NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Hypoxic perinatal brain injury is caused by lack of oxygen to a baby's brain during labour and/or delivery. It can lead to death or permanent brain damage. Therapeutic hypothermia aims to cool the brain (soon after birth and for several days) to prevent permanent brain damage. Hypothermia may be induced by whole body cooling (using a mattress or blanket filled with cooled fluid or air) or by head cooling (using a cap filled with cooled fluid or air). Throughout the procedure, the baby's temperature is measured using a thermometer inside the body (either the rectum or the gullet) to help ensure that cooling is adequate but not excessive. After cooling, the baby's body temperature is gradually returned to normal.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2009.

Procedure name

- Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Specialty societies

- Royal College of Paediatrics and Child Health
- British Association of Perinatal Medicine.

Description

Indications and current treatment

Hypoxic perinatal brain injury is caused by a decrease in the amount of oxygen supplied to an infant's brain close to the time of birth (usually during labour and/or delivery). It can result in stillbirth or neonatal death. Infants who survive may develop hypoxic-ischaemic encephalopathy (HIE) which can lead to severe lifelong disability or death. Hypoxic perinatal brain injury may be associated with multi-organ failure affecting the heart, lungs, liver and kidneys in some infants.

Hypoxic perinatal brain injury is characterised by fetal distress, metabolic acidosis and the need for artificial ventilation from birth. The initial diagnosis of hypoxic perinatal brain injury is made using a combination of clinical features, birth history and, if available, paired umbilical arterial and venous blood gas measurements. Amplitude-integrated electroencephalography (aEEG) may also be used.

A variety of scales have been used to measure the degree of disability among children who survive hypoxic perinatal brain injury. These include the Bayley Psychomotor Development Index, the Bayley Mental Developmental Index, and the Gross Motor Function Classification System.

There is no specific treatment for hypoxic perinatal brain injury. Therapy focuses on supportive care after the injury has occurred.

What the procedure involves

Therapeutic hypothermia aims to cool the brain to several degrees below the baseline temperature, usually between 33°C and 35°C, with the intention of preventing continued neuronal loss that occurs in the days after brain injury.

Treatment is started as soon as possible after diagnosis, usually within 6 hours of birth. Hypothermia may be induced by a number of methods including selective cooling of the head using a cap placed over the infant's head, or by whole body cooling using a blanket or mattress. Fluid or air is circulated through the cap, blanket or mattress and a thermostat may be used to maintain the desired temperature. A rectal or nasopharyngeal thermometer is used to measure the intracorporeal temperature as a proxy for brain temperature. The temperature is measured continuously throughout the procedure.

Treatment is continued for 72 hours and the infant is then slowly warmed to normal body temperature.

Efficacy

A systematic review and meta-analysis of 8 randomised controlled trials (RCTs) and a total of 638 infants compared selective head cooling or whole

body cooling with standard care. Overall there was a lower risk of death within the first 18 months of life in cooled infants compared with infants who had standard care (relative risk [RR] 0.74; 95% confidence interval [CI] 0.58 to 0.94) and of major neurodevelopmental disability in infants at 18–22 months of age (RR 0.68; 95% CI 0.51 to 0.92) (results from four RCTs)[1].

Restricting the meta-analysis to studies using whole body cooling, cooled infants had lower risks of both death and major neurodevelopmental disability than control infants (RR 0.66; 95% CI 0.47 to 0.93 and RR 0.60; 95% CI 0.40 to 0.92 respectively). In the meta-analysis of studies using selective head cooling, there was no statistically significant difference between the groups[1].

The first 2 studies[2, 3] described in the following section were included in the systematic review and meta-analysis referred to above.

In an RCT of selective head cooling (n = 234), 13% (15/116) of cooled infants died during the cooling period compared with 16% (19/118) of control infants in the same time period. Of 218 infants who were followed-up, after 18 months, 55% (59/108) of cooled infants and 66% (73/110) of control infants had died or had severe neurodevelopmental disability (odds ratio [OR] 0.61; 95%CI 0.34 to 1.09)[2].

In an RCT of whole body cooling (n = 208), 13% (13/102) of cooled infants died during the 72-hour cooling period compared with 10% (11/106) of control infants in the same time period. Of 205 infants who were followed-up, after 18 to 22 months, 44% (45/102) of cooled infants and 62% (64/103) of control infants had died or had moderate or severe neurodevelopmental disability (RR 0.72; 95% CI 0.45 to 0.95)[3].

In an additional RCT of 325 infants, 45% (74/163) of whole body cooled infants died or had severe neurodevelopmental disability at 18 months compared with 53% (86/162) of infants in the control group (RR 0.86; 95% CI 0.68 to 1.07)[4]. 26% (42/163) of cooled infants died and 27% (32/120) survived with severe neurodevelopmental disability compared with 27% (44/162) and 36% (42/117) of infants, respectively, in the control group. Infants in the cooled group had a higher rate of survival without neurologic abnormality (44% [71/163] versus 28% [45/162] for non-cooled infants, RR 1.57; 95% CI 1.16 to 2.12). Among the survivors, cooled infants had a lower rate of cerebral palsy compared with non-cooled infants (28% [33/120] versus 41% [48/117], RR 0.67; 95% CI 0.47 to 0.96).

In an RCT of 50 infants, 78% (18/23) of head-cooled infants and 70% (19/27) of control infants had normal neurological development (assessed by Infant Mental Developmental Assessment Scale) at 6 months of age[5].

In a case series of 120 cooled infants (all but 3 underwent whole body cooling), the death rate was 26%. The daily encephalopathy score fell during the first 4 days after birth and 51% of infants established full oral feeding at a median of 9 days[6].

Safety

The systematic review reported increased risks of sinus bradycardia (RR 5.96; 95% CI 2.15 to 6.49), thrombocytopenia (RR 1.55; 95% CI 1.14 to 2.11) and hypotension requiring inotropic treatment (RR 1.17; 95% CI 1.00 to 1.38) in cooled infants compared with infants who had standard care[1].

In the RCT of 234 infants, there was a similar incidence of most adverse events in the cooled and control groups except minor cardiac arrhythmia (mostly sinus bradycardia) which was more common in cooled infants than control infants (9%, 10/112 and 1%, 1/118 respectively; p value = 0.004)[2].

