Appendix A: Search Strategies

Question #1:

PubMed: (Search Completed: January 2015)

("paramedic cooling"[TIAB] OR "field hypothermia"[TIAB] OR "hypothermia, induced"[MeSH] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB] OR "target temperature"[TIAB] OR "body temperature"[MeSH] OR “body temperature”[TIAB]) AND ("brain injuries"[MeSH] OR “brain injury”[TIAB] OR “brain injuries”[TIAB] OR “neurological status”[TIAB] OR “neurological outcome”[TIAB] OR “neurological outcomes”[TIAB] OR “functional outcome”[TIAB] OR “functional outcomes”[TIAB] OR neuroprotect*[TIAB] OR "hypoxia-ischemia, brain"[MeSH] OR “hypoxic-ischemic encephalopathy”[TIAB] OR “cognitive impairment”[TIAB] OR “cognitive impairments”[TIAB] OR “cognitive function”[TIAB] OR "outcome and process assessment (health care)"[MeSH] OR "treatment outcome"[MeSH] OR "Glasgow Outcome Scale"[MeSH]))) AND ("out-of-hospital cardiac arrest"[MeSH] OR “out of hospital cardiac arrest”[TIAB] OR “out-of-hospital cardiac arrest”[TIAB] OR "return of spontaneous circulation"[TIAB] OR ROSC[TIAB] OR "heart arrest"[MeSH] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "advanced cardiac life support"[MeSH] OR "advanced cardiac life support"[TIAB] OR "ACLS"[TIAB] OR "ventricular fibrillation"[MeSH] OR "cardiopulmonary resuscitation"[MeSH] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "heart massage"[MeSH]) NOT ((animal[MeSH] NOT humans[MeSH])) NOT ("letter"[publication type] OR "comment"[publication type] OR "editorial"[publication type] or “Case Reports”[publication type])

Embase: (Search Completed: January 2015)

('heart arrest'/exp OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR 'heart ventricle fibrillation'/exp OR “out of hospital cardiac arrest”:ti,ab OR “out-of-hospital cardiac arrest”:ti,ab OR 'return of spontaneous circulation'/exp OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR 'resuscitation'/exp OR resuscitat*:ti,ab OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR CPR:ti,ab OR 'heart massage'/exp) AND (hypothermia:ti,ab OR "targeted temperature management":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR cool*:ab,ti OR 'induced hypothermia'/exp OR "paramedic cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR ‘cooling’/de OR 'body temperature'/exp OR “body temperature”:ti,ab) AND ('brain injury'/de OR “brain injury”:ti,ab OR “brain injuries”:ti,ab OR “neurological status”:ti,ab OR neuroprotect*:ti,ab OR 'hypoxic ischemic encephalopathy'/exp OR “hypoxic-ischemic encephalopathy”:ti,ab OR

“neurological outcome”:ti,ab OR “neurological outcomes”:ti,ab OR “functional outcome”:ti,ab OR “functional outcomes”:ti,ab OR 'cognitive defect'/exp OR “cognitive impairment”:ti,ab OR “cognitive impairments”:ti,ab OR “cognitive function”:ti,ab OR 'treatment outcome'/exp OR 'Glasgow outcome scale'/exp))) NOT ('animal'/exp NOT 'human'/exp) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [Embase]/lim

Cochrane: (Search Completed: January 2015)

("paramedic cooling":ti,ab OR "field hypothermia":ti,ab OR [mh "hypothermia, induced"] OR "targeted temperature management":ti,ab OR "therapeutic hypothermia":ti,ab OR "hypothermia therapy":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR "target temperature":ti,ab OR [mh "body temperature"] OR “body temperature”:ti,ab) AND ([mh "brain injuries"] OR “brain injury”:ti,ab OR “brain injuries”:ti,ab OR “neurological status”:ti,ab OR “neurological outcome”:ti,ab OR “neurological outcomes”:ti,ab OR “functional outcome”:ti,ab OR “functional outcomes”:ti,ab OR neuroprotect*:ti,ab OR [mh "hypoxia-ischemia, brain"] OR “hypoxic-ischemic encephalopathy”:ti,ab OR “cognitive impairment”:ti,ab OR “cognitive impairments”:ti,ab OR “cognitive function”:ti,ab OR [mh "outcome and process assessment (health care)"] OR [mh "treatment outcome"] OR [mh "Glasgow Outcome Scale"]))) AND ([mh "out-of-hospital cardiac arrest"] OR “out of hospital cardiac arrest”:ti,ab OR “out-of-hospital cardiac arrest”:ti,ab OR "return of spontaneous circulation":ti,ab OR ROSC:ti,ab OR [mh "heart arrest"] OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR [mh "advanced cardiac life support"] OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR [mh "ventricular fibrillation"] OR [mh "cardiopulmonary resuscitation"] OR "cardiopulmonary resuscitation":ti,ab OR CPR:ti,ab OR [mh "heart massage"])

Question #2:

PubMed: (Search Completed: January 2015)

("paramedic cooling"[TIAB] OR "field hypothermia"[TIAB] OR "hypothermia, induced"[MeSH] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB]) AND ("brain injuries"[MeSH] OR “brain injury”[TIAB] OR “brain injuries”[TIAB] OR “neurological status”[TIAB] OR neuroprotect*[TIAB] OR "hypoxia-ischemia, brain"[MeSH] OR “hypoxic-ischemic encephalopathy”[TIAB] OR impair*[TIAB] OR impare*[TIAB]))) AND ("heart arrest"[MeSH] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "advanced cardiac life support"[MeSH] OR "advanced cardiac life support"[TIAB] OR "ACLS"[TIAB] OR "ventricular fibrillation"[MeSH] OR "cardiopulmonary resuscitation"[MeSH] OR

"cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "heart massage"[MeSH]) AND (initiat*[TIAB] OR induc*[TIAB] OR early[TIAB] OR earlie*[TIAB] OR late[TIAB] OR later[TIAB] OR length[TIAB] OR prolong*[TIAB] OR hour*[TIAB] OR hrs[TIAB] OR minute*[TIAB] OR rapid*[TIAB] OR fast*[TIAB] OR quick*[TIAB] OR slow*[TIAB] OR time[TIAB] OR timing[TIAB] OR speed[TIAB] OR rate[TIAB] OR "time factors"[MeSH] OR "time-to-treatment"[MeSH] OR delay*[TIAB] OR "emergency medical technicians"[MeSH] OR “emergency medic”[TIAB] OR “emergency medical”[TIAB] OR “EMS”[TIAB] OR “EMT”[TIAB] OR "pre-hospital"[TIAB] OR prehospital[TIAB] OR paramedic*[TIAB] OR “out-of-hospital”[TIAB] OR “out of hospital”[TIAB]) NOT ((animal[MeSH] NOT humans[MeSH]) OR rabbit*[TIAB] OR mouse[TIAB] OR mice[TIAB] OR swine[TIAB] OR pig[TIAB] OR pigs[TIAB] OR dog[TIAB] OR “animal model”[TIAB] OR “animal models”[TIAB]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or “case reports”[ptyp])

Embase: (Search Completed: January 2015)

(('heart arrest'/exp OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR 'heart ventricle fibrillation'/exp OR 'resuscitation'/exp OR resuscitat*:ti,ab OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR CPR:ti,ab OR 'heart massage'/exp) AND (initiat*;ti,ab OR induc*:ti,ab OR early:ti,ab OR earlie*:ti,ab OR late:ti,ab OR later:ti,ab OR length:ti,ab OR prolong*:ti,ab OR hour*:ti,ab OR hrs:ti,ab OR minute*:ti,ab OR rapid*:ti,ab OR fast*:ti,ab OR quick*:ti,ab OR slow*:ti,ab OR time:ti,ab OR timing:ti,ab OR speed:ti,ab OR rate:ti,ab OR delay*:ti,ab OR ‘therapy delay’/exp OR 'time'/exp OR 'time to treatment'/exp OR 'rescue personnel'/exp OR “emergency medic”:ti,ab OR “emergency medical”:ti,ab OR “EMS”:ti,ab OR “EMT”:ti,ab OR "pre-hospital":ti,ab OR prehospital:ti,ab OR paramedic*:ti,ab OR “out-of-hospital”:ti,ab OR “out of hospital”:ti,ab) AND (hypothermia:ti,ab OR "targeted temperature management":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR cool*:ab,ti OR 'induced hypothermia'/exp OR "paramedic cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR ‘cooling’/de) AND ('brain injury'/de OR “brain injury”:ti,ab OR “brain injuries”:ti,ab OR “neurological status”:ti,ab OR neuroprotect*:ti,ab OR 'hypoxic ischemic encephalopathy'/exp OR “hypoxic-ischemic encephalopathy”:ti,ab OR impair*:ti,ab OR impare*:ti,ab)))) OR ('heart arrest'/exp OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR 'heart ventricle fibrillation'/exp OR 'resuscitation'/exp OR resuscitat*:ti,ab OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR CPR:ti,ab OR 'heart massage'/exp) AND ((‘therapy delay’/exp OR 'time'/exp OR 'time to treatment'/exp OR 'rescue personnel'/exp OR “emergency medic”:ti,ab OR “emergency medical”:ti,ab OR “EMS”:ti,ab OR “EMT”:ti,ab OR "pre-hospital":ti,ab OR prehospital:ti,ab OR paramedic*:ti,ab OR “out-of-hospital”:ti,ab OR “out of hospital”:ti,ab) AND ('induced hypothermia'/exp OR "paramedic cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab OR ‘cooling’/de) AND ('brain injury'/de OR “brain injury”:ti,ab OR “brain injuries”:ti,ab OR “neurological status”:ti,ab OR neuroprotect*:ti,ab OR 'hypoxic ischemic encephalopathy'/exp OR “hypoxic-ischemic encephalopathy”:ti,ab OR impair*:ti,ab OR impare*:ti,ab))) OR ((initiat* OR induc* OR

