

## **An update: systematic review for the treatment of traumatic brain injury using therapeutic hypothermia**

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### **Citation**

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### **Review question(s)**

The purpose of this review is to update the evidence base for the use of therapeutic hypothermia in adult patients with traumatic brain injury following the recent publication of two randomised controlled trials.

### **Searches**

The following electronic resources will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- EMBASE
- MEDLINE
- PubMed

### **Other notes:**

- Only foreign articles published in the English language will be included.
- The electronic search will span from January 2011 to March 2016 and so will be complementary to the current evidence base (<http://www.ncbi.nlm.nih.gov/pubmed/?term=crossley+andrews+traumatic+brain+injury>).

### **Types of study to be included**

This review will only include randomised clinical trials.

### **Condition or domain being studied**

The condition being studied is adult traumatic brain injury sustained following acute closed head trauma. Therapeutic hypothermia is the intervention of interest.

For the purpose of this review therapeutic hypothermia is defined as any intervention with the intention of reducing core body temperature to below the physiological norm (36 degrees Celsius).

Patient outcomes at follow-up will be assessed according to mortality and morbidity data. There will be a particular emphasis on outcomes recorded on a scale, for example, the Glasgow Outcome Scale or Ranchos Los Amigos Scale.

## **Participants/ population**

### **Inclusion Criteria:**

- Randomisation.
- Control group.
- Use of therapeutic hypothermia
- Adult patients, taken as the legal age of consent in the country of trial origin.
- Closed head injury.

### Exclusion Criteria:

- No control group.
- Neonatal or paediatric patients.
- Open head injuries, including gunshot wounds.

Only articles meeting all inclusion criteria and no exclusion criteria will be included.

### Intervention(s), exposure(s)

The intervention of interest is therapeutic hypothermia.

### **Inclusion:**

- Any method of temperature reduction.

### **Exclusion:**

- No article will be excluded on the basis of their cooling technique.

For all articles the method of cooling will be detailed during data extraction. Other intervention factors that the authors may feel relevant, e.g. use of barbiturates, will also be noted during data extraction.

### Comparator(s)/ control

This review will only include studies that detail a normothermic or no temperature reduction control group.

## **Context**

Adult patients with moderate (Glasgow Coma Scale (GCS) 9-12) and severe (GCS  $\leq$ 8) acute traumatic brain injury and admitted to an intensive care unit.

## **Outcome(s)**

### **Primary outcomes**

The primary outcomes that will be assessed are mortality and morbidity, including, new pneumonia. Morbidity will

be assessed using the Glasgow Outcome Scale Extended or Glasgow Outcome Scale at six months.

Death or discharge Modified Oxford handicap scale will be used at 28 days.

### **Secondary outcomes**

The following will be investigated as secondary hypotheses:

- a) Duration of cooling over 48 hours confers improved outcomes compared to less than 48 hours duration.
- b) The re-warming of patients at a rate of greater than 1 degree Celsius every four hours increases the risk of poor outcome.
- c) Those patients cooled to below 35 degrees Celsius will have a better outcome at follow-up compared to more moderate cooling of 35-36 degrees Celsius.
- d) An increasing time between injury onset and temperature reduction is associated with a poorer outcome.
- e) Hypothermia intervention is not more effective when the control group is managed to normothermia.

Poor outcome at six months with the GOSE dichotomised 1-5 and 6-8.

### **Data extraction, (selection and coding)**

The PRISMA statement will be followed at all stages.

There are four co-authors that will be involved with abstract screening, full-text review and data extraction.

A minimum of two independent reviewers will assess each title/abstract found by the searches against the defined inclusion and exclusion criteria. Any discrepancies will be resolved by one of the senior co-authors. Reasons for exclusion will be noted.

All included abstracts will then undergo full-text review and data extraction by two of the co-authors. As before, any discrepancies will be resolved by one of the senior co-authors.

Risk of bias (quality) assessment

**The following proforma will be used to assess the risk of bias:**

**A) Allocation Concealment**

The randomisation methodology will be defined as adequate, inadequate or unclear. Definitions:

i. Adequate - Neither the investigator nor participant knows or could influence the intervention group prior to participant enrollment.

ii. Inadequate - Any indication that there was influence over the intervention group or use of a poor randomization technique employed, for example, unsealed envelopes etc.

iii. Unclear - No information on randomisation methodology.

