water	○ No	○ Yes
Q65		Central nervous system tumor with ongoing chemotherapy	○ No	○ Yes
Q66		Previous enrollment in P-ICECAP trial	○ No	○ Yes
Q67		Prisoner	○ No	○ Yes
Q68		Chronic hypothermia	○ No	○ Yes
Q69		New post-cardiac arrest diabetes insipidus	○ No	○ Yes
Q70		Known pregnancy	○ No	○ Yes

Other reason for screen failure

D01	*If B01 is D*	Other reason patient was not randomized	

General comments

If this is a source document, sign and date: _____ *Print name* _____ *Signature* __-__-____ *dd-mmm-yyyy*

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Forms You Need to Enter Into WebDCU in Order to Enroll

- **FIRST**: Subject Enrollment Form - *Generates the subject ID*
- **SECOND**: Eligibility Form - *Documents that the patient meets all inclusion and no exclusion criteria*
- **THIRD**: Randomization Form - *Once this form is submitted treatment assignment will appear on the form*

FIRST: Subject Enrollment Form

There are only 2 pieces of information needed:

- Date of Birth
- Date of Informed Consent Signature
- **Submitting this form gets you your Study ID!**

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Subject Enrollment CRF

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Subject Enrollment Version 1 (23-Mar-2022) Page 1 of 1

Q01	Site name	
Q02	Subject ID *Assigned by WebDCU.*	
P51	Birth sex assigned *Derived from Form 296 Demographics Q01.*	○ Male ○ Female
Q04	Ethnicity *Derived from Form 296 Demographics Q04.*	○ Hispanic or Latino ○ Not Hispanic or Latino ○ Unknown
Q05	Race *Check all that apply* *Derived from Form 296 Demographics Q05.*	☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Unknown
P52	Day of birth *Programming note: 1 – 31*	
P53	Month of birth *Programming note: 1 – 12*	
P54	Year of birth	_____
Q07	Informed consent was obtained prior to study participation	○ No ○ Yes
Q08	Date of informed consent	__ __-__ __ __-__ __ __ __ dd-mmm-yyyy

General comments

If this is a source document, sign and date:	_____ *Print name*	_____ *Signature*	__ __-__ __ __-__ __ __ __ *dd-mmm-yyyy*

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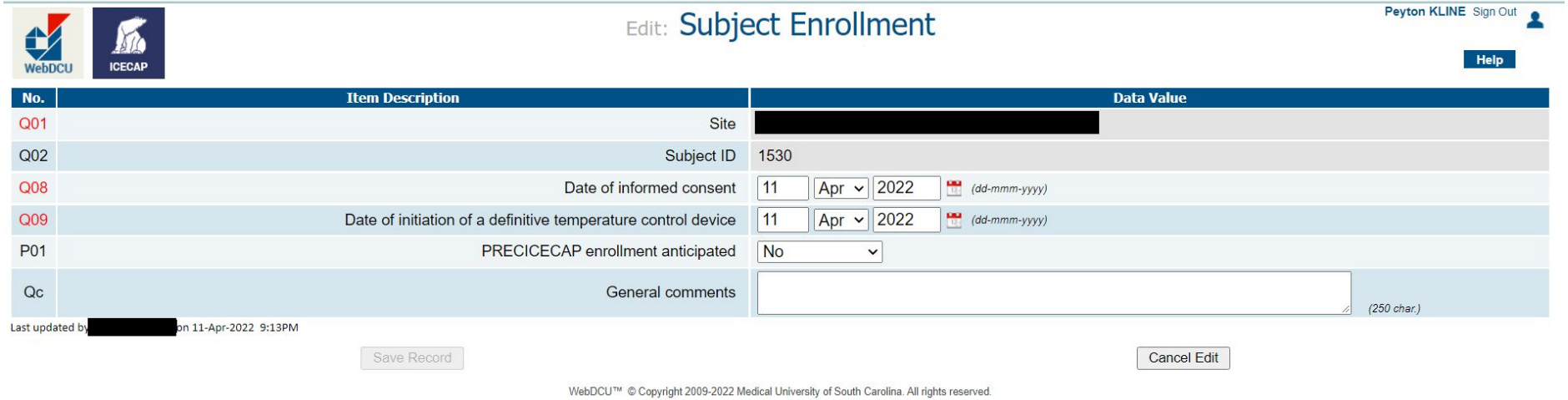
Entering Enrollment information in WebDCU
(Disclaimer - this is from ICECAP)



WebDCU ICECAP

Edit: Subject Enrollment

Peyton KLINE Sign Out

Help

No.	Item Description	Data Value
Q01	Site	[redacted]
Q02	Subject ID	1530
Q08	Date of informed consent	11 Apr 2022 (dd-mmm-yyyy)
Q09	Date of initiation of a definitive temperature control device	11 Apr 2022 (dd-mmm-yyyy)
P01	PRECICECAP enrollment anticipated	No
Qc	General comments	(250 char.)

Last updated by [redacted] on 11-Apr-2022 9:13PM

Save Record Cancel Edit

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Third Truth/Lie about Moni

My husband and I are twins

Second Eligibility Form

- All inclusion criteria must be YES, according to the information you have at the time.
- All exclusion criteria must be NO, according to the information you have at the time.
- First and last name of the person confirming eligibility

Randomization Form

- Confirmation that patient meets all eligibility requirements
- Date of definitive temperature control device initiation
- Time of definitive temperature control device initiation
- Confirmation that this randomization is within 6 hours of ROSC

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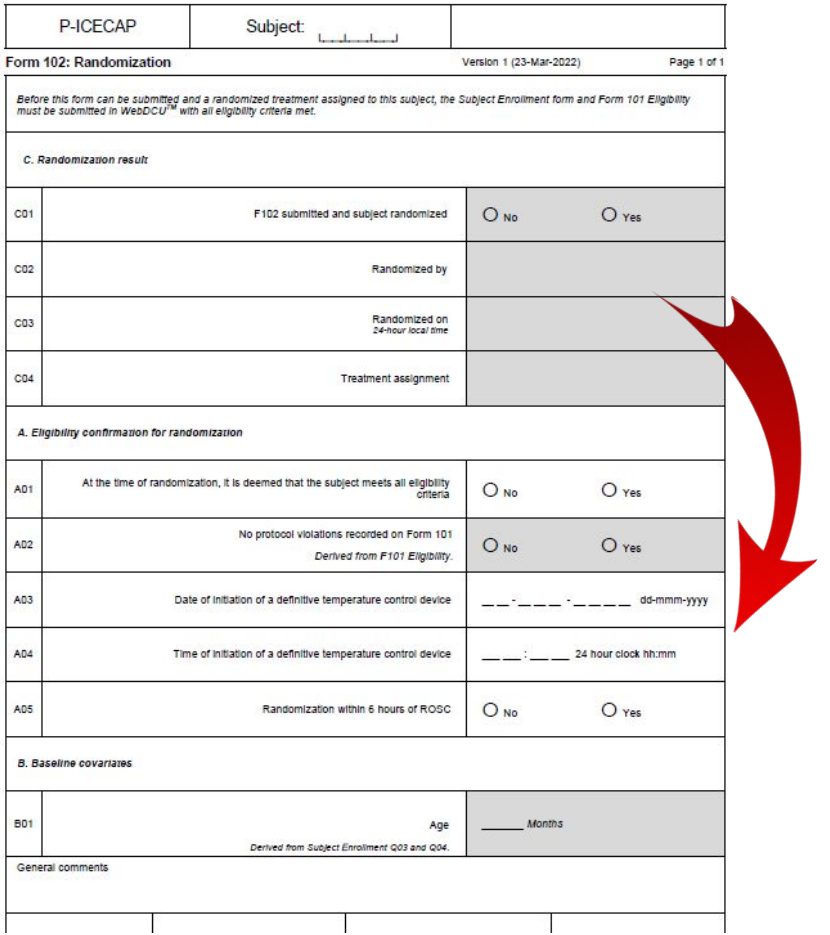
Randomization CRF



P-ICECAP	Subject: ____	

Form 102: Randomization Version 1 (23-Mar-2022) Page 1 of 1

Before this form can be submitted and a randomized treatment assigned to this subject, the Subject Enrollment form and Form 101 Eligibility must be submitted in WebDCU™ with all eligibility criteria met.

C. Randomization result

C01	F102 submitted and subject randomized	○ No ○ Yes
C02	Randomized by	
C03	Randomized on *24-hour local time*	
C04	Treatment assignment	

A. Eligibility confirmation for randomization

A01	At the time of randomization, it is deemed that the subject meets all eligibility criteria	○ No ○ Yes
A02	No protocol violations recorded on Form 101 *Derived from F101 Eligibility.*	○ No ○ Yes
A03	Date of initiation of a definitive temperature control device	__ __-___ -____ dd-mmm-yyyy
A04	Time of initiation of a definitive temperature control device	__ __ : __ __ 24 hour clock hh:mm
A05	Randomization within 6 hours of ROSC	○ No ○ Yes

B. Baseline covariates

B01	Age *Derived from Subject Enrollment Q03 and Q04.*	_____ *Months*

General comments

Other Things You'll Learn for Enrollment

Informed Consent (stay tuned… Coming after the break!)

- The Do's and Don'ts
- E-Consent process (also a Future RC Zoom session…)

Building rapport with a stressed family

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2 Truths and a Lie About Moni

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Questions?

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Protocol: Cooling Basics, Clinical Considerations, and Phases of Care

Dr. Frank Moler

Overview

- This talk reviews basic temperature (temp) related information needed for P-ICECAP.
- There is much information to know. Key content is repeated. (Sorry, no “Greatest Movies of All Time” trivia breaks as in THAPCA). Periodic review will be required during the trial.
- The information presented will assist the research team in safe monitoring and application of cooling in our study subjects.
- ‘Just in time’ reviews with the clinical teams will be optimal, especially for the Induction of cooling and the Rewarming phases of P-ICECAP.

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Outline

- Definitions
- Thermoregulation - basics
- Physiologic and other clinical effects of hypothermia/cooling
- Central temperature measurement
- Factors impacting target temperature
- Cooling protocol through 120 hours
- Review/Checklist (extra)
- Cases (extra)

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Definitions



Polderman
CCM 2009

Table 1. Proposed terms and definitions surrounding therapeutic hypothermia

Therapeutic temperature management definitions	
Hypothermia	Core temperature <36.0°C regardless of the cause
Induced hypothermia	An intentional reduction of a patients' core temperature below 36.0°C
Therapeutic hypothermia	Controlled induced hypothermia: i.e., induced hypothermia with the potentially deleterious effects, such as shivering, being controlled or suppressed
Controlled normothermia/therapeutic normothermia	Bringing down core temperature in a patient with fever, and maintaining temperature within a range of 36.0°C–37.5°C, with the potentially deleterious effects, such as shivering, being controlled or suppressed
Temperature range definitions	
Mild therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 34.0°C–35.9°C
Moderate therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 32.0°C–33.9°C
Moderate/deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 30.0°C–31.9°C
Deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to <30.0°C
Mild hyperthermia	Core temperature 37.5°C–38.0°C
Moderate hyperthermia	Core temperature 38.1°C–38.5°C
Moderate/severe hyperthermia	Core temperature 38.6°C–38.9°C
Severe hyperthermia	Core temperature ≥39.0°C

TEMPERATURE CONTROL SYSTEMS. A complex system is needed to monitor and regulate the heat exchanges that occur

Table 71-1. Fahrenheit to Celsius Temperature Conversions

°C	°F
45	113.0
44	111.2
43	109.4
42	107.6
41	105.8
40	104.0
39	102.2
38	100.4
37	98.6
36	96.8
35	95.0
34	93.2
33	91.4
32	89.6
31	87.8
30	86.0
28	82.4
26	78.8
25	77.0
24	75.2
23	73.4
22	71.6
21	69.8
20	68.0

Therapeutic Normothermia
= Normothermia
TTM 36.0-37.5°C (36.8)

Therapeutic Hypothermia
= Cooling
TTM 32.0-34.0°C (33.0)

***Concern for arrhythmias at temp < 30°C. Rewarm STAT to goal**

****<u>Greatly</u> increased risk of VF and other arrhythmias < 28°C. STAT rewarming required.**

Irwin and Rippe. Intensive Care Medicine, 4th ed, 1999

Thermoregulation Basics 101

Normal Thermoregulation

- Heat production
  - Normal heat production from metabolic processes in liver, viscera, and muscle
  - During exercise or shivering, muscle primary source of heat generation, may be very large
- Heat elimination
  - Radiation = heat from skin to object without contact (NA)
  - Convection = airflow across skin (minor P-ICECAP)
  - Conduction = skin to object in contact (#1 in P-ICECAP)
  - Evaporation = sweating (NA in P-ICECAP)

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Normal Thermoregulation

- Hypothalamus regulates body T°
  - Afferent inputs to hypothalamus
    - Skin*, abdomen, thorax, spinal cord, brain
  - Hypothalamus processes based on its setpoint
  - Central temp below hypothalamic setpoint results in efferent responses
    - Cutaneous vasoconstriction
      - impedes heat transfer through skin
    - Shivering
      - generates heat (muscles)

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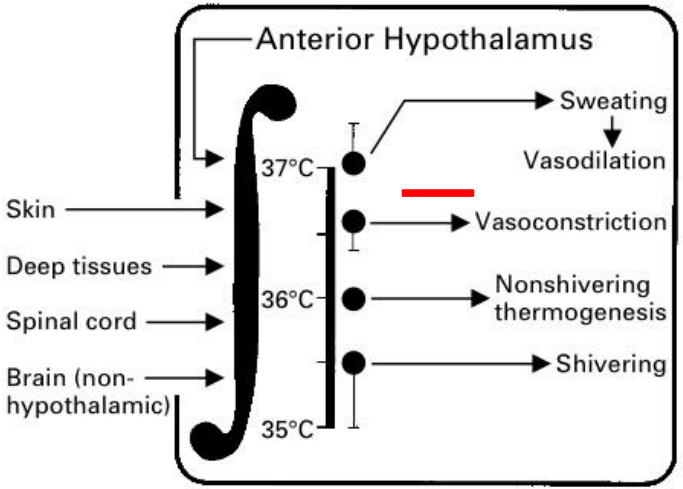

Figure 1. Thermoregulatory Control by the Hypothalamus.

The hypothalamus, the primary thermoregulatory control center in mammals, is shown as a large square. The skin surface, deep abdominal and thoracic tissue, spinal cord, and nonhypothalamic portions of the brain each contribute very roughly 20 percent of the input that is integrated by the hypothalamus in the control of autonomic thermoregulatory defenses (this input is shown entering the hypothalamus from the left of the figure). The temperature of the hypothalamus itself also contributes roughly 20 percent of the information used in thermoregulatory control. In the hypothalamus, the integrated body temperature is compared with threshold temperatures that trigger specific thermoregulatory responses. Values higher than the threshold for responses to warmth (i.e., sweating) or lower than the threshold for responses to cold (i.e., vasoconstriction and shivering) initiate the appropriate defense. Values between the thresholds for sweating and vasoconstriction lie in the interthreshold range — the range of temperatures that do not trigger any thermoregulatory defenses. The interthreshold range is normally only 0.2°C. Because thermoregulatory defenses are generally effective, human body temperature rarely deviates more than a few 10ths of a degree from the target value set by the hypothalamus. The thresholds for sweating, vasoconstriction, and shivering are from Lopez et al.[6] and are shown as means ±SD. The threshold for nonshivering thermogenesis is an estimated value.

Sessler DI. NEJM 1997:336;1730-7

Thermoregulation

- Pediatrics
  - Smaller infants / children
    - Larger SA/volume compared to adults
    - Reduced shivering response < 1 yr
    - Easier/shorter time to induce hypothermia (cooling) and temp control in very young
- Shivering decreases at approximately 33.5°C
  - P-ICECAP goal 33.0°C in hypothermia (cooled) groups

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Normal thermoregulation

- Normothermia Phase
  - If hypothalamic set point is elevated (e.g., fever at 39°C) relative to a goal temp 36.8°C, one will see similar physiologic responses as Therapeutic Hypothermia (cooling) induction phase
    - Vasoconstriction
    - Shivering
  - Common etiologies of increased set point (fever)
    - Post-cardiac arrest syndrome
    - Infection
- Normal temp range is ~36.5-37.5°C during a day.
  - Cooling devices sensitive to approx. ± 0.2°C from set point.
  - They will attempt to warm and cool normal subjects!

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Physiologic and Other Effects of Cooling in P-ICECAP

List of Physiologic Effects

1. Shivering
2. Hypovolemia (during cooling and rewarming)
3. CV including bradycardia
4. Potassium
5. Glucose
6. Other chemistries (Mg, PO4, etc.)
7. LFTs, amylase/lipase, lactate
8. Plts/Coags
9. WBC/Inflammation/Infection
10. Drug metabolism
11. Metabolic rate
12. Blood gases
13. Skin

Modified from:
- Polderman, CCM 2009
- ILCOR, Circulation, 2008

1. Shivering

- Frequent, causes heat generation and rewarming
- Tx (REQUIRED)
- Suggested agents
  - Opioids (e.g., fentanyl)
  - Benzodiazepines (e.g., midazolam) and others
  - NMB (e.g., vecuronium)
- Shivering response decreases at ~ 33.5°C
- Shivering response less in young (< 1 yr)
- Will see shivering in both hypothermia (cooled) and normothermia phases, if hypothalamic set point is greater than goal temperature
- May or may not be visible

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1. Shivering – drugs to inhibit

- Benzodiazepines* (midazolam - example)
  - Sedative
  - Vasodilation (+/-)
  - Antiepileptic effects
  - Decrease shivering
- Opiods* (fentanyl - example)
  - Analgesia, sedation
  - Vasodilation (+/-)
  - Decrease shivering
- NMB* (vecuronium, rocuronium and others). Cis-Atracurium has temperature dependent metabolism, prolonged with cooling (Hofmann Reaction). Twitch monitoring with infusions.
  - Inhibits shivering, facilitates cooling and temperature control
  - Masks sedation level and seizures

*ILCOR, Circulation 2008 – drug classes recommended

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Induction of Hypothermia without sedation

- If hypothalamic set point normal at 37.0°C
  - Vasoconstriction - 36.5°C
  - Shivering - 35.5°C
  - -↑HR
  - -↑Metabolic rate (40-100%)
  - -↑Stress response
- Undesirable in patients with neurologic and/or post hypoxic injury
- Increased risk of adverse cardiac events

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Polderman
CCM 2009

Induction of Hypothermia with sedation/analgesia

- ↓Shivering
- ↓HR
- ↓ Metabolic rate
- ↓ Stress response
- Improved neurologic outcome compared to no sedation/analgesia.

- ‘Proper sedation & analgesia are important for successful use of cooling’ (Polderman 2009).

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2. CV: Hypovolemia

- Hypovolemia – common during the cooling Induction Phase
  - often due to cold diuresis (renal);
  - results in tachycardia and hypotension;
  - requires tx
  - Note: if patient cooled and HR not reduced, may be sign of hypovolemia
- Hypovolemia – also common during Rewarming Phase
  - Vasodilation; may result in tachycardia and hypotension; requires tx

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3. CV effects

- Cardiovascular (assuming pt deeply sedated and euvolemic)
  - □BP (MAP), □CVP, □M_V02
  - □HR
  - □CO (due to HR), but improved O_2 supply/demand ratio
    - Case series – cooling used for low cardiac output states (LCOS)
    - Used for JET post op ped cardiac patients

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3. CV effects

- ECG changes –
  - Bradycardia (□HR) common (□PR, □ QRS,□QT intervals)
  - No specific tx usually required for □HR, if temp >30°C and otherwise stable
    - Atropine ineffective
    - If hypothermic without □HR, consider hypovolemia or inadequate sedation as cause
  - Other arrhythmias uncommon if temp > 30°C!
  - Arrhythmias at temps < 30°C
    - 28-30 °C - □ (AF & VF)
    - < 28 °C - □□VF.
    - STAT rewarming required if <30°C (MANUAL Mode required for Blanketrol-III)

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4. Electrolytes (Potassium = K+)

- Close monitoring of K^+ required post arrest due to AKI risk
- Electrolytes q 6 hr during cooling and rewarming phases and q 12 hr during other phases
  - **Induction Phase** - serum K^+ <u>decreases</u>
    - Careful replacement as needed
  - **Rewarming Phase** - serum K^+ <u>increases</u>
    - Slow rewarming results in less elevation in K^+
    - If patient received insulin for hyperglycemia and extra K^+ replacement given, this may result in greater ↑ K^+ on rewarming – be careful
    - Consider removing K^+ from IV fluids during rewarming; supplement prn only if needed

5. Hyperglycemia (GLU)

- Common post arrest due to stress response
- Relative insulin resistance with cooling
- Significance & optimal range for GLU unknown
- Neonatal, adult and THAPCA RCTs did not use tight control
- Often improves without tx in first 24 hr
- Important: if insulin for hyperglycemia used during cooling, will need more K^+ replacement. This may lead to HYPERkalemia and HYPOglycemia on rewarming as insulin resistance resolves.
- Protocol suggests <200 mg/dl (range 80-200) acceptable
    - consider reducing glucose in IV solutions, insulin only as needed for GLU > 200.
- Monitor q 6-12 hr. More often if insulin used.

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6. Chemistries (other)

- ☐ Phosphate, Magnesium, Calcium
  - Each may decrease during cooling
  - Monitored at least daily
  - Replace if indicated

7. LFTs, Amylase/Lipase, Lactate

- ☐ Amylase, lipase, liver enzymes
- ☐ Lactate (up to 6 mmol/L)
  - Monitor at least daily
  - No tx generally required
  - Elevations also commonly associated with cardiac arrest

8. Hematology/Coagulation

- Platelets
  - Mildly reduced numbers common
  - May require tx [platelet transfusion] if level too low for clinical setting (e.g., chest tube bleeding).
- Mild abnormalities coagulation studies ~ 33°C
  - NOT seen when measured in lab (37°C)
  - Usually requires no tx [FFP transfusion]
- Clinical trials including THAPCA-IH did not describe increased bleeding with cooling.
- Monitor at least daily

9. Hematologic (Neutropenia)/Infection

- □ WBC (neutropenia) may occur
- Impaired inflammatory response with cooling
- Potentially higher risk of infection
- Out of hospital cardiac arrests commonly associated with VAP and/or BSI in adults
- THAPCA overall positive cultures 39-46% (lung, blood and urine). Drowning subgroup 43-67%
- **<u>IMPORTANT</u>:**

  Consider antibiotic prophylaxis in BOTH cooled & normothermia groups as fever will be masked in both.

10. Drug Metabolism

- Drug clearance often dependent on enzyme reactions
- Hypothermia is expected to be associated with slower drug clearance and potentially higher drug levels (opiates, benzos, NMBs, etc.).
  - Follow levels if available (i.e., phenobarb)
  - Titrate sedation drugs to effect
  - Consider cautious use of drugs that cause bradycardia (i.e., dexmedetomidine?)

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11. Metabolic Rate

- Reduced with cooling (32-34°C)

  ~8-10% per degree C

- Caloric requirements decrease during cooling

  ~30-40%

- Do not over feed

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12. Blood Gases

- P_aO_2 and P_aCO_2 solubility differs by temp
- Controversial if correction should be done
- P-ICECAP, like THAPCA, will not temp correct ABGs
- Report at standard body temp 37.0°C
- A rough estimate of temp correction to 33°C
  - ~ P_aCO_2 = ↓2 torr/°C = ~ 8 torr
  - ~ P_aO_2 = ↓5 torr/°C = ~20 torr

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13. Skin

- Closely observe skin and provide good nursing care during 120 hrs. of temperature management.
  - Cooling not associated with skin break down in Neonatal cooling trials up to 72 hr. or THAPCA 48 hr.
- Larger, malnourished, immobile patients may be at greater risk

Central Temperature Measurement

Temperature Measurement

- Central temperature measurement required to estimate blood temp (Gold Standard)
- Delay in a central site to reflect blood temp in real time is associated with overshoot of cooling
  - Ideal site = accurate, short time lag
- Dual central temp measurements required for all patients (Primary to cooling device; Secondary to bedside monitor or cooling device).
- **Exception** - ECMO cases – 1 central temp (or venous circuit blood) only required

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- **Esophageal** (Preferred primary site – attached to the cooling devise (Arctic Sun, Blanketrol, other). Used as sole temp site in NICHD neonatal trials
  - Accuracy: High level
  - Time lag: Shortest = 5 min (2-10 min)
  - Insertion: easy, but need to verify position
  - IMPORTANT: Correct placement in lower 1/3 of esophagus is critical
    - If in stomach, temp may measure low by 1-3°C
    - If tube feeds (gastric) and reflux, may make measurement inaccurate
    - Vented G-tube accuracy?

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- **Rectal** (secondary probe– to monitor)
  - Accuracy: Moderate level
  - Time lag: Moderate = 15 min (10-40 min)
  - Insertion: Easy
  - Dislocation: Common. Monitor for it.
- **Bladder** (secondary probe – to monitor)
  - Accuracy: Moderate level
  - Time lag: Moderate = 20 min (10-60 min)
  - Insertion: Easy
  - Dislocation: Uncommon. Low urine output may result in less accurate measurements
  - Not available for smallest infants

*If Esophageal probe is not used as primary probe, then Rectal or Bladder will need to be selected.

- **Skin** sites (skin, axillary, etc)
  - Accuracy: Inaccurate – not a central temperature. Do not use.
  - Time lag: Moderate = 20 min (10-60 min)
  - Insertion: Easy
  - Dislocation: Uncommon
- **Tympanic** membrane (better than Skin)
  - Accuracy: Moderate, may be inaccurate
  - Time lag: Moderate = 10 min (10-20 min)
  - Insertion: Easy; quick
  - Dislocation: NA
  - Other: not continuously measured

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Central Temp Differences

- Two central temps for safety
- If within ± 1°C - acceptable
- If consistently > 1°C, escalating action required
  - Notify the site PI
  - Verify probe placement (esophageal, rectal)
  - Verify YSI 400 compatible probes used
  - Stomach feeds/GE reflux (esophageal probe)
  - Low urine output (temp sensing Foley)
  - Determine which probe is most accurate to be Primary connected to the cooling device.

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Factors influencing ability to maintain goal temperature

1. Patient factors

- Patient factors impeding cooling
  - Size (larger, obesity)
  - Shivering (commonly subclinical)
    - Sedation/analgesia/NMB (Inadequate)
    - Sepsis/Infection
  - Seizures
  - Extremely reduced CO/poor skin perfusion

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2. Skin surface area for cooling

- Surface area for contact (Conduction)
  - 2 vs. 1 blankets (i.e., anterior/posterior vs. posterior)
  - Positioning of patient (i.e., side vs. back)
  - Probably less of issue with Arctic Sun pads
- Extraneous materials between patient and blankets/pads (Maxi-Therm Lite or Arctic Sun pads)
  - Minimize, none required, no sheets

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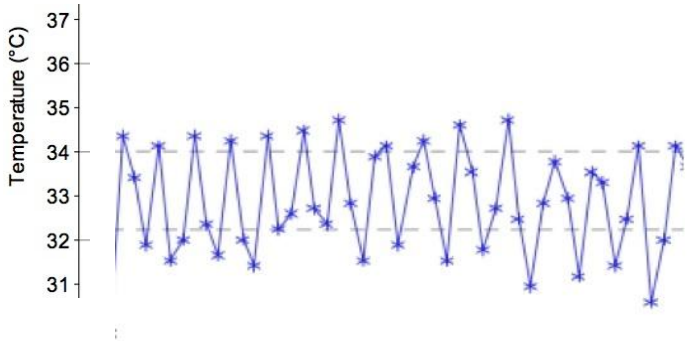
3. Cooling Devices

- Know how to use your cooling device per the manufacturer's recommendations!
- Also, know important limitations of your device
- Most common devices used in P-ICECAP are:
  1) Blanketrol-III: Gentherm (formerly CSZ) has improved educational materials and videos on website.
     https://www.gentherm.com/en/medical/hyper-hypothermia/blanketrol-3
  2) Arctic Sun: BD outstanding hands-on customer service
  3) Other (Criticool, etc.)
- Unlike THAPCA, we are not instructing on the use of any device. Examples used are for discussion purposes only.

3. Cooling Equipment: Example of modes – Blanketrol-III

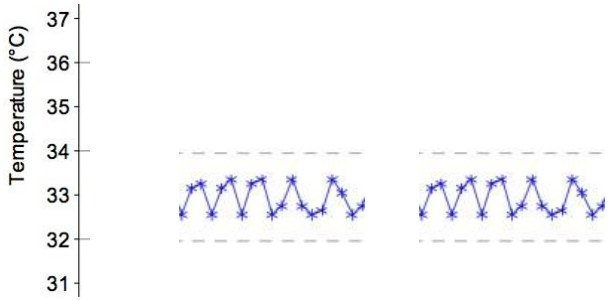
- **AUTO CONTROL Mode**
  - Warms or cools water to max range of 4 - 42°C when patient's central temp +/- 0.2°C from Blanketrol Set Point temp.
  - For large patients.
- **GRADIENT VARIABLE MODE (Plus SMART MODE)**
  - Warms or cools water to narrower range; dampens temp fluctuation compared to AUTO CONTROL Mode.
  - For smaller patient sizes.
  - Example (assume patient 34°C and set point 33°C)
    - AUTO CONTROL: 4 - 42°C For large patients
    - Gradient Variable 20°C: 14 - 42°C
    - Gradient Variable 10°C: 24 - 42°C. For smallest patients
- Defer to manufacturer/vendor for optimal set up and use

Temperature Tracings (from Primary Probe)



Not in range

- **AUTO Mode**
- **NMB, Sedation**



In range

- **GRADIENT VARIABLE Mode 10º C**
- **NMB, sedation**

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3. Blanketrol and SMART MODE

- **GRADIENT VARIABLE with SMART MODE** – Blanketrol-III
- A modification to the GRADIENT VARIABLE MODE.
- SMART MODE will decrease the water temperature set in GRADIENT VARIABLE MODE by 5°C if the goal temperature is not achieved within 30 minutes.
- It reverts to the GRADIENT VARIABLE MODE once the target temperature goal is achieved.
- This mode is suggested to be used by the manufacturer (Gentherm).

See User Guide and Inservice videos updated since THAPCA.

https://www.gentherm.com/en/medical/hyper-hypothermia/blanketrol-3

3. Blanketrol-III

- **Manual Mode** - Blanketrol-III
  - Not normally used except for emergencies
  - IMPORTANT: Key fact to know for Blanketrol! Manual mode is required if patient's (pt) tempis ever ≤30°C
    - None of the other Blanketrol Modes function if patient temp is ≤30°C
    - Suggest setting the Manual Mode to highest (warmest) setting (42°C) briefly until the pt temp is 33°C. Then use Auto Control of a Gradient Variable SMART Mode depending on patient size

*IMPORTANT - In the Manual Mode, the bedside nurse must continuously observe the pt's temp. The pt is 100% dependent on careful temp titration by nurse.

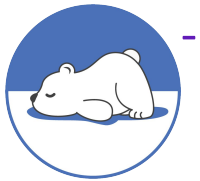
Protocol Overview Through 120 Hours

Overview – from 37,000 feet

- Example – University of Michigan PICU
- PICU fellow is contacted re: an OHCA from outside ED or our UM ED.
- The research team on call is immediately notified of a pending OHCA admit.
- Research team discusses with clinical team the case summary, arrival time, and approach for consent
- Order for nursing to get cooling equipment to bedside:
  - Blanketrol-III, two Maxi-Therm Lite cooling blankets (Ped or Adult), 2 hoses, 2 temperature probes and temp sensing Foley of correct size
- On pt arrival, clinical team stabilizes, places CVC, art line.
- Cooling device started as soon as it is safe to do so.
- Clinical team initiates their usual TTM target between 33-37°C before consent.

Overview – from 37,000 feet

- Research team gets informed consent and randomizes to 1 of 3 cooling durations (24, 48 or 72 hrs) for first 150 pts (“burn-in” phase).
- Subject enrollment = time randomized to a study cooling duration.
- TTM 33°C will be set as the target temp no later than 15 min following randomization.
  - If it was started prior to randomization, then the start time for cooling will be when a target 32-34°C range was set.
- Protocol goal is to achieve a temp range of 32-34°C no later than 2 hr. after randomization.
  - Sedation and NMB for induction phase results in fastest time to goal



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Overview – from 37,000 feet

- Cooling duration is equal to the combined time of the Induction plus Maintenance phases.
- After the cooling duration is completed, slow rewarming over at least 16 hrs. is done.
- Then normothermia 36.8°C for rest of 120 hr.

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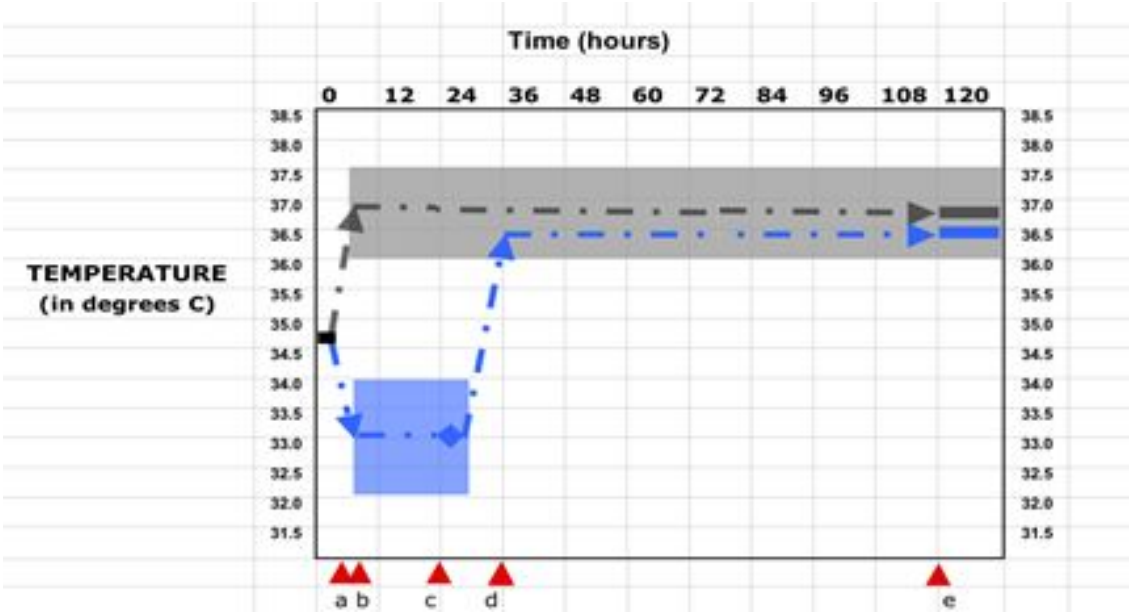
Durations of Cooling in P-ICECAP

Patient Timeline 0 - 120 Hours

Cooling Duration

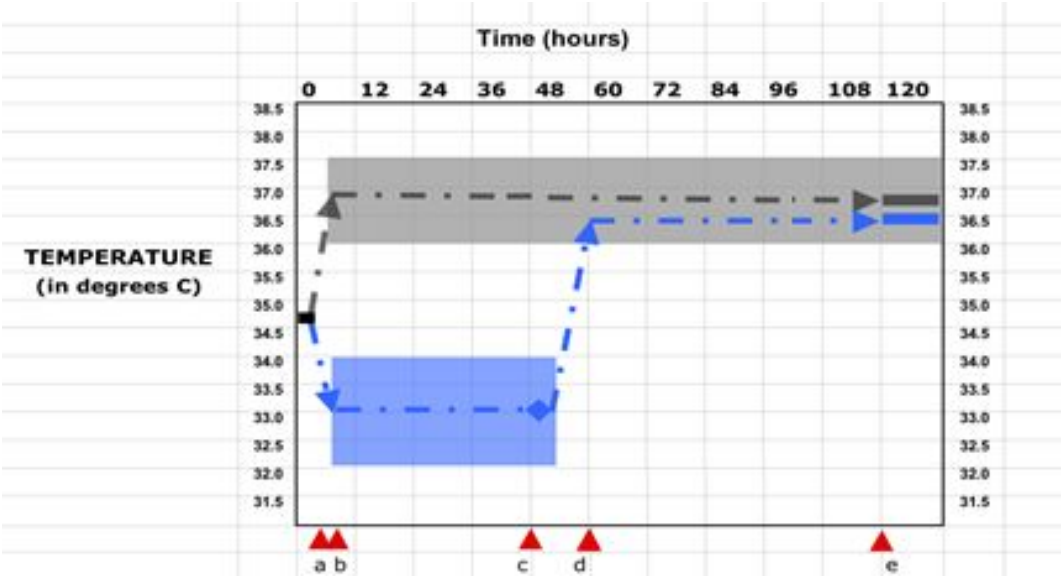
- Different than how it was defined in THAPCA.
- Cooling duration - Induction Phase + Maintenance Phase combined times. Starts when cooling device is set at target of 33°C [32-34 °C]. Ends when planned rewarming starts.
- Induction phase – starts when cooling device is set to the target temperature of 33° C post randomization (or 32-34°C range pre-randomization) and ends when the range of 32-34°C is achieved. Goal < 2 hrs.
- Maintenance phase – the remaining time to complete the assigned cooling duration. Ends at the start of rewarming.
- For the first 150 patients in P-ICECAP, the cooling durations will be 24, 48 or 72 hours only. (All patients cooled). Other cooling durations (0 to 96 hrs.) will be added in Year 3.
- DCC will provide sites with the exact time to begin rewarming.