In the RCT of 208 infants, the incidence of serious adverse events was similar in the cooled and control groups. Hypotension requiring treatment was more common in the cooled group than the control group (41% [42/102] and 33% [35/106] respectively), as was hypocalcaemia (27% [28/102] and 19% [20/106] respectively; p values not reported). In addition, 4 infants in the cooled group had various skin changes which resolved spontaneously[3].

The RCT of 325 infants reported no significant differences between the cooled and control groups with regard to adverse events[4].

The RCT of 50 infants found no significant differences between the cooled and control groups in blood pressure, cardiac function, renal function or other adverse outcomes. However, cooled infants had a significant decrease in heart rates at 24, 48 and 72 hours compared with controls ($p < 0.05$)[5].

There were 2 additional case reports of adverse events associated with therapeutic hypothermia. In the first report, an infant who underwent whole body cooling using a water-filled mattress developed sclerema on his back, in the area in contact with the cooling mattress. The sclerema resolved without scarring after 3 months[7]. In the second report, an infant who underwent whole body cooling using ice packs applied to the skin developed subcutaneous fat necrosis where the ice packs were applied. At 9 months of age, asymptomatic firm nodules with no calcification were present[8].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. Searches were conducted of the following databases, covering the period from their commencement to 21/09/09: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with hypoxic perinatal brain injury.
Intervention/test	Therapeutic hypothermia with intracorporeal temperature monitoring.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 1135 infants from 1 systematic review, 2 RCTs that were included in the systematic review, 2 additional RCTs, 1 case series and 2 case reports.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing assessments of this procedure

The Swedish Council on Technology Assessment in Healthcare (SBU) published a report on therapeutic hypothermia following perinatal asphyxia in February 2009 (www.sbu.se/200901e).

The report concludes that ‘therapeutic hypothermia reduces the risk of death or severe functional impairment in the child. However, the scientific evidence is insufficient to appraise the method’s effect beyond 18 months.

Scientific evidence is insufficient to draw firm conclusions on the adverse effects and complications related to therapeutic hypothermia. No serious adverse effects or complications have been identified in the studies reviewed for this report, but the studies were not specifically designed to investigate this.

The optimum way (best practice) to deliver treatment is not clear. Hence, it is important to monitor the experiences and outcomes of treatment, eg, via a central quality register. Also, continued research is essential to gain knowledge about best practices as well as the potential complications and adverse effects.'

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Table 2 Summary of key efficacy and safety findings on therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.

Study details

Azzopardi DV et al (2009)[4]

Study type: RCT

Country: UK, Hungary, Sweden, Israel, Finland

Study period: 2002–2006
Study population: newborn infants
n = 325
Sex: cooled group = 62% male, control group = 54% male

Inclusion criteria: gestational age ≥ 36 weeks and enrolled within 6 hours of birth; Apgar score ≤ 5 at 10 minutes; continued need for resuscitation at 10 minutes after birth, or acidosis within 60 minutes of birth; moderate-to-severe encephalopathy and either hypotonia, abnormal reflexes, absent or weak suck, or clinical seizures; abnormal background activity of ≥30 minutes duration or seizures on amplitude-integrated electroencephalography; no major congenital abnormality requiring surgery or suggestive of chromosomal anomaly or syndromes that involve brain dysgenesis.

Technique: whole body cooling to a rectal temperature of 33–34°C for 72 hours using a cooling blanket (initiated during transport to treatment centre). Infants were slowly warmed to a maximum 37±0.2°C (0.5°C per hour). Control infants received standard care.

Key efficacy findings

Main neurodevelopmental outcomes at 18 months

	Cooled group	Control group	RR (95% CI)
Death or severe neuro-developmental disability *(primary outcome)*	45% (74/163)	53% (86/162)	0.86 (0.68 to 1.07)
Death	26% (42/163)	27% (44/162)	0.95 (0.66 to 1.36)
Severe neuro-developmental disability	27% (32/120)	36% (42/117)	0.74 (0.51 to 1.09)
Survival without neurologic abnormality	44% (71/163)	28% (45/162)	1.57 (1.16 to 2.12)
Multiple neuro-developmental disabilities	19% (21/112)	30% (33/110)	0.63 (0.39 to 1.01)
Bayley MDI score < 70	24% (28/115)	35% (38/110)	0.70 (0.47 to 1.06)
Bayley MDI score ≥ 85	70% (81/115)	55% (60/110)	1.29 (1.05 to 1.59)
Bayley PDI score < 70	24% (27/114)	34% (37/109)	0.70 (0.46 to 1.60)
Bayley PDI score ≥ 85	68% (78/114)	53% (58/109)	1.29 (1.04 to 1.60)
GMF score 0 (no abnormality)	71% (85/120)	54% (63/117)	1.32 (1.07 to 1.61)
GMF score 3–5	20% (24/120)	31% (36/117)	0.65 (0.41 to 1.02)

Key safety findings

Adverse events

	Cooled group (n = 163)	Control group (n = 162)
Persistent hypotension (mean blood pressure ≤40 mm Hg)	77% (126/163)	83% (134/162)
Prolonged coagulation time	41% (67/163)	45% (72/161)
Thrombo-cytopaenia	58% (94/163)	50% (80/161)
Intracranial haemorrhage	39% (25/64)	31% (21/67)
Pneumonia	3% (5/163)	3% (5/162)
Pulmonary air leak	6% (9/163)	2% (3/162)
Pulmonary haemorrhage	3% (5/163)	2% (3/162)
Pulmonary hypertension	10% (16/163)	6% (9/162)
Necrotising enterocolitis	<1% (1/163)	0% (0/162)
Cardiac arrhythmia	5% (8/163)	2% (3/162)
Culture-proven sepsis	12% (20/163)	12% (20/162)

There were no significant differences between the groups with regard to adverse events.

Intracranial haemorrhage was identified on magnetic resonance imaging.

Comments

Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial.

2 infants were lost to follow-up (1 in each group).

Assignment to treatment group was done by central telephone randomisation or a secure web-based system.

Baseline characteristics were broadly similar between the 2 groups.

Estimated sample size of 236 infants needed to detect RR of 0.6 to 0.7 for primary outcome (death or severe neurodevelopmental disability at 18 months), with 80% power, at 2-sided significance level of 5% and assuming 10% loss to follow-up.