**B) Blinding**

Blinding of investigators: Yes/No/Not stated

Blinding of participants: Yes/No/Not stated

Blinding of outcome assessor: Yes/No/Not stated

Blinding of data analysis: Yes/No/Not stated

**C) Intention-to-Treat Analysis (Yes/No/Not stated)**

Yes - 1. Specifically reported by the authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment; 2. Not stated, but confirmed on study assessment.

No - 1. Not reported and lack of intention-to-treat analysis confirmed on study assessment\*; 2. Stated but not confirmed upon study assessment.

\*(For example, patients who were randomised but not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation).

**D) Completeness of follow-up** will be documented as the percentage of patients excluded or lost to follow-up.

The quality of individual studies may be assessed using the Downs and Black Quality Checklist (1998).

**Strategy for data synthesis**

The data used will be aggregate with both quantitative and qualitative analysis.

With respect to temperature data the difference in means will be calculated with 95% confidence intervals. If the quality of trials allows then a meta-analysis of weighted mean difference will be calculated. A statistical significance level of 0.05 will be used for all hypothesis testing. Statistical heterogeneity will be tested for by means of the Q test and I-squared index. Depending on the outcomes forthcoming from applying these procedures, relative risk and 95% confidence intervals for all-cause mortality an improved neurological outcome will be calculated using a random-effects model or fixed effect model. Subsequent models may be applied should the data be suitable for meta-analysis. When appropriate, sensitivity analyses as based on study quality (risk of bias) will be conducted.

## **Analysis of subgroups or subsets**

Specific subgroups that may be analysed are:

- Earlier versus more recent trial data to determine whether there is a change of effect over time.
- Controlled normothermia or no temperature control.
- Trials that used propofol sedation.

## **Dissemination plans**

Peer review publication; local, national and possibly international presentation; uploading to Eurotherm3235Trial

website; inclusion in HTA monograph on HTA project 11/01/30 Eurotherm3235.

## **Contact details for further information**

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Organisational affiliation of the review

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<http://www.nhslothian.scot.nhs.uk/Pages/default.aspx>

## **Review team**

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Details of any existing review of the same topic by the same authors

Crossley S, Reid J, McLatchie R, Hayton J, Clark C, MacDougall M, Andrews PJ. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. Crit Care. 2014 Apr 17;18(2):R75. doi: 10.1186/cc13835.

**Anticipated or actual start date**

04 March 2016

Anticipated completion date

06 March 2017

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**Conflicts of interest**

None known

**Language**

English

**Country**

Scotland

Subject index terms status

Subject indexing assigned by CRD

**Subject index terms**

Brain Injuries; Humans; Hypothermia, Induced

Stage of review                      Ongoing

**Date of registration in PROSPERO**

27 October 2016

**Date of publication of this revision**

27 October 2016

**Stage of review at time of this submission**

	<b>Started</b>	<b>Completed</b>
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

## Search strategies:

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Thank you to Ms Shiela Fiskien of the University of Edinburgh Library for her help in both developing our search strategies and in accessing the databases that were used.

The search terms that have been used are complimentary to those from Crossley 2014.

A full alphabetical list of our search terms may be found below our individual strategies.

