East of England Neonatal ODN

(Hosted by Cambridge University Hospitals)

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Guidelines for Management of Infants with Suspected Hypoxic Ischaemic Encephalopathy (HIE)

Abbreviations:

aEEG Amplitude integrated electroencephalogram
BAPM British Association of Perinatal Medicine
CFM Cerebral function monitoring
CUS Cranial Ultrasound
HIE Hypoxic Ischaemic Encephalopathy
MRI Magnetic Resonance Imaging
MRS Magnetic Resonance Spectroscopy
NE Neonatal Encephalopathy
NICE National Institute of Clinical Excellence
NLS Newborn Life Support
PaNDR Paediatric and Neonatal Decision Support and Retrieval Service
TH Therapeutic Hypothermia

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Assurance Statement

The purpose of this protocol is to clarify the regional agreement on the use and practice of Therapeutic Hypothermia in the treatment of infants with Hypoxic-Ischaemic Encephalopathy in the East of England Neonatal Operational Delivery Network.

1. Neuroprotection Care Pathway

These guidelines form part of an integrated neonatal neuroprotection care pathway and are designed to be used in conjunction with the Neuroprotection Care Pathway document. The care pathway integrates a checklist of steps that should be undertaken to ensure that cooling is safely initiated and maintained.

To allow for the most appropriate medical management of infants and accurate data collection, all sections of this form should be completed. Copy of the initial care pathway should be sent along with the baby to the regional centre and original filed in the case notes/electronically.

Alongside this guideline there are also separate guidelines for cerebral function monitoring, magnetic resonance imaging and management of seizures.

2. Introduction

2.1. Neonatal Encephalopathy

Neonatal encephalopathy is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes [1].

There are many potential causes of neonatal encephalopathy, the commonest of which follows a hypoxic-ischaemic insult. However, it is not always possible to document a clear hypoxic-ischaemic episode during labour, and several other important aetiologies should be considered as being a primary or contributory cause of the encephalopathy.

Other causes of NE include:

- infection
- perinatal stroke
- intracranial haemorrhage
- congenital brain malformations
- Neurometabolic
- Genetic syndromes

Investigation of these conditions will depend on the presentation, history, and clinical presentation of individual cases.

2.2. Hypoxic Ischaemic Encephalopathy

HIE in the term or near-term infant refers to acute brain dysfunction following critical lack of cerebral blood flow and oxygen delivery.

Perinatal asphyxia severe enough to cause HIE occurs in approximately 1/1000 – 3.5/1000 births in the UK [2, 3]. Infants with HIE are often very sick with multi-organ failure requiring intensive care. Without therapeutic hypothermia (TH), the risk of death or severe handicap in survivors of moderate or severe HIE is approximately 25 and 75% respectively, and children with and without motor impairments have lower cognitive scores on long term follow-up, poorer scholastic attainment in independent National Attainment Tests, and often need educational support [4]. Perinatal hypoxia-ischaemia thus creates a major burden for the individual, the family and for society.

Current evidence shows that therapeutic hypothermia (33-34^{o}C) with intracorporeal monitoring started within 6 hours after birth improves neurological outcome at 18 months and at 6 years of age, reducing mortality from 25% to 9% and disability from 20% to 16% [5, 6] and is now recommended as the standard of care in the UK [4, 7].

However, cooling is not performed in isolation and should be part of a package of neurocritical care that enables appropriate investigation, treatment and imaging to be undertaken prior to long-term follow-up being arranged for surviving infants.

3. Clinical Management

The clinical management of infants with HIE is a combination of therapeutic hypothermia (where appropriate) and supportive management, dependent on the extent of organ compromise. Each baby's management should be individualised, with close monitoring of cardiorespiratory status and early identification and treatment of multi-organ system complications where appropriate.

3.1. Resuscitation

Resuscitation should be carried out following the Newborn Life Support (NLS) guidelines. Resuscitation should be initiated using room air. For infants requiring and surviving extensive resuscitation, early

thought should be given to therapeutic hypothermia. Therapeutic hypothermia is most effective when commenced as close as possible in time to the hypoxic-ischaemic event. Cooling should only be considered once cardiorespiratory stability has been achieved including heart rate and oxygen saturation.

Recommendations

- Maintain normothermia (avoiding hyperthermia) until a decision to treat with cooling is made by a senior clinician post cardiorespiratory stability.
- Infants starting any form of TH, including switching the resuscitaire heater off, should have their temperature continuously monitored ideally using an intracorporeal (e.g., rectal) temperature probe.