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.						
Study details	**Key efficacy findings**				**Key safety findings**	**Comments**
Follow-up: **18 months** Conflict of interest: none	Cerebral palsy	28% (33/120)	41% (48/117)	0.67 (0.47 to 0.96)		
	Hearing loss not corrected by aids	4% (4/114)	6% (7/108)	0.54 (0.16 to 1.80)		
	No useful vision	7% (8/119)	11% (12/114)	0.64 (0.27 to 1.50)		
	Seizures requiring anticonvulsive agents	10% (12/116)	14% (16/116)	0.75 (0.37 to 1.51)		

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.

Study details	Key efficacy findings	Key safety findings	Comments
Jacobs et al (2007) [1] **Study type: systematic review** Country: international Study period: not reported Study population: newborn infants **n = 638 (8 RCTs)** Sex: not reported Inclusion criteria: • evidence of birth asphyxia (Apgar score ≤5 at 10 minutes; mechanical ventilation or resuscitation required at 10 minutes or cord or arterial pH <7.1) and • evidence of encephalopathy and • no major congenital abnormalities. Technique: • Method of cooling: whole body (6 studies) or selective head cooling (2 studies) vs standard care (no cooling). • Duration of cooling: 72 hours (7 studies) or 48 hours (1 study) • Degree of cooling: various target temperatures ranging from 32.5–36.5°C • Warming: 0.5°C per hour for 4 hours (6 studies), 0.5°C every second hour for 8 hours (1 study), spontaneous warming at room temperature for up to 12 hours (1 study). Follow-up: **various** Conflict of interest: none reported	*All outcomes are for cooled group vs standard care* ***Death or major neurodevelopmental disability at age 18–22 months*** **RR (95% CI)** / **Risk difference (risk in the treated group minus risk in the control group) (95% CI)** Total (4 studies): 0.76 (0.65 to 0.89) / -0.15 (-0.24 to -0.07) *Subgroup analysis: method of cooling* Head (2 studies): 0.85 (0.69 to 1.05) / -0.09 (-0.21 to 0.03) Whole body (2 studies): 0.69 (0.55 to 0.86) / -0.21 (-0.33 to -0.09) ***Death within first 18 months of life*** **RR (95% CI)** / **Risk difference (95% CI)** Total (8 studies): 0.74 (0.58 to0.94) / -0.09 (-0.16 to -0.02) *Subgroup analysis: method of cooling* Head (4 studies): 0.83 (0.59 to 1.16) / -0.05 (-0.14 to 0.04) Whole body (4 studies): 0.66 (0.47 to 0.93) / -0.13 (-0.23 to -0.02) ***Major neurodevelopmental disability in survivors at age 18–22 months*** **RR (95% CI)** / **Risk difference (95% CI)** Total (4 studies): 0.68 (0.51 to 0.92) / -0.13 (-0.23 to -0.03) *Subgroup analysis: method of cooling* Head (2 studies): 0.77 (0.51 to 1.17) / -0.09 (-0.24 to 0.05) Whole body (2 studies): 0.60 (0.40 to 0.92) / -0.17 (-0.31 to -0.03)	***Adverse events*** *Only adverse events with statistically significant differences in cooled infants compared to standard care infants are reported here.* • Increased sinus bradycardia (5 studies; RR 5.96; 95% CI 2.15 to 6.49), • Increased hypotension requiring inotropes (borderline significance) (5 studies; RR 1.17; 95% CI 1.00 to 1.38) • Increased thrombo-cytopaenia (4 studies; RR 1.55; 95% CI 1.14 to 2.11)	Apgar score: method of assessing newborns' heart rate, respiratory effort, muscle tone, skin color, response to catheter in nostril (10 = infant is in the best possible condition, 0–3 = infant needs immediate resuscitation). Major neurodevelopmental disability was defined as: • cerebral palsy • developmental delay (Bayley or Griffith mental development assessment > 2 standard deviations below the mean) • intellectual impairment (IQ > 2 standard deviations below the mean) • blindness (< 6/60 in both eyes) • sensorineural deafness requiring amplification. There was no evidence of heterogeneity in all outcomes (I-squared = 0%) except for major neurodevelopmental disability by method of cooling (mild heterogeneity - 16%)

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Gluckman et al (2005) [2]

Study type: RCT
Country: international (multi-centre)
Study period: July 1999 – Jan 2002
Study population: newborn infants
n = 234

Sex: not reported

Inclusion criteria:
• gestational age ≥ 36 weeks
• Apgar score ≤ 5 10 minutes after birth or continued need for resuscitation or severe acidosis (pH <7 pr base deficit 16 mmol/L in any blood sample within 60 minutes of birth)
• evidence of encephalopathy
• abnormal aEEG
• no major congenital abnormalities.

Technique: selective head cooling to a rectal temperature of 34–35°C for 72 hours using a CoolCap cooling cap (Olympic Medical) (n = 116). After cooling infants were slowly warmed to 36.8–37.2°C (0.5°C per hour) over 6 hours. Control infants received standard care (n = 118).

Follow-up: 18 months</td>
<td>Death or severe disability at age 18 months
<table>
<tr><th></th><th>Cooled group</th><th>Control group</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Died or severe neurodevelopmental disability (primary outcome)</td><td>55% (59/108)</td><td>66% (73/110)</td><td>0.61 (0.34 to 1.09)</td></tr>
<tr><td>Died</td><td>33% (36/108)</td><td>38% (42/110)</td><td>0.81 (0.47 to 1.41)</td></tr>
<tr><td>Severe neuromotor disability (GMF level 3–5)</td><td>19% (14/72)</td><td>31% (21/68)</td><td>0.54 (0.25 to 1.17)</td></tr>
<tr><td>Bayley MDI score <70</td><td>30% (21/70)</td><td>39% (24/61)</td><td>0.66 (0.32 to 1.36)</td></tr>
<tr><td>Bayley PDI score <70</td><td>30% (21/69)</td><td>41% (23/56)</td><td>0.63 (0.30 to 1.31)</td></tr>
<tr><td>Bilateral cortical visual impairment</td><td>10% (7/72)</td><td>16% (11/64)</td><td>0.52 (0.19 to 1.39)</td></tr>
</table>
Mortality
<table>
<tr><th>Time period</th><th>Cooled group</th><th>Control group</th></tr>
<tr><td>76-hour monitoring period</td><td>13% (15/116)</td><td>16% (19/118)</td></tr>
<tr><td>First week of life</td><td>23% (27/116)</td><td>22% (26/118)</td></tr>
</table>
Secondary outcomes