24 Hour Cooling Duration



Timepoints	
a	randomization to Hypothermia (blue) or Normothermia (gray)
a - b	interval to assigned temperature goal range
a - c	duration of cooling assigned in hr
c - d	rewarming of cooled group
d - e	interval of controlled normothermia through 120 hr
e	end of study temperature control

48 Hour Cooling Duration



Timepoints	
a	randomization to Hypothermia (blue) or Normothermia (gray)
a - b	interval to assigned temperature goal range
a - c	duration of cooling assigned in hr
c - d	rewarming of cooled group
d - e	interval of controlled normothermia through 120 hr
e	end of study temperature control

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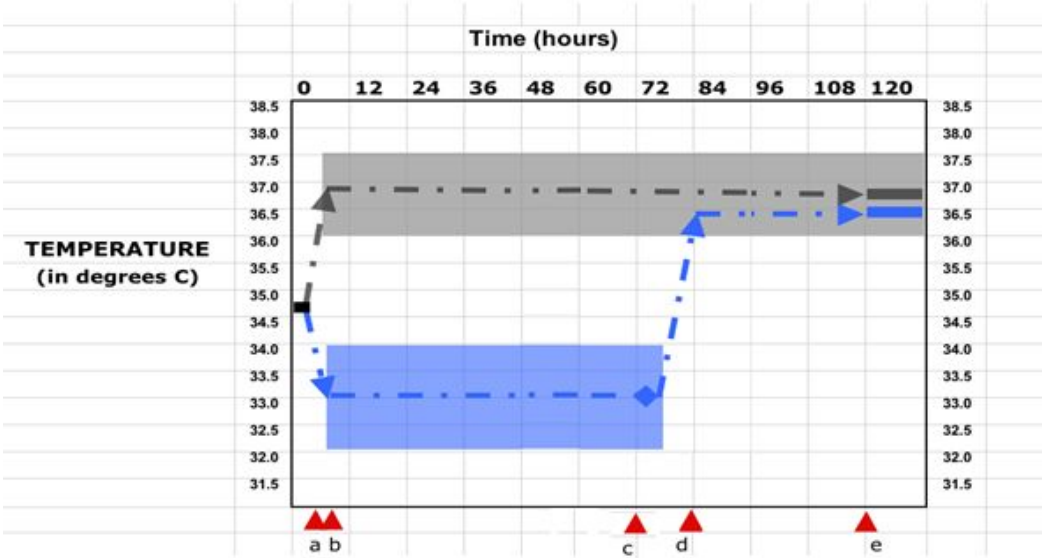
72 Hour Cooling Duration



Timepoints

a	randomization to Hypothermia (blue) or Normothermia (gray)
a - b	interval to assigned temperature goal range
a - c	duration of cooling assigned in hr
c - d	rewarming of cooled group
d - e	interval of controlled normothermia through 120 hr
e	end of study temperature control

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Review: Cooling Duration

- Duration of cooling starts when the target temperature on the cooling device is set to 33°C (range 32-34°C)
- Goal: start 33°C target temperature <15 minutes post randomization.
- If cooling device's set temp is between 32-34°C before randomization (because this is the site TTM practice), then the start time for duration of cooling is pre-randomization. After randomization, the target should be set at 33°C.
- Duration of cooling ends at the start of planned rewarming
- Equals Induction + Maintenance combined time

Temperature Monitoring and Management

HYPER-HYPOTHERMIA

Blanketrol® III

Patient Temperature Management Solutions

The Blanketrol® III hyper-hypothermia system offe
regulation while still keeping control in the hands o
program minimizes fluctuations in water temperatu
temperature.

Request More Information

Blanketrol® III Quick Reference Guide

Blanketrol® III User Guide

Blanketrol® III Inservice Video

HYPER-HYPOTHERMIA

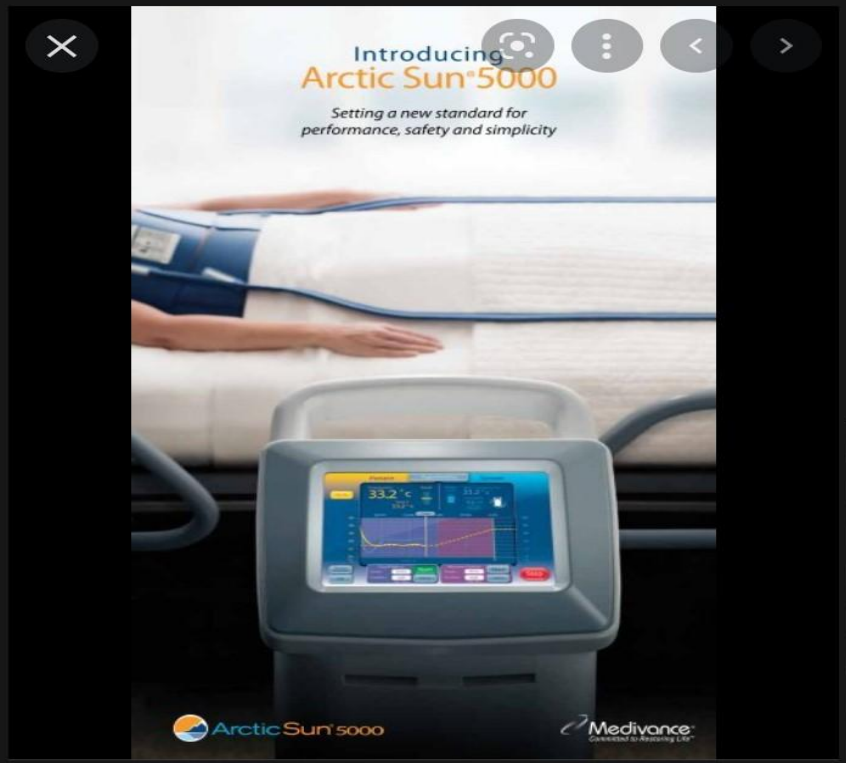
Maxi-Therm® Lite Blankets

Single-Use Hyper-Hypothermia Blankets

Gentherm's Maxi-Therm® Lite hyper-hypothermia blankets have a strong bonded pattern in the blanket resulting in a long lasting seal during usage.

The white material provides a comfortable, clean feel, and in today's hospitals where hospital acquired infections are an important issue, having a white blanket helps notify the caregiver when the blanket is soiled and needs to be changed.

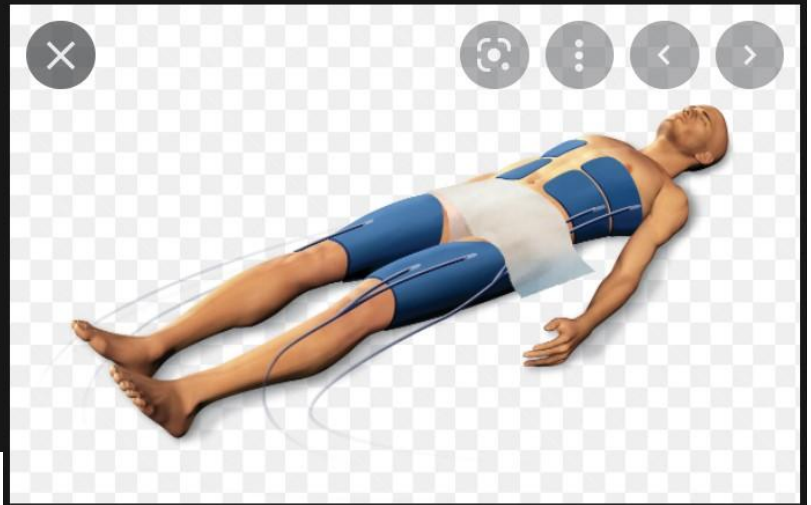
Request More Information



Yumpu

Arctic SunÂ®5000

Visit



BD

ArcticGel™ Pad Kit, Medium, 1 per case - 31707 | BD

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Neonatology Intensive Care Trauma & Emergency

CritiCool®

FEATURES RESOURCES DISPOSABLES REQUEST INFO

Targeted Temperature Management Has Never Been Easier

Operating CritiCool is simple, with quick and easy setup, and is both user- and patient-friendly. Clinicians just have to:

- Set the desired temperature on the CritiCool device
- Wrap the appropriately sized CureWrap garment around the patient
- Cool the patient to the set temperature
- Rewarm the patient through controlled, monitored rewarming

Monitoring: TTM 33°C (32-34°C)

- Two central temperature probes.
  - Primary to cooling device (Blanketrol-III, Arctic Sun, other).
    - *This temperature is entered into the case report form (CRF).
  - Secondary to bedside monitor or device (safety).

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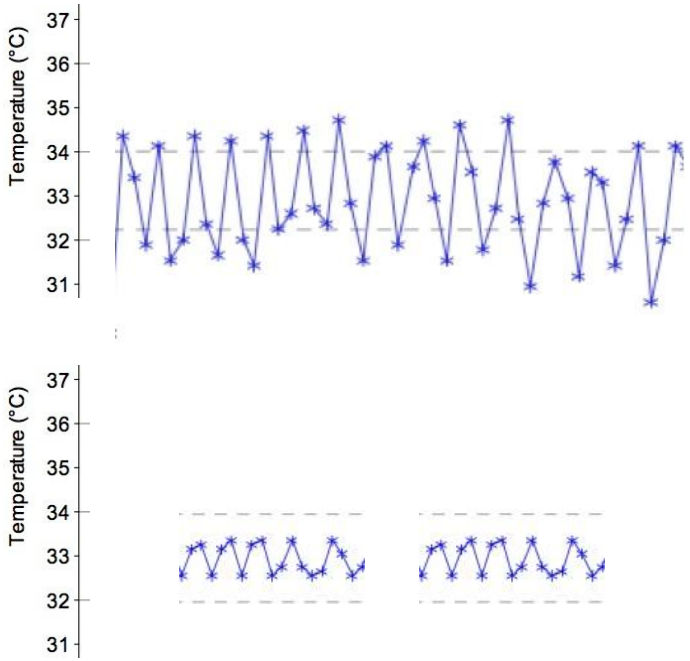
Monitoring: TTM 33°C (32-34°C)

- Cooling device's target temp is 33°C (range 32-34°C) until rewarming. Different devices have different settings/modes for small to large sized patients.
  - If temp is not staying in the 32-34°C range, need to adjust cooling device per manufacture (e.g., next slide).
    - Arctic Sun (excellent hands-on support)
    - Blanketrol-III (good online instructions & videos)
    - Both have 24/7 hotline numbers for support.
  - The on-call P-ICECAP team has 24/7 hotline that is available for other study questions.
  - We will collect temp information hourly after the first central temp probe is placed until end of TTM or the probe is removed. (FDA request).

Temperature tracings from small child (primary probe)



Not in 32-34°C range

- **AUTO Mode**
- **NMB, Sedation**

In range

- **GRADIENT VARIABLE Mode 10°C**
- **NMB, sedation**

Temperature Management

- A major goal in P-ICECAP is to achieve the desired phase target temperatures for the 120-hour intervention while preventing shivering.
- Sedation and analgesia are generally used throughout the120 hours while a patient remains intubated.
- NMB use for Induction and Rewarming phases. Other times PRN.
- Subclinical shivering is common. In patients with difficult to maintain temperature, consider sedation with NMB trial.

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Temperature Management

- Sedation/analgesia and NMB for Induction Phase until a stable goal 33°C target.
  - The goal clinical response is "sluggish or no response to noxious stimulus."
    - Common sedatives midazolam and dexmedetomidine.
    - Common analgesics fentanyl and morphine.
    - Common NMB agents vecuronium and rocuronium.
      - Twitch monitoring as needed
    - Infusions and intermittent dosing per site practice
- After the goal temperature range is achieved and stable, may hold NMB and dose prn through the Maintenance Phase. Titrate sedation/analgesia to above goal.

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Temperature Management

- Sedation/analgesia and NMB are also key during the Rewarming Phase. This facilitates slow controlled temp increase to the normothermia target 36.8 °C.
- Increased doses of sedatives/analgesics and NMBs may be required during rewarming as drug clearance increases at higher temperatures.

See Clinical Practice Guidelines

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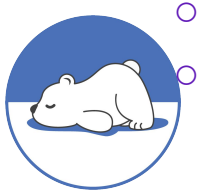
P-ICECAP Trial: Cooling, Rewarming and Normothermia Phases

Cooling Groups: 24, 48, and 72 hour

Induction Phase (I)

- Time from start of TTM 33°C (or 32-34°C if pre randomization) until the goal range (32-34°C) is reached.
- Use the recommended cooling modes described by manufactures for the patient's size.
  - Blanketrol III - AUTO CONTROL or GRADIENT VARIABLE SMART MODE – per manufacturer.
  - Arctic Sun – per manufacturer.
- Induction will require sedation + analgesia and NMB
- Likely time of maximum BP instability following OHCA since closest to event
- Hypovolemia, Hypokalemia and Hyperglycemia may occur during this period
- Review issues with clinical team optimal



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Cooling Groups: 24, 48, and 72 hour

Maintenance Phase (II)

- Steady state period with target temperature 33°C (32-34°C) until assigned study cooling duration is completed and planned rewarming starts.
- Adjust the cooling device mode as needed per manufacturer.
- Titrate sedation/analgesia to achieve/maintain "sluggish or no response to noxious stimulus."
- NMB prn after stable 32-34°C temp range is achieved.
- Similar clinical issues as Induction Phase possible (Hypovolemia, Hypokalemia and Hyperglycemia).

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Cooling Groups: 24, 48, and 72 hour

Rewarming Phase (III)

- This is a critical time – it needs to be done slowly.
- Begins with the initiation of planned increase of device target temperature toward 36.8°C (normothermia) goal.
- Should be done over ≥16 hrs
- For Blanketrol-III: AUTO CONTROL or GRADIENT VARIABLE SMART MODE
  - Manually **Increase** temp set goal 0.7 °C every 4 hrs.
    - **33°C** (0 hr); **33.7°C** (0-4hr); **34.4°C** (4-8hr); **35.1°C** (8-12hr); **35.8°C** (12-16hr); then **36.8°C** (16+hr)
  - Goal temp of 36.8°C (36-37.5°C range) after 16 hrs
- For Arctic Sun – the rate of rewarming is programed to achieve the goal of 36.8°C (from 33°C) over 16-18 hr.

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Cooling Groups: 24, 48 and 72 hour

Normothermia Phase (IV)

- Goal temp is 36.8°C, range 36-37.5°C for remaining time to 120 hrs
- If clinical team determines they must check fever status, put in MONITOR ONLY Mode
- Return to the device's appropriate cooling mode if temp > 37.5° C, but only if the patient remains intubated. Sedation/analgesia and possibly NMB may be required to prevent shivering

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Cooling Groups: 24, 48, and 72 hour

Normothermia Phase (IV)

- Clinical team may elect to extubate patient if clinically awake and otherwise stable
  - Management of fever following extubation is limited to antipyretic agents (Tylenol). Will NOT be able to deeply sedate or use NMB to prevent shivering.
  - If afebrile, could use MONITOR Only Mode

*IMPORTANT: Do NOT extubate a patient until rewarmed! Cerebral edema, hypoglycemia, hyperkalemia, and hypotension are risks of rapid rewarming.

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Initial Site Enrollments

- For the first 2 patients enrolled from each site, we recommend you contact the on-call 247 P-ICECAP hotline to review the Induction Phase soon after device is set to 33°C. Call again just prior to start of the Rewarming Phase.
- This was done successfully in THAPCA.
- Since sites are using their own cooling devices, we are relying on sites and manufacturers to have expertise for using their cooling equipment safely. Contact your vendor for an in-service if you believe it would benefit your PICU/PCCM team.
- Arctic Sun may have already contacted you.
- Contact Gentherm (Blanketrol) and other manufactures as needed for in-services.

Questions?

Break

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Clinical Standardization

Dr. Alexis Topjian

CSG Team

- Alexis Topjian, MD, MSCE - Study PI - Pediatric Critical Care
- Frank Moler, MD, MS - Study PI - Pediatric Critical Care
- Vinay Nadkarni, MD, MS - Co-I - Pediatric Critical Care
- Faye Silverstein, MD – Co-I - Pediatric Neurology

Site PIs and Steering Committee Feedback and Input

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Objectives

- Discuss intent of clinical standardization guidelines
- Review clinical standardization guidelines for P-ICECAP
  - Targeted Temperature Management
  - Post Cardiac Arrest Care
  - Neuroprognostication/Withdrawal
  - Laboratory Studies and Imaging

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Why Clinical Standardization?

- Purpose: to minimize treatment variability of participants when possible in the P-ICECAP trial in order to optimally discern the effect of the study intervention.

- Goal-oriented strategy that maintains some flexibility in approach as long as a consistent target parameter is attained.

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Why Clinical Standardization?

- Made by consensus among a multidisciplinary clinical standardization team and vetting with feedback and revision among participating sites.
- Most have insufficient data, however national guidelines were utilized for some elements.

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Clinical Standardization is not…

- Intended to dictate clinical practice for patients that are not enrolled in P-ICECAP
- Best practice for all patients at all timepoints

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How to implement clinical standardization

- Adapt your local procedures
- Create P-ICECAP order set
- Educate study team and care providers
- Review cases and understand there will be variability but continue education to standardize care

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Definitions

- **Time of cardiac arrest:**
  - When the child's arrest starts (Often not known)
  - NOT when they are found

- **Time of initiation of Targeted Temperature Management**
  - When the button on the closed loop cooling device is pushed
  - Eligibility criteria

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Return of Spontaneous Circulation

- **ROSC** is operationally defined as the restoration of a palpable pulse or a measurable blood pressure. If cardiac monitoring is available, ROSC requires an organized cardiac rhythm.
- **Sustained ROSC** is when the patient has achieved ROSC with signs of circulation persisting for at least 20 consecutive minutes.

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Sustained ROSC example

- CPR from 2:00 to 2:10 pm
- ROSC is at 2:10 pm
- No additional CPR is provided for next 20 minutes
- Time of sustained ROSC is 2:10pm, but you don't know that until 2:30pm

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Time of initiation of cooling

- **Time of initiation of cooling is the start of intervention**
- The time the device is set to a temperature between 32-34℃
  - After randomization, set to 33℃ should be within 15 minutes of randomization
  - If prior to randomization, time of button push to a temp of 32-34℃

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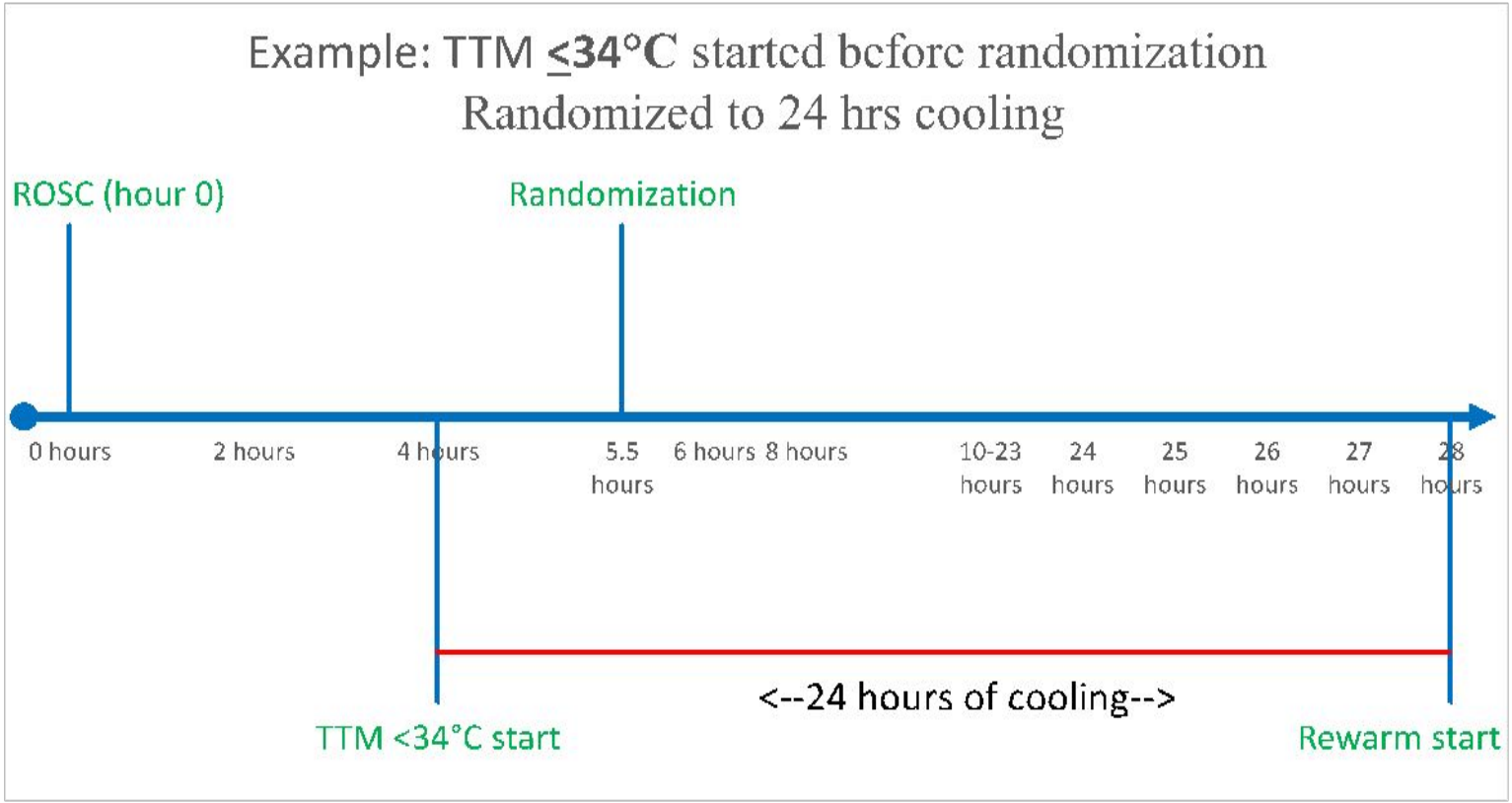
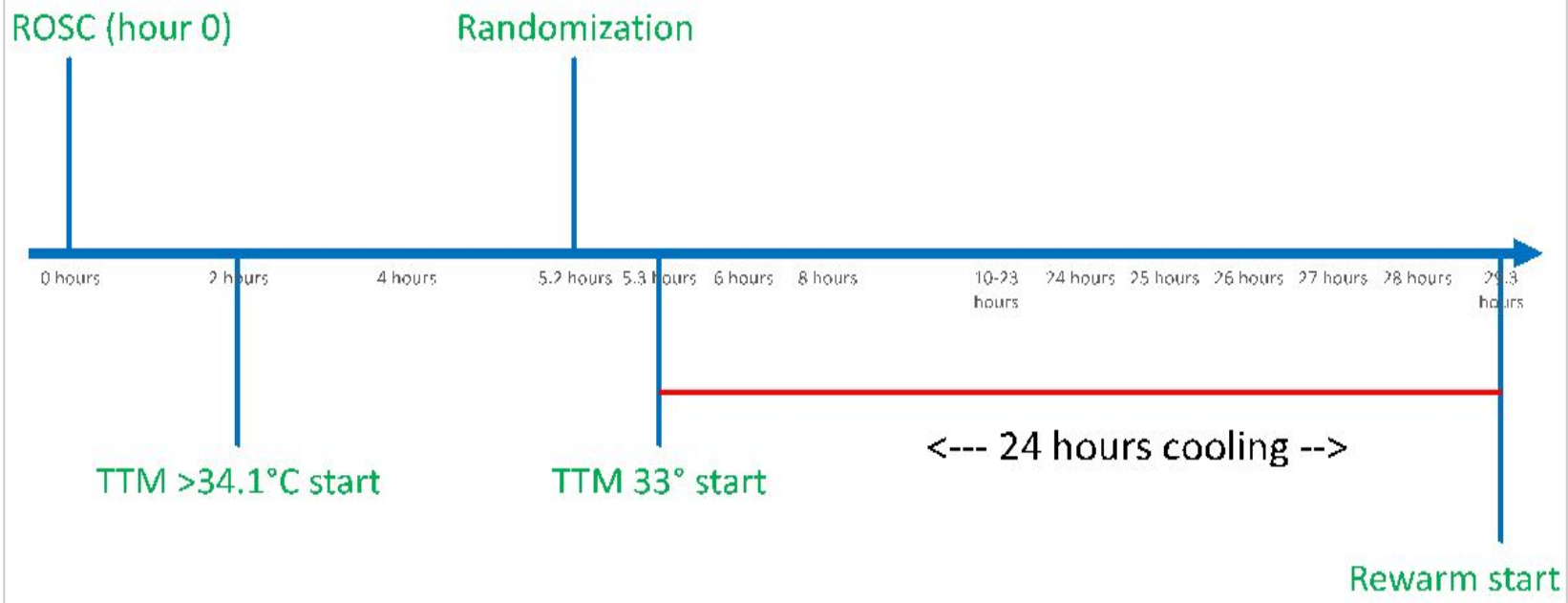

Example: TTM ≤34°C started before randomization
Randomized to 24 hrs cooling
ROSC (hour 0)
Randomization
0 hours
2 hours
4 hours
5.5 hours
6 hours
8 hours
10-23 hours
24 hours
25 hours
26 hours
27 hours
28 hours
<--24 hours of cooling-->
TTM <34°C start
Rewarm start

Example: TTM ≥34.1°C started before randomization
Randomized to 24 hours cooling



Temperature Management

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Temperature Monitoring

- Continuous from time of clinical initiation through end of intervention
- Core body temperature should be monitored at two core sites
  - Esophageal, bladder, rectal
- The esophageal probe is the preferred primary probe which will be connected to the surface cooling unit.

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Temperature Management Troubleshooting

Probe temps are within 1ºC of each other (A)	Probe temps are within 1-2ºC of each other (B)	Probe temps are more than 2ºC apart (C)
• Nothing needs to be done • Continue routine clinical verification of probe placement	• Verify probe placements • Verify all temp probes are YSI 400 compatible • Contact MD and site PI • Determine if primary probe (esophageal) is malfunctioning or yielding incorrect central temp (tube feeds reflux, in stomach, etc). • Determine if secondary probe is malfunctioning or yielding incorrect temp (displaced, low urine output, etc) • If probe ? malfunction - replace • If esophageal temp inaccurate and unable to resolve, switch to Foley or rectal probe as primary probe and plug it into Blanketrol unit. • If secondary probe believed inaccurate, consider switching to rectal or Foley site	• Notify MD and site PI immediately • Repeat steps in (B) • Verify esophageal probe position using x-ray if not already done • Strongly consider replacing probes • MD must determine which temp probe now reflects the true central temp. Consider checking a third site (rectal or foley). • If unable to determine which probe is most accurate, see **Rule 1** below. The temp probe determined to be most accurate, will become the primary probe connected to Blanketrol.

Rule 1: if unable to determine which probe accurately reflects central temperature:

1. Assume the lowest temperature is correct for Induction and Maintenance Phase of Therapeutic Hypothermia
2. Assume highest temperature is correct for all other phases of Therapeutic Hypothermia and Normothermia

Refer to Section X of the THAPCA protocol

Temperature Management

- Clinically used servo-regulated device
- Rarely ECMO
- No intravascular cooling, gastric cooling etc
- Can use acetaminophen as an adjunct

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Induction of Hypothermia

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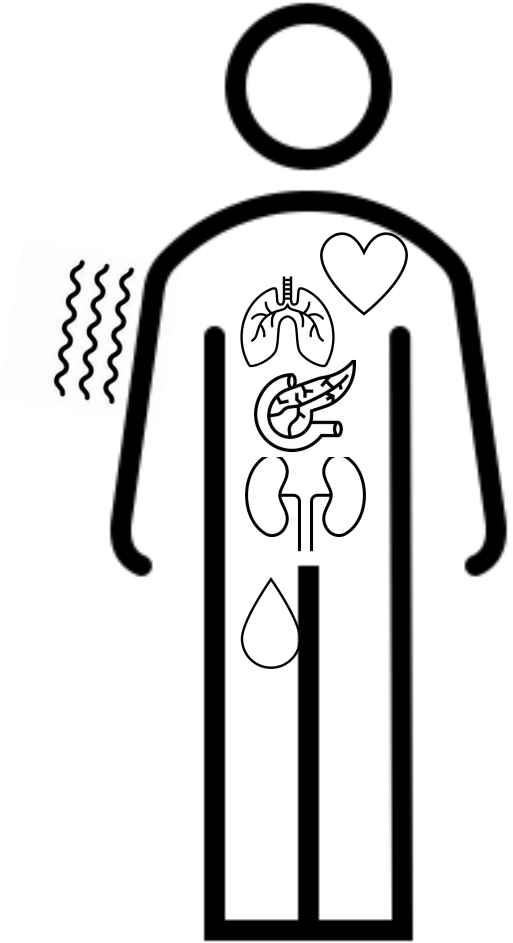
Induction Phase-Decrease in temperature to 33C



Endocrine/Metabolic
Hyperglycemia □ diuresis
↑ insulin resistance

Target
Euglycemia
Insulin infusion

Neuromuscular:
Shivering
↑ metabolic demand
Resolves < 34C

Sedate/paralyze

Coagulation:
Mild coagulopathy
Mild ↓ platelet count and function

Cardiac:
↓ Heart Rate
↑ Systemic vascular resistance
↓ Cardiac output
EKG: mildly prolonged PR, wide QRS, increased QT

Expect bradycardia
Expect cool extremities and poor cap refill

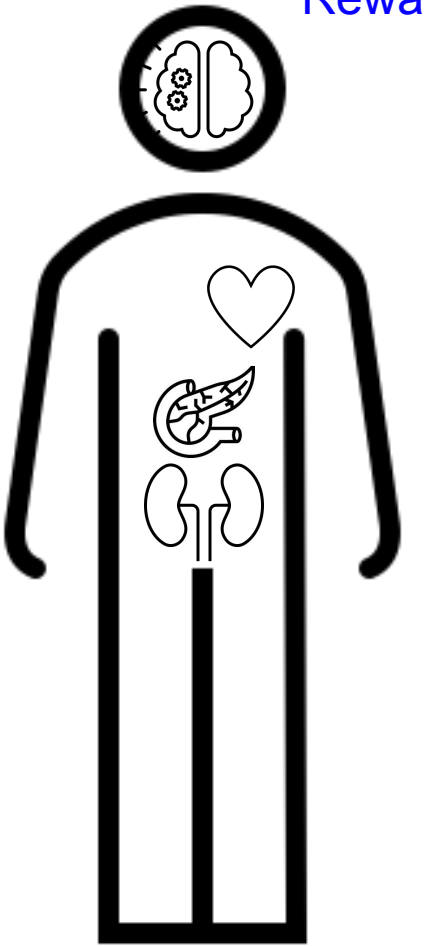
Renal:
"Cold diuresis"
↑ venous return, ↑ ANP,
↓ ADH, tubular dysfunction
Electrolyte abnormalities
- ↓ K
- ↓ Phos
- ↓ Mg

Monitor and replete electrolytes
Replete Fluids

Other:
Altered drug metabolism
Altered blood gas analysis
Mild increase in amylase, AST/ALT
↑ fat metabolism □ ↑ ketones and lactate □ ↓ pH

Rewarming Phase

Rewarm slowly over 16 hours to 36.8



Neuromuscular:
Shivering
↑ metabolic demand
Resolves < 34C

Sedate/paralyze

Other:
Altered drug metabolism
Altered blood gas analysis

Cardiac:
↓ Systemic Vascular Resistance
Vasodilation
Hypotension
Tachycardia

Replete fluids
Start vasopressors

Renal:
Electrolyte abnormalities
↑ K due to cellular shifts, stopping insulin,
Decreased urine output, and exogenous repletion

Monitor Potassium closely
Remove potassium from fluids
Treat hyperkalemia

Vascular Access

- Central Venous Catheters
  - PICC line
  - Temporary CVC
  - Broviac
- Arterial Line

(place ASAP , much harder when cold)

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Sedation and Analgesia

- Goal: Sedation scores are per your ICU with a target of "sluggish or no response to noxious stimulus."
  (e.g. SBS -2, RASS -4)
- Decisions regarding agents are at the jurisdiction of the clinical team with the following guidance

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Sedation and Analgesia

- Should be initiated as a continuous infusion with intermittent boluses to achieve goal sedation score.
- Titrate to achieve sedation score
- After rewarming is complete sedation goals are at the jurisdiction of the clinical team

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Sedation and Analgesia

- Goal: “sluggish or no response to noxious stimulus.”
- Common sedatives: dexmedtomidine and midazolam
- Common analgesics: narcotics
- If after the first 4 hours of intervention the patient has no clinical response to noxious stimulus sedative and analgesics can be weaned
- May wean off after 24 h if no response to noxious stimulus.