early OR earlie* OR late OR later OR length OR prolong* OR hour* OR hrs OR minute* OR rapid* OR fast* OR quick* OR slow* OR time OR timing OR speed OR rate OR delay*) NEAR/5 (hypothermia OR "targeted temperature management" OR "whole body cooling" OR "whole-body cooling" OR cool*)):ti,ab) NOT ('animal'/exp NOT 'human'/exp) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [Embase]/lim

Cochrane: (Search Completed: January 2015)

("paramedic cooling":ti,ab OR "field hypothermia"ti,ab OR [mh "hypothermia, induced"] OR "targeted temperature management":ti,ab OR "therapeutic hypothermia":ti,ab OR "hypothermia therapy":ti,ab OR "whole body cooling":ti,ab OR "whole-body cooling":ti,ab OR ((cool*:ti,ab OR cold:ti,ab) AND ([mh "brain injuries"] OR “brain injury”:ti,ab OR “brain injuries”:ti,ab OR “neurological status”:ti,ab OR neuroprotect*:ti,ab OR [mh "hypoxia-ischemia, brain"] OR “hypoxic-ischemic encephalopathy”:ti,ab OR impair*:ti,ab OR impare*:ti,ab))) AND ([mh "heart arrest"] OR "cardiac arrest":ti,ab OR "cardiac arrests":ti,ab OR "cardiovascular arrest":ti,ab OR "cardiovascular arrests":ti,ab OR "heart arrest":ti,ab OR "heart arrests":ti,ab OR "asystole":ti,ab OR "pulseless electrical activity":ti,ab OR "cardiopulmonary arrest":ti,ab OR "cardiopulmonary arrests":ti,ab OR [mh "advanced cardiac life support"] OR "advanced cardiac life support":ti,ab OR "ACLS":ti,ab OR [mh "ventricular fibrillation"] OR [mh "cardiopulmonary resuscitation"] OR "cardiopulmonary resuscitation":ti,ab OR CPR:ti,ab OR [mh "heart massage"]) AND (initiat*;ti,ab OR induc*:ti,ab OR early:ti,ab OR earlie*:ti,ab OR late:ti,ab OR later:ti,ab OR length:ti,ab OR prolong*:ti,ab OR hour*:ti,ab OR hrs:ti,ab OR minute*:ti,ab OR rapid*:ti,ab OR fast*:ti,ab OR quick*:ti,ab OR slow*:ti,ab OR time:ti,ab OR timing:ti,ab OR speed:ti,ab OR rate:ti,ab OR [mh "time factors"] OR [mh "time-to-treatment"] OR delay*:ti,ab OR [mh "emergency medical technicians"] OR “emergency medic”:ti,ab OR “emergency medical”:ti,ab OR “EMS”:ti,ab OR “EMT”:ti,ab OR "pre-hospital":ti,ab OR prehospital:ti,ab OR paramedic*:ti,ab OR “out-of-hospital”:ti,ab OR “out of hospital”:ti,ab)

Question #3:

PubMed: (Search Completed: January 2015)

("hypothermia, induced"[MeSH] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB]) AND ("brain injuries/prevention and control"[MeSH] OR neuroprotection[TIAB] OR "hypoxia-ischemia, brain/prevention and control"[MeSH] OR “hypoxic-ischemic encephalopathy”[TIAB]))) AND ("heart arrest"[MeSH] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "advanced cardiac life support"[MeSH] OR "advanced cardiac life support"[TIAB] OR "ACLS"[TIAB] OR "ventricular fibrillation"[MeSH] OR "cardiopulmonary resuscitation"[MeSH] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "heart massage"[MeSH]) AND (prolong*[TIAB] OR hour*[TIAB] OR hrs[TIAB] OR

duration*[TIAB] OR "time factors"[MeSH]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or “case reports”[ptyp])

Embase: (Search Completed: January 2015)

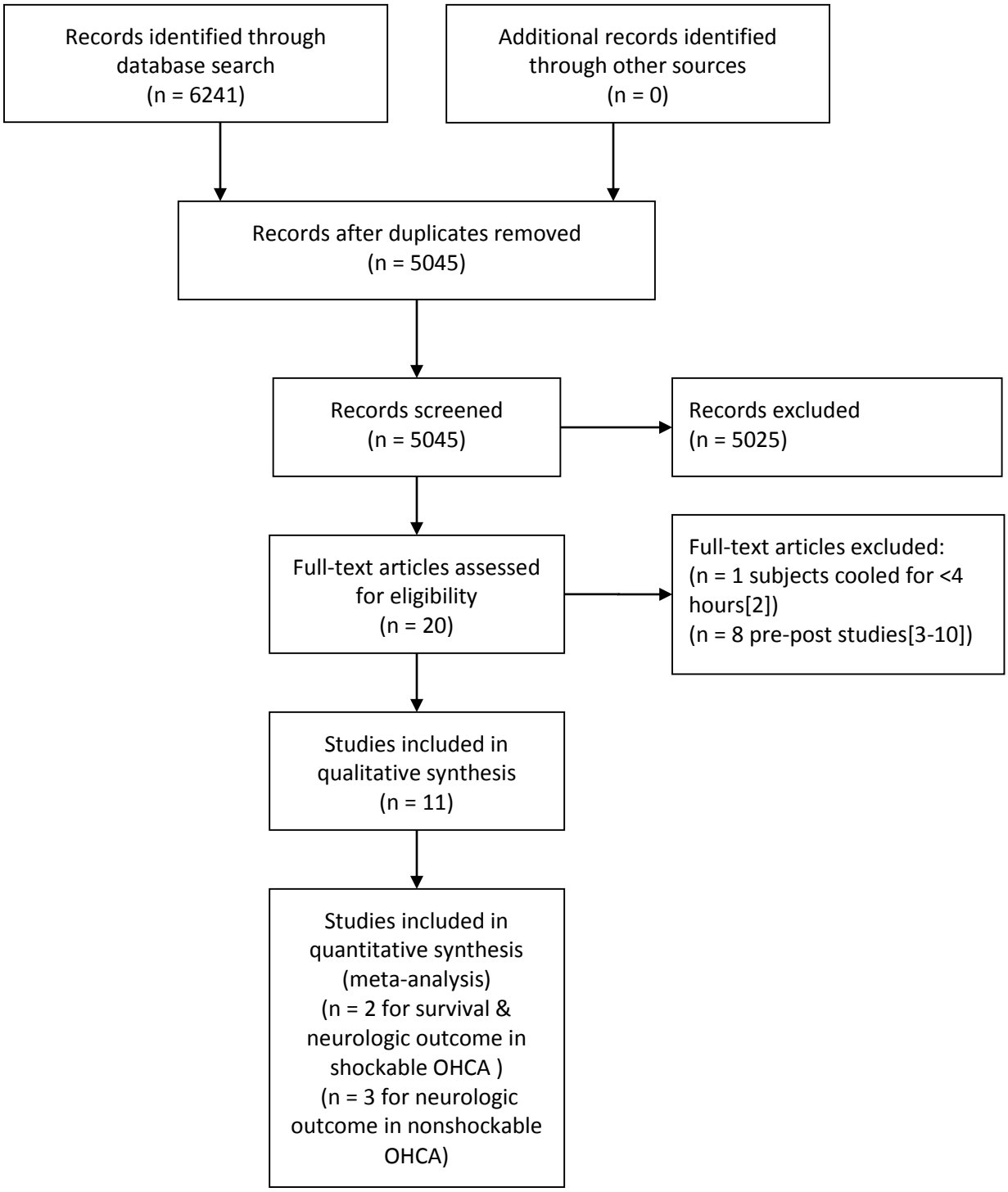
('dose time effect relation'/exp OR 'time'/exp OR “thermal dose”:ab,ti OR ((duration* OR hour* OR hr* OR prolong* OR short* OR long*) NEAR/10 (hypotherm* OR cool*)):ab,ti) AND ('induced hypothermia'/exp OR "targeted temperature management":ab,ti OR "therapeutic hypothermia":ab,ti OR "hypothermia therapy":ab,ti OR "whole body cooling":ab,ti OR "whole-body cooling":ab,ti OR ((cool*:ab,ti OR cold:ab,ti) AND ('brain injury'/exp OR 'neuroprotection'/exp OR neuroprotection:ab,ti OR 'hypoxic ischemic encephalopathy'/exp OR “hypoxic-ischemic encephalopathy”:ab,ti))) AND ('out of hospital cardiac arrest'/exp OR 'heart arrest'/exp OR "heart arrest":ab,ti OR "heart arrests":ab,ti OR "cardiac arrest":ab,ti OR "cardiac arrests":ab,ti OR "cardiovascular arrest":ab,ti OR "cardiovascular arrests":ab,ti OR "asystole":ab,ti OR "pulseless electrical activity":ab,ti OR "cardiopulmonary arrest":ab,ti OR "cardiopulmonary arrests":ab,ti OR 'cardiopulmonary arrest'/exp OR 'resuscitation'/exp OR "cardiopulmonary resuscitation":ab,ti OR CPR:ab,ti OR 'heart stimulation'/exp) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [Embase]/lim