There were no significant differences between the study groups in the odds ratio of the following outcomes:
- multi-organ dysfunction
- multiple disabilities
- bilateral sensorineural hearing loss.
- epilepsy</td>
<td>Adverse events
<table>
<tr><th></th><th>Cooled group</th><th>Control group</th></tr>
<tr><td>Scalp oedema*</td><td>28% (32/116)</td><td>1% (1/118)</td></tr>
<tr><td>Mean heart rate during 72-hour cooling period *</td><td>114 bpm</td><td>145 bpm</td></tr>
<tr><td>Major cardiac arrhythmia</td><td>0</td><td>0</td></tr>
<tr><td>Major venous thrombosis</td><td>0</td><td>2% (2/118)</td></tr>
<tr><td>Severe hypotension</td><td>3% (3/112)</td><td>3% (3/116)</td></tr>
<tr><td>Minor cardiac arrhythmia (mostly sinus bradycardia)*</td><td>9% (10/112)</td><td>1% (1/118)</td></tr>
<tr><td>Abnormal renal function</td><td>65% (73/112)</td><td>70% (83/118)</td></tr>
<tr><td>Systemic infection</td><td>3% (3/112)</td><td>3% (3/118)</td></tr>
<tr><td>Coagulopathy</td><td>19% (21/112)</td><td>14% (17/118)</td></tr>
<tr><td>Hypoglycaemia</td><td>13% (14/112)</td><td>17% (20/118)</td></tr>
<tr><td>Hypocalcaemia</td><td>44% (49/112)</td><td>43% (51/118)</td></tr>
</table>
* Significant difference between groups

1 cooled infant (who died of other causes) had skin breakdown and local haemorrhage under the cooling cap.</td>
<td>This study is included in the Cochrane systematic review (Jacobs et al 2007)

Treatment assignment: random allocation stratified by centre.

4 infants allocated to cooling were not cooled and 1 infant allocated to standard care was cooled briefly.

Safety data are based on all infants that were enrolled (n = 234). Efficacy data are based on 218 infants that were followed up. (8 infants in each group were lost to follow-up.)

Severe neurodevelopmental disability was defined as one of:
• GMF level 3–5
• Bayley MDI < 70
bilateral cortical visual impairment.</td>
</tr>
</table>

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Conflict of interest: study funded by manufacturer	***Sub-group analyses*** Of infants with severe aEEG changes at baseline (n = 46), there was no significant difference between study groups in death or severe neuromotor disability. Of all other infants (i.e. with moderate aEEG changes; n = 172), there were significant differences between study groups in severe neuromotor disability and in combined death and severe disability.		

Abbreviations used: MDI, mental development index; HIE, hypoxic-ischaemic encephalopathy, GMF, gross motor function, PDI, psychomotor development index;

Study details

Shankaran (2005)[3]

Study type: RCT
Country: USA (multi-centre)
Study period: July 2000 – May 2003
Study population: newborn infants
n = 208

Sex: not reported

Inclusion criteria:

- gestational age ≥ 36 weeks and enrolled within 6 hours of birth
- blood pH ≤ 7.0 or base deficit ≥ 16 mmol/L within 60 minutes of birth, or acute perinatal event and either 10 minute Apgar score ≤ 5 or assisted ventilation initiated at birth and continued for at least 10 minutes
- diagnosis of encephalopathy or seizures
- no major congenital abnormalities.

Treatment assignment: random allocation by telephone, stratified by centre.

Technique: whole body cooling to an oesophageal temperature of 33.5°C for 72 hours using a Blanketrol cooling blanket (Cincinatti Sub-Zero). Infants were slowly warmed to 36.5°C (0.5°C per hour) over 6 hours. Control infants received standard care.

Follow-up: **20 months (median)**

Conflict of interest: none stated

Key efficacy findings

Death or disability at age 18–22 months (number of infants)

	Cooled group (n = 102)	**Control group (n = 106)**	**Adjusted RR (95% CI)**
Died or moderate or severe neuro-developmental disability *(prim. outcome)*	44% (45)	62% (64)	0.72 (0.45 to 0.95)
Died	24% (24)	37% (38)	0.68 (0.44 to 1.05)
Bayley MDI score <70	25% (19)	39% (24)	0.71 (0.43 to 1.17)
Bayley PDI score <70	27% (20)	35% (22)	0.80 (0.48 to 1.33)
Disabling cerebral palsy	19% (15)	30% (19)	0.68 (0.38 to 1.22)
Blindness	7% (5)	14% (9)	0.50 (0.17 to 1.44)
Severe hearing impairment	4% (3)	6% (4)	0.54 (0.10 to 3.02)

RRs were adjusted for study centre.
Percentages were based on the number of infants for whom data were available.

Mortality

Time period	**Cooled group**	**Control group**
72-hour intervention period	13% (13/102)	10% (11/106)
Hospital course	19% (19/102)	27% (29/106)

Key safety findings

Adverse events

	Cooled group (n = 102)	**Control group (n = 106)**
During 72-hour intervention period		
Mean heart rate	109 bpm	140 bpm
Cardiac arrhythmia	0	0
Persistent acidosis	1	2
Bleeding	0	0
Skin changes	4% (4/102)	0
During hospital course		
Hypotension requiring treatment	41% (42/102)	33% (35/106)
Cardiac arrhythmia	2% (2/102)	1% (1/106)
Persistent pulmonary hypertension	25% (25/102)	22% (23/106)
Hepatic dysfunction	20% (20/102)	15% (16/106)
Sepsis	5% (5/102)	6% (6/106)
Disseminated intravascular coagulopathy	18% (18/102)	11% (12/106)
Hypoglycaemia	12% (12/102)	15% (16/106)
Hypocalcaemia	27% (28/102)	19% (20/106)

There was a similar incidence of serious adverse events in both groups.

Comments

This study is included in the Cochrane systematic review (Jacobs et al 2007)

3 infants were lost to follow-up.

Severe disability was defined as one of:

- GMF level 3–5
- Bayley MDI <70
- hearing impairment requiring aids
- blindness.

Moderate disability was defined as:

- Bayley MDI 70–84 and
- GMF level 2, or
- persistent seizure disorder, or
- hearing impairment with no amplification.