### Pubmed search strategy:

(((((randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR randomly[Title/Abstract] OR random order[Title/Abstract] OR random sequence[Title/Abstract] OR random allocation[Title/Abstract] OR randomly allocated[Title/Abstract] OR at random[Title/Abstract])) OR randomized controlled trial[MeSH Terms]) NOT ((models, animal[MeSH Terms] OR animals[MeSH Terms] OR animal experimentation[MeSH Terms] OR disease models, animal[MeSH Terms] OR animals, laboratory[MeSH Terms]) NOT (humans[MeSH Terms]))) AND Humans[Mesh] AND (((((hypotherm\*[Title/Abstract] OR normotherm\*[Title/Abstract] OR cool\*[Title/Abstract] OR cold\*[Title/Abstract] OR temperature\*[Title/Abstract] OR cryother\*[Title/Abstract] OR cryogen\*[Title/Abstract] OR cryotreat\*[Title/Abstract]))) OR (((((refrigeration\*[Title/Abstract] OR cryo\*[Title/Abstract]) AND anaesthes\*[Title/Abstract]) OR ((cool\*[Title/Abstract] OR cold\*[Title/Abstract]) AND (therap\*[Title/Abstract] OR device\*[Title/Abstract] OR equipment\*[Title/Abstract]))) OR (temperature[Title/Abstract] AND (reduc\*[Title/Abstract] OR low\*[Title/Abstract]))) OR ((cool\*[Title/Abstract] OR cold\*[Title/Abstract]) AND (blanket\*[Title/Abstract] OR neck collar\*[Title/Abstract] OR helmet\*[Title/Abstract] OR hood\*[Title/Abstract]))) OR (intravenous[Title/Abstract] AND (cold\*[Title/Abstract] OR cool\*[Title/Abstract]) AND (fluid\*[Title/Abstract] OR catheter\*[Title/Abstract]))) OR (((induced hypothermia[MeSH Terms]) OR cryotherapy[MeSH Terms]) OR hypothermia[MeSH Terms]) AND (((((((((((CranioCerebral Trauma[MeSH Terms]) OR Brain Edema[MeSH Terms]) OR Glasgow Coma Scale[MeSH Terms]) OR glasgow outcome scale[MeSH Terms]) OR Unconsciousness[MeSH Terms]) OR Cerebrovascular Trauma[MeSH Terms]) OR intracranial hypertension[MeSH Terms]) OR (((head[Title/Abstract] OR cranial[Title/Abstract] OR cerebral[Title/Abstract] OR capitis[Title/Abstract] OR brain[Title/Abstract] OR forebrain\*[Title/Abstract] OR skull\*[Title/Abstract] OR Hemisphere\*[Title/Abstract] OR intra-cran\*[Title/Abstract] OR inter-cran\*[Title/Abstract]) AND (injur\*[Title/Abstract] OR trauma[Title/Abstract] OR damag\*[Title/Abstract] OR wound\*[Title/Abstract] OR fracture\*[Title/Abstract] OR contusion\*[Title/Abstract] OR concuss\*[Title/Abstract] OR pressure\*[Title/Abstract]))) OR (((head[Title/Abstract] OR cranial[Title/Abstract] OR cerebral[Title/Abstract] OR capitis[Title/Abstract] OR brain[Title/Abstract] OR forebrain\*[Title/Abstract] OR skull\*[Title/Abstract] OR hemisphere\*[Title/Abstract] OR intra-cran\*[Title/Abstract] OR inter-cran\*[Title/Abstract] OR tentori\*[Title/Abstract]) AND (haematoma\*[Title/Abstract] OR hematoma\*[Title/Abstract] OR haemorrhag\*[Title/Abstract] OR hemorrhag\*[Title/Abstract] OR Bleed\*[Title/Abstract] OR hernia\*[Title/Abstract] OR oedema\*[Title/Abstract] OR edema\*[Title/Abstract] OR swell\*[Title/Abstract]))) OR ((glasgow[Title/Abstract] AND (scale[Title/Abstract] OR score[Title/Abstract]) AND (outcome[Title/Abstract] OR coma[Title/Abstract]))) OR ranchos Los amigos[Title/Abstract]) OR diffuse axonal injur\*[Title/Abstract]) OR ((unconscious[Title/Abstract] OR coma\*[Title/Abstract] OR concuss\*[Title/Abstract] OR persistent vegetative state[Title/Abstract]) AND (injur\*[Title/Abstract] OR trauma[Title/Abstract] OR damag\*[Title/Abstract] OR wound\*[Title/Abstract] OR fracture\*[Title/Abstract]))))

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## Ovid Embase and Medline search strategy:

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1. exp Craniocerebral Trauma/
2. Brain Edema/
3. glasgow coma scale/ or glasgow outcome scale/
4. exp Unconsciousness/
5. exp Cerebrovascular Trauma/
6. exp Intracranial Hypertension/
7. ((head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or hemispher\* or intrac-cran\* or inter-cran\*) adj3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or concuss\* or pressure\*)),ti,ab.
8. ((head or cran\* or cerebr\* or capitis or tentori\* or brain\* or forebrain\* or hemispher\* or intra-cran\* or inter-cran\*) adj3 (haematoma\* or hematoma\* or hemorrhag\* or haemorrhag\* or bleed\* or hernia\* or oedema\* or edema\* or swell\*)),ti,ab.
9. (Glasgow adj3 (coma or outcome\*) adj3 (scale\* or score\*)),ti,ab.
10. "Rancho Los Amigos".ti,ab.
11. "diffuse axonal injur\*".ti,ab.
12. ((unconscious\* or coma\* or concuss\* or 'persistent vegetative state\*') adj3 (injur\* or trauma\* or damag\* or wound\* or fracture\*)),ti,ab.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp hypothermia, Induced/
15. exp Cryotherapy/
16. exp Profound Induced Hypothermia/
17. (hypotherm\* or normother\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\*).ab,ti.
18. ((refrigeration\* or cryo\*) adj3 anaesthes\*).ab,ti.
19. ((cool\* or cold\*) adj3 (therap\* or device\* or equipment\*)),ab,ti.
20. (temperature adj3 (reduc\* or low\*)),ab,ti.
21. (intravenous adj3 (cold\* or cool\*) adj3 (fluid\* or catheter\*)),ab,ti.
22. ((cool\* or cold\*) adj3 (blanket\* or neck collar\* or helmet\* or hood\*)),ab,ti.
23. exp Hypothermia/
24. or/14-23
25. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial\*).tw,hw.
26. clinical trial.pt.
27. randomized controlled trial.pt.
28. or/25-27
29. exp models, animal/
30. exp animals/
31. exp animal experimentation/
32. exp animals, laboratory/
33. or/29-32
34. Humans/
35. 33 not 34
36. 28 not 35
37. 13 and 24 and 36