Cochrane: (Search Completed: January 2015)

([mh "hypothermia, induced"] OR "targeted temperature management":ab,ti OR "therapeutic hypothermia":ab,ti OR "hypothermia therapy":ab,ti OR "whole body cooling":ab,ti OR "whole-body cooling":ab,ti OR ((cool*:ab,ti OR cold:ab,ti) AND ([mh "brain injuries/prevention and control"] OR neuroprotection:ab,ti OR [mh "hypoxia-ischemia, brain/prevention and control"] OR “hypoxic-ischemic encephalopathy”:ab,ti))) AND ([mh "heart arrest"] OR "cardiac arrest":ab,ti OR "cardiac arrests":ab,ti OR "cardiovascular arrest":ab,ti OR "cardiovascular arrests":ab,ti OR "heart arrest":ab,ti OR "heart arrests":ab,ti OR "asystole":ab,ti OR "pulseless electrical activity":ab,ti OR "cardiopulmonary arrest":ab,ti OR "cardiopulmonary arrests":ab,ti OR [mh "advanced cardiac life support"] OR "advanced cardiac life support":ab,ti OR "ACLS":ab,ti OR [mh "ventricular fibrillation"] OR [mh "cardiopulmonary resuscitation"] OR "cardiopulmonary resuscitation":ab,ti OR CPR:ab,ti OR [mh "heart massage"]) AND (prolong*:ab,ti OR hour*:ab,ti OR hrs:ab,ti OR duration*:ab,ti OR [mh "time factors"])

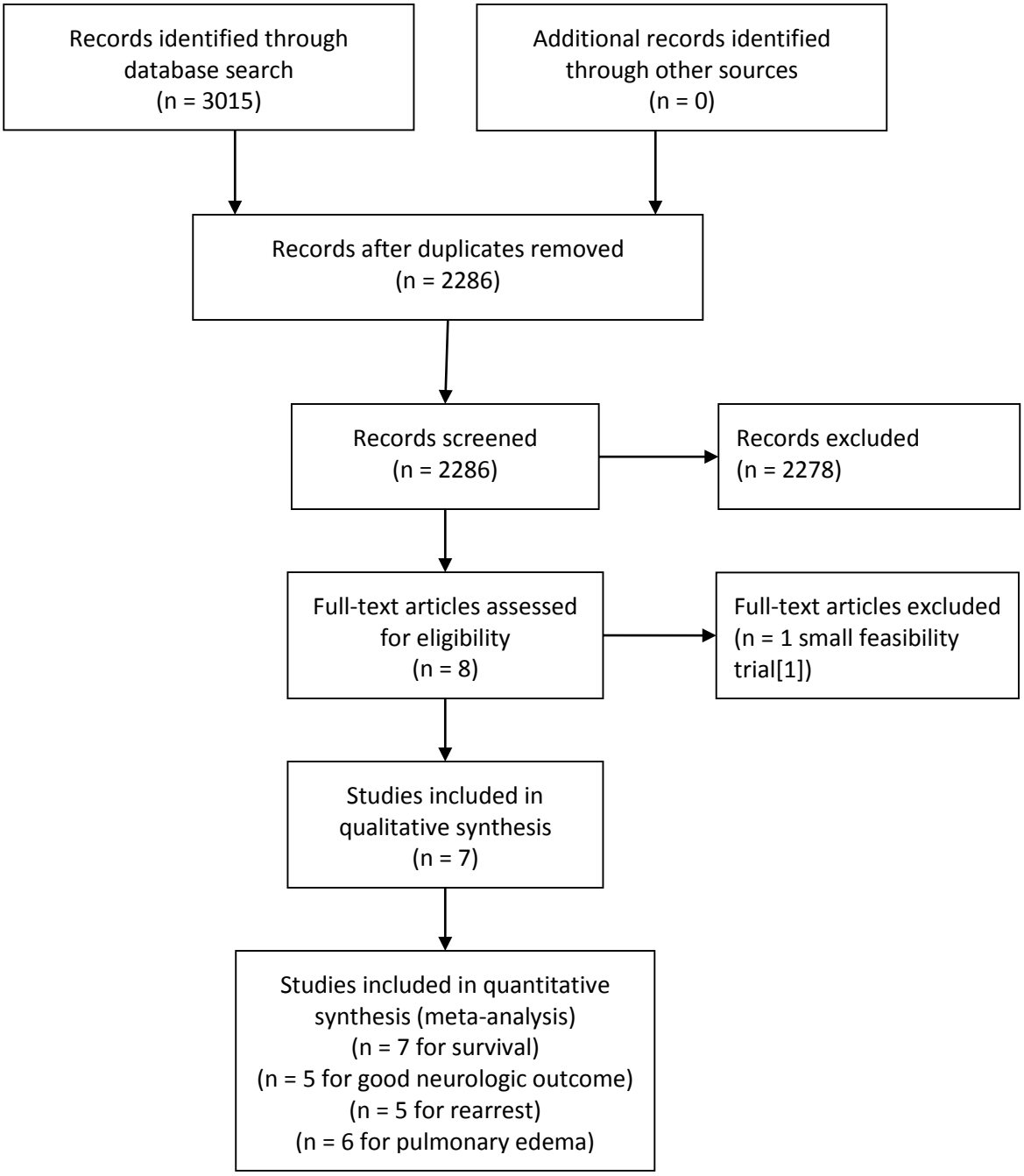
Appendix B: Selection of Articles

Question #1:

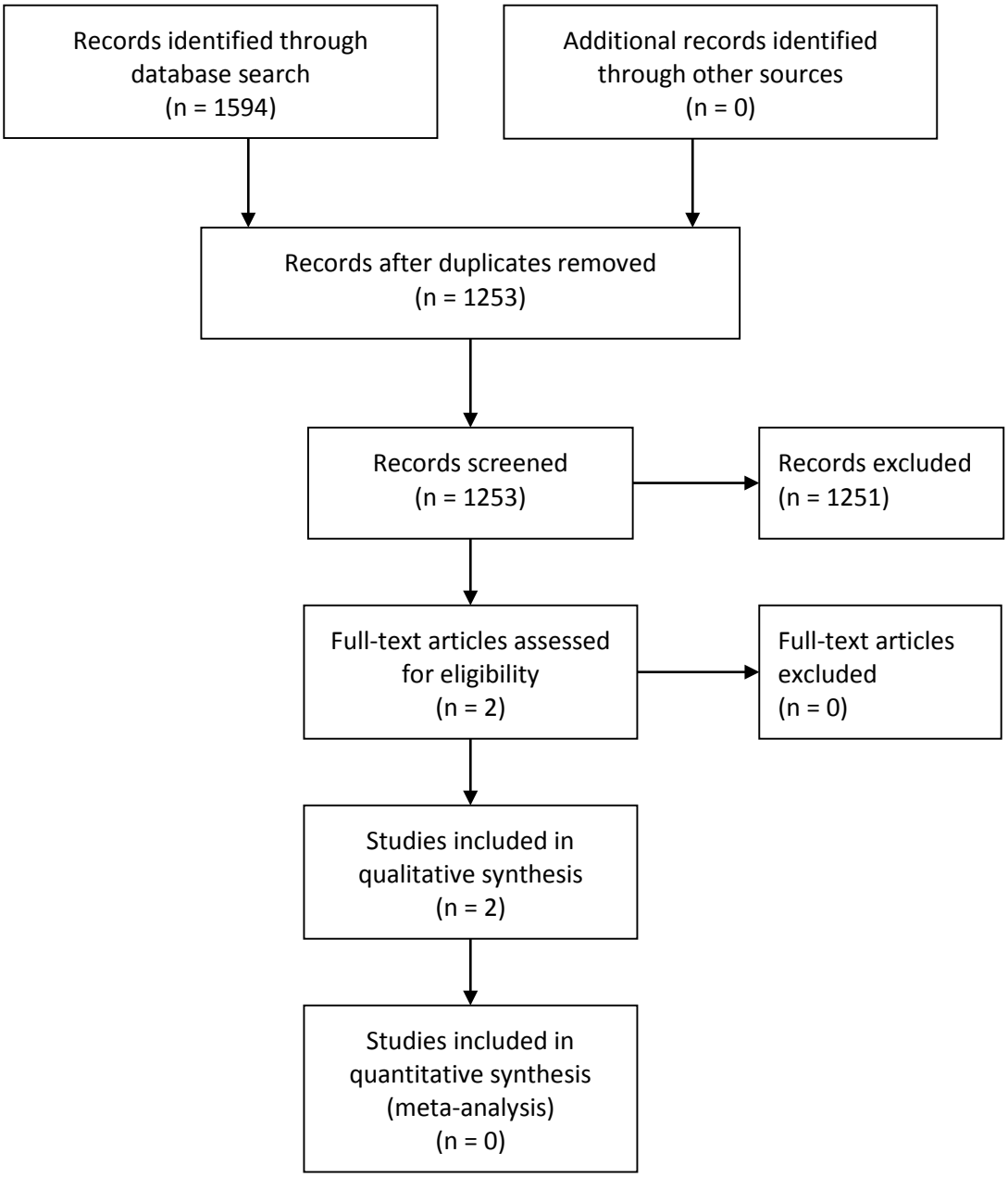


OHCA indicates out-of-hospital cardiac arrest; RCT: randomized controlled trial.

Question #2:


Records identified through database search (n = 3015)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 2286)
Records screened (n = 2286)
Records excluded (n = 2278)
Full-text articles assessed for eligibility (n = 8)
Full-text articles excluded (n = 1 small feasibility trial[1])
Studies included in qualitative synthesis (n = 7)
Studies included in quantitative synthesis (meta-analysis)
(n = 7 for survival)
(n = 5 for good neurologic outcome)
(n = 5 for rearrest)
(n = 6 for pulmonary edema)

Question #3:


Records identified through database search (n = 1594)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 1253)
Records screened (n = 1253)
Records excluded (n = 1251)
Full-text articles assessed for eligibility (n = 2)
Full-text articles excluded (n = 0)
Studies included in qualitative synthesis (n = 2)
Studies included in quantitative synthesis (meta-analysis) (n = 0)

Appendix C: Overview of Studies

Question #1:

Study	No. of Patients Analyzed	No. of Patients Screened	Inclusion Criteria	Exclusion Criteria	Experimental Intervention	Control Group	Primary Outcome	Main Clinical Results (Intervention vs Control)
Randomized controlled trials								
HACA (2002)[11]	275	3551	Age 18–75 y, OHCA, witnessed arrest, initial shockable rhythm, presumed cardiac origin, collapse-to-CPR interval >5 to <15 min, collapse-to-ROSC interval <60 min	Initial temperature <30°C, pre–cardiac arrest coma, pregnancy, following commands, hypotension >30 min, severe hypoxia >15 min, pre–cardiac arrest terminal illness, unlikely to follow up, concomitant enrollment in another study, EMS-witnessed arrest, preexisting coagulopathy	Surface cooling to 32°C to 34°C within 4 h of ROSC, maintenance for 24 h, then passive rewarming	Normothermia (not otherwise defined)	Good neurologic status at 6 mo (CPC 1–2)	55% vs 39% (*P*=0.009) Adjusted RR 1.47 (95% CI, 1.09–1.82)
Bernard et al. (2002)[12]	77	84	OHCA, initial shockable rhythm, persistent coma	Female age <50 y and male age <18 y, systolic blood pressure <90 mm Hg despite vasopressor support, other possible causes of coma, unavailable ICU bed at hospital	Prehospital initiation of surface cooling to 33°C after ROSC, maintenance for 12 h, then active rewarming for 6 h	Target core temperature of 37°C, passive rewarming if spontaneously hypothermic	Good functional status at hospital discharge (discharge to home or acute rehabilitation)	49% vs 26% (*P*=0.046) Adjusted OR 5.25 (95% CI, 1.47–18.76)
Laurent et al. (2005)[13]	61	244	Age 18–75 y, OHCA, initial shockable or asystolic rhythm, collapse-to-CPR <10 min, collapse-to-ROSC <50 min, presumed cardiac origin	Pregnancy, following commands, preexisting terminal illness	Hemofiltration plus active cooling with replacement fluid to 32°C to 33°C for 24 h, then passive rewarming	Hemofiltration with replacement fluid set to 37°C	Mortality at 6 mo	32% vs 45% (*P*=0.28)
Zhang et al. (2005)[14]	16	Not reported	Received CPR for cardiac arrest	Previous history of cardiac arrest, trauma	Surface cooling to 33°C for 72 h, then rewarming at 1°C/h	No temperature management	Secondary outcome: functional status at 3 mo	Barthel Index score: 86±6 vs 52±12 (*P*<0.01)

Lopez-de-Sa et al. (2012)[15]	36	73	Age >18 y, OHCA, witnessed arrest, presumed cardiac cause, initial shockable or asystolic rhythm, collapse-to-ROSC ≤ 60 min	GCS >8, pregnancy, initial PEA rhythm, preceding terminal illness, other possible causes of coma, shock despite 30 min of administration of inotropes	Induction with ice-cold crystalloid and maintenance of 32°C with endovascular device for 24 h, then rewarming at 0.1°C to 0.3°C/h	Induction with ice-cold crystalloid and maintenance of 34°C with endovascular device for 24 h, then rewarming at 0.1°C to 0.3°C/h	Good functional status at 6 mo (Barthel Index score ≥60)	44% vs 11% (*P*=0.12)
Nielsen et al. (2013)[16]	939	1431	OHCA, any initial rhythm, GCS <8	Obvious or suspected pregnancy, known bleeding diathesis, suspected or confirmed acute intracranial bleeding or acute stroke, unwitnessed cardiac arrest with initial rhythm asystole, known limitations in therapy and do-not-resuscitate order, known disease that would make 180-d survival unlikely, known prearrest CPC 3 or 4, >4 h from ROSC to screening, systolic blood pressure <80 mm Hg in spite of fluid loading/vasopressor and/or inotropic medication/ intra-aortic balloon pump, temperature on admission <30°C	Cooling via any method as rapidly as possible to 33°C, maintenance for 28 h, then rewarming ata maximum of 0.5°C/h to 37°C, then active fever prevention until 72 h after the cardiac arrest	Cooling via any method as rapidly as possible to 36°C, maintenance for 28 h, then rewarming at maximum 0.5°C/h to 37°C, then active fever prevention until 72 h after the cardiac arrest	All-cause mortality through the end of the trial	50% vs 48% (*P*=0.51) Hazard ratio 1.06 (95% CI, 0.89–1.28)
Observational studies								
Testori et al. (2011)[17]	374	N/A	Age >18 y, nontraumatic OHCA in a registry, witnessed, initial nonshockable rhythm	Died <24 h after ROSC, GCS >8, prearrest CPC 3–5, CVA cause of arrest, initial temperature <30°C	Cooling via any method to 32°C to 34°C for 24 h	No temperature management	Good functional status at 6 mo (CPC 1–2)	35% vs 23% (*P*=0.02) Adjusted OR 1.84 (95% CI, 1.08–3.13)
Dumas et al. (2011)[18]	437	N/A	OHCA patients in a registry, initial nonshockable rhythm	Trauma	Surface cooling to 32°C to 34°C for 24 h, then passive rewarming for additional 24 h	No temperature management	Good functional status at hospital discharge (CPC 1–2)	15% vs 17% (*P*=0.48) Adjusted OR 0.71 (95% CI, 0.37–1.36)