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Shivering

- Occurs during induction and rewarming when above 34 C
- Shivering will slow cooling to a goal temperature.
- Makes it more difficult to maintain target temperature
- May be uncomfortable for patients
- Adversely affect the patient's metabolic needs

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Shivering

- Goal: prevent and treat shivering
- May be subclinical and difficult to detect
- May be difficult to differentiate from seizures or myoclonus
- Sites that have shivering scores and protocols can use them
- Treatments: Dexmedtomidine, Demerol, shin counterwarming, neuromuscular blockade

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Physiological Goals and Management

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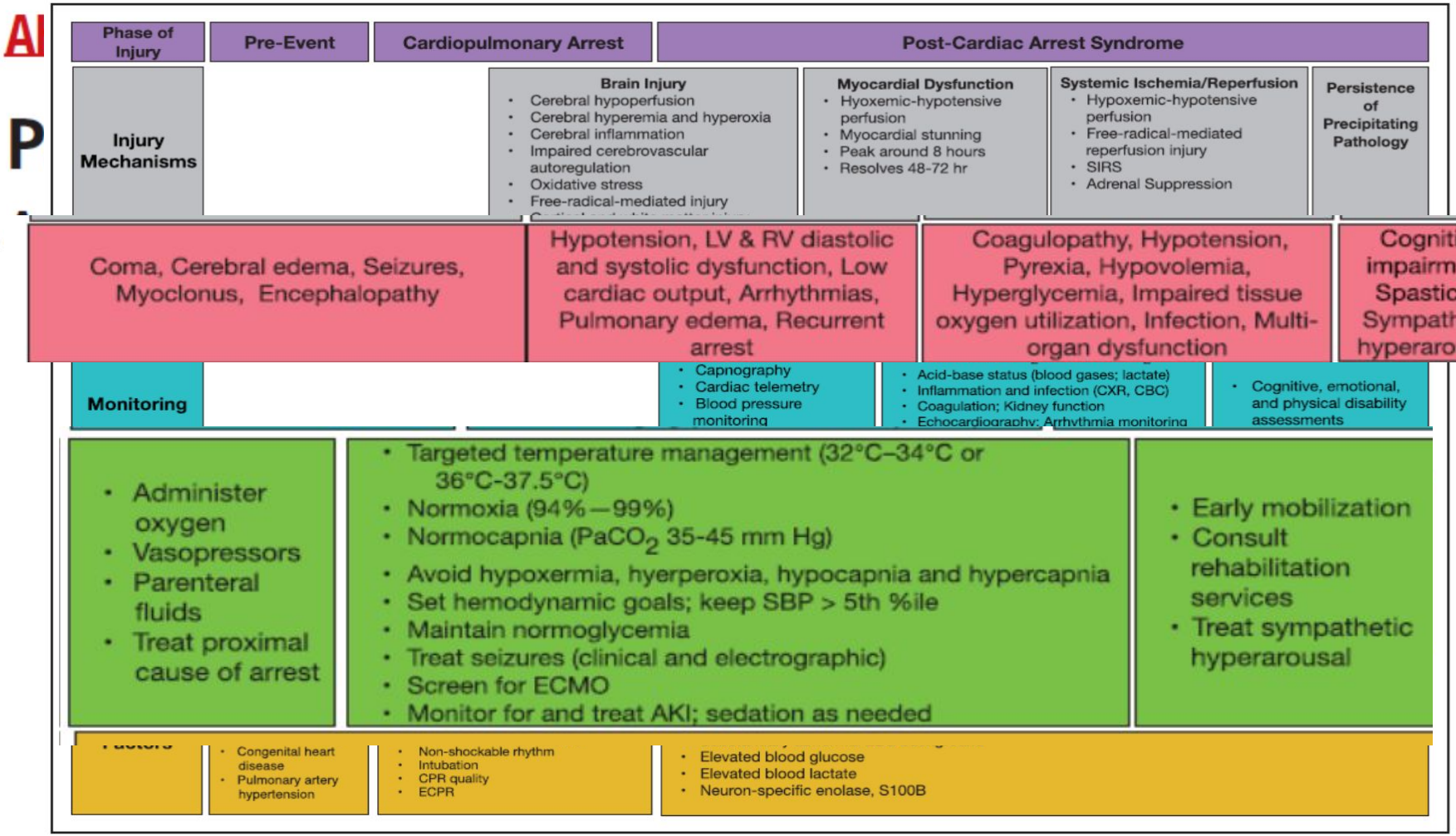
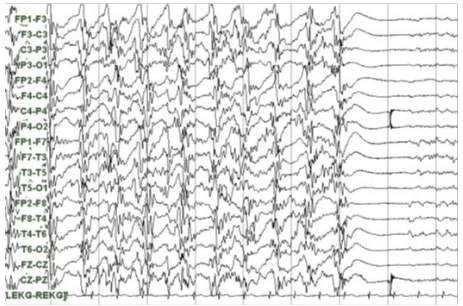
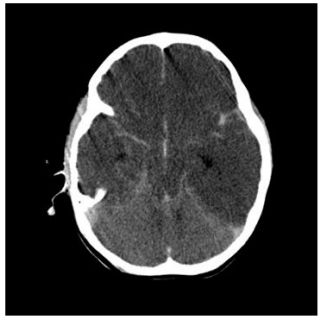

Phase of Injury
Pre-Event
Cardiopulmonary Arrest
Post-Cardiac Arrest Syndrome
Injury Mechanisms
Brain Injury
Cerebral hypoperfusion
Cerebral hyperemia and hyperoxia
Cerebral inflammation
Impaired cerebrovascular autoregulation
Oxidative stress
Free-radical-mediated injury
Myocardial Dysfunction
Hyoxemic-hypotensive perfusion
Myocardial stunning
Peak around 8 hours
Resolves 48-72 hr
Systemic Ischemia/Reperfusion
Hypoxemic-hypotensive perfusion
Free-radical-mediated reperfusion injury
SIRS
Adrenal Suppression
Persistence of Precipitating Pathology
Coma, Cerebral edema, Seizures, Myoclonus, Encephalopathy
Hypotension, LV & RV diastolic and systolic dysfunction, Low cardiac output, Arrhythmias, Pulmonary edema, Recurrent arrest
Coagulopathy, Hypotension, Pyrexia, Hypovolemia, Hyperglycemia, Impaired tissue oxygen utilization, Infection, Multi-organ dysfunction
Cognitive impairment, Spasticity, Sympathetic hyperarousal,
Monitoring
Capnography
Cardiac telemetry
Blood pressure monitoring
Acid-base status (blood gases; lactate)
Inflammation and infection (CXR, CBC)
Coagulation; Kidney function
Cognitive, emotional, and physical disability assessments
Administer oxygen
Vasopressors
Parenteral fluids
Treat proximal cause of arrest
Targeted temperature management (32°C–34°C or 36°C-37.5°C)
Normoxia (94%—99%)
Normocapnia ($PaCO_2$ 35-45 mm Hg)
Avoid hypoxermia, hyerperoxia, hypocapnia and hypercapnia
Set hemodynamic goals; keep SBP > 5th %ile
Maintain normoglycemia
Treat seizures (clinical and electrographic)
Screen for ECMO
Monitor for and treat AKI; sedation as needed
Early mobilization
Consult rehabilitation services
Treat sympathetic hyperarousal
Congenital heart disease
Pulmonary artery hypertension
Non-shockable rhythm
Intubation
CPR quality
ECPR
Elevated blood glucose
Elevated blood lactate
Neuron-specific enolase, S100B

Post Arrest Brain Injury

Seizures



Myoclonus



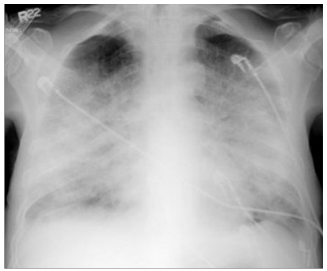
Coma

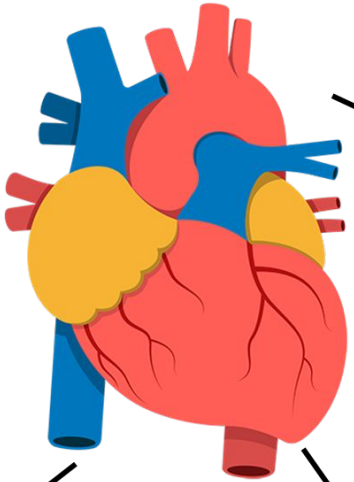
Cerebral Edema

Neumar 2008, Topjian 2019

Post Arrest Myocardial Dysfunction

Pulmonary Edema

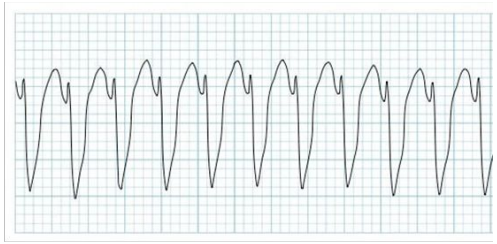




Low cardiac output

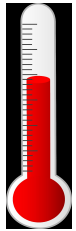
Hypotension

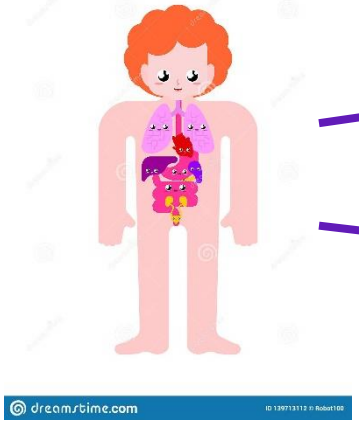
Arrhythmia



Neumar 2008, Topjian 2019

Post Arrest Systemic Ischemia/Perfusion





Pyrexia

Coagulopathy

Hyperglycemia

Adrenal Suppression

Hypovolemia

Infection

Vasoplegia

End Organ Dysfunction

Neumar 2008, Topjian 2019

Blood Pressure

Goal: target a blood pressure higher than at least the 25th percentile in order to avoid hypotension < 5th percentile.

Treatment: Fluids, vasopressors and inotropes at the discretion of the clinical team to meet the goal

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AHA PALS Guidelines: Blood Pressure

After ROSC, we recommend that parenteral fluids and/or vasoactive drugs should be used to maintain a **systolic blood pressure greater than fifth percentile for age**

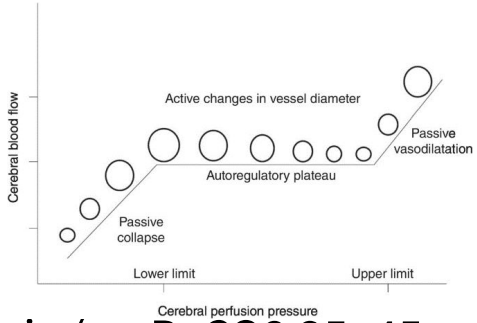
When appropriate resources are available, continuous arterial pressure monitoring is recommended

Topjian, Circulation, 2020

Oxygenation

- **Goal**
  - For patients with expected baseline SpO2 >94%, should be maintained oxygen saturation 94 -98%
  - For patients with baseline lower saturations due to an underlying condition (e.g cyanotic heart disease), target saturations appropriate to the patient's underlying condition
- **Treatment**: Titrate FiO2, ventilator rate, volume, or peak end expiratory pressure (PEEP) at discretion of the clinical team.

Ventilation



- **Goal**
  - If pre-arrest baseline PaCO2 35-45, target normocapnia (eg.PaCO2 35–45 mm Hg), limiting exposure to severe hypercapnia and hypocapnia while accounting for appropriate pH.
  - If pre-arrest higher baseline PCO2 due to an underlying condition target pCO2 appropriate to the patient's baseline PCO2, limiting exposure to relative hypercapnia and hypocapnia, while accounting for appropriate pH.
- **Treatment**: at the discretion of the clinical team.

Euglycemia

- **Goal:** Serum glucose is between 80 to 200 mg/dL, prevent hypoglycemia
- **Treatment**
  - Administering glucose containing fluids and titrating insulin or removing dextrose from fluids.
  - Be aware: On rewarming, insulin resistance lessons and hypoglycemia may develop rapidly.
  - Insulin can cause hypokalemia, closely monitor during induction to replete and during rewarming remove potassium if insulin stopped

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Seizure Monitoring

- Seizures are common after cardiac arrest.
- When resources are available, continuous electroencephalography (EEG) monitoring is recommended for the detection of seizures and evaluation of treatment efficacy (AHA 1, LOE C-LD)
- If continuous EEG is not available, intermittent screening EEG can be used.
- Duration of monitoring at the discretion of the clinical team.

Seizure Treatment

- Treatment is recommended for clinical and electrographic seizures (AHA 1 , LOE C-LD).
- Treatment of electrographic status epilepticus should optimally occur in conjunction with neurologists (AHA 2a, LOE C-EO).
- Selection of anti-seizure medication(s) is at the discretion of the attending physician(s).
- Side effects of antiseizure medication should be considered.

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Monitoring and Assessments

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- Laboratory testing will be conducted at baseline and throughout the intervention period (0 to 120 hours).
- Basic metabolic panel, glucose, calcium, mag, phos for safety
  - Q6 hours during induction and rewarming
  - Q12 during maintenance hypothermia and normothermia periods:

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- Daily
  - Complete blood count (CBC),
  - Liver function tests (LFTs)
  - Daily coagulation profile: prothrombin time (PT) and International Normalized Ratio (INR), partial thromboplastin time (PTT),
  - Arterial Blood Gas At least, daily for the first 72 hours.

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Cultures & Imaging

- Blood cultures
  - Randomization, days 2 and 4
  - Baseline respiratory culture
- Chest xray
  - Daily to confirm esophageal probe location

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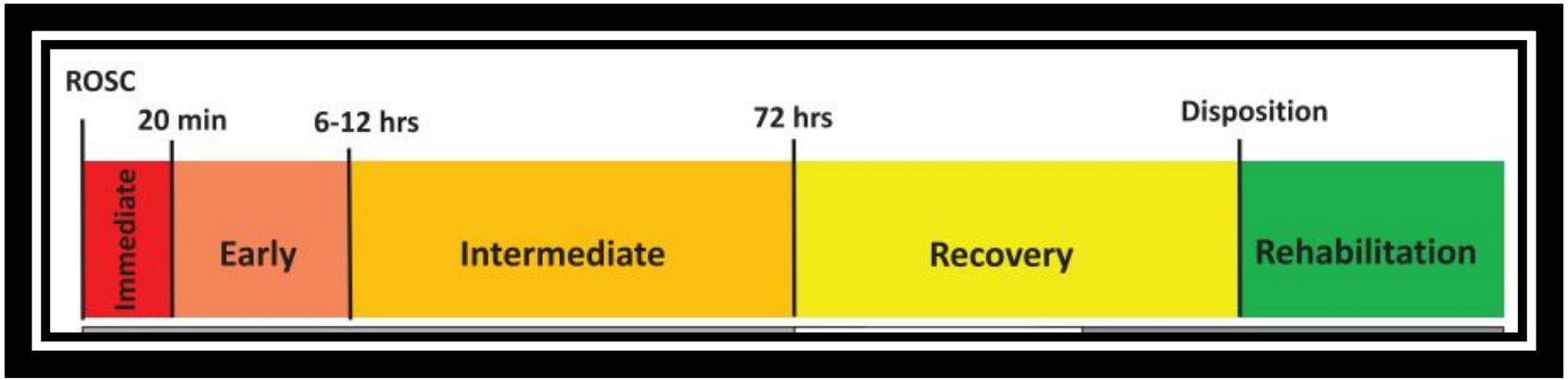
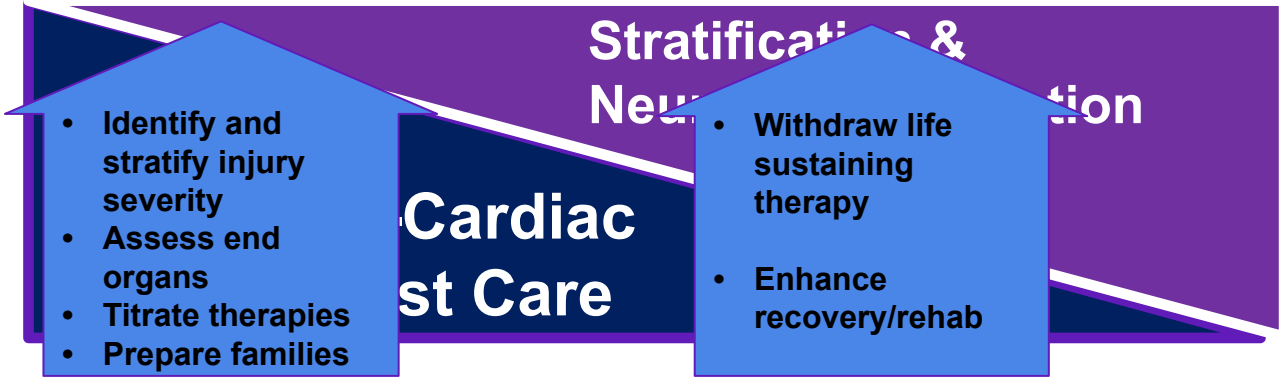
Post-Arrest Care Continuum





Withdrawal from intensive care and life support

- Patients are ineligible for this study if an early withdrawal of life support (prior to 120 hours) is consistent with goals of care

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Withdrawal of life sustaining therapies <u>prior</u> to 120 hours after randomization

- After cooling and rewarming and sedatives are off for an appropriate period of time.
- Brain Death Evaluation
  - Consistent with institutional brain death pathway
  - Patients should be rewarmed and off sedation and paralytics >24 hours
- *In individuals who have undergone cooling for more than 24 hours a longer time interval prior to initiation of a brain death evaluation should be considered.*

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Withdrawal of life sustaining therapies prior to 120 hours after randomization

- *Neurologic Futility*:
  - In select cases (eg. herniation on neuroimaging, or > 24 h fixed non-reactive pupillary responses, with absent motor responses to painful stimuli in the absence of paralytics or sedation).
  - Consultation with neurology and documentation of criteria upon which the decision to withdraw life-sustaining therapies should be considered in this setting.

Withdrawal of life sustaining therapies prior to 120 hours after randomization

- *Non-neurological Prognosis*: Life support may be withdrawn prior to 120 hours for futility or otherwise poor prognosis based on non-neurological problems

- *Changes in Goals of Care:* Changes in goals of care are not to be pursued with the parent or LAR prior to 120 hour from randomization.

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Withdrawal of life sustaining therapies <u>after</u> 120 hours from randomization

- *Determination of neurologic prognosis:* If the clinical team feels that the neurologic prognosis is most consistent with irreversible injury such that a favorable outcome is no longer possible, they may undertake testing for neurologic prognostication. Neurologic prognostication of unfavorable outcome is a common basis for withdrawal of life sustaining therapies that invariably leads to death.

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Approach to surgical procedures or imaging

- For brief imaging (eg. head CT) closely monitor temperature during transport; temperature may drop below intended range.
- More prolonged imaging is unlikely to be performed as neuroprognostication will not occur until after 120 hours.
- If procedures or surgeries are clinically necessary during the cooling intervention, clinicians and proceduralists should consider the impact of cooling (eg. bleeding risk) on the participant and determine if rewarming is necessary based on what is best for the patient.

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Tracking and Reporting of Clinical Guideline Variations and Excursions

- There will be tracking of excursions and feedback to sites for improvement

- More to come…

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Order Set Creation

- Create and order set
- Can share through epic via userweb

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Summary

- Standardized post cardiac arrest care will minimize the risk of losing the true signal of the study
- Work and educate your clinical team

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Consenting Lessons from THAPCA

Dr. Alexis Topjian & Moni Weber

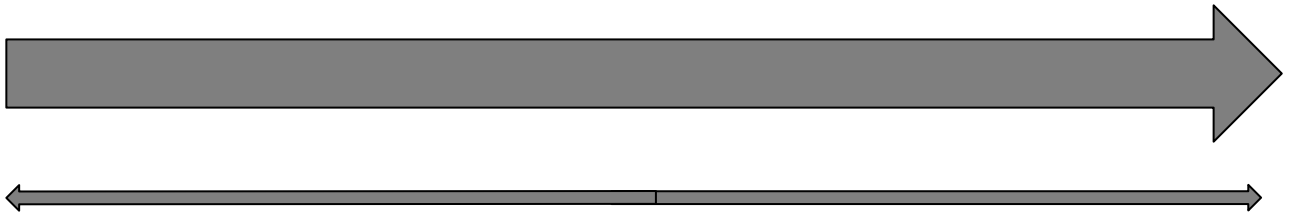
Consenting Timeline and To Do's

TIME 0

ROSC

TIME 6

Randomization



PREP

PREPPING THE CLINICAL TEAM
CONFIRMING THE CLINICAL TEAM HAS SPOKEN WITH THE FAMILY
KNOWLEDGE ABOUT PATIENT AND ARREST
DETAILS ABOUT THE FAMILY

CONSENT

SELL IT JUST RIGHT
ENTHUSIASM & CONFIDENCE
INSTILL TRUST
BE CURRENT ON CONDITION
GIVE TIME FRAME

P-ICECAP

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

SIREN

Consenting for research in Pediatric Emergency Situations is hard!

- It can be any time of day or night.
- The child just died, and came back to life.
- The event was unexpected.
- The family is stressed.
- The unit is busy caring for the child.
- Many people are talking to the family and the research team may be new faces in an already long line of medical personnel.

- But there are some tips of the trade that previous studies like THAPCA have taught us.

P-ICECAP

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SIREN

Prep before you enroll that first patient

EDUCATE EDUCATE EDUCATE

- Educate the medical team members about the study.
- Educate PICU staff members that most families want their child to participate in a study that may benefit for their child.
- Find ‘champions’ willing to learn more details about the study and can help if they are on shift when a study patient comes in.

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Before you approach the family

- Know the consent document! Practice ahead of time. Role play is good.
- Know the child's first name and gender.
- Confirm that the child's attending has briefed the family on the patient's condition.
- Get into the right frame of mind. Not an ask, but an opportunity to participate in a study that may have benefit.
- Have the family placed in a quiet area and limit family members.

They should hear this from their doctor first, not you!

Ask the team to use clear language that the family will hear again from you during the consent discussion

“Your child had a cardiac arrest when their heart stopped. They received CPR and it was restarted.”

“You child has brain injury because their brain did not have normal, blood flow during CPR. “

“We want to decrease the chance that brain injury will become brain damage.”

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Talking with the Family

- Have someone from the care team introduce you to the family.
- Address clinical issues first. Talk about child's condition. Mention the risk for brain injury after cardiac arrest.
- Use the word 'study', not 'investigation' or 'research' when introducing the study.
- All arms of the study have active temperature control.

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Talking with the Family

- Emphasize patient safety with concrete examples. “If your child needs to go to the OR, then X will happen.”
- Remind them that the study is voluntary.
- Mention adult and neonatal studies done previously.
- Mention number of patients enrolled so far and that there is ongoing independent review of safety data.

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Delivery

- Don’t over- or undersell. Hit it down the middle. Don’t come on too strongly or forcefully.
- Show enthusiasm and confidence in the study.
- Assure that the main goal is to give their child the best care possible.
- Instill trust. Be current on child’s condition, current plan and clinical team’s plan going forward.
- Speak in simple terms.

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Delivery

- Have coordinator mention something if you forgot.
- Listen closely to any questions the family has and answer concisely.
- Give the family about 30 minutes to decide, if you have that time. Give them a set time you will return.
- Stress that it is important to get the treatment started as soon as possible after an arrest.

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Benefits

Potentially reduces brain injury after an arrest.

Research staff is reviewing labs/images and following care. This is an ‘extra pair of eyes’ on your child.

Child would be on a regimented protocol and is under strict guidelines.

Free follow up neurologic evaluation at one year…

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Risks

Bleeding, infection, cardiac rhythm can be affected by cooling

Lab values (electrolytes, glucose) can be affected by cooling

Fever: short durations of cooling may not prevent fever as well as longer durations

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Risks continued

Keeping child comfortable and preventing shivering may require additional medication.

Skin problems related to cooling device requiring treatment.

When mentioning risks, might follow with statement on how the risk is minimized. (“*we minimize this by….*” or “*It is standard of care, whether your child is in the study or not, to…., so it will be watched very closely*.”)

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Consent process follow up

- Get the answer from one of the family members you spoke with.
- Do not accept “the family said no” from bedside nurse or family you have not yet met.
- If the family member shares why they want to decline the study, there may be opportunities to answer more questions.
- Children come to centers like yours for cutting edge care and studies that improve outcomes for children.

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Debrief

- Debrief with coordinator and other research team members who were present for the consent discussion.
- What seemed to work well and what was problematic?
- Was there a phrase used that made the family skeptical / reassured them?
- Did you forget something?
- Did you over-stress or under-stress a risk or benefit?

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Questions and Discussion

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WebDCU for Everyone

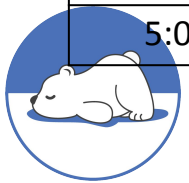
Sara Butler

Lunch

NHLBI UG3HL159134, U24HL159132

The Afternoon

Time	Topic	Speaker
12:10 PM	**Lunch**	
1:10 PM	Protocol and Standardization Game - Kahoot!	Dr. William Meurer, MD, & Moni Weber, RN, BSN, CCRP
2:10 PM	Adverse Event Reporting	Dr. Robert Silbergleit, MD
2:50 PM	Baseline & Central-Measured Outcome	Dr. Beth Slomine, PhD
3:35 PM	**Break**	
3:45 PM	Neurological Outcomes	Dr. Faye Silverstein, MD
4:00 PM	Central IRB and E-Consent	Dr. Robert Silbergleit, MD, & Deneil Harney, MPH, MSW
4:15 PM	Adaptive Design	Dr. John VanBuren, PhD
5:00 PM	**Adjourn Day 2**	



P-ICECAP

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

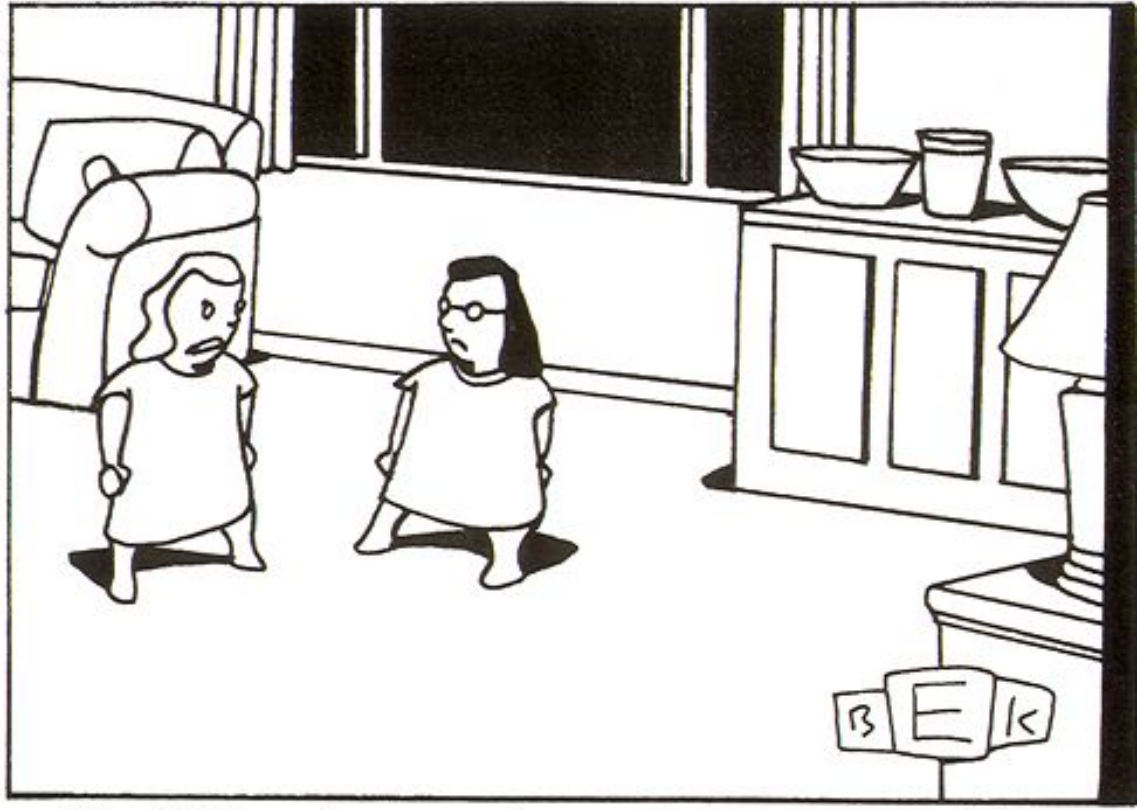
SIREN

Protocol and Standardization Game - Kahoot!

Dr. William Meurer & Moni Weber

Adverse Event Reporting

Dr. Robert Silbergleit



"Try falling down and scraping your knee. Then you can talk to me about pain."

Adverse Event Reporting in P-ICECAP

Adverse

Serious

Severity

Relatedness

Reporting - timelines

Naming

Event type - Expectedness

Narratives

What is adverse?

Adverse Events (AEs) are ". . . any untoward medical occurrence in a subject that was not previously identified which does not necessarily have a causal relationship to the study drug…"

Abnormal lab values are only AE when they are deemed clinically significant by the site investigator.

What is serious?

Adverse events that…

- Are Fatal
- Are Life-threatening
- Cause or prolong hospitalization
- Result in disability/congenital anomaly
- Require intervention to prevent permanent impairment

Report all SAE.

Report only non-serious occurring in the first 120 hours (5 days)

What is severity?

Is a grade of “how bad” - from 1 to 5

Use the CTCAE dictionary for event-specific **severity** when possible

Use the CTCAE general scheme for events not in the dictionary

Do **NOT** use the CTCAE dictionary for anything else.

NIH NATIONAL CANCER INSTITUTE

What is severity?

Non-event specific severity

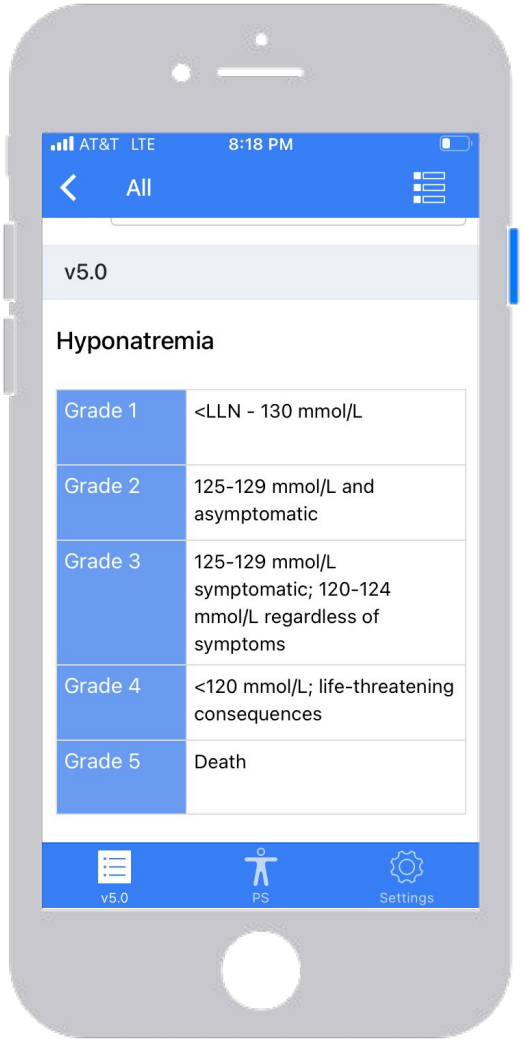
Grade refers to the severity of the AE. The Common Terminology Criteria for Adverse Events (CTCAE) dis
descriptions of severity for each AE based on this general guideline:

- *Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention no*
- *Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instru*
- *Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolong*
  limiting self care Activities of Daily Living.
- *Grade 4 - Life-threatening consequences; urgent intervention indicated.*
- *Grade 5 - Death related to AE.*

Q02		Grade	○ Grade 1 ○ Grade 2 ○ Grade 3 ○ Grade 4 ◉ Grade 5

What is severity?

Event specific severity



What is relatedness?

Not Related
- The timing is wrong and there was clearly another cause

Unlikely (both of the following, but timing doesn't matter)
- Another cause is possible
- Not something the intervention is known to cause

Reasonable Possibly (2 of 3)
- Timing is suggestive.
- Not readily caused by something else
- This is something the intervention is known to cause.

Definitely (must have all 3)
- Timing suggests intervention caused the problem.
- No other possible cause.
- This is something the intervention is known to cause.

What is relatedness?

The intervention in P-ICECAP is **duration** of cooling

Not use of a temperature control device or TTM per se

What not to report…

Do not report events EXISTING PRIOR to randomization
(unless there is a change in severity)

Do not report “just in case”

Repeated occurrences that are really part of a single event

How to report

Form 104 – Adverse Event Case Report Form (CRF)

One AE per CRF

Data Entry Timelines

Non-serious AEs must be entered and **submitted** within 5 days of study team discovery.

SAEs must be entered and **submitted** within 24 hours of discovery by the study team.

Naming

Report the DIAGNOSIS, not the symptoms:

Fever, cough, chest pain, crackles = pneumonia

Report the PATHOLOGY, not the outcome or treatment

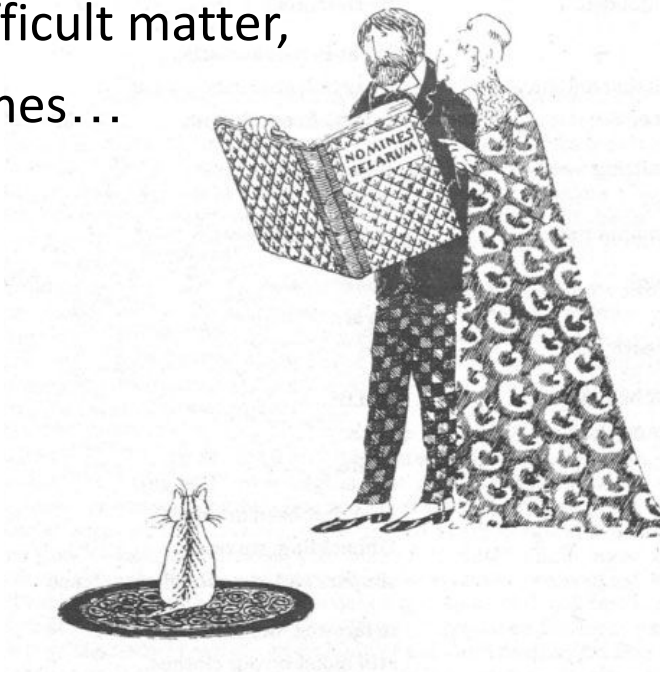
Not ‘death’ but the event that caused death

Not ‘intubation’ but the event that required it

The MedDRA dictionary

Naming

Like T.S. Eliot’s cats, the naming of events is a difficult matter, and like his cats, events have three different names…



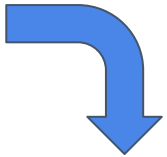
Event name

LLT - lowest level term

Preferred term

Naming

No.	Item Description	Data V
	This CRF is optional and should only be completed if the subject experiences a reportable Adverse Event. Reportable AEs include: *All non serious adverse events are collected through day 4.* *All serious adverse events (SAEs) occurring until participation in study has ended.*	
Q01	Adverse Event Name *Brief description of event*	Multisystem organ failure *(100 char.)*
LLT	AE MedDRA Term	Multiorgan failure *(100 char.)*



No.	Item Description	Data Value
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Q01	Adverse Event Name *Brief description of event*	Multisystem organ failure
LLT	AE MedDRA Term	Multiorgan failure
PT	AE preferred term	Multiple organ dysfunction syndrome

Naming when there is a procedure

Is getting cannulated and placed on ECMO an SAE?

Is getting renal replacement therapy an SAE?

Is placing a transthoracic cardiac pacemaker an SAE?

Naming fatal events

Is a death an SAE?

Provide the cause of death. Don’t use “synonyms” for death.

What if the cause of death is a pre-existing condition?

Is withdrawal-of-life-sustaining treatments ever an SAE?

AE of special interest (Q12 Event Type)

Pneumonia

Blood stream infection

Urinary tract infection

Cardiac arrhythmia requiring intervention

Neurological worsening

Hypokalemia

Neutropenia

Thrombocytopenia

Seizures

Repeated cardiac arrest

Other adverse event

Set apart by study-specific definitions - and are typically serious

Write good SAE narratives

Be concise but complete (not comprehensive) - think 1000 characters

- Include only the pertinent PMH and HPI
- Describe the event
- Describe the response
- Describe the outcome
- And say when each of those happened

Look for and respond to queries promptly

How are SAE narratives used?