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Zhou et al (2002)[5]

Study type: RCT

Country: China

Study period: July 1999 – Dec 2000

Study population: newborn infants

n = 50

Sex: not stated

Inclusion criteria:
• gestational age ≥ 37 weeks
• Apgar score < 5 at 5 minutes
• abnormal electrocardiography or clinical depression of nervous system within 6 hours of birth
• no major congenital abnormalities.

Treatment assignment: random allocation

Technique: selective head cooling to a nasopharyngeal temperature of 34°C for 72 hours using a cap of circulating water (Hengyuan, China) (n = 23). After cooling infants were spontaneously warmed in 12 hours to a normal temperature. Control infants received standard care (n = 27).

Follow-up: 6 months

Conflict of interest: none stated</td>
<td>Mortality

No deaths reported.

Neurodevelopmental outcomes

<table>
<tr><th></th><th>Cooled group</th><th>Control group</th></tr>
<tr><td>Abnormal CT scan at 5–7 days</td><td>100%</td><td>100%</td></tr>
<tr><td>Abnormal CT scan at 3 months</td><td>17% (4/23)</td><td>33% (9/27)</td></tr>
<tr><td>Abnormal EEG at baseline</td><td>74% (17/23)</td><td>67% (18/27)</td></tr>
<tr><td>Abnormal EEG at 3 months</td><td>17% (4/23)</td><td>30% (8/27)</td></tr>
<tr><td>Normal development at 6 months*</td><td>78% (18/23)</td><td>70% (19/27)</td></tr>
</table>
* As assessed by the Infant Mental Developmental Assessment Scale (the authors do not provide a description of this scale)</td>
<td>There was a significant decrease in heart rates at 24, 48 and 72 hours in cooled infants compared with controls ($p < 0.05$).

There were no significant differences between the groups in blood pressure, cardiac function, renal function or other adverse outcomes.</td>
<td>This study did not meet inclusion criteria for the systematic review (it did not describe method of treatment allocation and did not report any of the pre-specified outcomes).</td>
</tr>
</table>

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Azzopardi D et al (2009)[6]

Study type: case series

Country: UK (multi-centre)

Study period: 2006–2008

Study population: newborn infants

n = 120

Sex: not stated

Inclusion criteria:
• gestational age ≥ 36 weeks
• clinical evidence of birth asphyxia and moderate to severe encephalopathy

Technique: target rectal temperature of 33.5°C for 72 hours, using a certified or locally approved cooling device followed by gradual rewarming at a rate no faster than 0.5°C/h.

3 infants received selective head cooling (Cool Care, Olympic Medical), 3 were treated with CritiCool whole body cooling system (CritiCool, Charter Kontron) and the remaining infants were treated with Tecotherm wholly body cooling (Tecotherm, Inspiration Healthcare)

Follow-up: not stated

Conflict of interest: none</td>
<td>Before cooling, 54% (44/82) and 28% (23/82) infants had a severely or moderately suppressed amplitude integrated EEG, respectively. Clinical seizures were reported in 67% (74/110) infants.

Daily encephalopathy score during the first 4 days after birth (median, interquartile range):
• Day 1 after birth = 11 (6–15)
• Day 2 after birth = 9.7 (5–14)
• Day 3 after birth = 8 (5–13)
• Day 4 after birth = 7 (2–12)

51% of the infants established oral feeding before discharge or transfer from the treating hospital at a median of 9 days (range 4–24).

Magnetic resonance imaging was done in 60% (71/120) infants but reports were only available for 53 infants (44%). The findings were classified as normal or consistent with mild hypoxic-ischaemic injury in 30 infants, and consistent with moderate of severe injury in 23 infants.

Mortality = 26%</td>
<td>Complications during cooling period
<table>
<tr><th></th><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th></tr>
<tr><td>Seizures</td><td>90 (75%)</td><td>59 (49%)</td><td>40 (33%)</td><td>28 (23%)</td></tr>
<tr><td>Hypotension</td><td>41 (34%)</td><td>33 (28%)</td><td>22 (18%)</td><td>11 (9%)</td></tr>
<tr><td>Sepsis</td><td>20 (17%)</td><td>16 (13%)</td><td>15 (12%)</td><td>11 (9%)</td></tr>
<tr><td>Coagulo-pathy</td><td>32 (27%)</td><td>22 (18%)</td><td>15 (12%)</td><td>7 (6%)</td></tr>
<tr><td>Hypo-glycaemia</td><td>28 (23%)</td><td>13 (11%)</td><td>5 (4%)</td><td>1 (<1%)</td></tr>
<tr><td>Arrhythmia</td><td>3 (2%)</td><td>2 (2%)</td><td>3 (2%)</td><td>1 (<1%)</td></tr>
<tr><td>Respiratory support</td><td>99 (82%)</td><td>75 (62%)</td><td>59 (49%)</td><td>40 (33%)</td></tr>
</table>
NB. Before cooling, clinical seizures were reported in 67% (74/110) of infants.

Complications recorded during admission period
• Pulmonary hypertension = 6% (7/120)
• Air leak = 3% (4/120)
• Late sepsis (no further details) 3% (4/120)
• Pulmonary haemorrhage = 2% (3/120)
• Necrotising enterocolitis = 2% (2/120)
• Pneumonia = 0.8% (1/120)

The treating physicians did not consider any of these complications to be related to therapeutic hypothermia.</td>
<td>Prospective study.

Infants were registered with the UK TOBY cooling register, which was established on completion of enrolment to the TOBY RCT.

Conditions other than hypoxic-ischaemic encephalopathy were subsequently diagnosed in 5 infants (1 chromosomal disorder, 1 neuromuscular disorder, 2 early onset group B streptococcal meningitis, 1 group B streptococcal septicaemia diagnosed on day 3).

Cooling was started more than 6 hours after birth in 18% (21/120) of infants – the authors state that any neuroprotective benefit from hypothermia may be diminished by this time.</td>
</tr>
</table>

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Navarini-Meury et al (2007)[7] **Study type*:* case report** Country: Switzerland Study period: not reported Study population: new born infant delivered at term with birth asphyxia **n = 1** Sex: male Technique: whole body cooling using a water-filled mattress to 34.5°C for 72 hours Follow-up: not stated Conflict of interest: none reported		The infant survived without apparent brain damage but developed sclerema on his back, in the area in contact with the cooling mattress (at 3-week follow-up). The sclerema resolved without scarring after 3 months.	