Vaaher-salo et al. (2013)[19]	223	N/A	Age >18 y, OHCA, initial nonshockable rhythm, admitted to the ICU	Noncomatose patients	Cooling to 33°C, primarily via endovascular devices although not mandated	No temperature management	Poor functional status (CPC 3, 4, or 5, or death) 1 y after discharge	77% vs 82% Adjusted OR 1.16 (95%CI, 0.33–4.12)
Nichol et al. (2013)[20]	8316	N/A	IHCA on general inpatient ward in a registry, index event	Trauma, unknown time of arrest	Coded as "induced hypothermia" in registry. Cooling methods not described	Not coded as "induced hypothermia" in registry	Survival to hospital discharge	27% vs 31% (*P*=0.29) Adjusted OR 0.90 (95% CI, 0.65–1.23)
Mader et al. (2014)[21]	1830	N/A	CARES registry; Age > 18 y, OHCA, initial nonshockable rhythm, presumed cardiac etiology	Missing data on temperature management or outcome, cardiac arrest at long-term care facility, EMS-witnessed	Coded as "therapeutic hypothermia" in CARES	Not coded as "therapeutic hypothermia" in CARES	Poor functional status at hospital discharge (CPC 3-5)	85% vs. 78% (P<0.0001) Adjusted OR1.44 (95% CI, 1.04-2.01)

CARES indicates Cardiac Arrest registry to Enhance Survival; CI, confidence interval; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; EMS, emergency medical service; GCS, Glasgow Coma Scale; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; N/A, not applicable; OHCA, out-of -hospital cardiac arrest; OR, odds ratio; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; RR, risk ratio.

Question #2:

Study	No. of Patients Analyzed	No. of Patients Screened	Inclusion Criteria	Exclusion Criteria	Experimental Intervention	Control Intervention	Clinical Outcome	Main Clinical Results (Intervention vs Control)
Kim et al. (2007)[22]	125	559	OHCA with ROSC, intubation, IV access, esophageal temperature probe (temperature ≥34°C), unresponsive, any initial rhythm	Traumatic arrest, age <18 y	Prehospital rapid infusion of up to 2 L of 4°C normal saline	Standard of care (60/97 admitted patients in the combined group received surface cooling in the hospital)	Survival to hospital discharge	21/63 (33%) vs 18/62 (29%)
Kamaraine n et al. (2009)[23]	37	44	OHCA with ROSC, >9 min until ROSC, age ≥18 y, GSC ≤5, any initial rhythm	Pregnancy, traumatic arrest, arrest due to intoxication, persistent initial hypotension after ROSC	Prehospital rapid infusion of 4°C Ringer's acetate at a rate of 100 mL/min (10 of 19 received in-hospital TTM)	13 of 18 received in-hospital TTM	Hospital survival and good neurologic outcome at discharge (CPC 1–2)	Hospital survival: 8/19 (42%) vs 8/18 (44%) CPC 1–2: 42% vs 44%
Castren et al. (2010)[24]	194	Unknown	OHCA, ≥ 18 y, witnessed, CPR initiated by EMS within 20 min, any initial rhythm	Trauma, drug overdose, cerebrovascular accident, known coagulopathy, asphyxia or known requirement for supplemental oxygen, electrocution, hypothermia, do-not-attempt-resuscitation order, and intranasal obstruction. ROSC before randomization	Prehospital intra-arrest transnasal cooling	In-hospital cooling (modality according to "institutional standards," not otherwise specified)	ROSC rate, survival to discharge, good neurologic outcome at discharge (CPC 1–2)	ROSC: 35/94 (38%) vs 43/101 (43%) (*P*=0.48) Survival to discharge in those admitted alive: 14/32 (44%) vs 13/42 (31%) (*P*=0.26) CPC 1–2 in those admitted alive: 11/32 (34%) vs 9/42 (21%) (*P*=0.21)

Bernard et al. (2010)[25]	234	6730	OHCA with ROSC, ventricular fibrillation, systolic blood pressure >90 mm Hg, cardiac arrest time >10 min, age ≥15 y, and IV access	Not intubated, poor prearrest functional status, hypothermic, or pregnant	Prehospital rapid infusion of up to 2 L of ice-cold lactated Ringer's solution	In-hospital rapid infusion of 40 mL/kg ice-cold lactated Ringer's solution	Good functional status at hospital discharge (discharge to home or to rehabilitation)	56/118 (48%) vs 61/116 (53%) (*P*=0.43)
Bernard et al. (2012)[26]	163	6730	OHCA with ROSC, PEA or asystole, systolic blood pressure >90 mm Hg, cardiac arrest time >10 min, age ≥15 y, and IV access available	Not intubated, poor prearrest functional status, hypothermic, pregnant, or traumatic arrest	Prehospital rapid infusion of 40 mL/kg (up to 2 L) ice-cold Hartmann's solution	In-hospital cooling with rapid infusion of 40 mL/kg ice-cold Hartmann's solution, and surface cooling	Good functional status at hospital discharge (discharge to home or to rehabilitation)	10/82 (12%) vs 7/81 (9%) (*P*=0.50)
Kim et al. (2014)[27]	1359	5696	OHCA with ROSC, intubation, IV access, esophageal temperature probe (temperature ≥34°C), unresponsive, any initial rhythm	Traumatic arrest, age <18 y,	Prehospital rapid infusion of up to 2 L of 4°C normal saline (224 of 292 patients with VF received in-hospital cooling; no information provided for non-VF patients)	Standard of care (224 of 291 patients with VF received in-hospital cooling; no information provided for non-VF patients)	Hospital mortality and good neurologic outcome at discharge	Survival to discharge: VF: 63% vs 64% (*P*=0.69) Non-VF: 19% vs 16% (*P*=0.30) Good neurologic outcome: VF: 58% vs 62% (*P*=0.59) Non-VF: 14% vs 13% (*P*=0.74)
Debaty et al. (2014)[28]	245	1559	OHCA, > 18 y, eligible for resuscitation	Trauma, hemorrhage, asphyxia, hypothermia, pregnant, ROSC before randomization	Intra-arrest up to 2 L < 8°C saline at 100mL/min with pressure bag and gel pads surface cooling. Aim for 32-34°C. In-hospital TTM	In-hospital TTM with cold saline infusion, cooling mattress, cold air circulation or extra corporeal life support	Survival at 30 days	5.7% vs 4.1% (P=0.58)

CPC indicates cerebral performance category; EMS, emergency medical service; GCS, Glasgow Coma Scale; IV, intravenous; OHCA, out-of -hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; TTM, targeted temperature management; VF, ventricular fibrillation.

Question 3:

Study	No. of Patients Analyzed	Inclusion Criteria	Exclusion Criteria	Intervention	Clinical Outcomes	Results Related to Duration
Yokoyama et al. (2011)[29]	452	OHCA, receiving temperature management, age >18 y, stable hemodynamics, comatose, presumed cardiac cause of arrest	Pregnancy, aortic dissection, pulmonary embolism, drug addiction, poor daily activity before onset	Various durations of targeted temperature management	Neurologic outcome at 30 d	Duration of cooling in CPC 1–2: 24 (24–42) h vs CPC 3–5: 26 (24–45) h (Nonsignificant *P* value, exact *P* value not reported)
Lee et al. (2014)[30]	79	OHCA, unconscious asphyxia (i.e. preceding respiratory failure)	< 18 y, preexisting terminal illness, trauma, exsanguination, toxin other than tetrodotoxin	24 h at 33°C ± 1°C compared to 72 h at 32°C ± 1°C	Survival and good neurologic outcome (CPC 1-2) at 30 days	Survival: 49% vs. 47% (P=0.61) Good neurological outcome: 3% vs. 3% (P=1.00)

CPC indicates cerebral performance category; OHCA, out-of-hospital cardiac arrest.