Medical safety monitor

DSMB

Study Leadership

Example narrative (637 characters)

A 41 yo woman was resuscitated from asystolic cardiac arrest on 7/31/21. Cooling with a definitive device started at 10:07. Head CT at 10:57 showed edema and subsequent over-read indicated impending uncal herniation. FOUR score remained at a 0 throughout hospital stay. Clinical exam was consistent with brain death though determination was confounded by methadone ingestion, which also precluded an apnea trial. Following the planned duration of cooling and rewarming, a radionuclide brain perfusion scan was conducted on 8/2/21 at 09:40 which was consistent with brain death. Brain death was confirmed and she died on 8/2/21 at 09:40.

Too much (2357 characters)

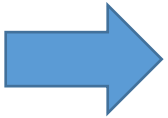
73-year-old male with no known past medical history who presented with an out-of-hospital witnessed cardiac arrest on September 8, 2020. He had bystander CPR, AED was placed and had a shockable rhythm defibrillated twice. EMS, patient was found to be in PEA and CPR was continued and was given ACLS until ROSC was achieved. Patient was intubated in the field and initial ECG reportedly showed ST elevations. However, the patient was evaluated by cardiology and was thought tdid not meet criteria for a STEMI. As result, targeted temperature management was started. Cooling duration of 12 hours and rewarming over 12 hours per ICECAP protocol. Rewarming was completed 9/9 @16:09 On September 10, purposeful movement was noted and His neurologic examination today was reported as being reassuring. Patient was being diuresed, however his urine output dropped. Also, lactate was noted to be elevated intermittently, highest of the day was 3. Creatinine was up to 1.19 from 0.8. LFTs were only minimally elevated. His distal extremities were somewhat cool, more proximally they were lukewarm. over the course of the day, the patient had a new norepinephrine requirement as well as dobutamine. Transthoracic echocardiogram was done on 9/9/2020 and showed an LVEF of 24%. RV was not well visualized but probably normal. No significant valvular lesions noted. There is mild concentric LVH. There is severe global

~~Too much~~ - Just enough

73-year-old male was resuscitated following PEA arrest 9/8/20. Cooling with a definitive cooling device was initiated 9/8/20 at HH:MM and he completed the protocol 9/9/20 at 16:09. TTE 9/9/20 revealed LVEF 24% with severe global hypokinesis. On 9/10/20, the patient began to have decreased urine output, elevated lactate, increased creatinine and developed a vasopressor and inotrope requirement. The patient was taken for a coronary angiogram and intra-aortic balloon pump. The angiogram was without evidence of significant obstructive lesions. The IABP was removed 9/13, and the patient was taken off pressors 9/14/20. The patient's clinical status continues to improve.

Too much - resolution

73-year-old male with no known past medical history who presented with an out-of-hospital witnessed cardiac arrest on September 8, 2020. He had bystander CPR, AED was placed and had a shockable rhythm defibrillated twice. EMS, patient was found to be in PEA and CPR was continued and was given ACLS until ROSC was achieved. Patient was intubated in the field and initial ECG reportedly showed ST elevations. However, the patient was evaluated by cardiology and was thought tdid not meet criteria for a STEMI. As result, targeted temperature management was started. Cooling duration of 12 hours and rewarming over 12 hours per ICECAP protocol. Rewarming was completed 9/9 @16:09 On September 10, purposeful movement was noted and His neurologic examination today was reported as being reassuring. Patient was being diuresed, however his urine output dropped. Also, lactate was noted to be elevated intermittently, highest of the day was 3. Creatinine was up to 1.19 from 0.8. LFTs were only minimally elevated. His distal extremities were somewhat cool, more proximally they were lukewarm. over the course of the day, the patient had a new norepinephrine requirement as well as dobutamine. Transthoracic echocardiogram was done on 9/9/2020 and showed an LVEF of 24%. RV was not well visualized but probably normal. No significant valvular lesions noted. There is mild concentric LVH. There is severe global hypokinesis. Troponins were noted to be 8.49 at their peak, downtrending 2.16. PA catheter was placed and the patient's RA pressure was measured at approximately 14, PA pressure was 70/54, PA saturation was 56, cardiac output was 3.27, cardiac index is 1.62, SVR was 905. PA pulsatility index was 0.67, cardiac power output is 0.44. Due to the patient's decreased urine output, increasing pressor and inotrope requirement, and decreased ejection fraction in the setting of a presumed VF arrest, the patient was taken for expedited coronary angiogram as well as placement of an intra-aortic balloon pump. The coronary angiogram was without evidence of significant obstructive lesions. . Update: 9/14. pt doing much better. hemodynamically stable, off pressors. balloon pump and PAC removed 9/13, urine output and CL improved. Pt extubated, following commands and interacting, although still somewhat confused. Continues on broad spectrum abx.



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Not enough

- Blood culture positive for beta hemolytic strep, left peripheral line. Patient started Levaquin oral tablet qd x 10 days

~~Not~~ enough

- ~~Blood culture positive for beta hemolytic strep, left peripheral line. Patient started Levaquin 750 mg oral tablet qd x 10 days~~

- A 14 yo with epilepsy was enrolled on 3/15/17 at 9:02PM. On 3/17/17 she had fever, leukocytosis, and underwent a workup for an infectious source. Blood culture grew strep agalactiae sensitive to ceftriaxone and levofloxacin, but no other source was found. She was treated with ceftriaxone IV x 4 days, and levofloxacin PO x 10 days, and had no further fevers.

Style points

Use generic drug names

Use a spell checker

Have the site PI read critically

SAE review process

Site manager review

Internal quality reviewer

Independent medical safety monitor review

MedWatch

“I just have to create a few loose ends for other people to clear up, and then I can out of here.”

While being screened for enrollment in P-ICECAP, a 2 yo who had drowned has a prolonged seizure requiring treatment which resolves after several rounds of anticonvulsants. She is subsequently appropriately enrolled. Anticonvulsant medications are continued after enrollment as is continuous EEG monitoring.

Adverse event?	Yes / No	Related?	A. Not related
Serious?	Yes / No		B. Unlikely
Expected?	Yes / No		C. Reasonable Possibly
			D. Definitely

While being screened for enrollment in P-ICECAP, a 2 yo who had drowned has a prolonged seizure requiring treatment which resolves after several rounds of anticonvulsants. She is subsequently appropriately enrolled. Anticonvulsant medications are continued after enrollment as is continuous EEG monitoring. Brief electrographic seizures are seen. No AED are added or changed.

Adverse event?	Yes / No	Related?	A. Not related
Serious?	Yes / No		B. Unlikely
Expected?	Yes / No		C. Reasonable Possibly
			D. Definitely

While being screened for enrollment in P-ICECAP, a 2 yo who had drowned has a prolonged seizure requiring treatment which resolves after several rounds of anticonvulsants. She is subsequently appropriately enrolled. Despite continued anticonvulsants she develops more seizures in the ICU, and her propofol is titrated up from mild sedation to burst suppression.

Adverse event? Yes / No

Serious? Yes / No

Expected? Yes / No

Related? A. Not related

B. Unlikely

C. Reasonable Possibly

D. Definitely

An 8 yo with asthma arrests and aspirates while being endotracheally intubated. He is resuscitated and appropriately enrolled in P-ICECAP. On hospital day 3, he develops pneumonia and his PEEP is increased to improve recruitment. Three hours later he decompensates from a pneumothorax. A chest tube is placed without complications.

Adverse event? (Yes) / No

Serious? (Yes) / No

Expected? (Yes) / No

Related? A. Not related

(B. Unlikely)

C. Reasonable Possibly

D. Definitely

A 17 yo who arrested from an opioid overdose is resuscitated, appropriately enrolled in P-ICECAP, and randomized to 96 hours cooling duration. Temperature is monitored only with an esophageal probe. At 90 hours, his nurse notices that the esophageal probe has backed out into the pharynx. When advanced back into the esophagus, the temperature is noted to be 29 degrees, but then corrects to 33 over the next hour.

Adverse event? Yes / No

Serious? Yes / No

Expected? Yes / No

Related?

A. Not related

B. Unlikely

C. Reasonable Possibly

D. Definitely

An 12 yo with myocarditis induced arrest and resuscitation is appropriately enrolled. On ICU day 3 her routine metabolic panel shows a potassium of 3.2 and an AST of 99 for which she receives no specific intervention.

Adverse event(s)?	Yes / No	Related?	A. Not related
Serious?	Yes / No		B. Unlikely
Expected?	Yes / No		C. Reasonable Possibly
			D. Definitely

A 17 yo who arrested from an opioid overdose is resuscitated, and appropriately enrolled. After 7 days of diligent care, he remains unresponsive, head CT shows extensive cerebral edema with impending herniation. His parents opt for a transition to comfort care and he is terminally extubated and dies.

Adverse event(s)?	Yes / No	Related?	A. Not related
Serious?	Yes / No		B. Unlikely
Expected?	Yes / No		C. Reasonable Possibly
			D. Definitely

Baseline & Central-Measured Outcome

Dr. Beth Slomine

Agenda

- Study Hospital responsibilities necessary for outcomes assessment for…
  - The first 48 hours
  - 30 days or hospital discharge (whichever comes first)
  - 2 and 11 months
- 3 and 12-month telephone interview

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

Baseline Assessment for Outcomes

- *Understanding functioning prior to cardiac arrest is essential for outcome analysis*
  - Identify a primary caregiver as respondent
  - Rate of global neurological functioning and overall functioning based on medical records and/or caregiver report
  - Facilitate caregiver completion of 3 questionnaires
  - Collect data within 48 hours of enrollment

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

SIREN

Identifying and supporting respondent

- Respondent must be adult very familiar with everyday behavior of child (usually a parent).
- Identify obstacles: language, literary status, level of distress.
  - Language - If proficiency in English comprehension is poor and Spanish is respondent's primary language, use Spanish version of questionnaires.
  - Literacy - Must have sufficiently high reading skills to be able to read and understand questionnaires. If poor reading skills are suspected, read items to respondent.
  - Distress - If the family is distraught, it is suggested that a member of the study team sit down with the respondent, and, if necessary, read questionnaires and assist with completion.

Establishing Rapport

Establishing a relationship that encourages accurate, unbiased information is important for obtaining valid results. Take time to establish rapport:

- Briefly describe purpose of assessment: “Learning about [NAME’S] behavior and your family prior to this cardiac arrest will help us get a total picture of him/her”
- Explain their role: “Given that you have spent the most time with [NAME], you will be the important person who is going to give us the information about his/her behavior.”
- Explain the structure of the questionnaires: “You will be giving us information about [NAME’S] physical, emotional, social, and cognitive functioning as well as information about his/her family and household.”

Global Neurological and Overall Functioning

PCPC – Pediatric Cerebral Performance Category

POPC – Pediatric Overall Performance Category

- Review the medical record for the pre-CA level of impairment, medical conditions, AND etiology of delays in functional impairment.
- If records are not clear, ask the caregiver about any medical diagnoses the child had prior to the cardiac arrest AND ask whether each diagnosis limited child's functioning in any way.

PCPC/POPC Decision Tree

1. **Normal/Good** = If the child has no disability or medical conditions, and is functioning appropriately, they should be classified as “Normal” on the PCPC and “Good” on the POPC.
2. **Mild Disability** = If the child has minor delays or functional impairments and most skills are within age-appropriate limits, or the child has well-controlled medical conditions, they should be classified as “Mild Disability”.
3. **Moderate Disability** = If the child is significantly delayed or functionally impaired in most areas and demonstrates some level of independence in activities of daily living, they should be classified as “Moderate Disability”.
4. **Severe Disability** = If the child is responsive to the environment but dependent on others for daily support because of impaired brain functioning or other medical conditions (excluding age), the child is classified as “Severe Disability”.
5. **Coma/Vegetative State** = If the child has any degree of coma, is unaware and unresponsive, even if awake in appearance, without interaction with environment, they are classified as “Coma/Vegetative State”.

PCPC/POPC Decision Tree

- *Neurological Disease* is coded on the PCPC **and** the POPC. If the identified functional impairments are the result of *neurological disease (e.g. cerebral palsy),* the PCPC **and** POPC get coded based on level of functional impairments.

- If *non-neurological medical conditions* (e.g., asthma, amputation) impair functioning above and beyond any impairment caused by neurological disease, score disability **ONLY** on the POPC.

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3 Baseline Questionnaires

These questionnaires are to be answered by a primary caregiver about the subject's function PRIOR to cardiac arrest. Answers to these questions become less accurate with time.

1. Family and Household Information Form
2. PedsQL
3. Participant Contact Form

All these forms can be found in the P-ICECAP Toolbox and in WebDCU™

P-ICECAP

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1. Family and Household Information Form

- RC will hand the caregiver the user-friendly printed form for completion.
- If necessary, RC will sit with family and assist with completion.
- The completed form should be entered directly into WebDCU™.

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2. PedsQL

- Appropriate PedsQL form is based on the age of the child on the day the form is completed. Verify date of birth, date of administration and determine exact age, do not round up, in order to choose the appropriate form.

- From the options below, pick only one

  Infant Scales

  PedsQL Infant Scales (2 days – 12 months)

  PedsQL Infant Scales (13 months - < 2 years)

  OR

  Generic Core Scales

  PedsQL Generic Core – Toddler Version (2-4 years)

  PedsQL Generic Core – Child Version (5-7 years)

  PedsQL Generic Core – Child Version (8-12 years)

  PedsQL Generic Core – Teen Version (13-18 years)

2. PedsQL

- RC will hand caregiver the age-appropriate printed form.
- If necessary, RC will sit with family and assist with completion.
- The appropriate PedsQL form should be *uploaded to the UofM secure dropbox* so that Kennedy Krieger can score the measure and enter scores into WebDCU™.

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3. Baseline Participant Contact Form

- Study Hospital will obtain contact information from caregiver.
- Study Hospital should ask caregiver for all available contact information and alternates who can either complete the interview OR find a caregiver.
- Obtain names, telephone numbers, email, preferred contact method, time of day for interview and preferred language of primary caregiver.
- Keep this form at the Study Hospital.

P-ICECAP

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Baseline Assessment Data Entry

- The Study Hospital will:
  - Enter Baseline PCPC/POPC in WebDCU™
  - Enter Family and Household Information into WebDCU™
  - Upload PedsQL to secure UofM box for Kennedy Krieger to review and score
  - Store Participant Contact Form at the Study Hospital
- Kennedy Krieger will:
  - Enter PedsQL scores into WebDCU™

If these forms are not completed within 72 hrs of enrollment, an email reminder will be sent to Study Hospital

Hospital Discharge or 30 days Assessments
(Whichever comes first)

- PCPC/POPC score at time of Hospital Discharge or 30 days, whichever comes first, is required
- PCPC/POPC should be completed from information available in medical record or by consulting care team as close to Hospital Discharge/Day 30 as possible, or from family interview (within 24 hrs of Hospital Discharge/Day 30)
- Refer to PCPC/POPC Decision Tree while reviewing records for information about development and functional skills at time of discharge or 30 days

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3 Month Follow-Up: What is included?

- There is ONE component to the 3-month evaluation - 3-month **telephone interview** done by Kennedy Krieger
- *3-month data will be used for interim analyses and to add in adaptive allocation to cooling doses; collecting the VABS-3 in 3-month survivors is essential for trial success.*
- Kennedy Krieger has 3 months ± 2 weeks to complete the 3 months' assessment, thus it is important that the Study Hospital contact the family as soon as possible within the window (two to four weeks) prior to the 3-month date.

2 months after cardiac arrest

In preparation for the 3-month outcome

Pre-interview instruction for Study Hospitals

- 2-4 weeks prior to 3-month evaluation, contact caregiver to obtain vital status and if alive, update contact information.
- The Study Hospital can schedule interview time directly with caregiver.
- Please let caregiver know to expect interview will take between 30 minutes and up to 1.5 hours.

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2 months after cardiac arrest

In preparation for the 3-month outcome

Pre-interview instruction for Study Hospitals

- All attempts to contact family at 2 months must be documented on Contact Tracking Form
- There is no minimum or maximum number of contacts prescribed.
- If Study Hospital is having trouble reaching the family, please reach out to Beth Slomine (Slomine@kennedykrieger.org) and Nishta Amin (aminN@kennedykrieger.org) and/or Moni Weber (monij@umich.edu) for advice and suggestions.

2 months after cardiac arrest

In preparation for the 3-month outcome

For Subjects Who Are Living

- The UPDATED Participant Contact Form should be uploaded to secure UofM dropbox.
- To ensure that form has been received the Study Hospital should ALSO email Dr. Beth Slomine at Slomine@kennedykrieger.org and Nishta Amin at AminN@kennedykireger.org to confirm receipt.
- It is critical the subject ID/date of birth are entered correctly on form so that Kennedy Krieger enters information for the correct participant into WebDCU™.

2 months after cardiac arrest

In preparation for the 3-month outcome

For Subjects Who Are Deceased

- If the subject died between hospital discharge and the 3-month evaluation time point, DO NOT forward contact information to Kennedy Krieger.
- Kennedy Krieger will only be contacting caregivers of participants who survived.
- Study Hospitals must complete the End of Study Form in WebDCU™.

2 months after cardiac arrest
In preparation for the 3-month outcome

For Subjects Lost to Follow-Up

- Discuss difficulties connecting with local PI and Beth Slomine and/or Moni Weber
- If suggestions exhausted, participant will be considered lost to follow-up for the 3-month visit.
- **The participant will still be considered active and attempts should be made to contact the caregiver at 11 months**.

P-ICECAP

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12-Month Follow-Up: What is included?

- There are TWO components to the 12-month evaluation.
  1. 12-month **telephone interview** done by Kennedy Krieger
  2. On site 12-month **Neurologic Evaluation**, completed at the Study Hospital by a clinical neurologist.
- *The primary outcome is **VABS-3 Mortality Composite at 12 months*** collected via telephone interview
- *Collecting VABS-3 in 12-month survivors is essential for trial success* and should be completed PRIOR to the onsite neurological examination
- Kennedy Krieger has 12 months ± 2 weeks to complete the 12 months' assessment
- Contact caregiver as soon as possible within window (2-4 weeks prior to 11-month date).

11 months after cardiac arrest
In preparation for the 12-month outcome

Pre-interview instruction for Study Hospitals

- 2-4 weeks prior to 3-month evaluation, contact caregiver to obtain vital status and if alive, update contact information.
- The Study Hospital can schedule interview time directly with caregiver.
- Please let caregiver know (remind caregiver) to expect interview will take between 30 minutes and up to 1.5 hours.

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11 months after cardiac arrest

In preparation for the 12-month outcome

Pre-interview instruction for Study Hospitals

- All attempts to contact family at 11 months must be documented on Contact Tracking Form
- There is no minimum or maximum number of contacts prescribed.
- If Study Hospital is having trouble reaching the family, please reach out to Beth Slomine (Slomine@kennedykrieger.org) and Nishta Amin (aminN@kennedykrieger.org) and/or Moni Weber (monij@umich.edu) for advice and suggestions.

11 months after cardiac arrest

In preparation for the 12-month outcome

For Subjects Who Are Living

- 11-month Participant Contact Form will be uploaded to the secure UofM dropbox. To ensure that form has been received.
- Study Hospital should ALSO email Dr. Beth Slomine at Slomine@kennedykrieger.org and Nishta Amin at AminN@kennedykrieger.org to confirm receipt.
- It is critical the subject ID/Date of Birth are entered correctly on the contact form so that Kennedy Krieger enters information for the correct participant into WebDCU™.

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11 months after cardiac arrest

In preparation for the 12-month outcome

For Subjects Who Are Deceased

- If the participant died between hospital discharge and 12-month evaluation time point, DO NOT forward contact information to Kennedy Krieger.
- Kennedy Krieger will only be contacting families of known survivors.
- Study Hospitals must complete the End of Study Form in WebDCU™.

11-month Procedures

In preparation for the 12-month outcome

For Subjects Lost to Follow-Up

- Discuss difficulties connecting with local PI and Beth Slomine and/or Moni Weber
- If suggestions exhausted, participant will be considered lost to follow-up for the 12-month visit.
- Study Hospital will complete the End of Study Form in WebDCU™, indicating that the 12-month assessment was not done and when queried will explain that the family could not be contacted.

12-month Onsite Neurologic Evaluation

Instructions for Study Hospitals prior to administration

- The neurologic examination must be completed **AFTER** the 12-Month Kennedy Krieger Evaluation.
- Schedule the Month 12 Neurologic Evaluation.
- Remind the participant/caregiver of the appointment at the time of contact for the 12-month evaluation and discuss site specific reimbursement policies for travel costs with the caregiver.
- Provide a paper copy of the correct neurologic exam form to the neurologist. There are two versions of the form (< 3 years of age, ≥ 3 years of age at the time of evaluation)

12-month Onsite Neurologic Evaluation

Instructions for Study Hospitals after administration

- Collect Neurology Exam Form as soon as possible after exam completion. A copy should be retained by neurologist.
- Ensure all elements of Global Assessment Score are complete and ask neurologist to provide any missing or unclear information.
- Enter information from Neurology Exam Form directly into WebDCU™.
- Retain Neurology Exam Form with research files.
- Upload a copy to secure UofM dropbox for review by Drs. Silverstein or Ichord.
- Drs. Silverstein/Ichord will reach out to site neurologists if there are questions or concerns.
- If necessary, site neurologist will correct form and site RC will revise WebDCU™ entries.
- Once the Neurology Exam is completed, complete the End of Study CRF.

What will we do with these outcomes?

- Vineland Adaptive Behavior Scale (VABS-3) at 12 months is highest priority
- VABS-3 Mortality Composite at 12 months is the primary outcome
- Pre-CA PCPC scores used to determine if child will be included in primary analysis
- Other measures are important for planned secondary analyses

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VABS-3

- **Adaptive Behavior Composite**
  - **Communication**
  - **Daily Living Skills**
  - **Socialization**

  - Motor Skills

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Health-related Quality of Life

- PedsQL – child functioning
  - Infant Scales or Core
  - Cognitive functioning
- PedsQL Family Impact Module – caregiver and family functioning
  - Parent functioning
  - Family functioning

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PCPC/POPC

- Brief Interview
- Captures diagnoses/medical problems
- AND functional impairments associated with each diagnosis/problem

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3-month telephone interview

Measure	Domain	Collection Method	Time
Vineland Adaptive Behavior Scale – Third Edition (VABS-3)	Neurobehavioral Functioning	Caregiver interview via phone	30-60 min
PedsQL Core or Infant Scales	Health Related Quality of Life	Caregiver report via phone	3-5 min
PedsQL cognitive functioning	Cognitive Functioning	Caregiver report via phone	1-3 min
PedsQL Family Impact Module (family functioning scales only)	Family Burden	Caregiver report via phone	1 min
PCPC/POPC	Neurological and global functioning	Caregiver report (based on VABS-3 responses and any clarifying questions)	2-5 min

12-month telephone interview

Measure	Domain	Collection Method	Time
VABS-3 – Primary study outcome	**Neurobehavioral Functioning**	**Caregiver interview via phone**	**30-60 min**
PedsQL Core or Infant Scales	Health Related Quality of Life	Caregiver report via phone	3-5 min
PedsQL cognitive functioning	Cognitive Functioning	Caregiver report via phone	1-3 min
PedsQL Family Impact Module (entire scale)	Family Burden	Caregiver report via phone	3-5 min
PCPC/POPC	Neurological and global functioning	Caregiver report (based on VABS-3 and any clarifying questions)	0-5 min

Challenges and Solutions

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Methods Used To Maximize Follow-up: Lessons Learned from the Therapeutic Hypothermia After Pediatric Cardiac Arrest Trials

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Before Sites Go Live

- Discuss scientific rationale for study and potential impact study could have on patient population.
- Emphasize consequences of lost to follow-up on primary outcome.
- Orient study teams to detailed protocol and procedures.
- Many additional strategies (Gildea et la., 2020, supplemental table 1)

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Thank you for your attention!

Questions and Discussion

Break

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Neurological Outcomes

Dr. Faye Silverstein

Background

- In the THAPCA trials we implemented a scoring method to evaluate long-term neurological outcomes after pediatric cardiac arrest resuscitation
- Neurological exams were performed by neurologists at each participating site and scored by each examiner
- Two neurologists reviewed all scoring forms and addressed any scoring problems that arose

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Global Assessment Score

- Measure of assessment of function in major neurobehavioral domains
  - sensorimotor function, language, cognition, behavior
- Scores reflect clinical judgment of the examiner
- Scores in each domain: 0 - 3

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Scoring and Interpretation

- Pediatric neurologists perform conventional, detailed age- and function-appropriate neurological exams
- Based on the exam, in some cases supplemented by history from the parent(s), the examiner assigns scores from 0 - 3 in 7 categories
  0 = normal 3 = severely abnormal
- Total score 0 = normal
- Total score 21 = most severe abnormalities in all categories
- Based on our initial data review, we defined five categories for comparison with VABS-2 scores

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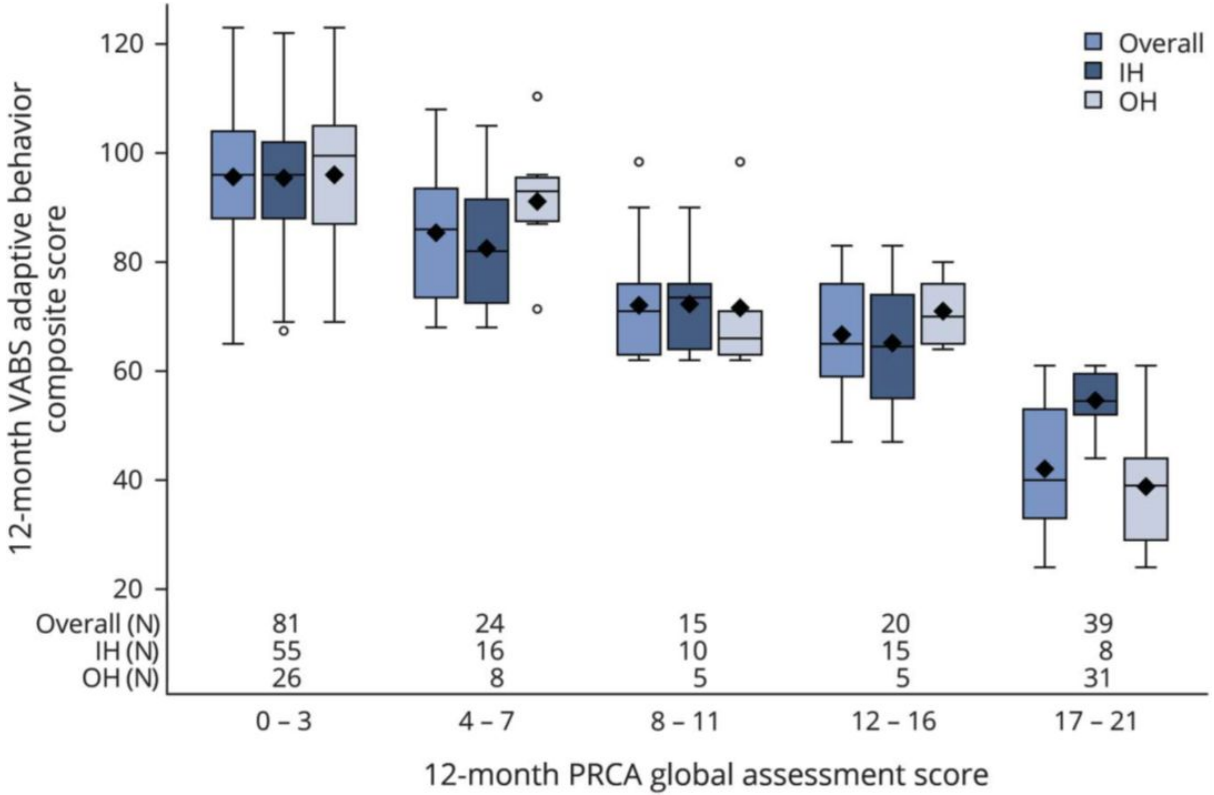
Correlation With VABS-2



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Normal Outcomes

- 16/75 OH-CA survivors had normal neurological exams one year later, including 4 who required over 20 minutes of CPR

- 34/104 IH-CA survivors had normal neurological exams one year later, including 13 who required over 20 minutes of CPR

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P-ICECAP vs. THAPCA

- We anticipate that we'll have better overall outcomes and more normal outcomes in P-ICECAP than in THAPCA-OH
  - Broader inclusion criteria
    - Inclusion of cases with motor GCS = 5
  - Hopefully, we'll identify more effective treatment for some subjects

P-ICECAP

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Outcome Assessments

- WE NEED TO IDENTIFY AT LEAST ONE NEUROLOGIST AT EACH SITE WHO WILL DO THE EXAMS
- WE WILL SCHEDULE ZOOM MEETINGS THIS FALL TO REVIEW P-ICECAP, EXAM PROTOCOLS, AND SCORING
- Scoring forms have two versions:
  - Infant version – up to third birthday
  - Child version – age 3 and older

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Important Task

- Please identify at least one neurologist at your site by August 1 and send the name to Frank Moler (fmoler@med.umich.edu)
- If you prefer, it would be fine to identify two neurologists at your site
- We will have Zoom meetings in early fall to provide P-ICECAP overview and review the details of the neurological outcome evaluation plan

P-ICECAP

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Neurological Outcome Forms

- All will be reviewed by FSS or RI
- Any scoring questions will be addressed with the site neurologist
- Research coordinators at each site enter assessment score data in Web DCU
- No information about cooling duration is included in these forms

GLOBAL Assessment Score.

Summarize and grade your impressions in the following 7 categories. Circle the score in each category that best represents your final impression of your exam findings:

A. Sensorimotor Deficit - score each side separately

	A1.Left side	A2.Right side
None	0	0
Mild but no impact on function	1	1
Moderate with some functional limitations	2	2
Severe or Profound with missing function	3	3

For items scored in Category A1 and A2, identify all the of the types of Sensorimotor Deficits that you observed:

☐ Abnormality of tone ☐ Quadriparesis ☐ Hemiparesis ☐ Sensory deficit

☐ Global delay in gross motor skill attainment ☐ Global delay in fine motor skill attainment

B. Other motor or sensory deficit (includes cranial nerve deficits)

None	0
Mild but no impact on function	1
Moderate with some functional limitations	2
Severe or Profound with missing function	3

For items scored in Category B, identify all the of the types of Other Sensorimotor Deficits that you observed:

☐ Vision impairment ☐ Difficulty with drinking, chewing or swallowing ☐ Ataxia ☐ Movement disorder

☐ Other, describe:

GLOBAL Assessment Score.

C. Language Deficit – Production (include dysarthria)

None	0
Mild but no impact on function	1
Moderate with some functional limitations	2
Severe or Profound with missing function	3

D. Language Deficit - Comprehension

None	0
Mild but no impact on function	1
Moderate with some functional limitations	2
Severe or Profound with missing function	3

E. Cognitive Deficit

None	0
Mild (little impact on daily function)	1
Moderate with some functional limitations	2
Severe or Profound with missing function	3

F. Behavioural Deficit

None	0
Mild (little impact on daily function)	1
Moderate with some functional limitations	2
Severe or Profound with missing function	3

For Categories E and F, describe the Cognitive or Behavioral Deficits that you observed:

Other comments regarding scoring:

TOTAL SCORING: _____/ 21

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Questions

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Extra Slides

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PRCA NEUROLOGICAL OUTCOME MEASURE - INFANT VERSION (Up to 3 years old)

STANDARDIZED NEUROLOGICAL EXAM modified from PSOM-SNE (Revised 5.03.07)

Revised 4.13.09

IDENTIFYING DATA

ID# _____ **Site:** _____ **Date of assessment** (yyyy-mm-dd): _____

Date of birth: (yyyy-mm-dd): _____ **Location of Assessment:** ☐ In-patient ☐ Out-patient Clinic

SCORING INSTRUCTIONS:
Each item can be scored as Normal, Abnormal, or Not Done (includes items that are not age-appropriate or that were not assessed). For abnormal items, assess and score severity of abnormality (1- mild; 2- moderate; 3-severe), based on your best clinical judgment. Guidelines for Scoring are given as suggestions, and need not be viewed as absolute criteria for scoring.