Abbreviations used: GMF, gross motor function; HIE, hypoxic-ischaemic encephalopathy; MDI, mental development index; PDI, psychomotor development index.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Wiadrowski et al (2001)[8] **Study type: case report** Country: Australia Study period: not reported Study population: new born infant delivered at term with birth asphyixia **n = 1** Sex: female Technique: surface cooling using ice packs applied to the skin. Temperature (monitored via a rectal probe) was kept at 32–33°C for 24 hours, then raised to 35 degrees and then 37degrees over a 3 day period. Follow-up: **9 months** Conflict of interest: none reported		Pink woody odematous change was noted on the thighs and back of the infant, corresponding to the sites of applications of the ice packs. First noted at approximately 24 hours after birth and progressively worsening over 4 days. Subcutaneous fat necrosis was histologically diagnosed at 6 days. The infant was treated by rehydration, diuretics, prednisolone, etidronate and a low-calcium, low- vitamin D diet. At 9 months asymptomatic firm nodules were present and no calcification was present.	

Validity and generalisability of the studies

- The studies varied in the method of cooling used (some used selective head cooling and some used whole body cooling) as well as in the degree of cooling and the method used to monitor temperature.
- The systematic review also included studies with different cooling methods, selection criteria and outcome measures.
- Outcomes were assessed to a maximum follow-up of about 18 months only.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Prof David Edwards, Prof Henry Halliday, Prof Marianne Thoresen, Prof Andrew Whitelaw. Royal College of Paediatrics and Child Health.

- One Specialist Adviser thought the procedure was established practice and 2 thought it was novel and of uncertain safety and efficacy.
- All Advisers thought that there was no appropriate comparator because standard intensive care with normothermia was the only alternative.

Safety

- Theoretical or anecdotal adverse events included: pulmonary hypertension, cardiovascular instability, cardiac arrhythmia, cerebral haemorrhage, metabolic disturbances, blood hyperviscosity syndrome, increased infections and sclerema.
- Reported adverse events included: mild oedema, local skin injury and seizures during rewarming if it is carried out too quickly.
- The main concern with regard to safety was to ensure the procedure is carried out properly and in a suitable environment.

Efficacy

- Key efficacy outcomes included: improvement in survival without neurological impairment, reduction in severe disability, improvement in Motor and Psychomotor Development Index scores and reduction in cerebral palsy.
- Uncertainties about efficacy included: which infants should be selected for treatment (those with moderate or severe asphyxia) and whether there are long-term benefits (beyond 18 months).

Other comments

- All four Advisers thought that training in the use of cooling equipment was important.

- Two Advisers thought that the potential impact of the procedure on the NHS was moderate and one thought it was major.

Issues for consideration by IPAC

- Several Advisers and the Cochrane systematic review mentioned 2 additional trials, which are due to publish results within the next 2 years: the nnn-Hypothermia multi-centre trial in Europe (results due late 2008) and the ICE trial in Australia (results due late 2009).
- The TOBY group has set up a national register of cooling (http://www.npeu.ox.ac.uk/tobyregister).

References

1. Jacobs S, Hunt R, Tarnow M et al. (2007) Cooling for newborns with hypoxic ischaemic encephalopathy. The Cochrane Library

2. Gluckman PD, Wyatt JS, Azzopardi D et al. (2005) Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. Lancet 365: 663–670.

3. Shankaran SL (2005) Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. New England Journal of Medicine 353: 1574–1584.

4. Azzopardi DV, Strohm B, Edwards AD et al. (2009) Moderate hypothermia to treat perinatal asphyxia encephalopathy. New England Journal of Medicine 361: 1349–58.

5. Zhou W-H, Shao X-M, Yun C et al. (2002) Safety study of hypothermia for treatment of hypoxic-ischemic brain damage in term neonates. Acta Pharmacologica Sinica 23: 64–68.

6. Azzopardi D, Strohm B, Edwards AD et al. (2009) Treatment of asphyxiated newborns with moderate hypothermia in routine clinical practice: how cooling is managed in the UK outside a clinical trial. Archives of Disease in Childhood Fetal & Neonatal Edition 94: F260–4.

7. Navarini-Meury S, Schneider, J, Buhrer, C. (2007) Sclerema neonatorum after therapeutic whole-body hypothermia. Archives of Disease in Childhood Fetal & Neonatal Edition 92 (4) F307.

8. Wiadrowski TP, Marshman G. (2001) Subcutaneous fat necrosis of the newborn following hypothermia and complicated by pain and hypercalcaemia. Australasian Journal of Dermatology 42 (3) 207–210.