Appendix D: Bias Assessment

Question #1:

a. Bias Assessment: RCTs

Study	Allocation: Generation	Allocation: Concealment	Blinding: Participants	Blinding: Assessors	Outcome: Complete	Outcome: Selective	Other Bias
HACA (2002)[11]	Low	Low	High*	Low	Low	Low	Unclear†
Bernard et al. (2002)[12]	High‡	High‡	High*	Low	Low	Low	Unclear†
Laurent et al. (2005)[13]	Low	Low	High*	High§	Low	Low	Unclear†‖
Zhang et al. (2005)[14]	High§	High§	High*	High§	Low	High¶	High†#
Lopez-de-Sa et al. (2012)[15]	Low	Low	High*	Low	Low	Low	Unclear†**
Nielsen et al. (2013)[16]	Low	Low	High*	Low	Low	Low	Low

*Study participants and clinical teams not blinded.
†Clinician performing neurologic prognostication not blinded.
‡Allocation by day of week.
§Not described in manuscript.
‖All subjects received 8 hours of hemofiltration.
¶Did not report survival.
#Very limited patient information/baseline data provided.
**Some baseline imbalance between groups.

b. Bias Assessment: Observational Studies

Study	Eligibility Criteria	Exposure/Outcome	Confounding	Follow-Up
Testori et al. (2011)[17]	Low	Low	High*	Low
Dumas et al. (2011)[18]	Unclear†	Low	Low	Low
Nichol et al. (2013)[20]	High†	High‡	High§	Low
Vaahersalo et al. (2013)[19]	Unclear†	Low	High*	Low
Mader et al. (2014)[21]	Unclear**†	High#	High*	Low

*High risk of residual confounding.
†Patients with traditional targeted temperature management exclusion criteria not excluded before analysis.
‡Less than 3% of subjects received hypothermia, and inclusion criteria rely solely on coding in the registry.
§Independent documentation of therapeutic temperature was available for only 40% of patients cooled and was not always consistent with reaching target temperature for those reportedly cooled. Less than 3% of patients received the intervention, which causes high concern for confounding by indication.
**Limited data on how decision to use hypothermia was made
#No actual temperature data; exclusion criteria rely solely on coding in the registry

Question #2:

a. Bias Assessment: RCTs

Study	Allocation: Generation	Allocation: Concealment	Blinding: Participants	Blinding: Assessors	Outcome: Complete	Outcome: Selective	Other Bias
Kim et al. (2007)[22]	Low	Low	High*	Low	Low	Low	Low
Kamarainen et al. (2009)[23]	Low	Low	High*	High†	Low	Low	Low
Castren et al. (2010)[24]	Low	Low	High*	High‡	Low	Low	Low
Bernard et al. (2010)[25]	Low	Low	High*	Low	Low	Low	Low
Bernard et al. (2012)[26]	Low	Low	High*	Low	Low	Low	Low
Kim et al. (2014)[27]	Low	Low	High*	Low	Low	Low	Low
Debaty et al. (2014)[28]	Low	Low	High*	High†	Low	Low	Low

*Study participants and clinical teams not blinded.
†Outcome assessors not blinded.
‡According to the study, “assessment may not always have been performed by an individual blinded to the treatment group.”

Question #3:

a. Bias Assessment: Observational Studies

Study	Eligibility Criteria	Exposure/Outcome	Confounding	Follow-Up
Yokoyama et al. (2011)[29]	Low	Low	High*	Low
Lee et al. (2014)[30]	Low	Low	High†	Low

*No adjustment for any potential confounders.
†High risk of residual confounding, pre/post study, different temperature target

Appendix E: GRADE Tables

Question #1:

TTM compared with no TTM in adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC										
No. of Patients, No. of Studies, Follow-Up Period	**Quality Assessment**						**Summary of Findings**			
							No. of Patients		**Effect**	
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other***	**Overall Quality of Evidence**	**TTM**	**No TTM**	**Relative† (95% CI)**	**Absolute‡ (95% CI)**
Mortality										
352 patients 2 RCTs[11, 12] 6 mo/hospital discharge	Serious§‖	Not serious	Not serious	Serious¶	None	**Low**	78/180 (43%)	99/172 (58%)	**RR 0.75** (0.61–0.92)	144 fewer per 1000 (−224 to −46)
42 patients 1 RCT[13] 6 mo	Serious§	Not serious	Serious#	Serious¶	None	**Very low**	15/22 (68%)	11/20 (55%)	**RR 1.24** (0.76–2.02)	132 more per 1000 (−132 to 561)
Poor neurologic/functional outcome**										
350 patients 2 RCTs[11, 12] 6 mo/hospital discharge	Serious§‖	Not serious	Not serious	Serious¶	None	**Low**	83/179 (46%)	108/ 171 (63%)	**RR 0.73** (0.60–0.88)	171 fewer per 1000 (−253 to −76)

CI indicates confidence interval; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; TTM, targeted temperature management.

*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†The risk ratios represent the risk of the outcome in the treatment group (targeted temperature management) compared to the control group (no targeted temperature management) such that a risk ratio <1 indicates the outcome being less common in the intervention group. When more than 1 trial is included the pooled risk ratio is reported. See appendix F for forest plots.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (targeted temperature management) and the control group (no targeted temperature management) expressed as number of patients per 1000 patients treated. For the confidence interval, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

§Neurological prognosticators and clinical team not blinded.

‖One of the included trials used quasi-randomization (alternating days).[12] We did not consider this to introduce enough additional concern to increase the overall risk of bias to “very serious”.

¶Optimal information size not achieved. Based on a conservative alpha of 0.01, beta of 0.2, a control outcome rate of 55% and a relative risk reduction of 10% the optimal information size was calculated at 3,922 total patients.

#Simultaneous hemofiltration.

**Poor neurological/functional outcome defined as a cerebral performance category score of 3,4 or 5 or dead[11] or not being discharged home or to rehabilitation.[12]

TTM compared with no TTM in adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC										
No. of Patients, No. of Studies, Follow-Up Period	**Quality Assessment**						**Summary of Findings**			
							No. of Patients		**Effect**	
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other***	**Overall Quality of Evidence**	**TTM**	**No TTM**	**Relative† (95% CI)**	**Absolute‡ (95% CI)**
Mortality										
374 patients 1 observational[17] 6 mo	Serious§	Not serious	Not serious	Serious‖	None	**Very low**	82/135 (61%)	180/239 (75%)	**OR 0.56** (0.34–0.93)	122 fewer per 1000 (−244 to −14)
Poor neurologic outcome¶										
1034 patients 3 observational[17-19] 6 mo/1 y	Serious§	Not serious	Not serious	Serious#	None	**Very low**	365/466 (78%)	456/568 (80%)	**OR 0.90** (0.45–1.82)	17 fewer per 1000 (−156 to 78)
Poor neurologic outcome¶										
1830 patients 1 observational[21] Hospital discharge	Very serious**	Not serious	Not serious	Serious#	None	**Very low**	NA††	NA††	NE††	NE††

CI, confidence interval; NA, not available; NE, not estimable; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

*Include assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†Adjusted ORs are reported for mortality. For the outcome of poor neurologic outcome the pooled OR was used (see Appendix F for forest plot). The ORs represent the risk of the outcome in the treatment group (TTM) compared with the control group (no TTM) adjusted for various confounders.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (TTM) and the control group (no TTM) calculated based on the control group risk and the adjusted OR, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

§High risk of residual confounding.

‖Optimal information size not achieved. Based on a conservative α of 0.01, a β of 0.2, a control outcome rate of 75%, and a relative risk reduction of 10%, the optimal information size was calculated at 1748 total patients.

¶Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or dead.

#CI cannot exclude clinically relevant benefit or harm.

**Very high risk of residual confounding

†† Study reported multiple analyses with inconsistent results

\TTM compared with no TTM in adults with IHCA with any initial rhythm who remain unresponsive after ROSC										
No. of Patients No. of Studies Follow-Up Period	**Quality Assessment**						**Summary of Findings**			
							No. of Patients		**Effect**	
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other***	**Overall quality of evidence**	**TTM**	**No TTM**	**Relative† (95% CI)**	**Absolute‡ (95% CI)**
Mortality										
8316 patients 1 observational[20] Hospital discharge	Very serious§	Not serious	Not serious	Serious‖	None	**Very low**	156/ 214 (73%)	5648/ 8102 (70%)	**OR 1.11** (0.81–1.54)	22 more per 1000 (−45 to 83)
Poor neurologic outcome¶										
8316 patients 1 observational[20] Hospital discharge	Very serious§	Not serious	Not serious	Serious‖	None	**Very low**	174/ 214 (81%)	6511/ 8102 (80%)	**OR 1.08** (0.76–1.54)	11 more per 1000 (−48 to 59)

CI, confidence interval; IHCA, in-hospital cardiac arrest; OR, odds ratio; ROSC, return of spontaneous circulation; TTM, targeted temperature management.
*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.
†Adjusted ORs are reported for all relative effect measures. The ORs represent the risk of the outcome in the treatment group (TTM) compared with the control group (no TTM) adjusted for various confounders.
‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (TTM) and the control group (no TTM) calculated based on the control group risk and the adjusted OR, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.
§High risk of residual confounding, high risk of selection bias, and unclear exposure.
‖CI cannot exclude clinically relevant benefit or harm.
¶Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or dead.