LEVEL OF CONSCIOUSNESS

TEST ITEM	Normal	Abnormal	Notes
Level Of Consciousness			

BEHAVIOR, MENTAL STATUS

TEST ITEMS	Normal	Abnormal	Not Done	Guidelines for Scoring
Activity Level				Excessively quiet, hyperresponsive, fidgety – age dependent
Interpersonal Interaction				With parents and examiner
Cooperation				Age dependent
Attention				Age dependent
Affect				Extremely shy, withdrawn totally flat, gaze avoidance
Object Permanence				

LANGUAGE

TEST ITEMS	Normal	Abnormal	Not Done	Guidelines for Scoring
Receptive language				**6 mo** orients to sound **10 mo** inhibits to "no" **12 mo** one-step command with gesture **16 mo** one-step command without gesture, points to body parts **24 mo** two-step commands, points to named pictures
Expressive language development				**By 12 mos**. - 1-2 words **12-18 mos**. – 10-20 single words **2 years**. – 50 words, 2 word phrase **3 years** - 200 words, 3+ word sentences
Comments				

CRANIAL NERVES

TEST ITEMS		Normal	Abnormal	Not Done	Guidelines for Scoring
Visual Fields / Vision	Right				Facing patient at 2–3 ft encourage to stare at your eyes and tell when they see object come into view from side (or note gaze shifting toward object)
	Left				
Pupillary Light Reflex	Right				Direct and Consensual
	Left				
Funduscopy	Right				Note Abnormalities:
	Left				
Ocular Motility	Right				Move pen or red object or light smoothly from right to left and back testing full range. Watch for nystagmus or dysconjugate eye movements
	Left				
Facial Movements	Right				Observe smile, observe mouth symmetry during vocalization. Listen to speech quality, observe eye closure for symmetry
	Left				
Hearing	Right				Finger-rub for infants or whisper at 2 - 3 feet away.
	Left				
Swallow					Based on history or observation
Palate and gag	Right				Observe during open mouth crying or demonstrate with tongue protruded . 'Say 'ahhhhh.' Listen to voice quality
	Left				
Head/neck control					
Handling secretions					

GROSS MOTOR Testing

Developmental Gross Motor Use this table only for children who cannot walk independently

TEST ITEMS – Posture & Mobility Skills	Normal	Abnormal	Not Done	Comments
Central Tone: Head lag on 'pull-to-sit'				
Central Tone: Slip Thru On Vertical Suspension				
Central Tone: Ventral Suspension				
Rolls Over (Front To Back)				
Rolls Over (Back To Front)				
Sits Alone				
Moves From Laying To Sitting Unassisted				
Weight-Bearing, Supported				
Walks Holding On				
Walks Independently				

	POWER AND TONE				INVOLUNTARY MOVEMENTS*	
	Normal	Abnormal	Not Tested	Comments	Normal (None)	Abnormal (Present)
Neck/Trunk Muscles						
Right Arm						
Proximal						
Distal						
Left Arm						
Proximal						
Distal						
Right Leg						
Proximal						
Distal						
Left Leg						
Proximal						
Distal						

*Type(s) of Involuntary Movements Seen: Check all that are present

TYPE	COMMENT
Head/neck tremor	
Limb Tremor	
Choreoathetosis	
Dystonic Posturing	
Tics	
Myoclonus	

TENDON REFLEXES

TEST ITEMS		Normal	Abnormal	Not Done	Comments
Biceps	Right				
	Left				
Triceps	Right				
	Left				
Quadriceps	Right				
	Left				
Ankle Jerk	Right				
	Left				
Babinski	Right				
	Left				
Elicited ankle clonus	Right				
	Left				

FINE MOTOR / COORDINATION

TEST ITEMS		Normal	Abnormal	Not Done	Guidelines for Scoring
Pincer Grasp	Right				Encourage to pick up small 2–3 mm ball of rolled up paper
	Left				
Reaching for object	Right				Observe for unusual or asymmetric tremor on reaching for object
	Left				
Sitting Balance					
Standing Balance					
Comments:					

SENSORY

TEST ITEMS		Normal	Abnormal	Not Done	Comments
Light Touch	Right				
	Left				
Pin Prick or Cold	Right				
	Left				

GAIT

Test Only if walking without support

TEST ITEMS	Normal	Abnormal	Not Done *	Comments
Gait - Walking				
Gait - Running				
Climbing up 5 stairs				

**Not Done includes skills that are not developmentally appropriate for the child's current age.*

Other comments:

Central IRB & E-Consent

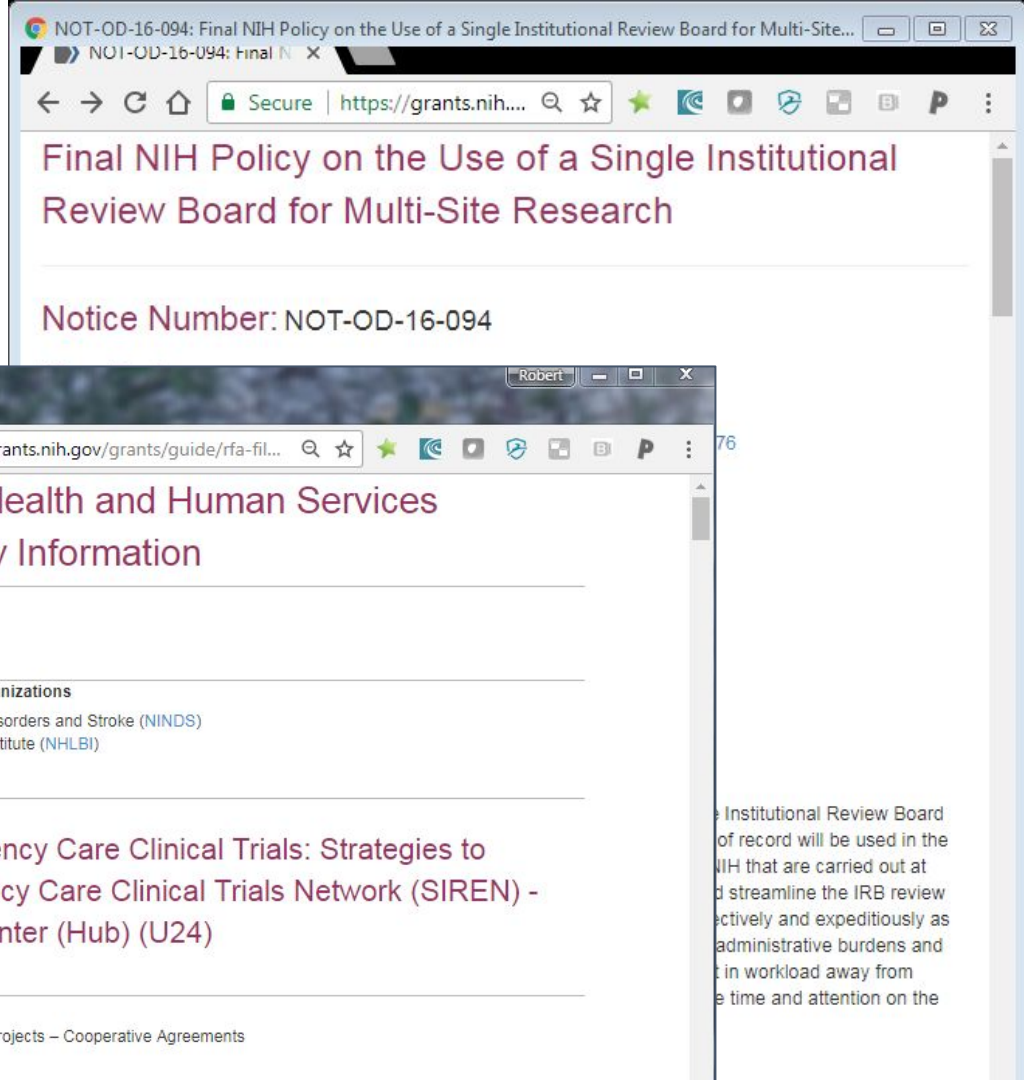
Dr. Robert Silbergleit

"This really is an innovative approach, but I'm afraid we can't consider it. It's never been done before."

Objectives

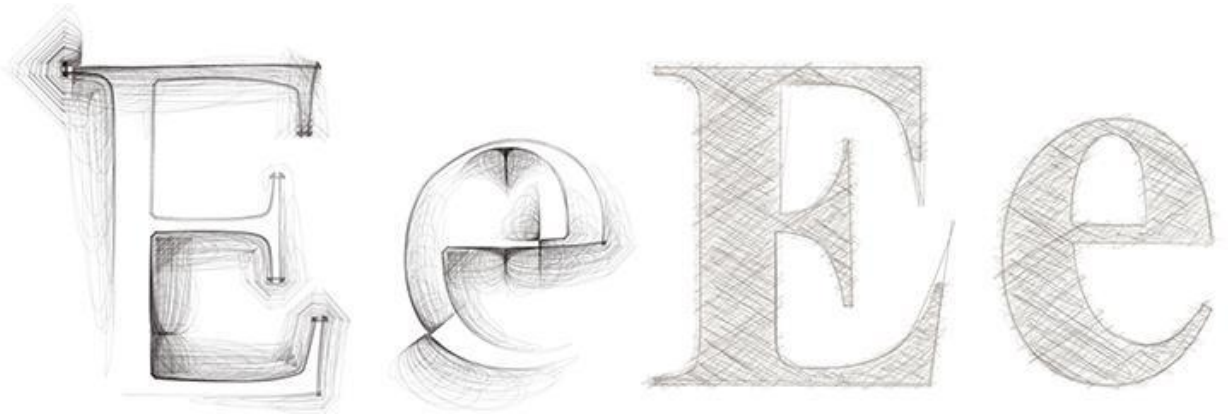
- Why a central IRB?
- What a CIRB is and is not.
- How it works.
- The e-consent platform

Why a central IRB?



Why a central IRB?

- Empowerment
- Equity
- Efficiency
- Expertise



What a CIRB is and is not

- It IS a replacement for your local IRB panel
  - Protocol review, consent review, site applications, AE's, ORIO's, SCR's

- It IS NOT a replacement for everything your local IRB office does
  - Contracts, staff training, certification, billing, COI, radiation comm, etc.

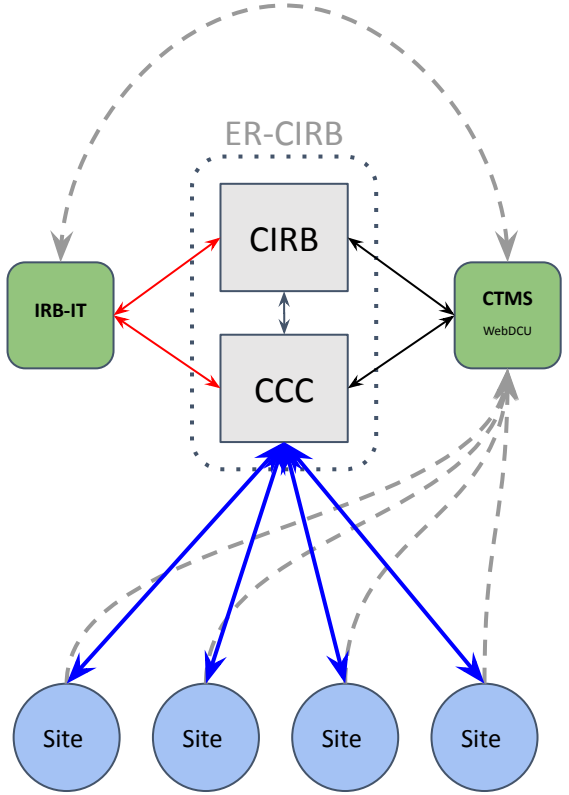
How it works

- Sponsor
- Reliance agreements
- Local processes
- Ceding documents

- Site applications
- Approvals
- AE and ORIO reporting
- SCR

How it works

- Communication
- Data flow
- Avoid triplicative data entry
- Avoid download/upload



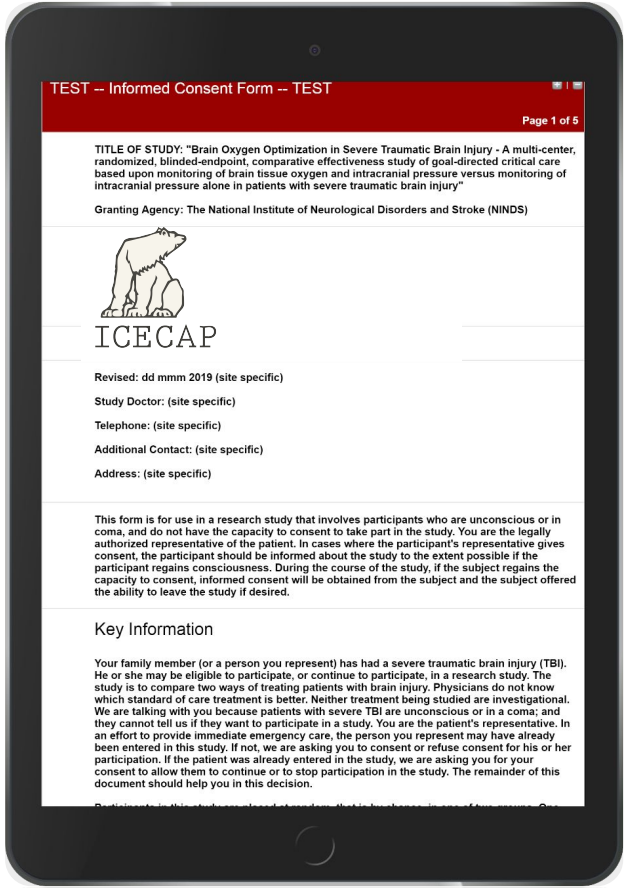
E-consent document

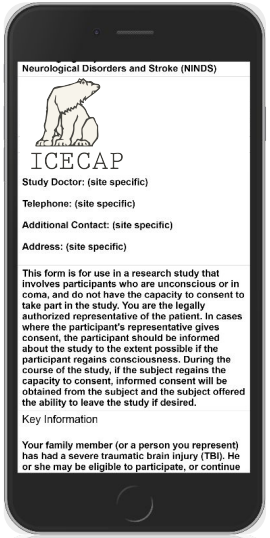
- Consent remains a human process
- Adjustable text size
- Error reduction
- Compliant remote consent documentation
- Completes the web based study binder
- Facilitate remote monitoring

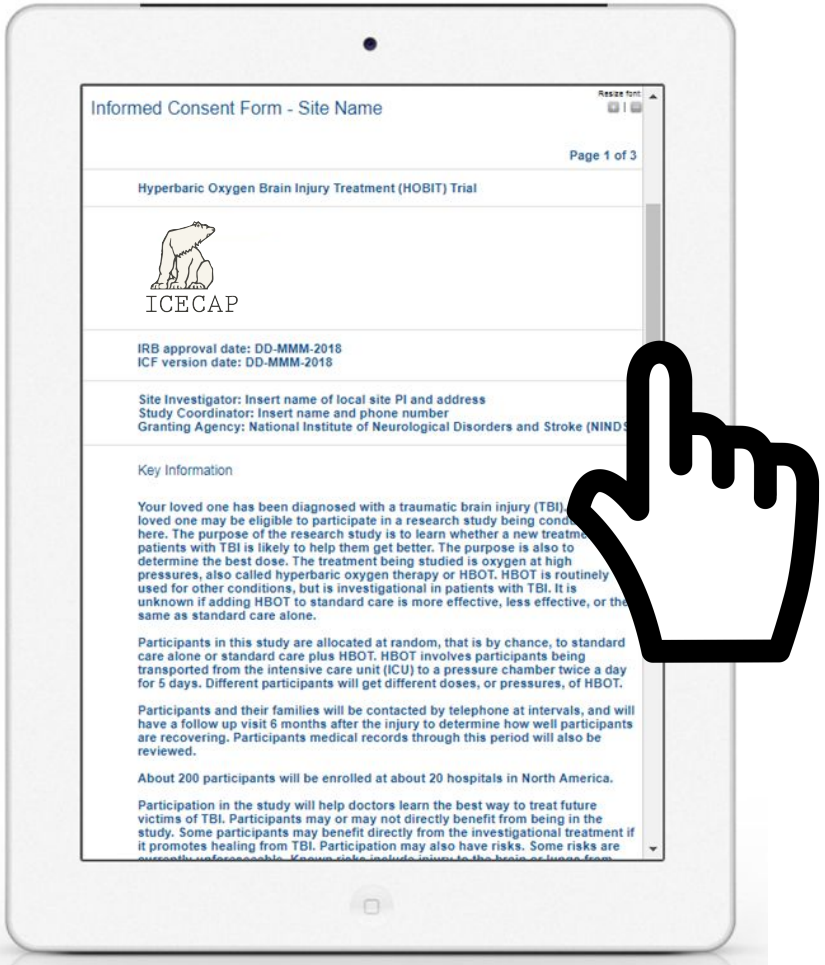
Link to test form

Link to simulator

- RedCap
- Compliant
- Web based






Informed Consent Form - Site Name
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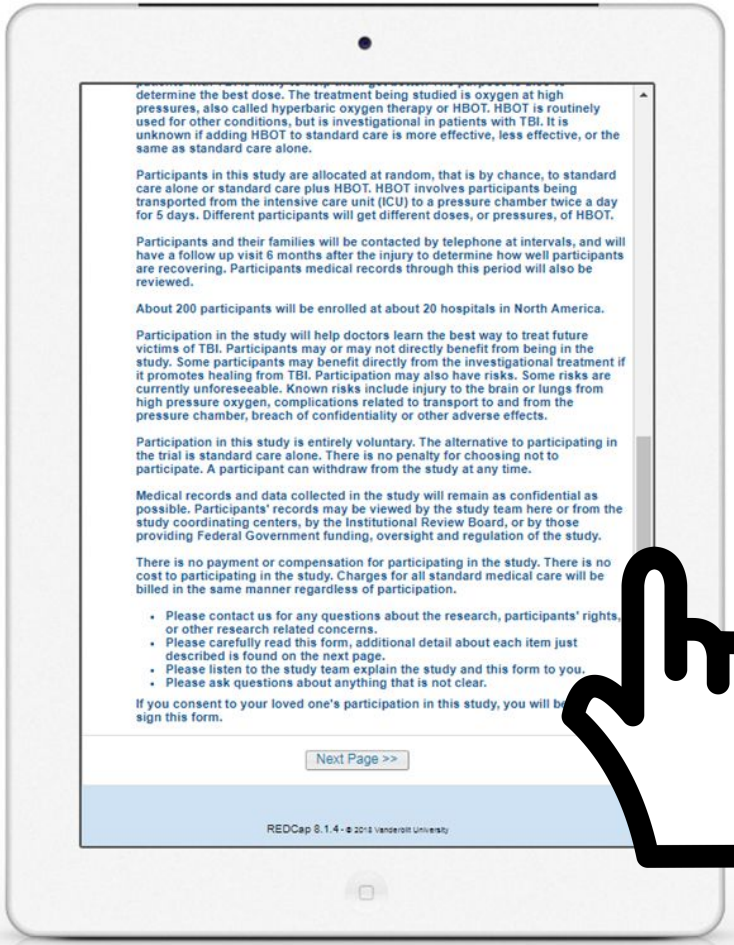
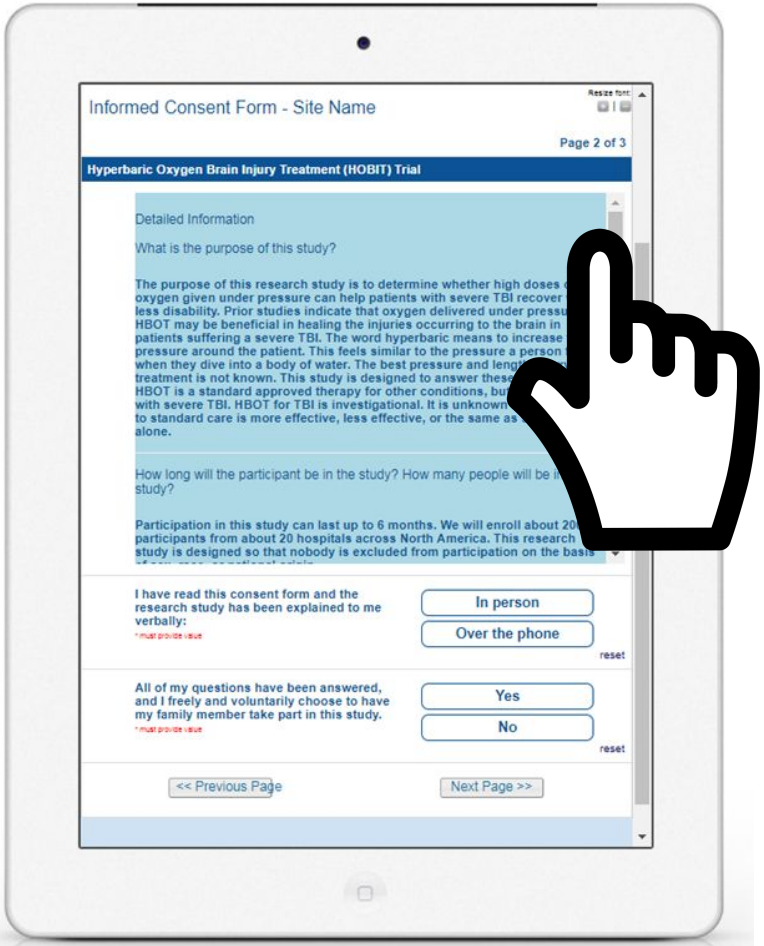
Page 1 of 3
Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial
ICECAP
IRB approval date: DD-MMM-2018
ICF version date: DD-MMM-2018
Site Investigator: Insert name of local site PI and address
Study Coordinator: Insert name and phone number
Granting Agency: National Institute of Neurological Disorders and Stroke (NINDS
Key Information
Your loved one has been diagnosed with a traumatic brain injury (TBI). loved one may be eligible to participate in a research study being cond here. The purpose of the research study is to learn whether a new treatm patients with TBI is likely to help them get better. The purpose is also to determine the best dose. The treatment being studied is oxygen at high pressures, also called hyperbaric oxygen therapy or HBOT. HBOT is routinely used for other conditions, but is investigational in patients with TBI. It is unknown if adding HBOT to standard care is more effective, less effective, or th same as standard care alone.
Participants in this study are allocated at random, that is by chance, to standard care alone or standard care plus HBOT. HBOT involves participants being transported from the intensive care unit (ICU) to a pressure chamber twice a day for 5 days. Different participants will get different doses, or pressures, of HBOT.
Participants and their families will be contacted by telephone at intervals, and will have a follow up visit 6 months after the injury to determine how well participants are recovering. Participants medical records through this period will also be reviewed.
About 200 participants will be enrolled at about 20 hospitals in North America.
Participation in the study will help doctors learn the best way to treat future victims of TBI. Participants may or may not directly benefit from being in the study. Some participants may benefit directly from the investigational treatment if it promotes healing from TBI. Participation may also have risks. Some risks are


determine the best dose. The treatment being studied is oxygen at high pressures, also called hyperbaric oxygen therapy or HBOT. HBOT is routinely used for other conditions, but is investigational in patients with TBI. It is unknown if adding HBOT to standard care is more effective, less effective, or the same as standard care alone.
Participants in this study are allocated at random, that is by chance, to standard care alone or standard care plus HBOT. HBOT involves participants being transported from the intensive care unit (ICU) to a pressure chamber twice a day for 5 days. Different participants will get different doses, or pressures, of HBOT.
Participants and their families will be contacted by telephone at intervals, and will have a follow up visit 6 months after the injury to determine how well participants are recovering. Participants medical records through this period will also be reviewed.
About 200 participants will be enrolled at about 20 hospitals in North America.
Participation in the study will help doctors learn the best way to treat future victims of TBI. Participants may or may not directly benefit from being in the study. Some participants may benefit directly from the investigational treatment if it promotes healing from TBI. Participation may also have risks. Some risks are currently unforeseeable. Known risks include injury to the brain or lungs from high pressure oxygen, complications related to transport to and from the pressure chamber, breach of confidentiality or other adverse effects.
Participation in this study is entirely voluntary. The alternative to participating in the trial is standard care alone. There is no penalty for choosing not to participate. A participant can withdraw from the study at any time.
Medical records and data collected in the study will remain as confidential as possible. Participants' records may be viewed by the study team here or from the study coordinating centers, by the Institutional Review Board, or by those providing Federal Government funding, oversight and regulation of the study.
There is no payment or compensation for participating in the study. There is no cost to participating in the study. Charges for all standard medical care will be billed in the same manner regardless of participation.
Please contact us for any questions about the research, participants' rights, or other research related concerns.
Please carefully read this form, additional detail about each item just described is found on the next page.
Please listen to the study team explain the study and this form to you.
Please ask questions about anything that is not clear.
If you consent to your loved one's participation in this study, you will b sign this form.
Next Page >>
REDCap 8.1.4 - © 2018 Vanderbilt University


Informed Consent Form - Site Name
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Page 2 of 3
Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial
Detailed Information
What is the purpose of this study?
The purpose of this research study is to determine whether high doses
oxygen given under pressure can help patients with severe TBI recover
less disability. Prior studies indicate that oxygen delivered under pressu
HBOT may be beneficial in healing the injuries occurring to the brain in
patients suffering a severe TBI. The word hyperbaric means to increase
pressure around the patient. This feels similar to the pressure a person
when they dive into a body of water. The best pressure and leng
treatment is not known. This study is designed to answer these
HBOT is a standard approved therapy for other conditions, bu
with severe TBI. HBOT for TBI is investigational. It is unknown
to standard care is more effective, less effective, or the same as
alone.
How long will the participant be in the study? How many people will be
study?
Participation in this study can last up to 6 months. We will enroll about 20
participants from about 20 hospitals across North America. This research
study is designed so that nobody is excluded from participation on the basis
I have read this consent form and the research study has been explained to me verbally:
* must provide value
In person
Over the phone
reset
All of my questions have been answered, and I freely and voluntarily choose to have my family member take part in this study.
* must provide value
Yes
No
reset
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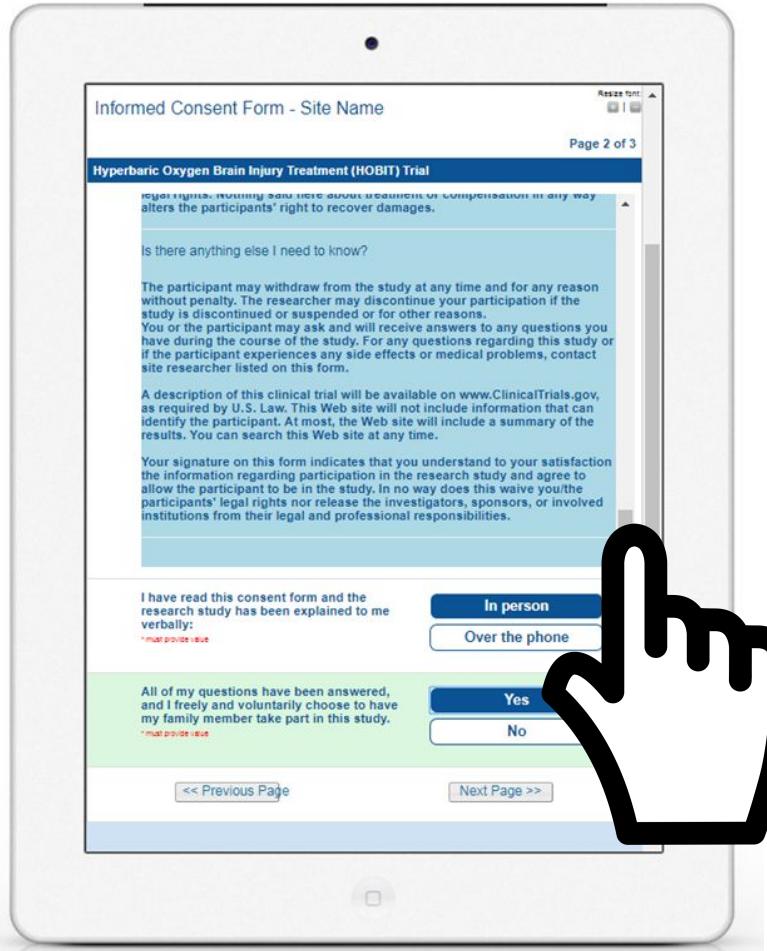
Informed Consent Form - Site Name
Resize font:
Page 2 of 3
Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial
alters the participants' right to recover damages.
Is there anything else I need to know?
The participant may withdraw from the study at any time and for any reason without penalty. The researcher may discontinue your participation if the study is discontinued or suspended or for other reasons.
You or the participant may ask and will receive answers to any questions you have during the course of the study. For any questions regarding this study or if the participant experiences any side effects or medical problems, contact site researcher listed on this form.
A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify the participant. At most, the Web site will include a summary of the results. You can search this Web site at any time.
Your signature on this form indicates that you understand to your satisfaction the information regarding participation in the research study and agree to allow the participant to be in the study. In no way does this waive you/the participants' legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.
I have read this consent form and the research study has been explained to me verbally:
* must provide value
In person
Over the phone
All of my questions have been answered, and I freely and voluntarily choose to have my family member take part in this study.
* must provide value
Yes
No
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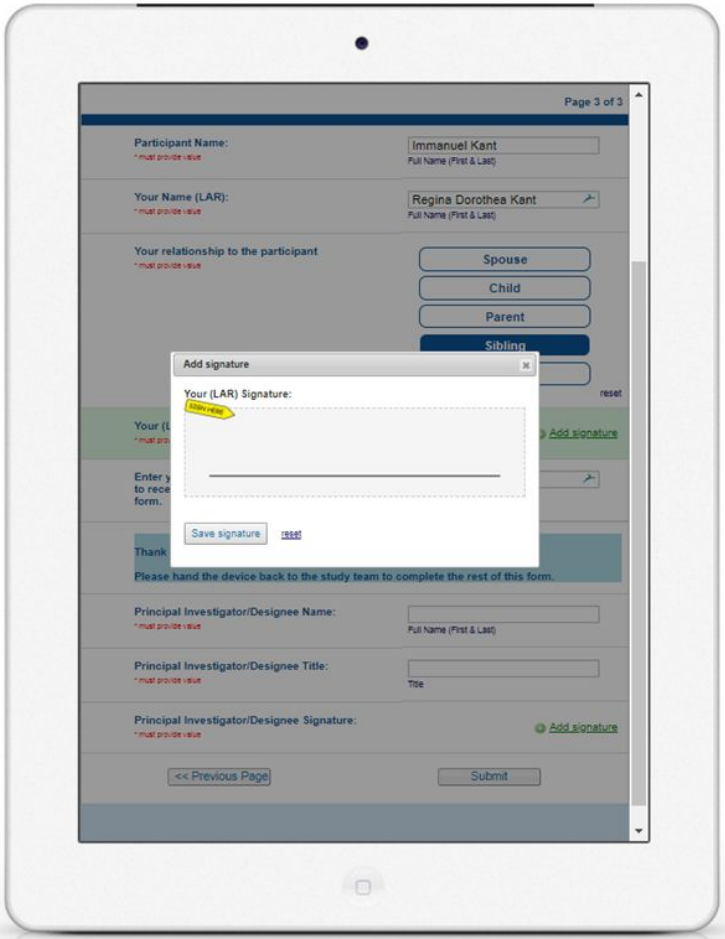
Next Page >>


Page 3 of 3
Participant Name:
Immanuel Kant
Full Name (First & Last)
Your Name (LAR):
Regina Dorothea Kant
Full Name (First & Last)
Your relationship to the participant
Spouse
Child
Parent
Sibling
Add signature
Your (LAR) Signature:
Sign Here
Save signature
reset
Please hand the device back to the study team to complete the rest of this form.
Principal Investigator/Designee Name:
Full Name (First & Last)
Principal Investigator/Designee Title:
Title
Principal Investigator/Designee Signature:
Add signature
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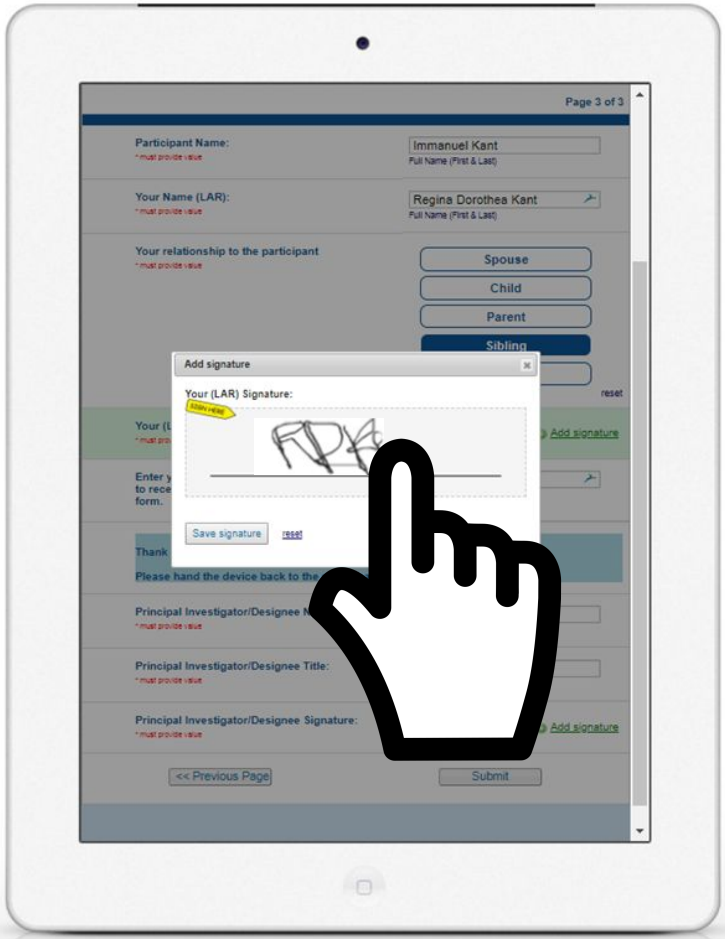
Submit


Page 3 of 3
Participant Name:
Immanuel Kant
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Your Name (LAR):
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Full Name (First & Last)
Your relationship to the participant
Spouse
Child
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Sibling
Add signature
Your (LAR) Signature:
Sign Here
Save signature
reset
Please hand the device back to the
Principal Investigator/Designee Title:
Principal Investigator/Designee Signature:
Add signature
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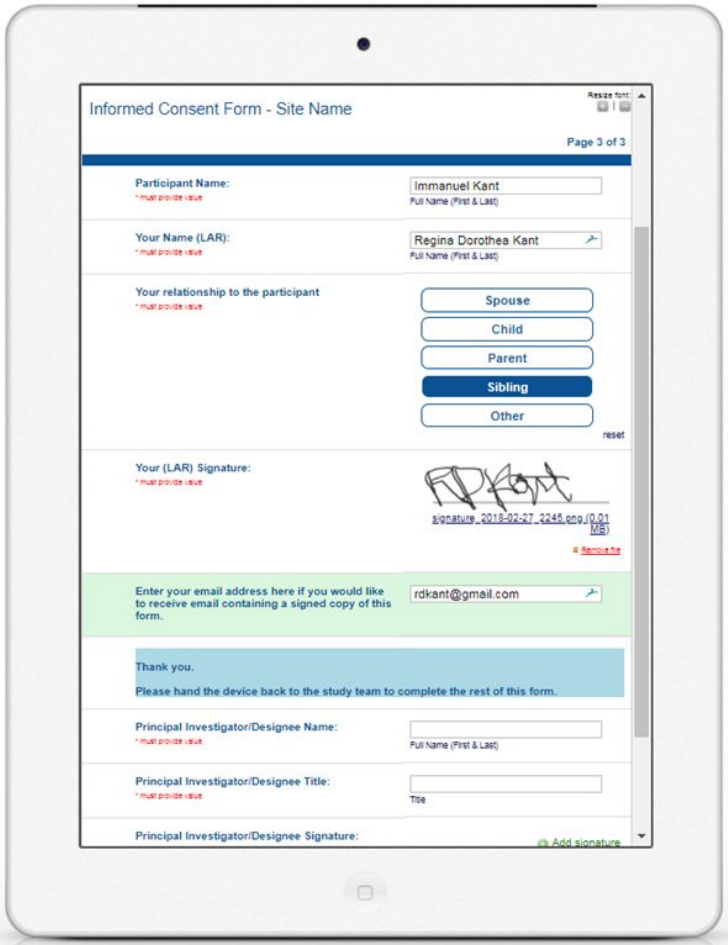
Informed Consent Form - Site Name
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Page 3 of 3
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Spouse
Child
Parent
Sibling
Other
reset
Your (LAR) Signature:
* must provide value
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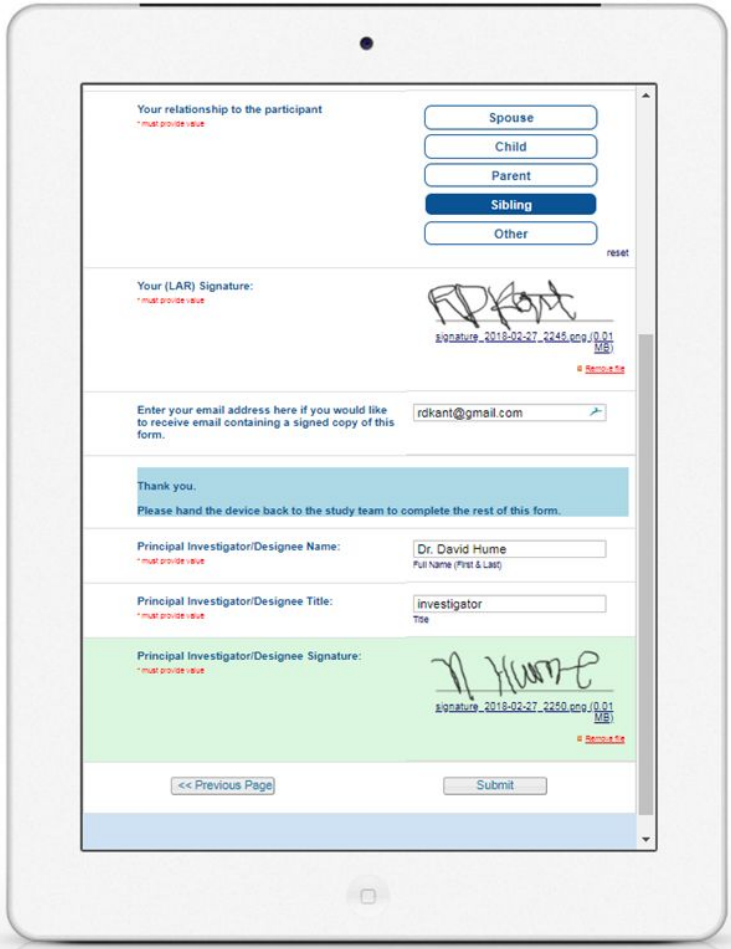
Enter your email address here if you would like to receive email containing a signed copy of this form.
rdkant@gmail.com
Thank you.
Please hand the device back to the study team to complete the rest of this form.
Principal Investigator/Designee Name:
* must provide value
Full Name (First & Last)
Principal Investigator/Designee Title:
* must provide value
Title
Principal Investigator/Designee Signature:
Add signature


Your relationship to the participant
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Spouse
Child
Parent
Sibling
Other
reset
Your (LAR) Signature:
* must provide value
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Enter your email address here if you would like to receive email containing a signed copy of this form.
rdkant@gmail.com
Thank you.
Please hand the device back to the study team to complete the rest of this form.
Principal Investigator/Designee Name:
* must provide value
Dr. David Hume
Full Name (First & Last)
Principal Investigator/Designee Title:
* must provide value
investigator
Title
Principal Investigator/Designee Signature:
* must provide value
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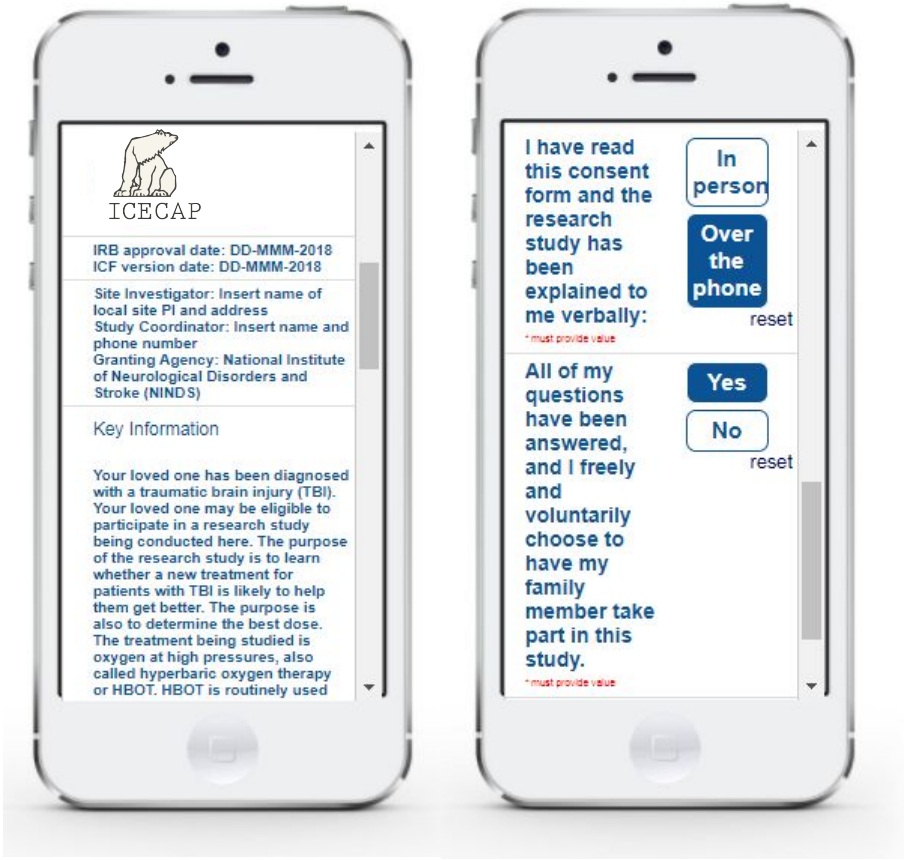
ICECAP
IRB approval date: DD-MMM-2018
ICF version date: DD-MMM-2018
Site Investigator: Insert name of local site PI and address
Study Coordinator: Insert name and phone number
Granting Agency: National Institute of Neurological Disorders and Stroke (NINDS)
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* must provide value
Yes
No
reset


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Google
Other
reset
Your (LAR) Signature:
* must provide value
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Remove file
Enter your email address here if you

Questions?