Appendix A: Additional papers on therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Akisu M. (2003) Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia. Prostaglandins Leukotrienes and Essential Fatty Acids 69 (1) 45–50.	n = 21 (RCT) Follow-up: not stated	No evidence of severe adverse events related to hypothermia. No cooled infants and 2 control infants (20%) died after 72 hours of life. No cooled infants and 3 control infants (30%) had clinical seizure activity. No cooled infants and 4 control infants (40%) had abnormal EEG patterns (P < 0.05).	Larger studies included in table 2.
Azzopardi D, Robertson NJ, Cowan FM et al. (2000) Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics 106: 684–694.	n = 10 Follow-up: not stated	3 infants (30%) died after intensive care was withdrawn. 1 infant had continuing neurological abnormalities at 6 months of age. 6 infants had normal neurological outcome on follow-up examination.	More recent study from same centre included in table 2.
Battin MR. (2001) Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. Pediatrics 107 (3) 480-484.	n = 40 RCT Follow-up: 18 months	3 infants died in each study group: 12% of cooled infants and 20% of control infants. 6/22 cooled infants and 1/12 control infants had impaired mental development or severe cerebral palsy at 18 months.	Larger studies included in table 2.
Battin MR. (2003) Treatment of term infants with head cooling and mild systemic hypothermia (35.0°C and 34.5°C) after perinatal asphyxia. Pediatrics 111: 244–251.	n = 13 (+ 13 controls) Follow-up: not stated	1 cooled infant died 2 days after rewarming, and 3 control infants died. 6 cooled infants (46%) and 5 control infants (38%) had normal EEG at 1 week.	More recent study from same centre included in table 2.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Battin MR, Thoresen M, Robinson E et al. (2009) Does head cooling with mild systemic hypothermia affect requirement for blood pressure support? Pediatrics 123:1031–6.	n = 230 (RCT) Follow-up: 76 hours	Cooling was associated with sinus bradycardia but did not affect blood pressure. There was an apparent change in physician behavior with slower withdrawal of therapy in cooled infants.	Secondary analysis of a study included in table 2.
Bhat MA. (2006) Re: Therapeutic hypothermia following perinatal asphyxia. Archives of Disease in Childhood: Fetal and Neonatal Edition 91 (6) F464.	n = 35 (RCT)	No significant difference in mortality between cooled infants (15%) and controls (33%; $p > 0.05$). Cooled infants were less likely to have abnormal neurological examination at discharge ($p < 0.001$; raw data not reported).	Data were reported in a letter to the journal not a full text original article.
Compagnoni G. (2002) Hypothermia reduces neurological damage in asphyxiated newborn infants. Biology of the Neonate 82: 222–227.	n = 10 (+ 11 controls) Follow-up: 18 months	No evidence of severe adverse events related to hypothermia. Significant ($p < 0.05$) reduction of major neurologic abnormalities at follow-up and abnormal MRI in cooled group.	Larger studies included in table 2.
Compagnoni G, Bottura C, Cavallaro G et al. (2008) Safety of deep hypothermia in treating neonatal asphyxia. Neonatology 93: 230–5.	n = 39 Non-randomised comparative study	Poor neurological outcomes and brain injury at MRI were reduced in the cooled groups, compared to control group. No statistically significant differences between deep hypothermia (body temperature between 30°C and 33°C) and mild hypothermia (body temperature between 32°C and 34°C).	Larger studies included in table 2.
Debillon T. (2003) Whole-body cooling after perinatal asphyxia: A pilot study in term neonates. Developmental Medicine and Child Neurology 45 (1) 17–23.	n = 25 Follow-up: 2 weeks	7 infants died. 13 infants (52%) had normal cerebral signal on MRI. Thrombocytopenia developed in 12 infants, including 7 with disseminated intravascular coagulation.	Larger studies included in table 2.
Eicher DJ, Wagner CL, Katikaneni LP et al. (2005) Moderate hypothermia in neonatal encephalopathy: Efficacy outcomes. Pediatric Neurology 32 (1) 11–17	n = 65 (RCT) Follow-up: 12 months	Death or severe motor disability at 12 months of age: cooled group: 52% (14/27), control group: 84% (21/25) [p = 0.019]	Larger studies included in table 2.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Eicher DJ, Wagner CL, Katikaneni LP et al. (2005) Moderate hypothermia in neonatal encephalopathy: Safety outcomes. Pediatric Neurology 32 (1) 18–24	n = 65 (RCT) Follow-up: 12 months	Cooled infants had a significantly higher incidence of bradycardia, requirements for plasma and platelet transfusions, stridor, tremors and seizures and had lower heart rates during treatment. 1 infant had an acute drop in blood pressure which responded to treatment. 1 infant had a rebleed into a previous haemorrhage site (possibly related to the hyperthermia treatment).	Larger studies included in table 2.
Gebauer CM. (2006) Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. Pediatrics 117: 843–850.	n = 7 Follow-up: not stated	Whole body hypothermia resulted in reduced cardiac output, which reached normal levels at the end of passive rewarming.	Larger studies included in table 2.
Gunn AJ. (2008) Therapeutic Hypothermia Changes the Prognostic Value of Clinical Evaluation of Neonatal Encephalopathy. Journal of Pediatrics 152: 55–58.	n = 234 Follow-up: 4 days	Hypothermia did not affect severity of encephalopathy at day 4. In infants with moderate encephalopathy at day 4, those cooled had a higher rate of favorable outcome (31/45 infants, 69%, p = 0.006) compared with standard care (12/33, 36%).	Secondary analysis of a study included in table 2.
Gunn AJ, Gluckman PD, and Gunn TR. (1998) Selective head cooling in newborn infants after perinatal asphyxia: a safety study. Pediatrics 102 (4 Pt 1) 885–892.	n = 22 Follow-up: not stated	There were no significant differences in the incidence of adverse events between the 3 groups of infants.	More recent study from same centre included in table 2.
Inder TE, Hunt RW, Morley C et al. (2004) Randomized trial of systemic hypothermia selectively protects the cortex on MRI in term hypoxic-ischemic encephalopathy. Journal of Pediatrics 145 (6) 835–837.	n = 27 (RCT) Follow-up: not stated	Cooled infants had less cortical gray matter signal abnormality MRI (1 cooled infant, 8% vs 7/14 control infants, 50%); p = .036).	Larger studies included in table 2.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Kilani RA. (2002) The safety and practicality of selective head cooling in asphyxiated human newborn infants, a retrospective study. Journal Medical Libanais 50: 17–22.	n = 14 (+ 12 controls) Follow-up: not stated	No significant differences in adverse effects between the groups.	Larger studies included in table 2.
Laptook A, Tyson J, Shankaran S et al. (2008) Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. Pediatrics 122;(3): 491–9.	n = 196 (RCT) Follow-up: not stated	Relatively high temperatures during usual care were associated with increased risk of adverse outcomes.	Secondary analysis of a study included in table 2.
Lin Z-L, Yu H-M, Lin J et al. (2006) Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: An experience from a single neonatal intensive care unit. Journal of Perinatology 26 (3) 180-184.	n = 58 (RCT) Follow-up: 10 days	Signs of moderate to severe encephalopathy on computed tomography scan at 5 to 7 days: 13% (4/30) of cooled infants vs 64% (18/28) of control infants ($p < 0.01$)	Larger studies included in table 2.
Parikh NA, Lasky RE, Garza CN et al. (2009) Volumetric and anatomical MRI for hypoxic-ischemic encephalopathy: relationship to hypothermia therapy and neurosensory impairments. Journal of Perinatology 29: 143–9.	n = 14 (RCT)	Relative volumes of subcortical white matter were significantly larger in cooled infants than control infants. Relative total brain volumes correlated significantly with death or neurosensory impairments.	Secondary analysis of a study included in table 2.
Robertson NJ, Nakakeeto M, Hagmann C et al. (2008) Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial. Lancet 372: 801–3.	n = 36 (RCT) Follow-up: 17 days	Whole body cooling is feasible and inexpensive in a low resource setting. 33% (7/21) cooled infants died, compared with 7% (1/15) control infants. Abnormal neurological exam on day 17 = 67% (8/12) cooled infants and 80% (4/5) controls.	Larger studies included in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Rutherford MA. (2005) Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy. Pediatrics 116: 1001–1006.	n = 34 (+ 52 controls) Follow-up: not stated	Cooling was not associated with unexpected or unusual cerebral lesions and the prevalence of intracranial hemorrhage was similar across study groups. Cooling was associated with a decrease in basal ganglia and thalamic lesions (which are predictive of abnormal outcome).	Larger studies included in table 2.
Schulzke SM, Rao S, Patole SK. (2007) A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy - Are we there yet? BMC Pediatrics 7 (30).	Systematic review n = 5 RCTs (552 infants) Follow-up: 18–22 months	Outcomes in cooled infants vs controls: Death or disability: RR: 0.78, 95% CI: 0.66–0.92) Death: RR: 0.75, 95% CI: 0.59–0.96 Neurodevelopmental disability aged 18-22 months: RR: 0.72, 95% CI: 0.53–0.98	Another systematic review of the same studies is included in table 2.
Shah PS. (2007) Hypothermia to treat neonatal hypoxic ischemic encephalopathy: Systematic review. Archives of Pediatrics and Adolescent Medicine 161 (10) 951-958.	Systematic review n = 8 RCTs (safety), 4 RCTs, 497 infants (efficacy) Follow-up: ≥ 12 months of age	Outcomes in cooled infants vs controls: Death or disability: RR: 0.76, 95% CI: 0.65–0.88) Death: RR: 0.74, 95% CI: 0.58–0.94	Another systematic review of 6 of the same studies is included in table 2.
Shankaran S, Pappas A, Laptook A et al. (2008) Outcomes of safety and effectiveness in a multicenter randomised controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. Pediatrics 122; e791–8.	n = 208 (RCT) Follow-up: 18 months	Data support the safety of whole body cooling when adhering to strict entry criteria and cooling initiated within 6 hours of age.	Another study reporting on the same infants is included in table 2 (Shankaran et al, 2005)
Shankaran S, Laptook A et al (2002) Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics 110 (2 Pt 1) 377–385.	n = 19 (RCT) Follow-up: not stated	2 (22%) cooled infants died after life support was withdrawn. 3 (30%) control infants died (1 after life support was withdrawn) 43% (3/7) of cooled infants and 43% (3/7) of control infants had abnormal MRI at follow-up (44 week postmenstrual age).	Larger studies included in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Simbruner G. (1999) Induced brain hypothermia in asphyxiated human newborn infants: A retrospective chart analysis of physiological and adverse effects. Intensive Care Medicine 25 (10) 1111–1117.	n = 21 (+ 15 controls) Follow-up:	4 cooled infants (19%) and 4 control infants (27%) died (not significant). There was no significant difference in neurological score within the first 2 days of life between the groups.	Larger studies included in table 2.
Thoresen M. (2000) Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics 106: 92–99.	n = 9 Follow-up: not stated	Cooling reduces heart rate and increases blood pressure (but not hazardously).	Larger studies included in table 2.
Whitelaw A,Thoresen M. (2001) Clinical experience with therapeutic hypothermia in asphyxiated infants. Developmental Medicine & Child Neurology - Supplemental 86: 30–31.	n = 9 Follow-up: not stated	Same study population and conclusion as previous study.	Larger studies included in table 2.
Wyatt JS. (2007) Determinants of outcomes after head cooling for neonatal encephalopathy. Pediatrics 119: 912–921.	n = 218 Follow-up: 18 months	n/a	Another study reporting on the same infants and outcomes is included in table 2 (Gluckman et al 2005).
Zanelli SA, Naylor M, Dobbins N et al. (2008) Implementation of a 'hypothermia for HIE' program: 2-year experience in a single NICU. Journal of Perinatology 28 (3) 171–175.	n = 21 Follow-up: not stated	4 infants (19%) died in the first 4 days after birth after ventilatory support was withdrawn. 15 infants (71%) had EEG-defined moderate or severe encephalopathy at 1–3 days of age. 5 infants (23%) had abnormal MRI at 3–24 months follow-up.	