33°C compared with 36°C for adults with OHCA who remain unresponsive after ROSC and receive TTM										
No. of Patients, No. of Studies, Follow-Up Period	**Quality Assessment**						**Summary of Findings**			
							No. of Patients		**Effect**	
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other***	**Overall Quality of Evidence**	**33°C**	**36°C**	**Relative† (95% CI)**	**Absolute‡ (95% CI)**
Mortality§										
939 patients 1 RCT[16] 180 d	Not serious‖	Not serious	Not serious	Serious¶	None	**Moderate**	226/473 (48%)	220/466 (47%)	**RR 1.01** (0.88–1.16)	6 more per 1000 (−54 to 74)
Poor neurologic outcome#										
933 patients 1 RCT[16] 180 d	Not serious‖	Not serious	Not serious	Serious¶	None	**Moderate**	251/469 (54%)	242/464 (52%)	**RR 1.03** (0.91–1.16)	14 more per 1000 (−48 to 83)

CI indicates confidence interval; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio; TTM, targeted temperature management.

*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.

†The RRs represent the risk of the outcome in the 33°C group compared with the 36°C group.

‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (TTM) and the control group (no TTM) calculated based on the control group risk and the risk ratio, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.

§The authors also reported the results of a time-to-event analysis (hazard ratio, 1.06 [95% CI, 0.89–1.28]).

‖Although clinicians and patients were not blinded, we do not consider this to introduce enough bias to downgrade the evidence, because the neurologic prognosticators were blinded.

¶CI cannot exclude clinically relevant benefit or harm.

#Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or dead. The authors also reported poor neurologic outcome, defined as a modified Rankin scale score of 4 to 6 (RR 1.01 [95% CI, 0.89–1.14]).

32°C compared with 34°C for adults with OHCA who remain unresponsive after ROSC and receive targeted temperature management										
No. of Patients No. of Studies Follow-Up Period	**Quality Assessment**						**Summary of Findings**			
							No. of Patients		**Effect**	
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other***	**Overall Quality of Evidence**	**32°C**	**34°C**	**Relative† (95% CI)**	**Absolute‡ (95% CI)**
Mortality										
36 patients 1 RCT[15] 180 days	Very serious§	Not serious	Not serious	Serious‖	None	**Very low**	10/18 (56%)	16/18 (89%)	**RR 0.63** (0.40–0.97)	233 fewer per 1000 (−533 to −23)
Poor neurologic outcome¶										
36 patients 1 RCT[15] 180 days	Very serious§	Not serious	Not serious	Serious#	None	**Very low**	9/18 (50%)	14/18 (78%)	**RR 0.64** (0.38–1.09)	278 fewer per 1000 (−482 to 66)

CI, confidence interval; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio.
*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.
†The RRs represent the risk of the outcome in the 32°C group compared with the 34°C group .
‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (targeted temperature management) and the control group (no targeted temperature management) calculated based on the control group risk and the adjusted odds ratio, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.
§Neurologic prognosticators not blinded, and risk of confounding caused by unbalanced groups.
‖Optimal information size not achieved. See calculations above.
¶Poor neurologic outcome, defined as the best cerebral performance category score being 3, 4, or 5. The authors also reported death or severe dependence, defined as a Barthel score <60 (RR 0.32 [95% CI, 0.08–1.37]).
#CI cannot exclude clinically relevant benefit or harm.

Question #2:

Prehospital targeted temperature management compared with no prehospital targeted temperature management in adults with OHCA who remain unresponsive after ROSC										
No. of Patients No. of Studies Follow-Up Period	**Quality Assessment**						**Summary of Findings**			
							No. of Patients		**Effect**	
	Risk of Bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other***	**Overall Quality of Evidence**	**Prehospital**	**No Prehospital**	**Relative† (95% CI)**	**Absolute‡ (95% CI)**
Mortality										
2237 patients 7 RCTs[22-28] Hospital discharge	Serious§	Not serious	Not serious	Not serious	None	**Moderate**	640/1125 (57%)	638/1112 (57%)	**RR 0.98** (0.92–1.04)	13 fewer per 1000 (−51 to 26)
Poor neurologic/functional outcome‖										
1867 patients 5 RCTs[23-27] Hospital discharge	Serious§	Not serious	Not serious	Not serious	None	**Moderate**	629/939 (67%)	612/928 (66%)	**RR 1.00** (0.95–1.06)	0 more per 1000 (−33 to 33)
Rearrest										
1719 patients 5 RCTs[22, 23, 25-27] Prehospital	Serious¶	Serious#	Not serious	Not serious	None	**Low**	200/968 (21%)	161/948 (17%)	**RR 1.27** (1.10–1.47)	65 more per 1000 (24 to 114)
Pulmonary edema**										
1860 patients 6 RCTs[22, 23, 25-28] Prehospital/arrival	Serious¶	Serious#	Not serious	Not serious	None	**Low**	287/952 (30%)	219/909 (24%)	††	††

CI indicates confidence interval; OHCA, out-of-hospital cardiac arrest, RCTs, randomized controlled trials; ROSC, return of spontaneous circulation; RR, risk ratio.
*Includes assessment of publication bias, magnitude of the effect, dose-response gradient, and plausible residual confounding leading to spurious effect when no effect was observed or reduction of a demonstrated effect.
†Pooled RRs are reported for all relative effect measures. The RRs represent the risk of the outcome in the treatment group (prehospital targeted temperature management) compared with the control group (no prehospital targeted temperature management). The corresponding forest plots are presented in Appendix F.
‡Absolute effect is calculated as the absolute difference in the outcome between the treatment group (prehospital targeted temperature management) and the control group (no prehospital targeted temperature management) calculated based on the control group risk and the pooled RR, expressed as number of patients per 1000 patients treated. For the CI, positive numbers reflect more patients and negative numbers fewer patients with the outcome.
§Neurologic prognosticators and clinical team not blinded.
‖Poor neurologic outcome defined as a cerebral performance category score of 3, 4, or 5 or not being discharged home or to rehabilitation
¶Clinical team and outcome assessors not blinded.
#Very large variability in reported incidences.

**Pulmonary edema was assessed with initial radiography[22, 27] or “oxygen desaturation <90% with froth visible in the endotracheal tube” prehospital.[25, 26] Two studies did not report details related to assessment of pulmonary edema.[23, 28]
†† No pooled estimate was calculated. See Appendix F.

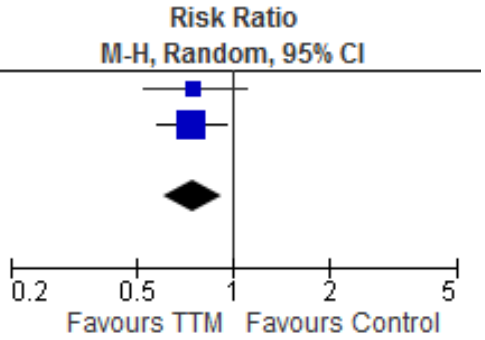
Appendix F: Forest Plots (meta-analyses)

Question #1:

A. Forest Plot – Outcome: Mortality

Study or Subgroup	TTM Events	TTM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bernard, 2002	22	43	23	34	31.2%	0.76 [0.52, 1.10]
HACA, 2002	56	137	76	138	68.8%	0.74 [0.58, 0.95]
Total (95% CI)		**180**		**172**	**100.0%**	**0.75 [0.61, 0.92]**
Total events	78		99			

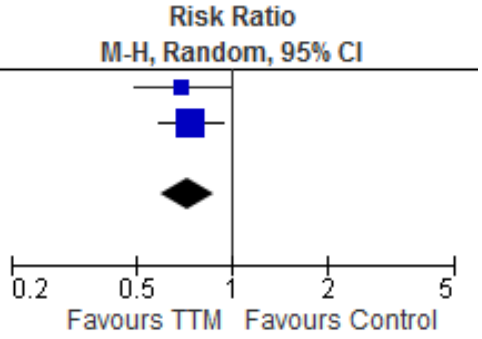
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)