Adaptive Design

Dr. John VanBuren

Outcome

- Primary outcome: 12-month VABS-3 Mortality Composite Score
  - Death at 12 months is scored a 0
  - VABS-3 score is used among survivors
- The 3-month VABS-3 Mortality Composite Score used in longitudinal modeling when no 12-month score available

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

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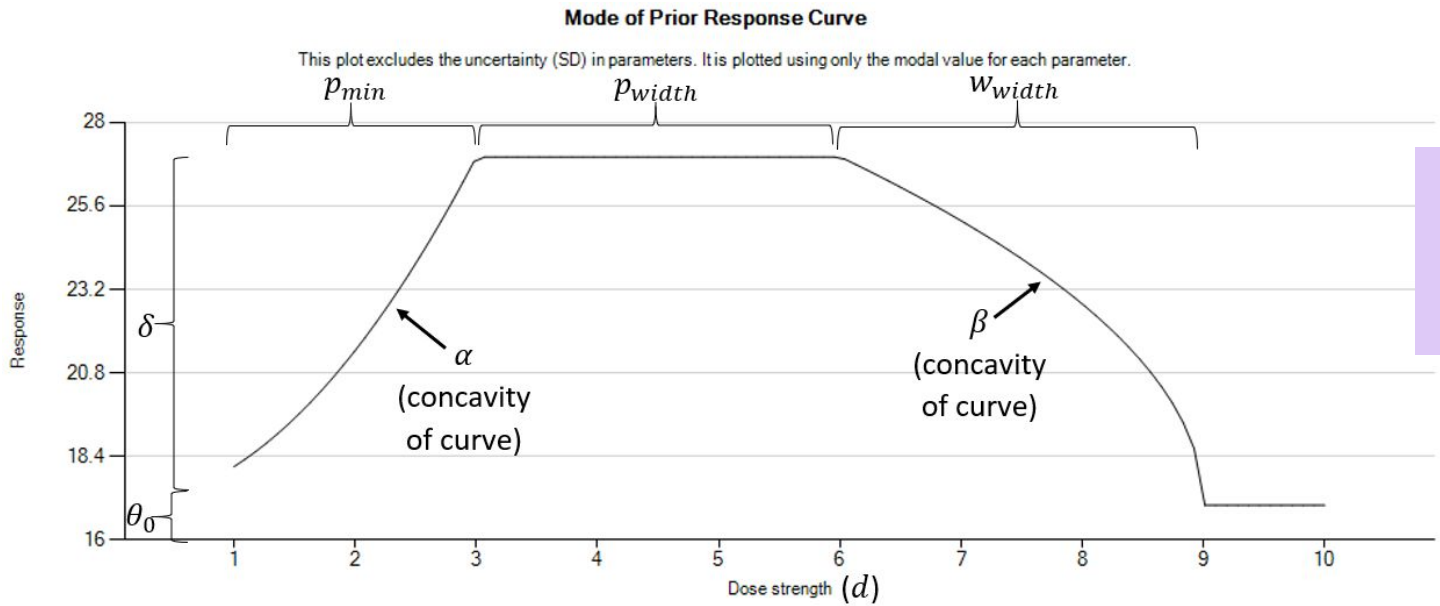
Dose Response Model



Optimal Dose:
The start of the plateau/peak

Interim Looks and Allocations

- First 150 subjects allocated equally to 24, 48, and 72 hours
- After 150 total enrolled, interims every 10 weeks
- Allocation proportions are the probability each cooling duration is optimal dose

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

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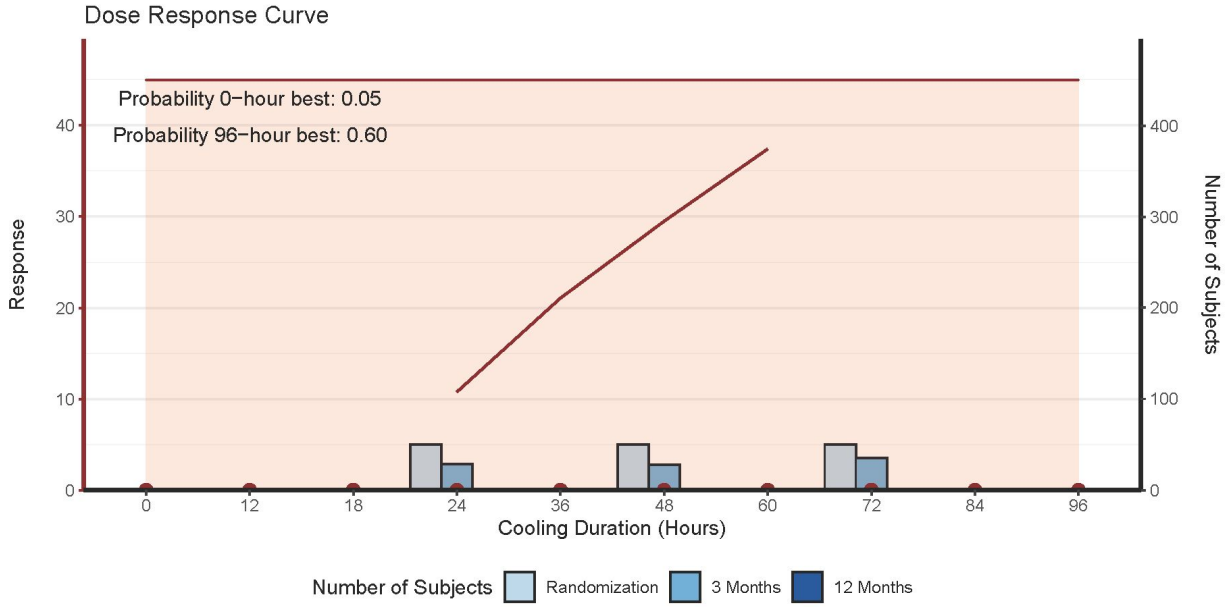
Example Trial

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655



Summary	0	12	18	24	36	48	60	72	84	96
N	0	0	0	50	0	50	0	50	0	0
3−month	0 NA	0 NA	0 NA	29 22.8 (31.2)	0 NA	28 25.7 (29.8)	0 NA	35 34.6 (34.3)	0 NA	0 NA
12−month	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA
New allocation	0.09	0.00	0.07	0.06	0.06	0.00	0.00	0.00	0.09	0.63

P-ICECAP

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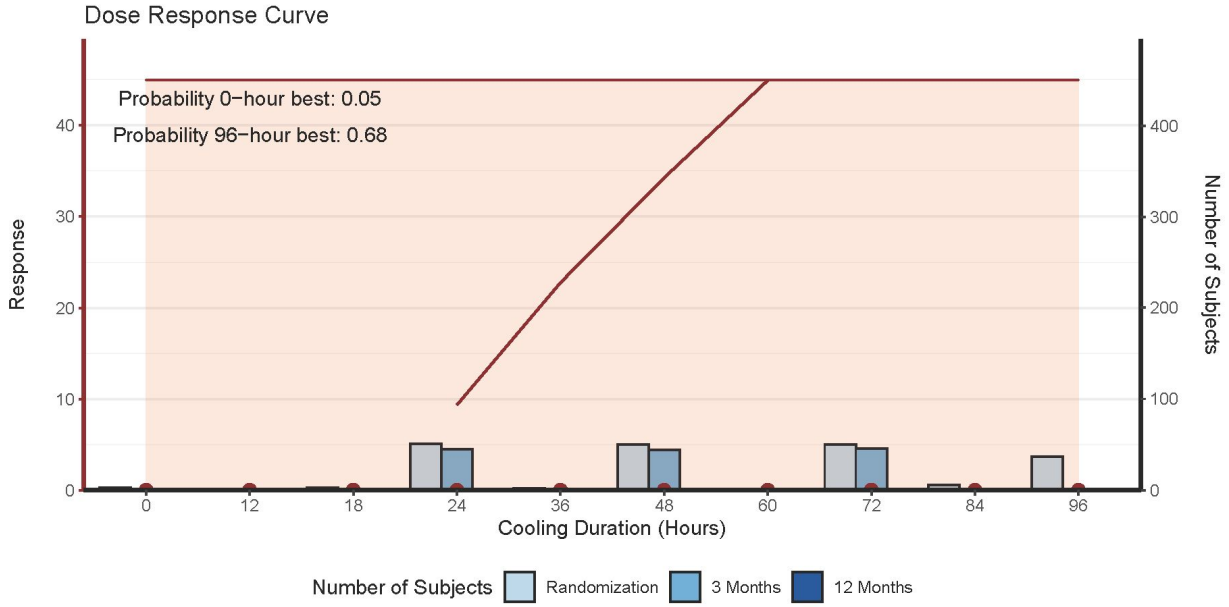

Summary	0	12	18	24	36	48	60	72	84	96
N	3	0	3	51	2	50	0	50	6	37
3−month	0 NA	0 NA	0 NA	45 29.9 (33.4)	0 NA	44 35.3 (33.7)	0 NA	46 40.9 (37.1)	0 NA	0 NA
12−month	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA
New allocation	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.13	0.78

P-ICECAP

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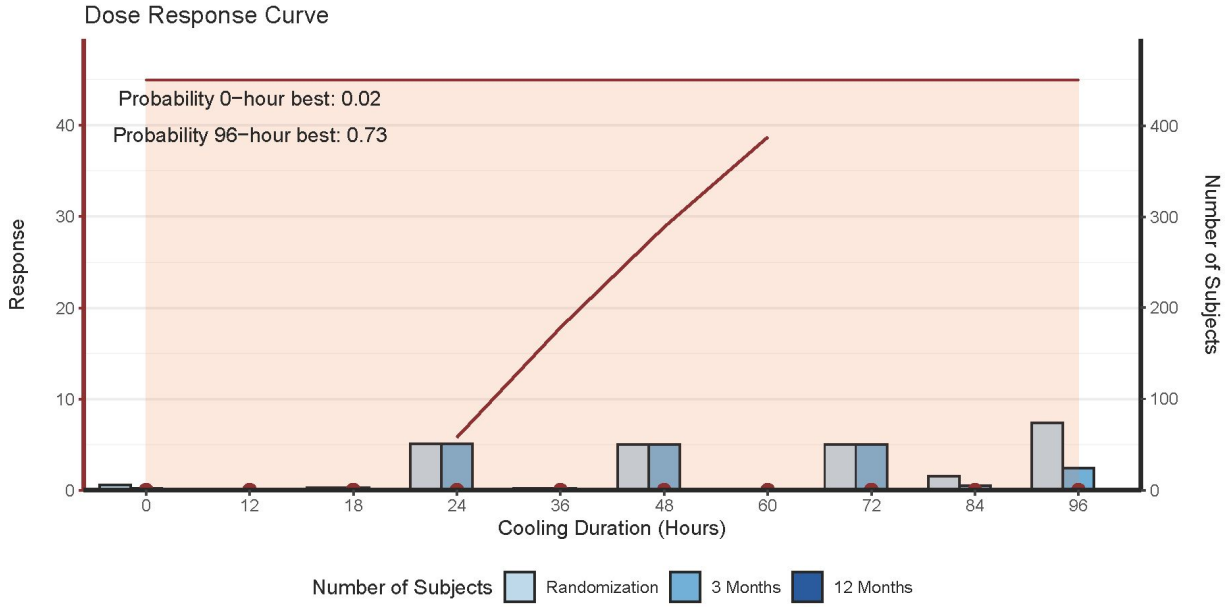

Summary	0	12	18	24	36	48	60	72	84	96
N	6	0	3	51	2	50	0	50	15	74
3−month	2 39.4 (55.7)	0 NA	3 24.0 (41.6)	51 31.8 (32.9)	2 28.5 (40.3)	50 35.5 (34.2)	0 NA	50 41.7 (36.7)	5 45.2 (43.6)	24 28.4 (32.5)
12−month	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA
New allocation	0.08	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.80

P-ICECAP

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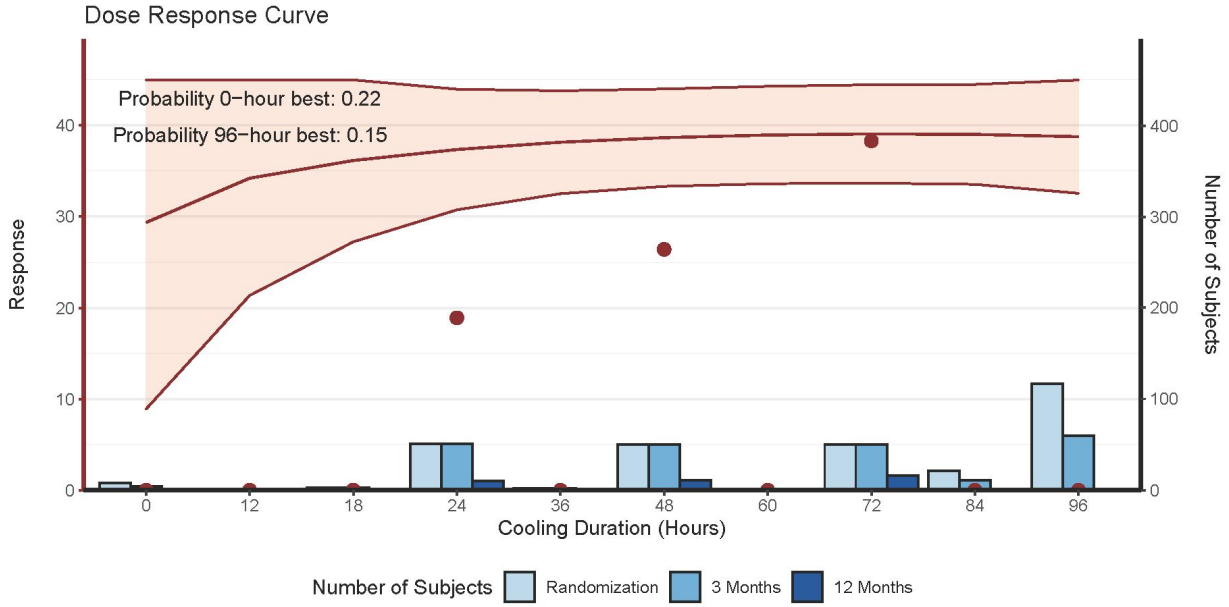

Summary	0	12	18	24	36	48	60	72	84	96
N	8	0	3	51	2	50	0	50	21	117
3−month	4 33.0 (39.5)	0 NA	3 24.0 (41.6)	51 31.8 (32.9)	2 28.5 (40.3)	50 35.5 (34.2)	0 NA	50 41.7 (36.7)	11 25.2 (36.7)	60 32.3 (34.5)
12−month	0 NA	0 NA	0 NA	10 18.9 (30.9)	0 NA	11 28.8 (35.4)	0 NA	16 38.3 (41.2)	0 NA	0 NA
New allocation	0.33	0.20	0.10	0.10	0.10	0.10	0.08	0.00	0.00	0.00

P-ICECAP

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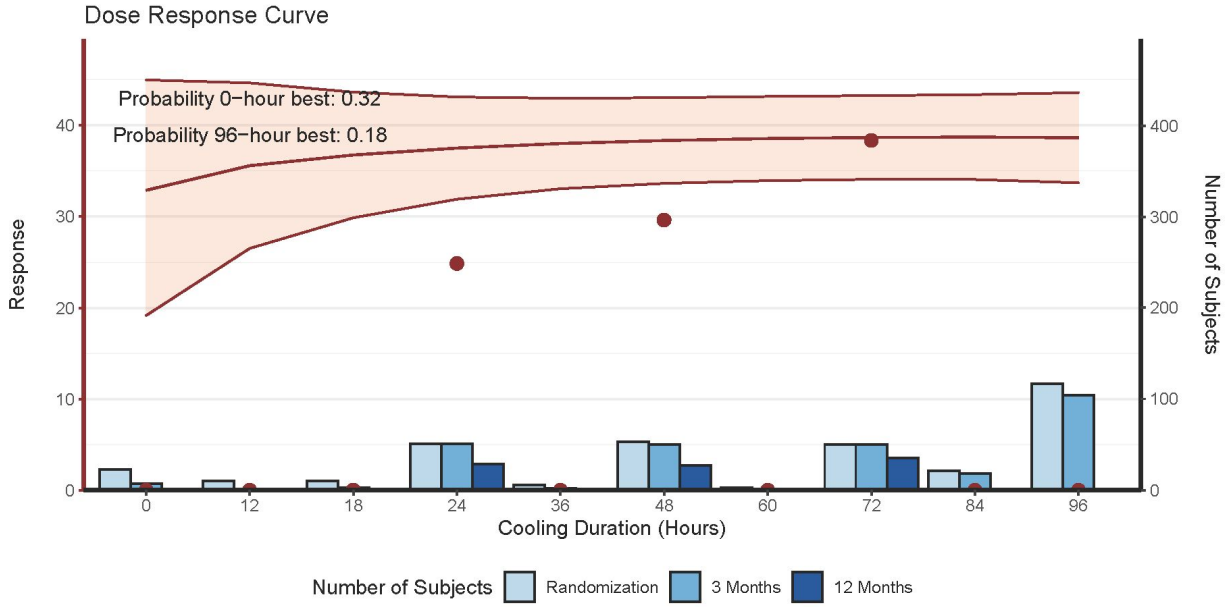

Summary	0	12	18	24	36	48	60	72	84	96
N	23	10	10	51	6	53	3	50	21	117
3−month	7 38.0 (36.3)	0 NA	3 24.0 (41.6)	51 31.8 (32.9)	2 28.5 (40.3)	50 35.5 (34.2)	0 NA	50 41.7 (36.7)	18 22.7 (35.2)	104 35.4 (34.2)
12−month	0 NA	0 NA	0 NA	29 24.9 (33.7)	0 NA	27 29.6 (33.1)	0 NA	35 38.4 (37.7)	0 NA	0 NA
New allocation	0.46	0.15	0.09	0.09	0.08	0.08	0.06	0.00	0.00	0.00

P-ICECAP

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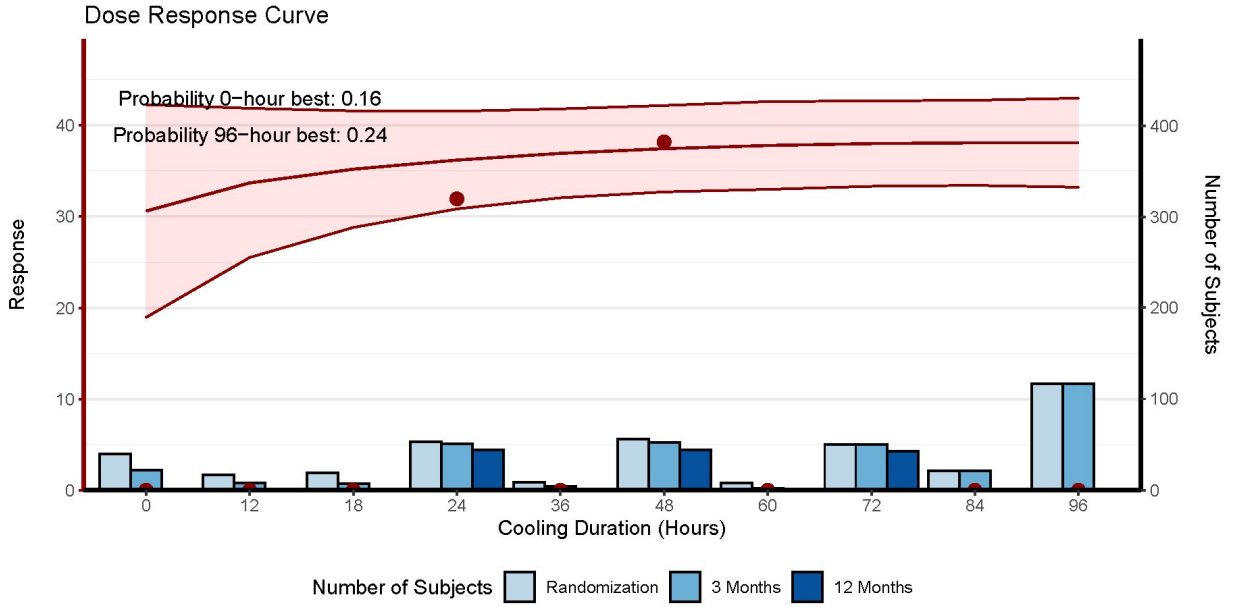

Summary	0	12	18	24	36	48	60	72	84	96
N	40	17	19	53	9	56	8	50	21	117
3−month	22 31.3 (37.0)	8 25.9 (49.9)	7 27.3 (35.2)	51 31.8 (32.9)	4 26.1 (30.4)	52 36.4 (34.0)	2 36.2 (51.1)	50 41.7 (36.7)	21 23.2 (35.6)	117 34.5 (34.5)
12−month	0 NA	0 NA	0 NA	44 31.0 (35.3)	0 NA	44 38.2 (36.1)	0 NA	43 42.7 (41.2)	0 NA	0 NA
New allocation	0.23	0.14	0.10	0.10	0.11	0.10	0.08	0.08	0.00	0.06

P-ICECAP

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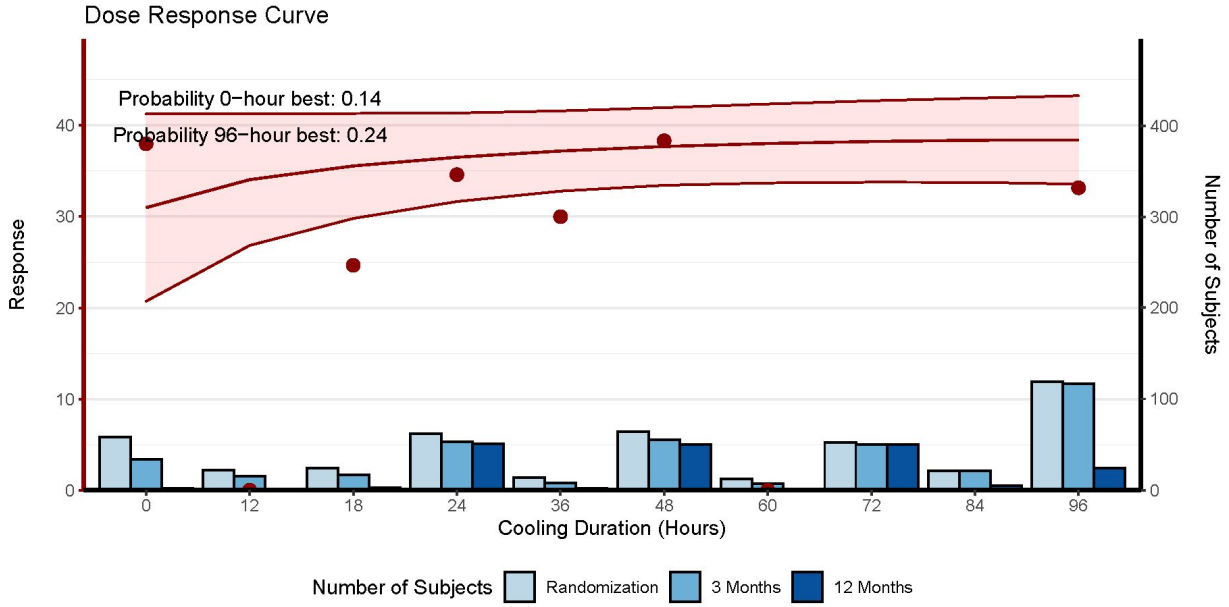

Summary	0	12	18	24	36	48	60	72	84	96
N	58	22	24	62	14	64	12	52	21	119
3−month	34 29.2 (35.7)	15 22.4 (41.1)	17 37.9 (33.3)	53 33.0 (32.9)	8 20.1 (27.9)	55 35.6 (34.0)	7 37.7 (35.7)	50 41.7 (36.7)	21 23.2 (35.6)	117 34.5 (34.5)
12−month	2 38.0 (53.7)	0 NA	3 24.7 (42.7)	51 34.6 (35.4)	2 30.0 (42.4)	50 38.3 (36.5)	0 NA	50 46.2 (40.6)	5 48.6 (46.6)	24 33.2 (37.9)
New allocation	0.21	0.14	0.12	0.10	0.10	0.10	0.08	0.08	0.00	0.06

P-ICECAP

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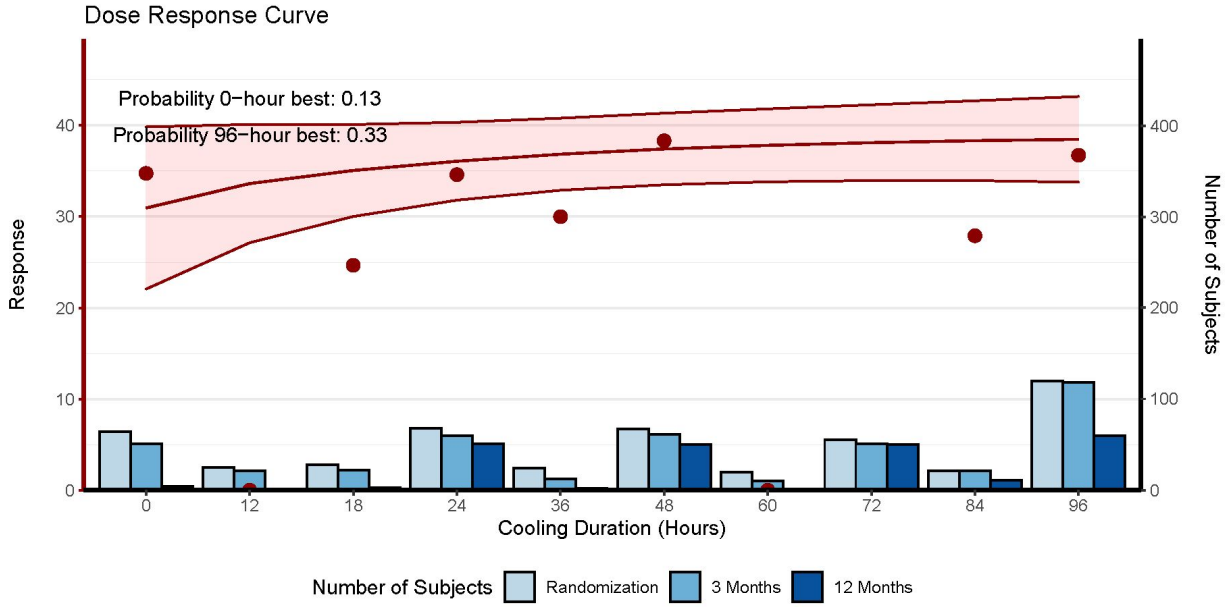
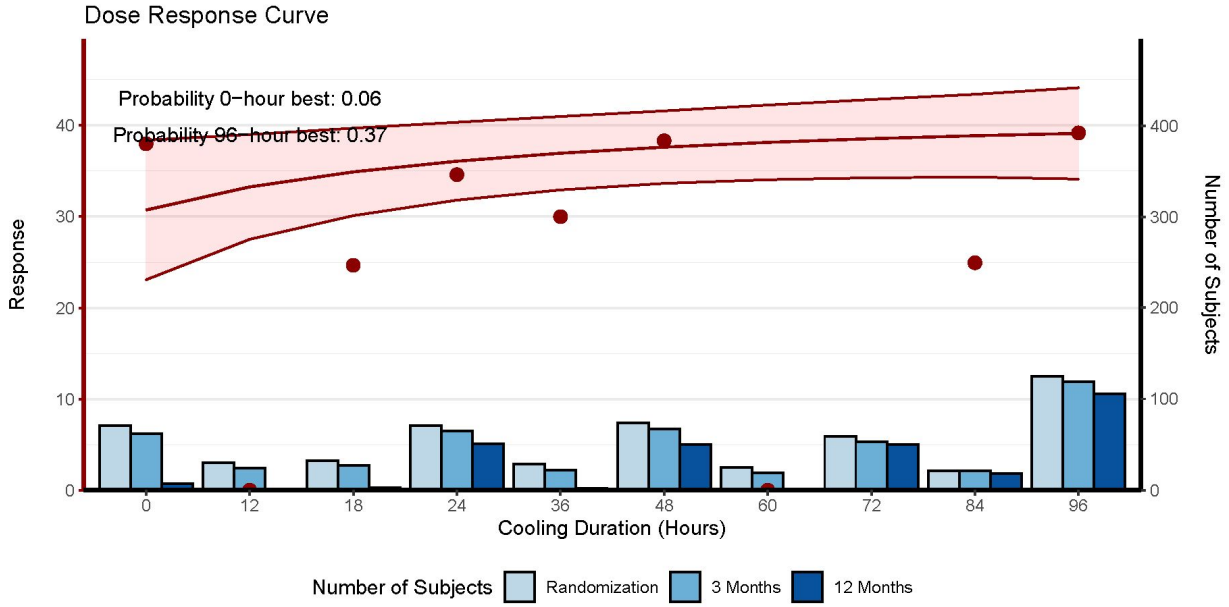


Summary	0	12	18	24	36	48	60	72	84	96
N	64	25	28	68	24	67	20	55	21	120
3−month	51 28.5 (33.9)	21 18.8 (36.9)	22 33.5 (32.2)	60 33.5 (32.9)	12 24.2 (30.4)	61 37.5 (33.7)	10 32.4 (34.4)	51 42.3 (36.6)	21 23.2 (35.6)	118 34.2 (34.5)
12−month	4 34.8 (40.5)	0 NA	3 24.7 (42.7)	51 34.6 (35.4)	2 30.0 (42.4)	50 38.3 (36.5)	0 NA	50 46.2 (40.6)	11 27.9 (40.0)	60 36.7 (39.0)
New allocation	0.19	0.13	0.08	0.08	0.11	0.10	0.11	0.10	0.00	0.09

P-ICECAP

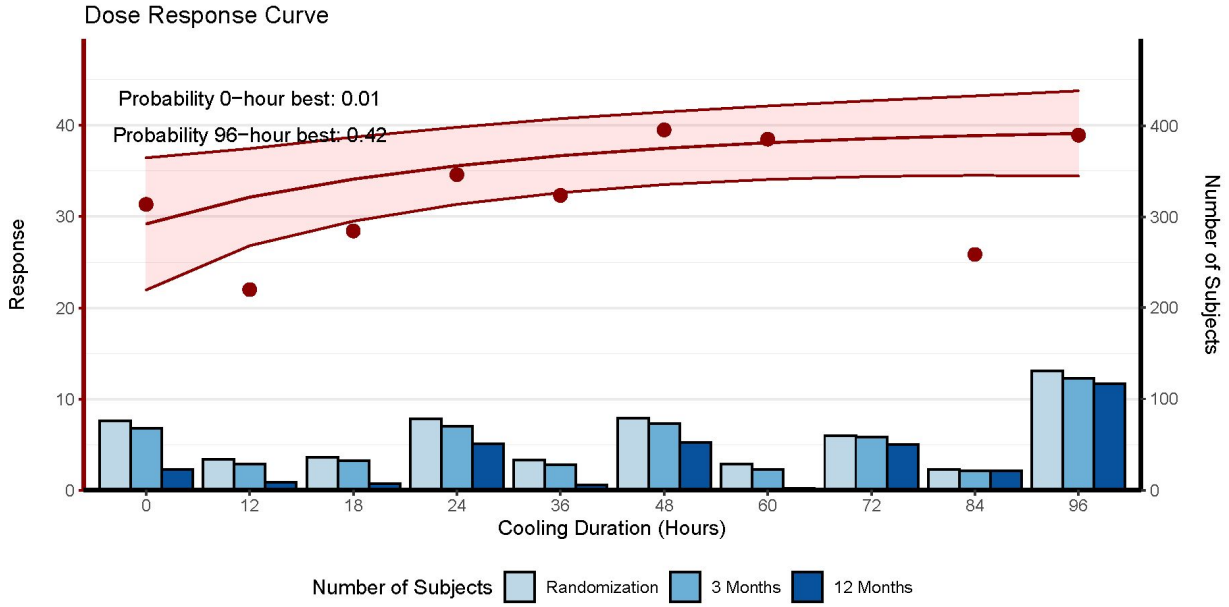
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	71	30	32	71	29	74	25	59	21	125
3−month	62 29.7 (33.9)	24 16.5 (35.0)	27 35.0 (33.5)	65 33.8 (32.7)	22 29.1 (31.8)	67 36.3 (34.0)	19 34.1 (38.1)	53 42.3 (36.9)	21 23.2 (35.6)	119 34.5 (34.5)
12−month	7 38.0 (35.9)	0 NA	3 24.7 (42.7)	51 34.6 (35.4)	2 30.0 (42.4)	50 38.3 (36.5)	0 NA	50 46.2 (40.6)	18 24.9 (38.1)	106 39.2 (38.3)
New allocation	0.10	0.06	0.10	0.11	0.12	0.10	0.11	0.11	0.08	0.11