## **Cochrane Central Register of Controlled Trials (Central) search strategy:**

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1. MeSH descriptor: [Craniocerebral Trauma] explode all trees
2. MeSH descriptor: [Brain Edema] explode all trees
3. MeSH descriptor: [Glasgow Coma Scale] explode all trees
4. MeSH descriptor: [Unconsciousness] explode all trees
5. MeSH descriptor: [Glasgow Outcome Scale] explode all trees
6. MeSH descriptor: [Cerebrovascular Trauma] explode all trees
7. MeSH descriptor: [Intracranial Hypertension] explode all trees
8. (head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intracran\* or inter-cran\*) near/3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\* or concuss\* or pressure\*)
9. (head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intracran\* or inter-cran\* or tentori\*) near/3 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or hernia\* or oedema\* or edema\* or swell\*)
10. (glasgow near/3 (coma or outcome) near/3 (scale or score))
11. "rancho los amigos scale"
12. (diffuse near/3 axonal near/3 injur\*)
13. (unconscious\* or coma\* or concuss\* or "persistent vegetative state") near/3 (injur\* or trauma\* or damag\* or wound\* or fracture\*)
14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
15. MeSH descriptor: [Hypothermia, Induced] explode all trees
16. MeSH descriptor: [Cryotherapy] explode all trees
17. MeSH descriptor: <sup>67</sup> explode all trees
18. (hypotherm\* or normotherm\* or cool\* or temperature\* or cryother\* or cryogen\* or cryotreat\*)
19. (refrigeration\* or cryo\*) near/3 anaesthes\*
20. (cool\* or cold\*) near/3 (therap\* or device\* or equipment\*)
21. temperature near/3 (reduc\* or low\*)
22. Intravenous near/3 (cold\* or cool\*) near/3 (fluid\* or catheter\*)
23. (cool\* or cold\*) near/3 (blanket\* or neck collar\* or helmet\* or hood\*)
24. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23)
25. (#14 and #24)
26. (#25)

## Search Terms

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The following are a list of the individual search terms used in each strategy to ensure sensitivity and specificity of each search for patient treatment and control group, as well as therapeutic management and trial design. Terms were re-evaluated for this review in May 2016 with Dr Jonathan Rhodes and Ms Shiela Fiskien.

allocated	damag*	neck
allocation	device*	normother*
anaesthes*	diffuse	oedema*
axonal	edema*	order
blanket*	equipment*	outcome*
bleed*	fluid*	'persistent vegetative state*'
brain edema	forebrain*	pressure*
brain*	fracture*	profound induced hypothermia
capitis	glasgow	rancho los amigos*
catheter*	glasgow coma scale	random
cerebr*	glasgow outcome scale	randomised
cerebrovascular trauma	haematoma*	randomized
clinical	haemorrhag*	randomized controlled trial
clinical trial	head	randomly
cold*	helmet*	reduc*
collar*	hematoma*	refrigeration*
coma	hemispher*	scale*
coma*	hemorrhag*	score*
concuss*	hernia*	sequence
controlled	hood*	swell*
contusion*	hypotherm*	temperature
cool*	hypothermia	temperature*
cran*	hypothermia, induced	tentori*
crani*	injur*	therap*
craniocerebral trauma	inter-cran*	trauma*
cryo*	intra-cran*	trial*
cryogen*	intrac-cran*	unconscious*
cryother*	intracranial hypertension	unconsciousness
cryotherapy	intravenous	wound*
cryotreat*	low*	