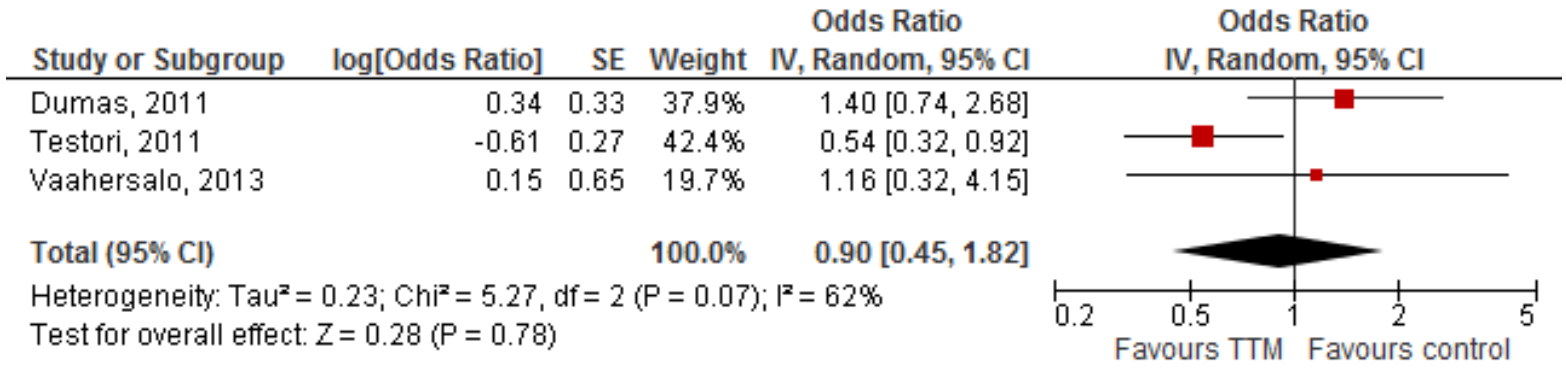
B. Forest Plot – Outcome: Poor Neurologic/Functional Outcome

Study or Subgroup	TTM Events	TTM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bernard, 2002	22	43	25	34	29.6%	0.70 [0.49, 0.99]
HACA, 2002	61	136	83	137	70.4%	0.74 [0.59, 0.93]
Total (95% CI)		**179**		**171**	**100.0%**	**0.73 [0.60, 0.88]**
Total events	83		108			

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 3.24 (P = 0.001)



C. Forest Plot – Nonshockable rhythm. Outcome: Poor Neurologic Outcome*



*Adjusted odds ratios and inverse variance weighting were used to calculate the pooled odds ratio. The study by Mader et al.[21] was not included in the meta-analysis given the very high risk of bias.

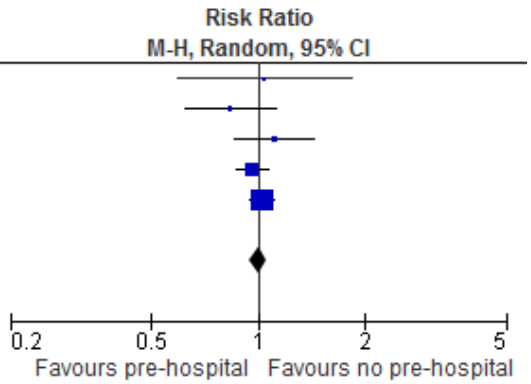
Question #2:

For the study by Castren et al.[24] only patients who had return of spontaneous circulation were included in the meta-analysis. The exclusion of the studies that initiated temperature management during cardiopulmonary resuscitation (Castren et al.[24] and Debaty et al.[28]) did not meaningfully change the pooled risk ratios for any of the outcomes (data not shown).

A. Forest Plot – Outcome: Poor Neurologic Outcome

	Pre-hospital TTM		No Pre-hospital TTM			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Kamarainen, 2009	11	19	10	18	1.1%	1.04 [0.59, 1.83]	2009
Castren, 2010	21	32	33	42	3.9%	0.84 [0.62, 1.12]	2010
Bernard, 2010	62	118	55	116	5.1%	1.11 [0.86, 1.43]	2010
Bernard, 2012	72	82	74	81	30.8%	0.96 [0.87, 1.07]	2012
Kim, 2014	463	688	440	671	59.2%	1.03 [0.95, 1.11]	2014
Total (95% CI)		**939**		**928**	**100.0%**	**1.00 [0.95, 1.06]**	
Total events	629		612				

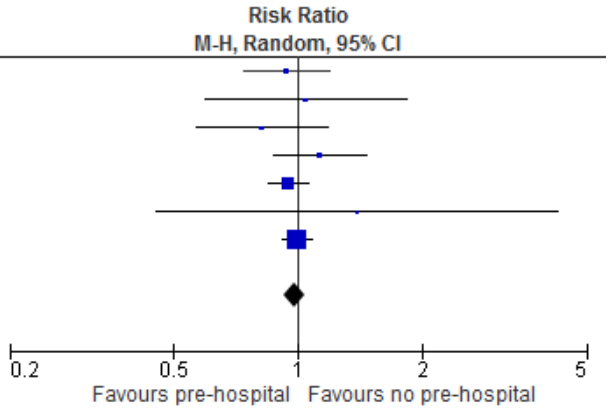
Heterogeneity: Tau² = 0.00; Chi² = 3.31, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)



B. Forest Plot – Outcome: Mortality

Study or Subgroup	Pre-hospital TTM Events	Total	No Pre-hospital TTM Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kim, 2007	42	63	44	62	6.5%	0.94 [0.74, 1.19]	2007
Kamarainen, 2009	11	19	10	18	1.1%	1.04 [0.59, 1.83]	2009
Castren, 2010	18	32	29	42	2.7%	0.81 [0.56, 1.18]	2010
Bernard, 2010	62	118	54	116	5.3%	1.13 [0.87, 1.46]	2010
Bernard, 2012	71	82	74	81	30.7%	0.95 [0.85, 1.06]	2012
Debaty, 2014	7	123	5	122	0.3%	1.39 [0.45, 4.26]	2014
Kim, 2014	429	688	422	671	53.4%	0.99 [0.91, 1.08]	2014
Total (95% CI)		**1125**		**1112**	**100.0%**	**0.98 [0.92, 1.04]**	
Total events	640		638				

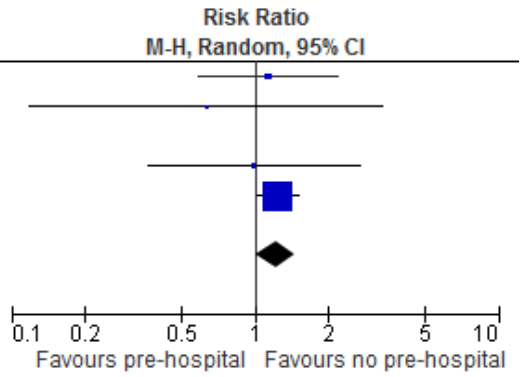
Heterogeneity: Tau² = 0.00; Chi² = 3.30, df = 6 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)



C. Forest Plot – Outcome: Rearrest

Study or Subgroup	Pre-hospital TTM Events	Total	No Pre-hospital TTM Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kim, 2007	15	63	13	62	7.8%	1.14 [0.59, 2.19]	2007
Kamarainen, 2009	2	19	3	18	1.2%	0.63 [0.12, 3.35]	2009
Bernard, 2010	0	118	0	116		Not estimable	2010
Bernard, 2012	7	82	7	81	3.3%	0.99 [0.36, 2.69]	2012
Kim, 2014	176	686	138	671	87.6%	1.25 [1.03, 1.52]	2014
Total (95% CI)		**968**		**948**	**100.0%**	**1.22 [1.01, 1.46]**	
Total events	200		161				

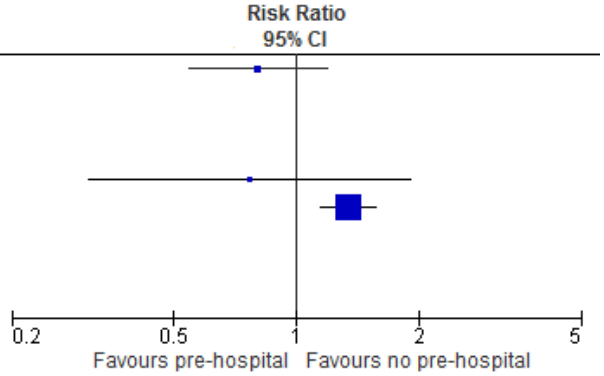
Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)



D. Forest Plot – Outcome: Pulmonary Edema*

Study or Subgroup	Pre-hospital Cooling Events	Total	No Pre-hospital Cooling Events	Total	Risk Ratio 95% CI	Year
Kim, 2007	24	54	27	49	0.81 [0.55, 1.19]	2007
Kamarainen, 2009	0	19	0	18	Not estimable	2009
Bernard, 2010	0	118	0	116	Not estimable	2010
Bernard, 2012	0	82	0	81	Not estimable	2012
Debaty, 2014	7	41	8	36	0.77 [0.31, 1.91]	2014
Kim, 2014	256	631	184	609	1.34 [1.15, 1.57]	2014
Total (95% CI)		**945**		**909**		
Total events	287		219			

Heterogeneity: Chi² = 6.77, df = 2 (P = 0.03); I² = 70%
Test for overall effect: Z = 3.14 (P = 0.002)



* Given that only three studies with high heterogeneity had pulmonary edema events reported no pooled analysis was performed. For the Debaty et al.[28] study only patients who survived to hospital admission were included.

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