P-ICECAP

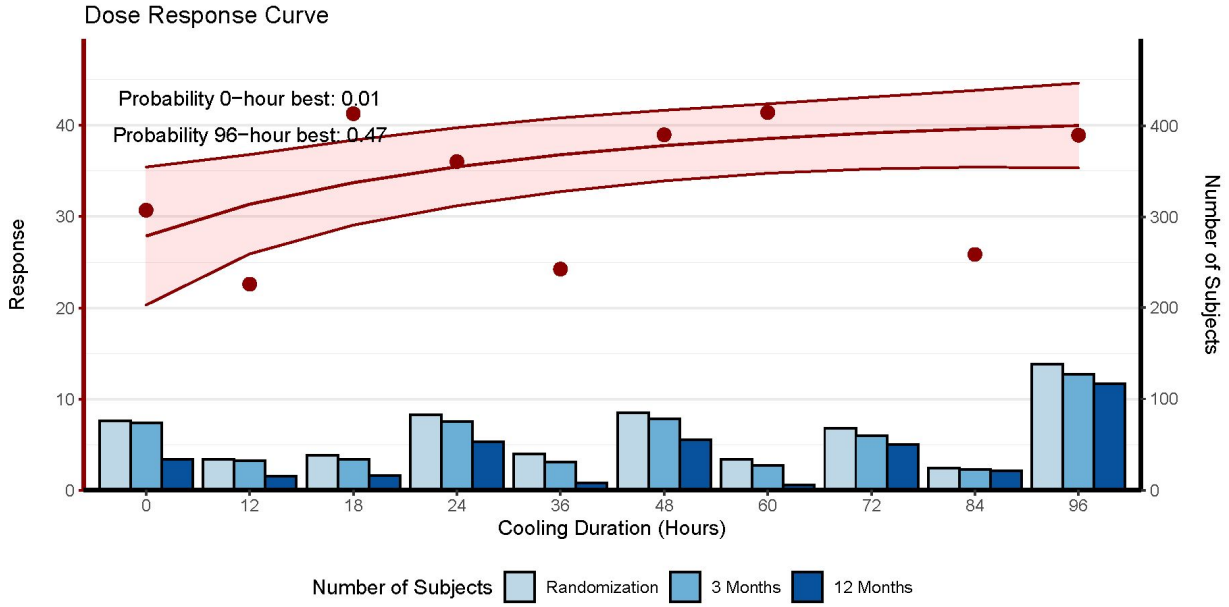
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	36	78	33	79	29	60	23	131
3−month	68 28.3 (33.2)	29 18.2 (34.8)	32 35.3 (33.0)	70 32.7 (32.5)	28 29.5 (31.7)	73 36.2 (34.2)	23 30.4 (36.7)	58 42.3 (37.0)	21 23.2 (35.6)	123 35.0 (34.5)
12−month	23 31.3 (37.8)	9 22.0 (44.9)	7 28.4 (36.4)	51 34.6 (35.4)	6 32.3 (36.5)	52 39.5 (36.4)	2 38.5 (54.4)	50 46.2 (40.6)	21 25.9 (39.2)	117 38.9 (38.7)
New allocation	0.00	0.00	0.08	0.12	0.16	0.14	0.16	0.17	0.07	0.12

P-ICECAP

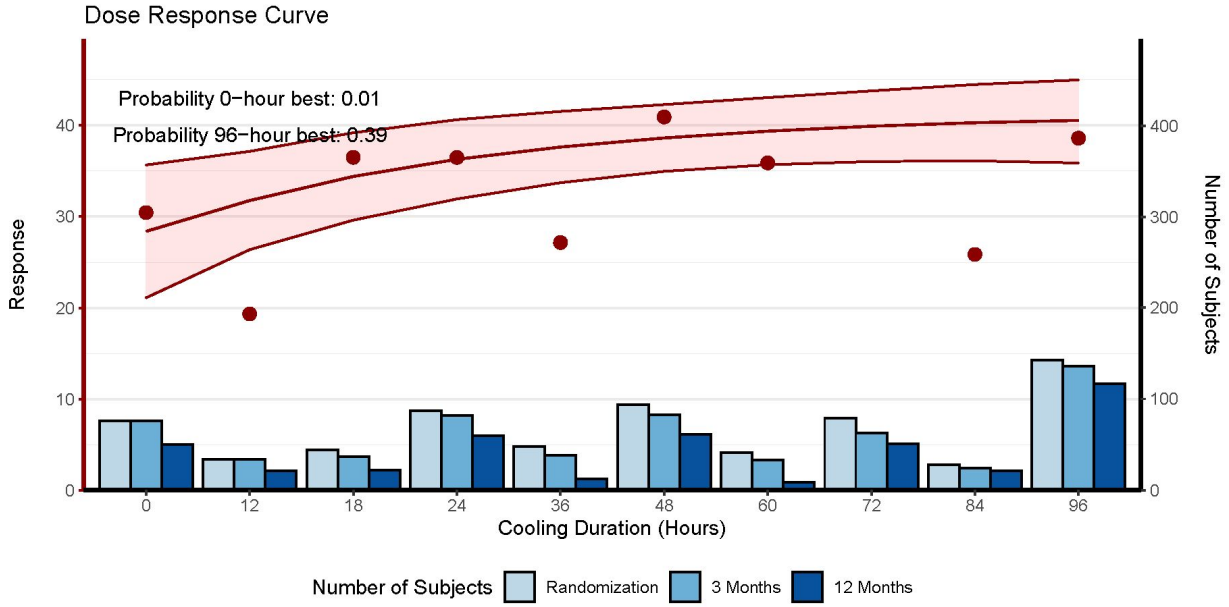
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	38	83	40	85	34	68	24	138
3−month	74 26.9 (32.9)	32 19.1 (35.3)	34 33.2 (33.1)	75 33.2 (32.7)	31 31.0 (32.2)	78 37.0 (34.6)	27 28.6 (36.2)	60 43.2 (36.7)	23 23.7 (35.0)	127 35.9 (34.3)
12−month	34 30.7 (36.6)	15 22.6 (40.3)	16 39.8 (37.0)	53 36.0 (35.5)	8 24.2 (34.3)	55 39.0 (36.8)	6 48.3 (37.6)	50 46.2 (40.6)	21 25.9 (39.2)	117 38.9 (38.7)
New allocation	0.00	0.00	0.06	0.09	0.12	0.13	0.15	0.20	0.12	0.13

P-ICECAP

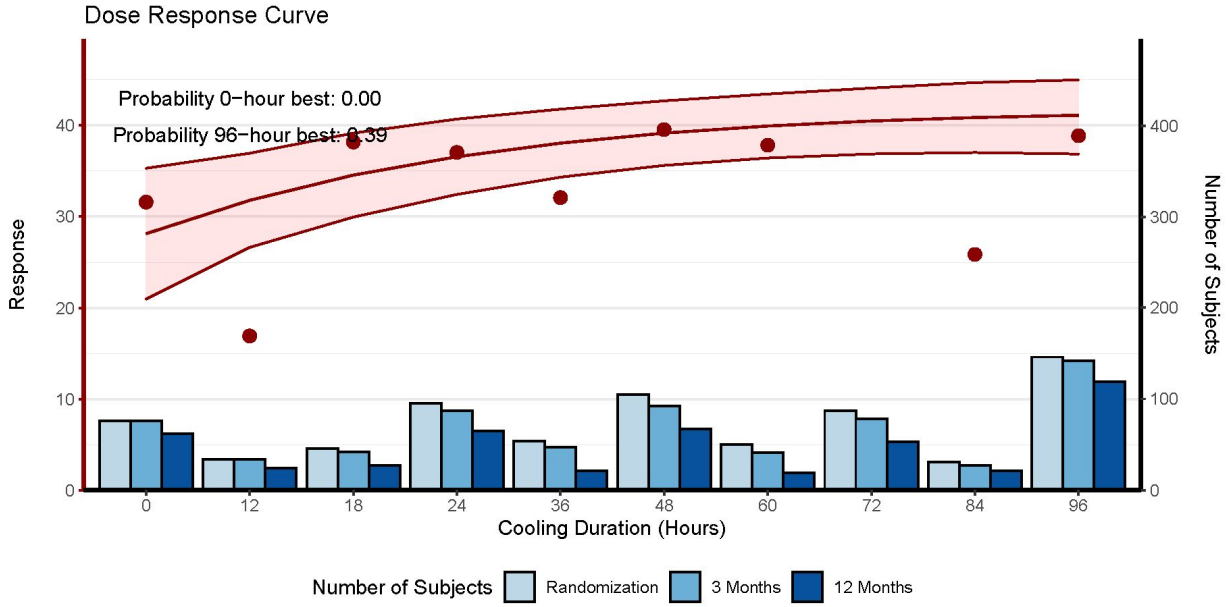
SIREN



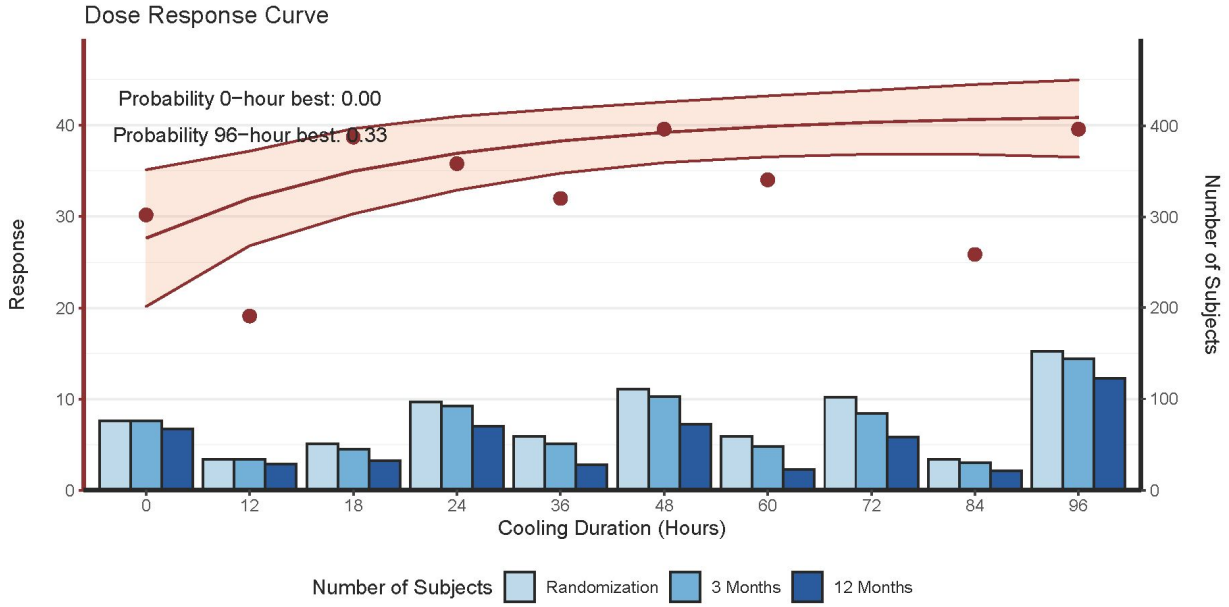
Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	44	87	48	94	41	79	28	143
3−month	76 27.2 (33.1)	34 18.8 (34.4)	37 33.7 (32.8)	82 34.6 (32.3)	38 36.8 (31.7)	83 36.2 (34.6)	33 27.9 (37.1)	63 43.5 (36.9)	24 25.5 (35.4)	136 36.7 (34.5)
12−month	50 31.1 (35.4)	21 19.3 (36.8)	22 36.5 (35.2)	60 36.5 (35.4)	12 27.2 (34.2)	61 40.9 (36.4)	9 39.9 (38.0)	51 46.9 (40.4)	21 25.9 (39.2)	117 38.9 (38.7)
New allocation	0.00	0.00	0.08	0.13	0.13	0.14	0.15	0.17	0.10	0.10

P-ICECAP

SIREN



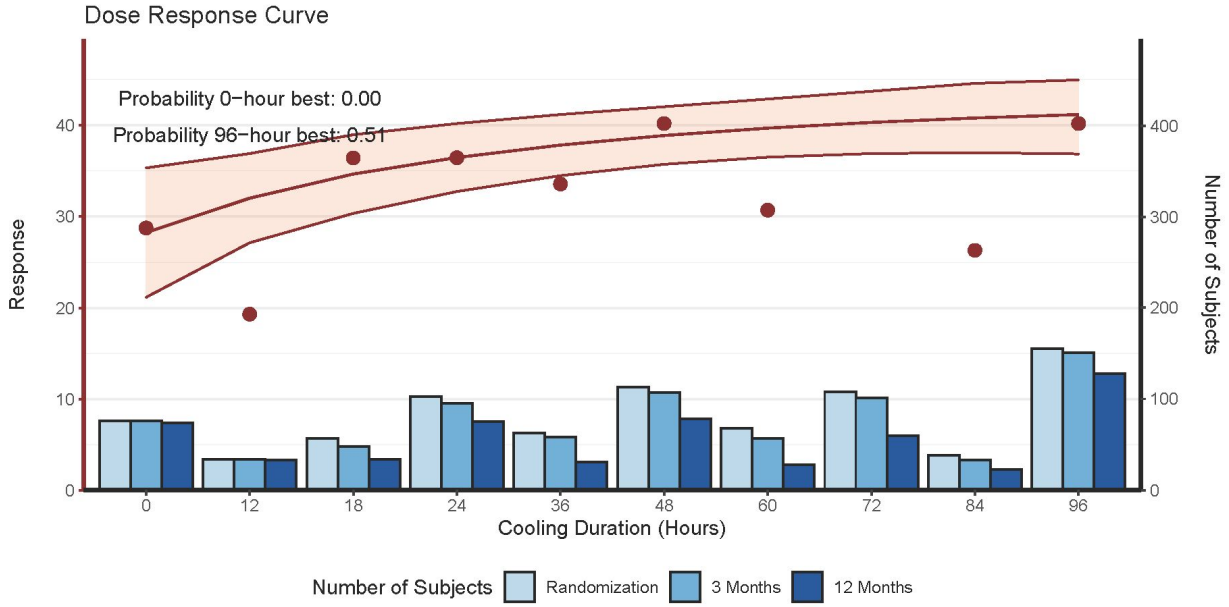
Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	46	95	54	105	50	87	31	146
3−month	76 27.2 (33.1)	34 18.8 (34.4)	42 35.6 (32.5)	87 33.9 (32.2)	47 33.3 (31.6)	92 36.8 (34.2)	41 32.2 (36.7)	78 43.0 (36.4)	27 28.0 (36.3)	142 36.7 (34.9)
12−month	62 31.6 (35.2)	24 16.9 (34.9)	27 38.2 (36.1)	65 37.0 (35.6)	21 30.7 (34.8)	67 39.6 (36.6)	19 37.8 (41.9)	53 46.9 (40.8)	21 25.9 (39.2)	119 38.9 (38.6)
New allocation	0.00	0.00	0.07	0.10	0.14	0.17	0.16	0.17	0.09	0.10



Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	51	97	59	111	59	102	34	152
3−month	76 27.2 (33.1)	34 18.8 (34.4)	45 35.9 (32.2)	92 34.3 (32.4)	51 33.5 (32.0)	103 36.8 (33.8)	48 33.5 (35.7)	84 41.4 (36.4)	30 25.2 (35.4)	144 36.7 (34.9)
12−month	67 30.6 (34.6)	29 19.1 (35.5)	32 38.7 (35.8)	70 35.8 (35.3)	28 32.0 (34.0)	72 38.9 (36.7)	23 34.0 (40.6)	58 46.9 (40.8)	21 25.9 (39.2)	123 39.6 (38.7)
New allocation	0.00	0.00	0.10	0.15	0.15	0.15	0.14	0.16	0.07	0.08

P-ICECAP

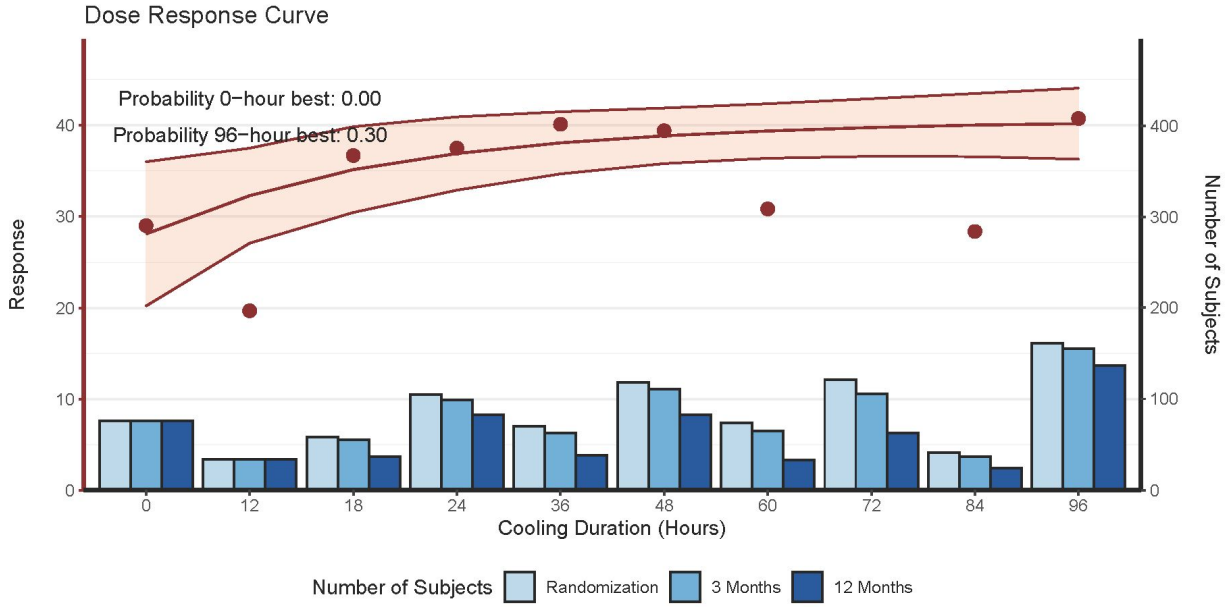
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	57	103	63	113	68	108	38	155
3−month	76 27.2 (33.1)	34 18.8 (34.4)	48 35.6 (31.7)	95 33.9 (32.4)	58 35.0 (32.3)	107 36.7 (33.8)	57 31.6 (35.3)	101 41.7 (36.7)	33 25.8 (36.5)	151 36.8 (34.8)
12−month	74 28.8 (34.4)	33 19.3 (35.6)	34 36.4 (35.9)	75 36.5 (35.6)	31 33.6 (34.3)	78 40.2 (37.3)	28 30.7 (39.6)	60 48.0 (40.6)	23 26.3 (38.5)	128 40.2 (38.5)
New allocation	0.00	0.00	0.08	0.09	0.10	0.12	0.15	0.23	0.11	0.13

P-ICECAP

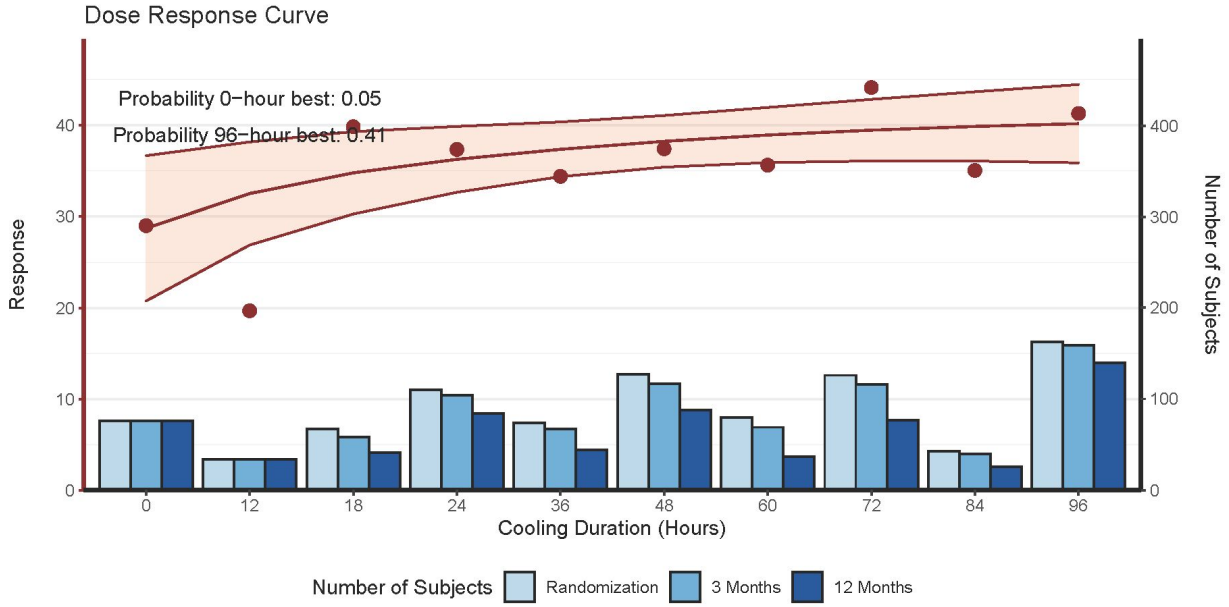
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	58	105	70	118	74	121	41	161
3−month	76 27.2 (33.1)	34 18.8 (34.4)	55 36.6 (31.4)	99 33.8 (32.4)	63 33.7 (33.0)	111 37.3 (33.9)	65 30.3 (35.5)	106 41.7 (36.6)	37 27.4 (37.4)	155 36.2 (34.7)
12−month	76 29.0 (34.5)	34 19.7 (35.1)	37 36.7 (35.5)	83 37.5 (35.2)	38 40.1 (34.2)	83 39.4 (37.2)	33 30.8 (40.6)	63 48.1 (40.4)	24 28.4 (39.0)	137 41.1 (38.6)
New allocation	0.00	0.00	0.14	0.16	0.16	0.14	0.12	0.13	0.06	0.08

P-ICECAP

SIREN



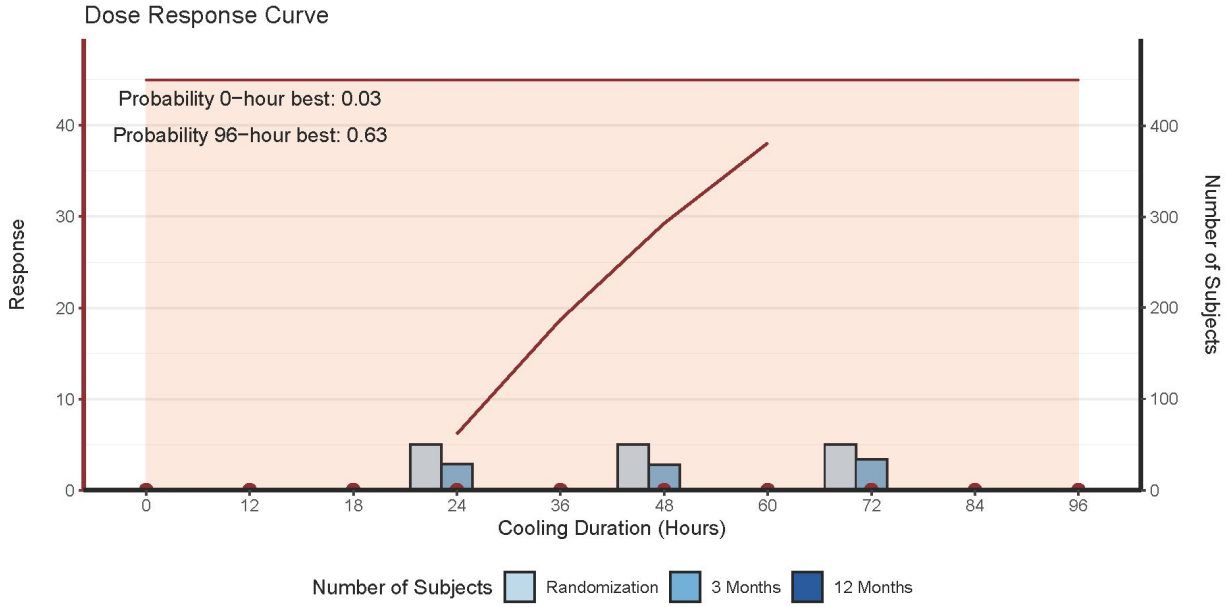
Summary	0	12	18	24	36	48	60	72	84	96
N	76	34	67	110	74	127	80	126	43	163
3−month	76 27.2 (33.1)	34 18.8 (34.4)	58 35.6 (31.4)	104 33.8 (32.3)	67 31.7 (32.9)	117 36.5 (33.9)	69 31.5 (35.6)	116 41.1 (36.6)	40 30.1 (37.3)	159 35.8 (34.5)
12−month	76 29.0 (34.5)	34 19.7 (35.1)	41 37.9 (35.1)	84 37.8 (35.1)	44 39.4 (34.4)	88 40.1 (36.8)	37 34.2 (41.3)	77 47.1 (40.0)	26 32.4 (40.5)	140 40.5 (38.5)
New allocation	0.00	0.00	0.14	0.16	0.16	0.14	0.12	0.13	0.06	0.08

P-ICECAP

SIREN

Example Trial 2

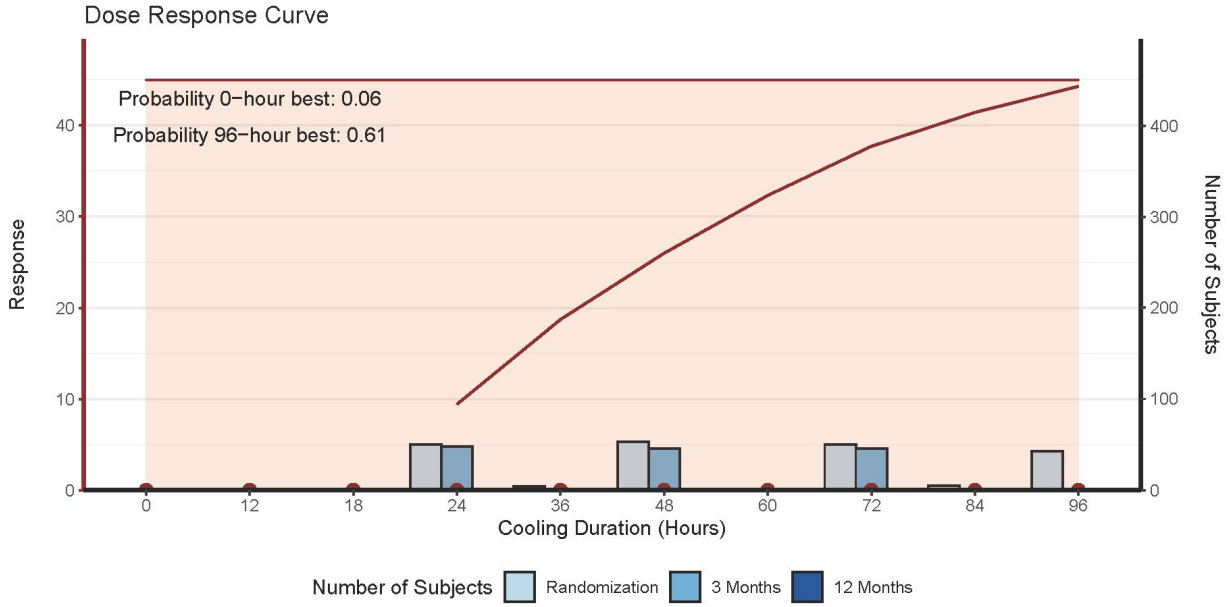
NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655



Summary	0	12	18	24	36	48	60	72	84	96
N	0	0	0	50	0	50	0	50	0	0
3−month	0 NA	0 NA	0 NA	29 27.2 (30.9)	0 NA	28 31.5 (32.6)	0 NA	34 28.1 (34.2)	0 NA	0 NA
12−month	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA
New allocation	0.00	0.00	0.07	0.00	0.07	0.07	0.06	0.00	0.10	0.63

P-ICECAP

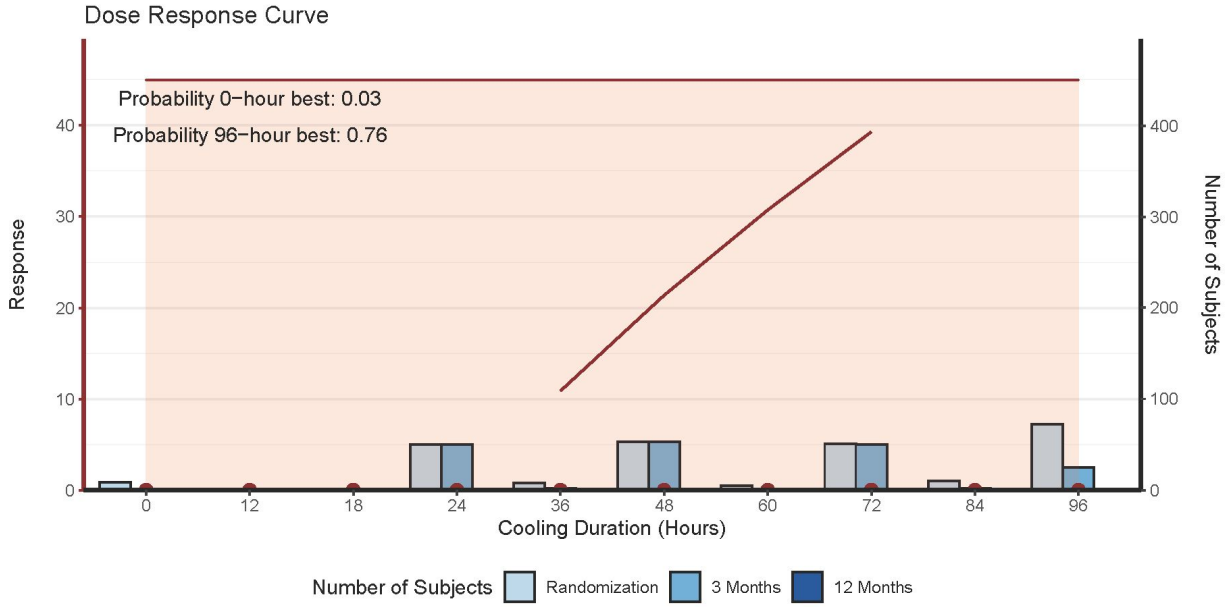
SIREN



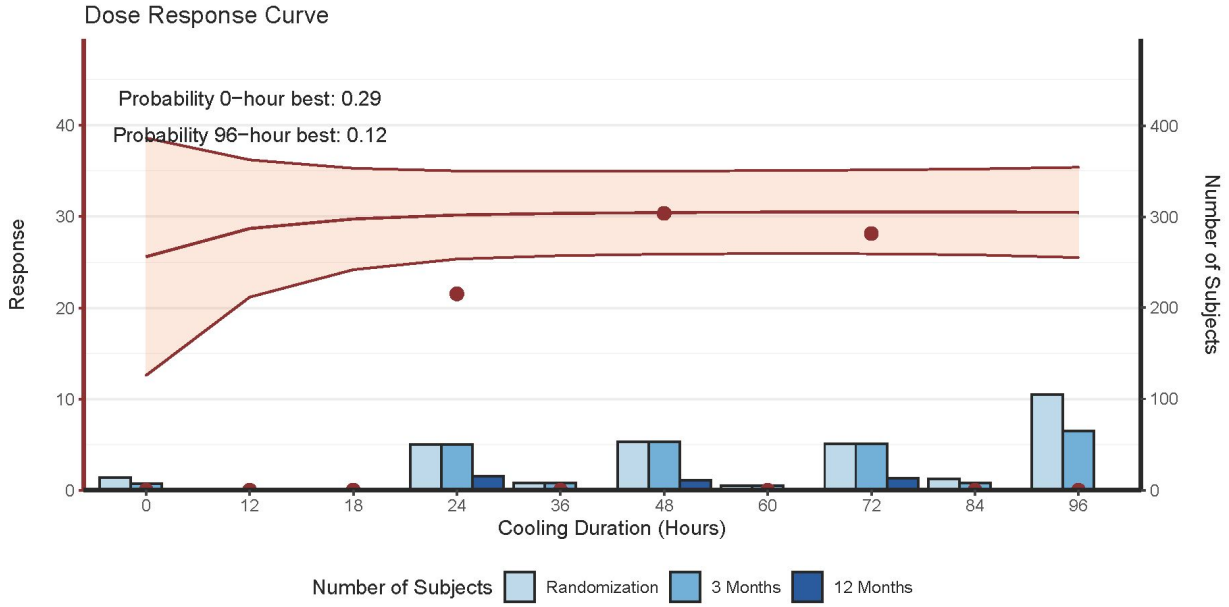
Summary	0	12	18	24	36	48	60	72	84	96
N	0	0	0	50	4	53	1	50	5	43
3−month	0 NA	0 NA	0 NA	48 34.7 (33.0)	0 NA	46 25.1 (31.0)	0 NA	46 22.9 (32.0)	0 NA	0 NA
12−month	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA
New allocation	0.09	0.00	0.00	0.00	0.06	0.00	0.06	0.06	0.12	0.60

P-ICECAP

SIREN



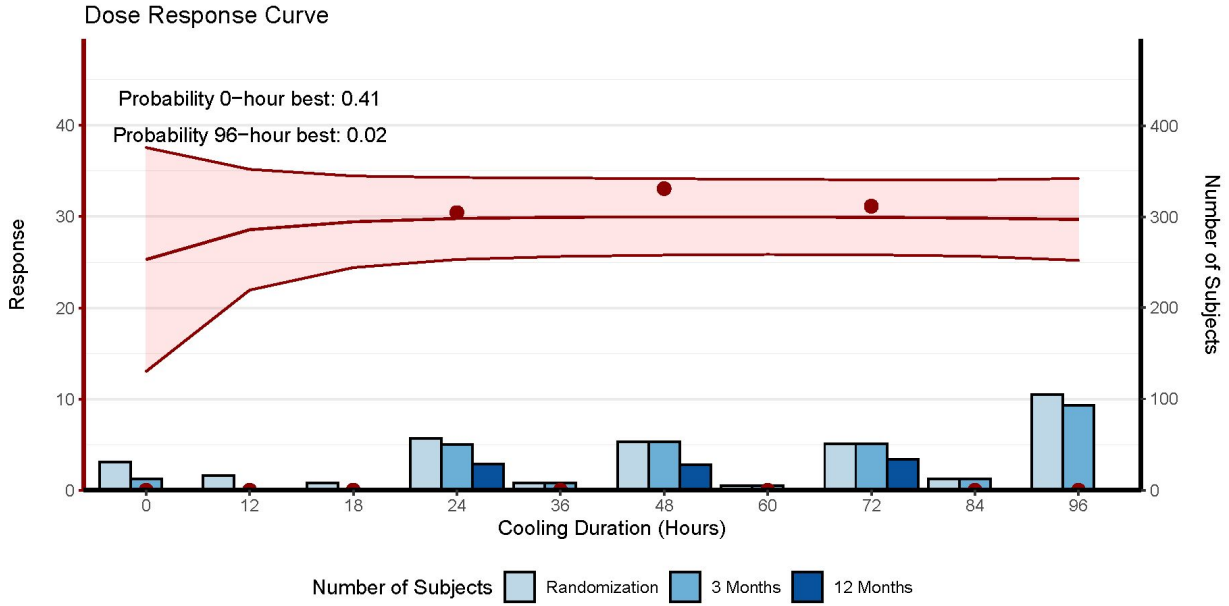
Summary	0	12	18	24	36	48	60	72	84	96
N	9	0	0	50	8	53	5	51	10	72
3−month	0 NA	0 NA	0 NA	50 34.1 (32.7)	2 0.0 (0.0)	53 24.9 (30.6)	1 71.3 (0.0)	50 23.1 (31.6)	2 48.6 (30.7)	25 33.6 (32.1)
12−month	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA	0 NA
New allocation	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.83