Appendix B: Related NICE guidance for therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/09/09	Issue 3, 2009
Database of Abstracts of Reviews of Effects – DARE (CRD website)	21/09/09	N/A
HTA database (CRD website)	21/09/09	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/09/09	Issue 3, 2009
MEDLINE (Ovid)	21/09/09	1950 to September Week 2 2009
MEDLINE In-Process (Ovid)	21/09/09	September 18, 2009
EMBASE (Ovid)	21/09/09	1980 to 2009 Week 38
CINAHL (NHS Evidence)	21/09/09	1981 to Present
BLIC (Dialog DataStar)	21/09/09	1995 to date

Trial sources searched on 14/09/09

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 14/09/09

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

1	exp Hypoxia-Ischemia, Brain/
2	Fetal Hypoxia/
3	Asphyxia Neonatorum/
4	Anoxia/
5	Apgar Score/

6	Respiratory Distress Syndrome, Newborn/
7	exp Brain Injuries/
8	(brain* adj3 injur*).tw.
9	(anoxi* or anoxemia* or hypoxi* or hypoxemia* or asphyxi* or encephalopath*).tw.
10	(apgar* adj3 scor*).tw.
11	(respirator* adj3 distres* syndrom*).tw.
12	or/1-11
13	exp Hypothermia, Induced/
14	Cryotherapy/
15	(Therapeut* adj3 hypother*).tw.
16	(cool* adj3 (brain* or body* or head* or neonatal*)).tw.
17	(cool* adj3 (cap* or blanket* or mattress*)).tw.
18	(hypotherm* adj3 induc*).tw.
19	cryothera*.tw.
20	or/13-19
21	Infant, Newborn/
22	(infant* adj3 newbor*).tw.
23	Perinat*.tw.
24	neonat*.tw.
25	(Fetus* or Fetal* or Foetus* or Foeta*).tw.
26	or/21-25
27	12 and 20 and 26
28	Animals/ not Humans/
29	27 not 28
30	2008*.ed.
31	2009*.ed.
32	or/30-31
33	29 and 32