Summary	0	12	18	24	36	48	60	72	84	96
N	14	0	0	50	8	53	5	51	12	105
3−month	7 26.9 (34.5)	0 NA	0 NA	50 34.1 (32.7)	8 21.3 (30.8)	53 24.9 (30.6)	5 50.1 (30.2)	51 22.6 (31.4)	8 18.1 (27.5)	65 29.9 (31.0)
12−month	0 NA	0 NA	0 NA	15 21.5 (33.6)	0 NA	11 30.4 (37.3)	0 NA	13 28.2 (37.4)	0 NA	0 NA
New allocation	0.46	0.27	0.17	0.10	0.00	0.00	0.00	0.00	0.00	0.00

P-ICECAP

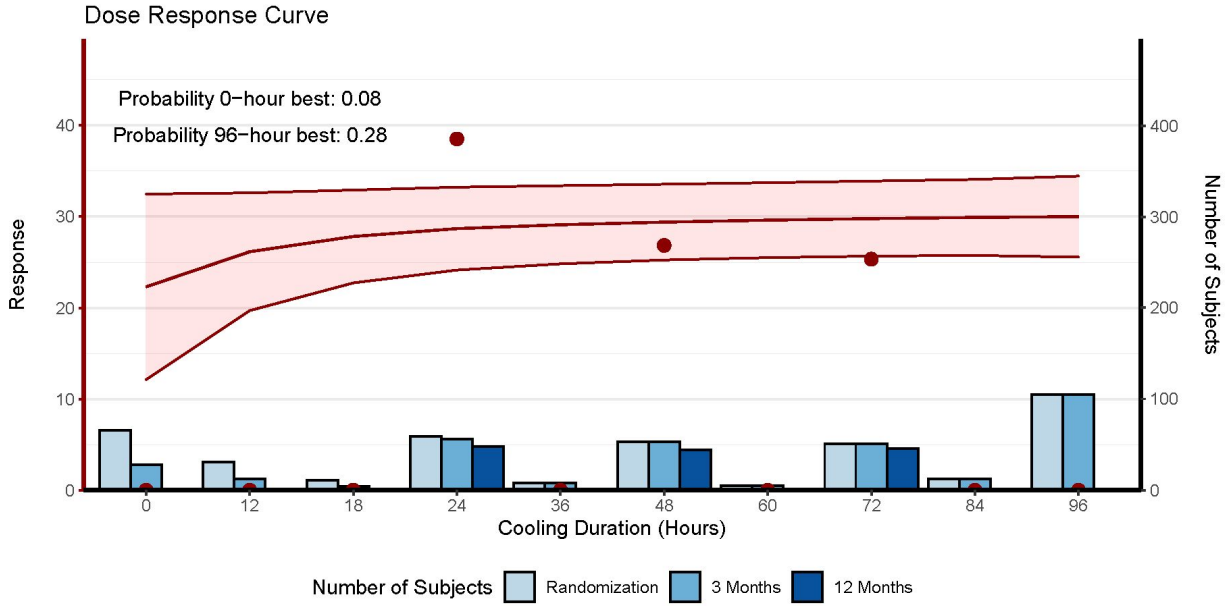
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	31	16	8	57	8	53	5	51	12	105
3−month	12 22.4 (29.5)	0 NA	0 NA	50 34.1 (32.7)	8 21.3 (30.8)	53 24.9 (30.6)	5 50.1 (30.2)	51 22.6 (31.4)	12 17.8 (28.5)	93 28.1 (30.4)
12−month	0 NA	0 NA	0 NA	29 30.4 (34.0)	0 NA	28 33.1 (33.9)	0 NA	34 31.1 (37.7)	0 NA	0 NA
New allocation	0.51	0.26	0.14	0.08	0.00	0.00	0.00	0.00	0.00	0.00

P-ICECAP

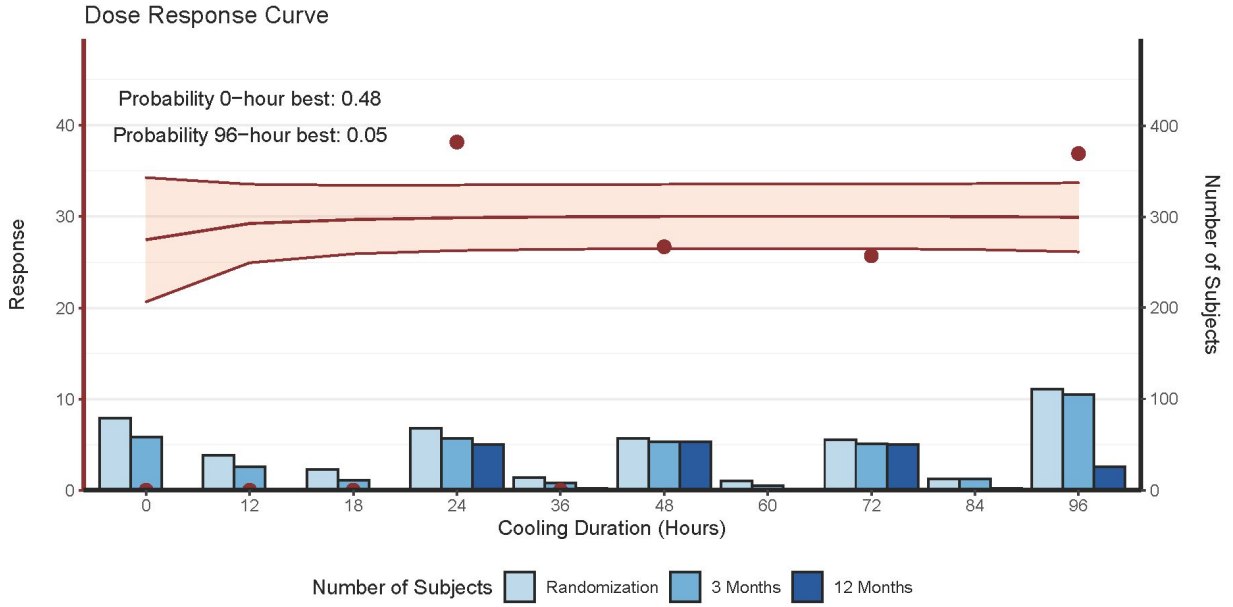
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	66	31	11	59	8	53	5	51	12	105
3−month	28 18.4 (26.0)	12 18.7 (28.0)	4 22.4 (44.9)	56 32.6 (32.5)	8 21.3 (30.8)	53 24.9 (30.6)	5 50.1 (30.2)	51 22.6 (31.4)	12 17.8 (28.5)	105 28.3 (30.5)
12−month	0 NA	0 NA	0 NA	48 38.5 (36.4)	0 NA	44 26.2 (32.3)	0 NA	46 25.3 (35.3)	0 NA	0 NA
New allocation	0.14	0.18	0.17	0.15	0.08	0.06	0.06	0.07	0.00	0.09

P-ICECAP

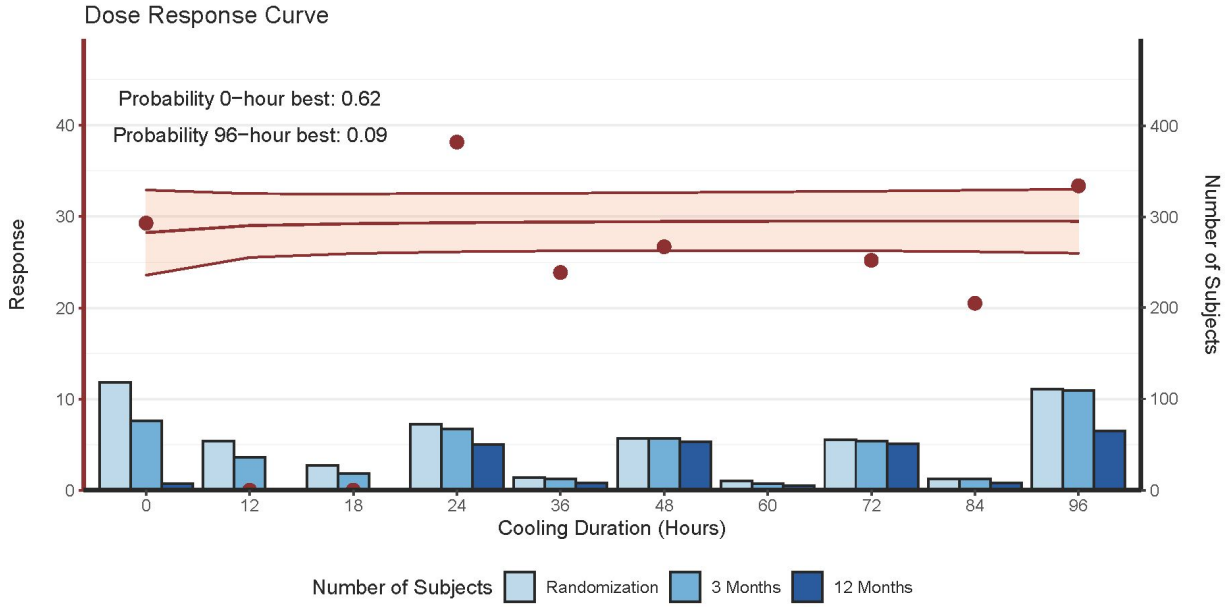
SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	79	38	23	68	14	57	10	55	12	111
3−month	58 23.6 (29.4)	26 27.5 (34.0)	11 23.2 (34.3)	57 32.0 (32.5)	8 21.3 (30.8)	53 24.9 (30.6)	5 50.1 (30.2)	51 22.6 (31.4)	12 17.8 (28.5)	105 28.3 (30.5)
12−month	0 NA	0 NA	0 NA	50 38.2 (36.2)	2 0.0 (0.0)	53 26.7 (32.5)	1 80.0 (0.0)	50 25.7 (34.9)	2 53.0 (35.4)	26 36.9 (36.9)
New allocation	0.60	0.24	0.10	0.06	0.00	0.00	0.00	0.00	0.00	0.00

P-ICECAP

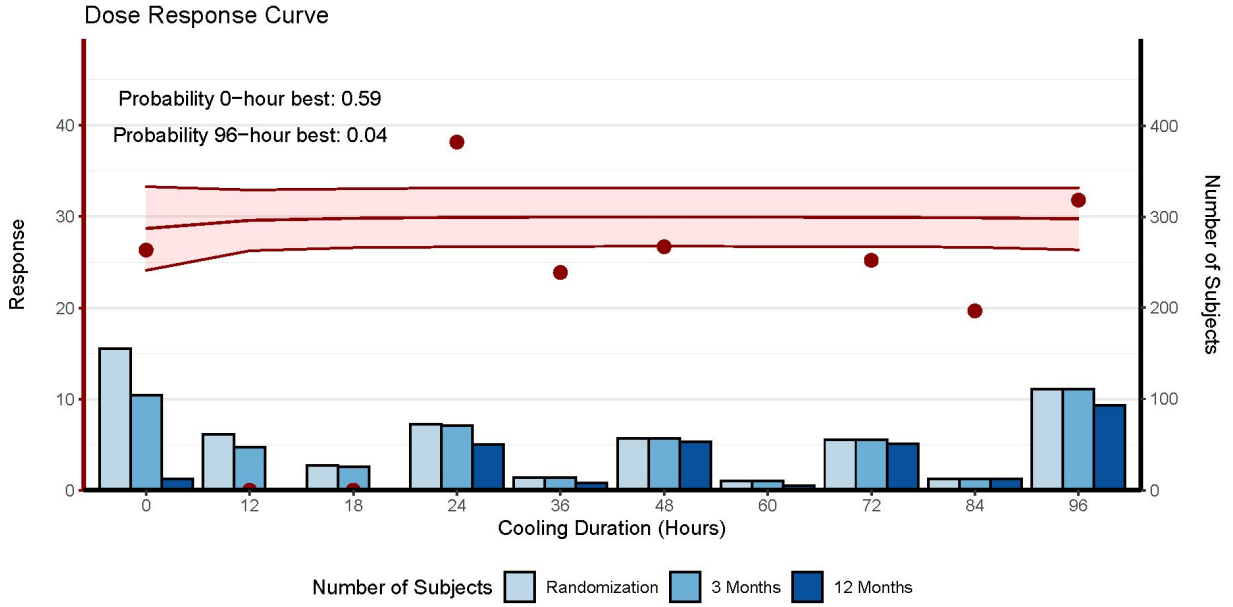
SIREN



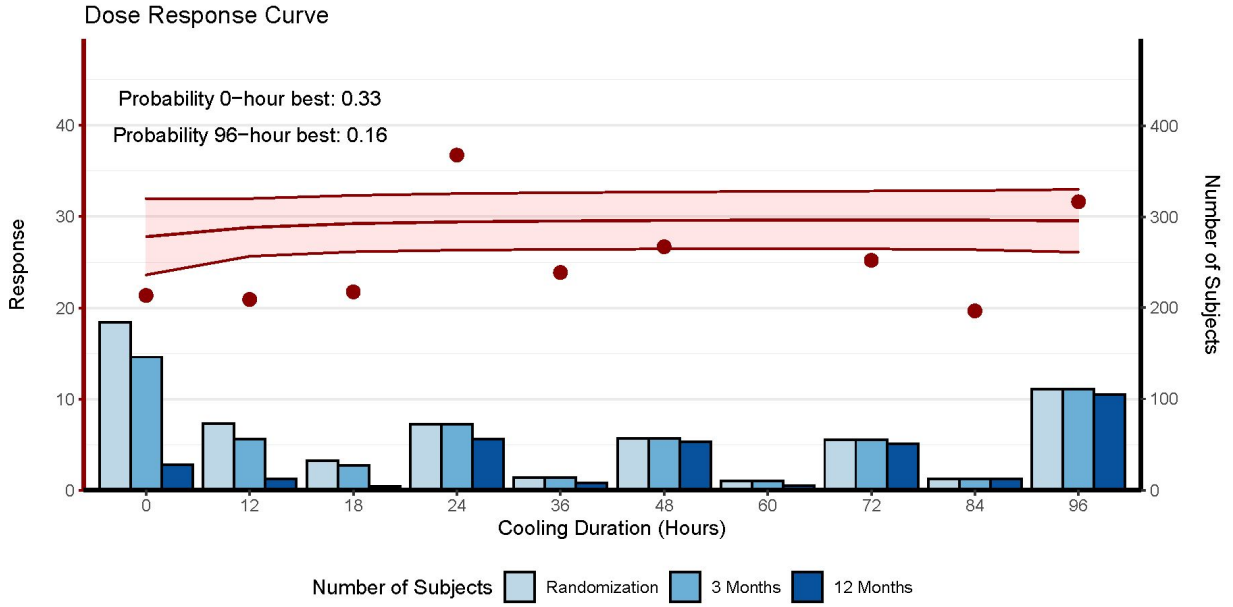
Summary	0	12	18	24	36	48	60	72	84	96
N	118	54	27	72	14	57	10	55	12	111
3−month	76 25.4 (30.0)	36 25.5 (33.5)	18 25.1 (33.8)	67 32.9 (31.7)	12 14.2 (26.7)	57 25.0 (30.4)	7 43.1 (31.1)	54 21.4 (30.9)	12 17.8 (28.5)	109 27.8 (30.4)
12−month	7 29.3 (37.0)	0 NA	0 NA	50 38.2 (36.2)	8 23.9 (33.3)	53 26.7 (32.5)	5 59.2 (34.6)	51 25.2 (34.8)	8 20.5 (31.3)	65 33.4 (34.7)
New allocation	0.84	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

P-ICECAP

SIREN



Summary	0	12	18	24	36	48	60	72	84	96
N	155	61	27	72	14	57	10	55	12	111
3−month	104 25.5 (30.3)	47 22.5 (32.5)	26 33.6 (36.4)	71 33.1 (32.0)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	12 26.3 (33.5)	0 NA	0 NA	50 38.2 (36.2)	8 23.9 (33.3)	53 26.7 (32.5)	5 59.2 (34.6)	51 25.2 (34.8)	12 19.7 (31.3)	93 31.8 (34.4)
New allocation	0.74	0.18	0.08	0.00	0.00	0.00	0.00	0.00	0.00	0.00



Summary	0	12	18	24	36	48	60	72	84	96
N	184	73	32	72	14	57	10	55	12	111
3−month	146 25.3 (30.0)	56 20.6 (31.1)	27 32.3 (36.3)	72 32.6 (32.0)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	28 21.4 (29.8)	12 20.9 (31.2)	4 21.8 (43.5)	56 36.8 (36.3)	8 23.9 (33.3)	53 26.7 (32.5)	5 59.2 (34.6)	51 25.2 (34.8)	12 19.7 (31.3)	105 31.6 (34.0)
New allocation	0.58	0.20	0.14	0.07	0.00	0.00	0.00	0.00	0.00	0.00

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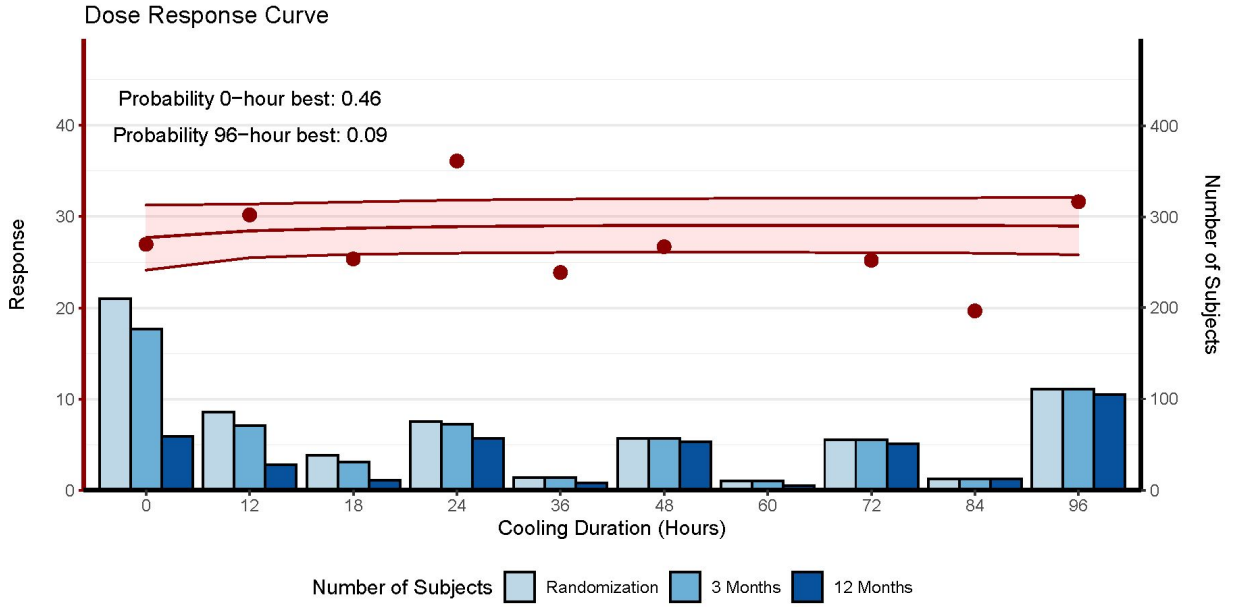
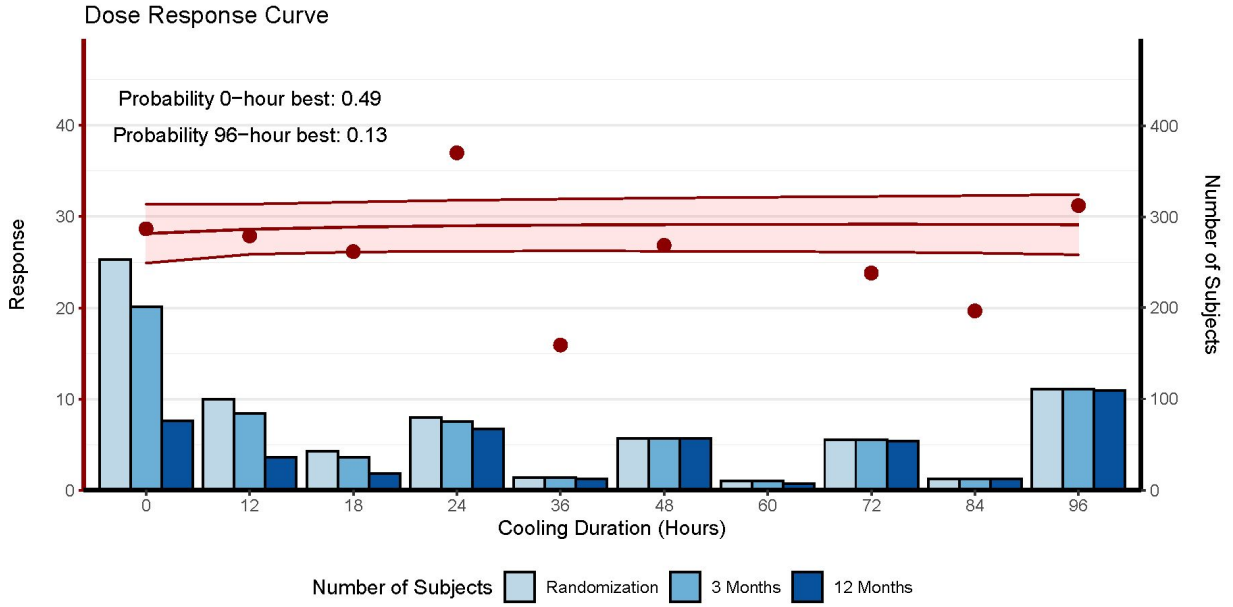
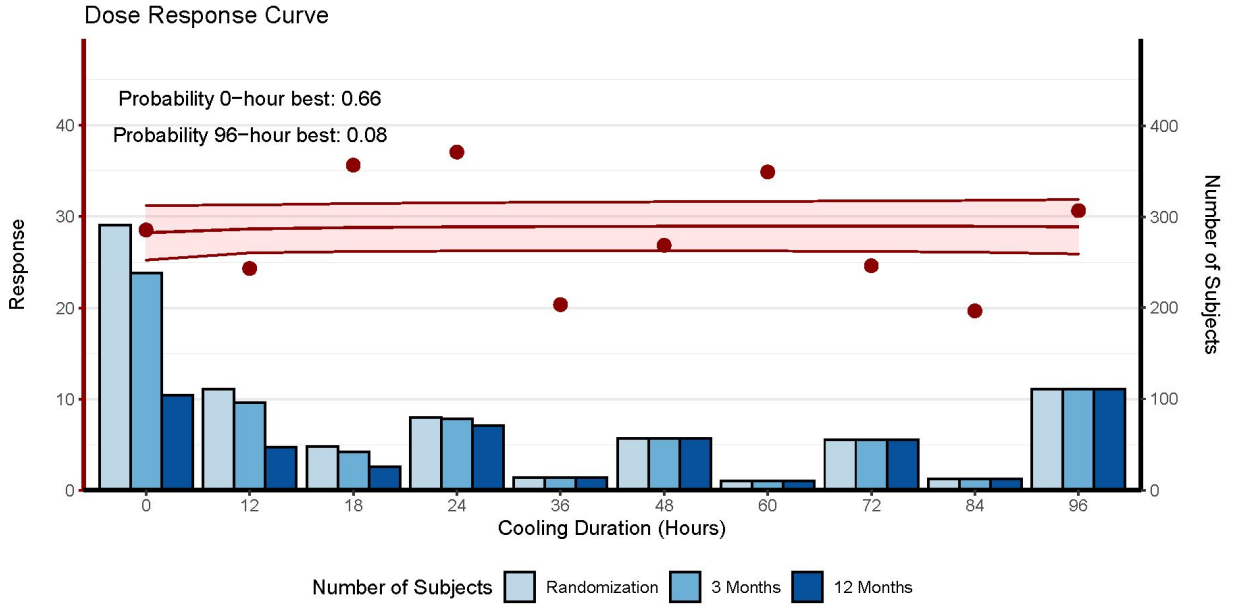


Summary	0	12	18	24	36	48	60	72	84	96
N	210	86	38	75	14	57	10	55	12	111
3−month	177 25.4 (30.0)	71 20.3 (30.6)	31 28.1 (35.5)	72 32.6 (32.0)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	59 27.6 (33.1)	28 30.7 (36.9)	11 25.4 (36.4)	57 36.1 (36.3)	8 23.9 (33.3)	53 26.7 (32.5)	5 59.2 (34.6)	51 25.2 (34.8)	12 19.7 (31.3)	105 31.6 (34.0)
New allocation	0.67	0.17	0.09	0.07	0.00	0.00	0.00	0.00	0.00	0.00



Summary	0	12	18	24	36	48	60	72	84	96
N	253	100	43	80	14	57	10	55	12	111
3−month	201 25.8 (30.5)	84 21.4 (30.9)	36 28.6 (34.3)	75 32.1 (31.9)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	76 28.7 (33.5)	36 27.9 (36.2)	18 26.2 (34.7)	67 37.0 (35.3)	12 15.9 (29.1)	57 26.9 (32.3)	7 49.9 (35.9)	54 23.8 (34.3)	12 19.7 (31.3)	109 31.2 (34.1)
New allocation	0.78	0.13	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00



Summary	0	12	18	24	36	48	60	72	84	96
N	291	111	48	80	14	57	10	55	12	111
3−month	238 26.4 (30.3)	96 22.6 (30.6)	42 29.0 (34.0)	78 30.8 (31.9)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	104 28.5 (33.7)	47 24.3 (34.8)	26 35.7 (38.2)	71 37.1 (35.5)	14 20.4 (30.5)	57 26.9 (32.3)	10 34.9 (37.9)	55 24.6 (34.5)	12 19.7 (31.3)	111 30.7 (34.1)
New allocation	0.88	0.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

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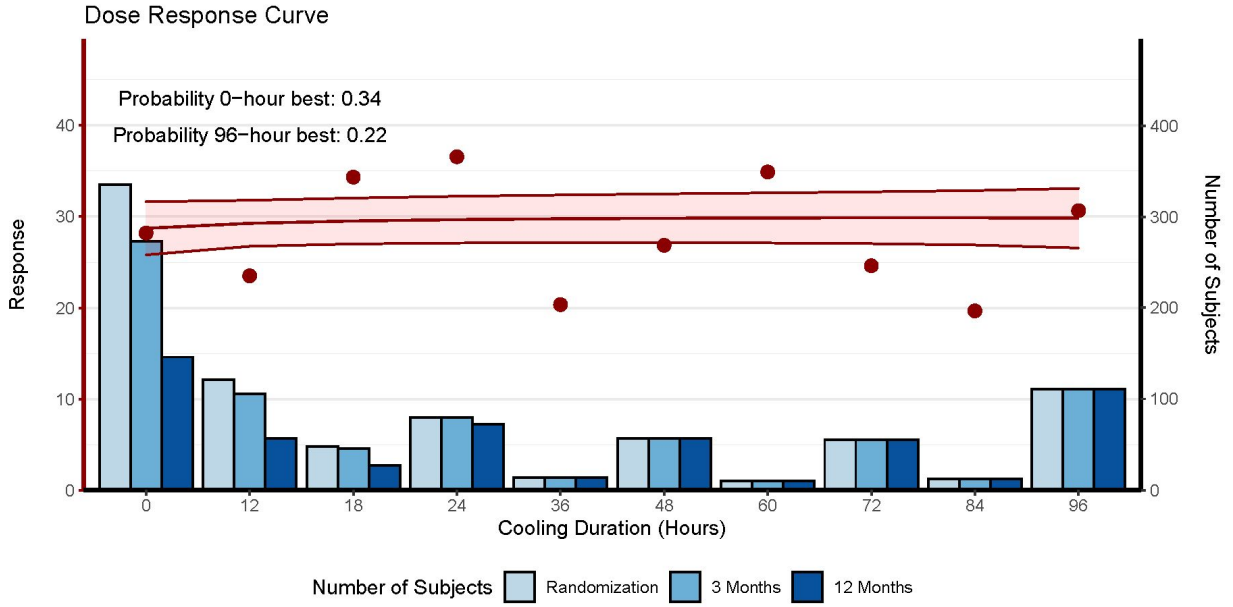
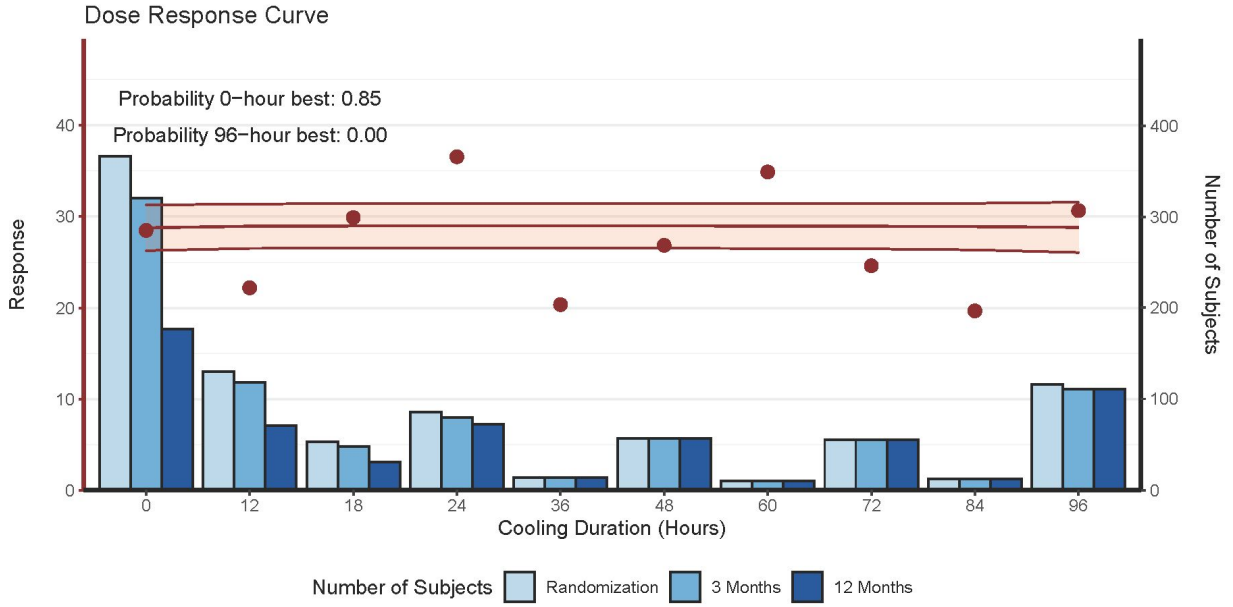


Summary	0	12	18	24	36	48	60	72	84	96
N	335	121	48	80	14	57	10	55	12	111
3−month	273 27.1 (30.4)	106 23.5 (30.7)	46 27.5 (33.4)	80 31.5 (31.8)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	146 28.4 (33.2)	57 23.5 (34.2)	27 34.3 (38.1)	72 36.6 (35.5)	14 20.4 (30.5)	57 26.9 (32.3)	10 34.9 (37.9)	55 24.6 (34.5)	12 19.7 (31.3)	111 30.7 (34.1)
New allocation	0.63	0.15	0.09	0.06	0.00	0.00	0.00	0.00	0.00	0.06



Summary	0	12	18	24	36	48	60	72	84	96
N	366	130	53	86	14	57	10	55	12	116
3−month	320 26.9 (30.5)	118 22.5 (30.3)	48 26.4 (33.1)	80 31.5 (31.8)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	177 28.5 (33.3)	71 22.2 (33.2)	31 29.9 (37.3)	72 36.6 (35.5)	14 20.4 (30.5)	57 26.9 (32.3)	10 34.9 (37.9)	55 24.6 (34.5)	12 19.7 (31.3)	111 30.7 (34.1)
New allocation	0.94	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

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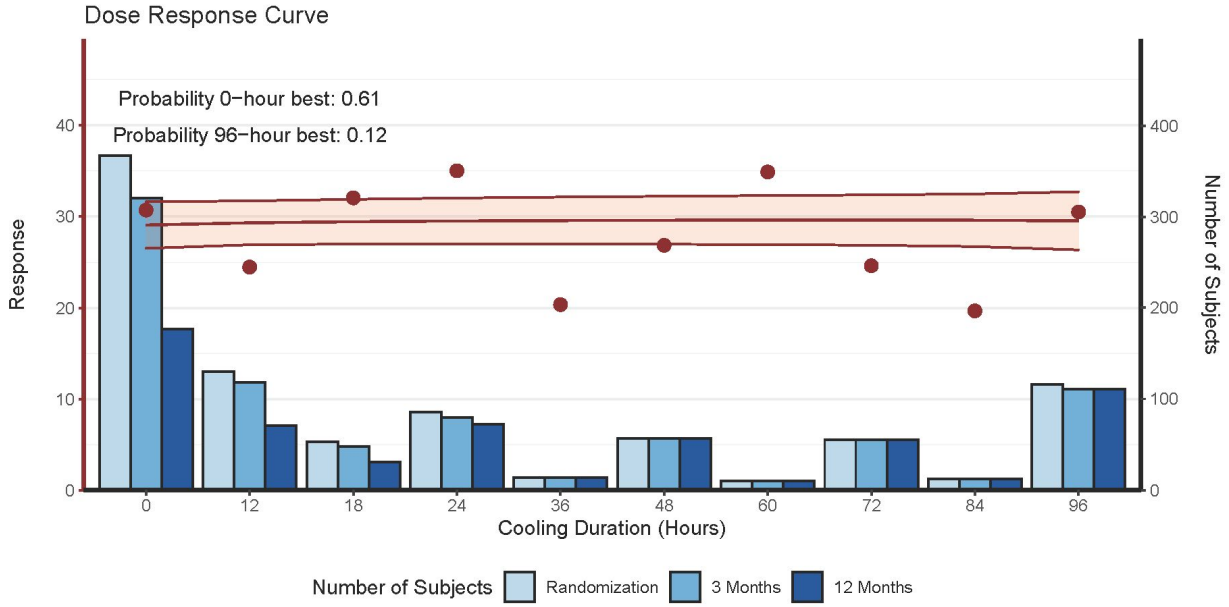

Summary	0	12	18	24	36	48	60	72	84	96
N	367	130	53	86	14	57	10	55	12	116
3−month	320 26.9 (30.5)	118 22.5 (30.3)	48 26.4 (33.1)	80 31.5 (31.8)	14 18.9 (29.0)	57 25.0 (30.4)	10 30.2 (32.8)	55 22.1 (31.2)	12 17.8 (28.5)	111 27.3 (30.3)
12−month	177 28.5 (33.3)	71 22.2 (33.2)	31 29.9 (37.3)	72 36.6 (35.5)	14 20.4 (30.5)	57 26.9 (32.3)	10 34.9 (37.9)	55 24.6 (34.5)	12 19.7 (31.3)	111 30.7 (34.1)
New allocation	0.94	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

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Summary

- The adaptations will be updated every 10 weeks based on the dose response curve
- At the end of the trial, we will identify optimal cooling durations based on the dose response curve
- Sites will be knowledgeable of individual patient arms, but blinded to overall randomization allocations

NHLBI UG3HL159134, U24HL159132 NINDS U24NS100659, U24NS100655

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Thank you!