3.2. Therapeutic Hypothermia – Cooling

3.2.1. Criteria for Cooling

Infants with suspected HIE who meet the following criteria A and B [4] should be considered for treatment with cooling: (See **appendix 1** for identification flowchart). Ideally early aEEG should be commenced and decision making can then include criteria C. Assessment of these criteria should be made by trained personnel. ***The decision to cool should not be delayed if aEEG is not readily available or if there is no one with suitable experience to read the aEEG.***

Criteria A

Infants ≥36 completed weeks' gestation who are **less than 6 hours old** with at least **one** of the following:

- Apgar score of ≤5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis – pH <7.00 in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth
- Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth

Criteria B

Moderate to severe encephalopathy, consisting of:

- Consciousness: Altered state of consciousness (lethargy, stupor or coma).

AND at least one of the following

- Abnormal reflexes including oculomotor or pupillary abnormalities
- Weak or absent suck
- Hypotonia
- Clinical seizures

Infants who meet criteria A and B should have assessment of global electrical brain activity measured using aEEG (read by trained personnel).

Criteria C

At least 30 minutes duration of amplitude integrated EEG recording that shows abnormal background aEEG activity or seizures.

There must be one of the following:

- Normal background with some seizure activity.
- Moderately abnormal activity
- Suppressed activity
- Continuous seizure activity

Notes on Practical Application of Cooling Criteria

- The term '*continued need for resuscitation including mask or endotracheal ventilation*' does NOT include infants who are receiving PEEP or CPAP alone.
- Neonatal encephalopathy evolves with time. Therefore, infants who meet at least one A criterion but on initial examination are neurologically normal should be reviewed atleast twice in the first 6 hours of life by a trained practitioner who is competent in neonatal neurological examination.
- It is also recognised that aEEG may not be available in all circumstances, and failure to obtain aEEG should not prevent or delay treatment if there is evidence from A and B criteria.

If an infant **meets** these criteria, but cooling is NOT offered, the reasons for this decision including discussions with PaNDR and regional NICU if appropriate, should be clearly documented in the medical notes.

In the event of an infant **not meeting** the criteria for cooling but where the local clinicians feel cooling may benefit the infant, PaNDR and regional NICU if appropriate should be contacted for further advice. Please see **Appendix 2** – Cooling Outside of Criteria Guidelines.

3.2.2. Exclusions

Cooling may not be appropriate if:

- The infant appears moribund or has persisting extremely severe encephalopathy such that further treatment is likely to be futile.
- The infant falls outside of the set criteria. Please see **Appendix 2**- Cooling Outside of Trial Criteria Guidelines and contact PaNDR and Regional NICU if appropriate for further advice.
- Known major chromosomal or other pre-existing abnormalities indicating poor long-term outcome
- Infants requiring surgery. This should be considered on an individual case by case basis and after full discussion with the surgeons, PaNDR and regional NICU as appropriate [8].

3.2.3. Neurological examination

The severity of encephalopathy should be assessed using the criteria in **Appendix 1**. This should be assessed many times in the first 6 hours. The initial score should be recorded on the NCP 1 prior to starting cooling and then daily for the first four days after birth.

As sedation and paralysis make the grading difficult, when assessing the infant, the type of medication, amount and time of last administration should be documented. Seizures could be missed in heavily sedated and paralysed infants and continuous aEEG monitoring is needed.

3.2.4. When to initiate cooling

- Passive or active cooling should be started after resuscitation is completed, post cardiorespiratory stability and eligibility is confirmed (see section 3.2.1) and baby is on the neonatal unit. Normothermia should be maintained till then.
- The decision to undertake therapeutic hypothermia should be prompt and made by a

practitioner who is competent in the above neurological assessments, their interpretation and criteria for cooling.

- It should always be discussed with a consultant and with the baby's parents unless this is not physically possible.
- Therapeutic hypothermia should not be started without continuous rectal temperature monitoring [4]
- Current evidence suggests that the maximum benefit can be derived from cooling when it is commenced within 6 hours of birth [4, 9]
- Therapeutic hypothermia is most effective when commenced as close as possible in time to the hypoxic-ischaemic event. Infants cooled within 3 hours of birth have better neurodevelopmental outcomes compared with infants whose cooling commences between 3 hours and 6 hours [10]. Hence initiation of cooling should not be delayed in infants who are clearly neurologically abnormal whilst awaiting aEEG data acquisition.
- At the same time, it would be better not to cool infants who recover quickly following perinatal adaptation and do not need TH. Hence senior input is needed along with repeated neurological examination.
- Currently there is no consensus regarding cooling beyond 6 hours and this should be discussed case by case with the PaNDR and regional NICU as appropriate, should be contacted for further advice. Please see **Appendix 2** – Cooling Outside of Criteria Guidelines

3.2.5. Temperature during therapeutic hypothermia

Core temperature (rectal) should be monitored continuously aiming for a core temperature of 33.5oC (range 33-34oC - do not allow it to drop below this). Cooling below 32^0C increases the mortality [11].

3.2.6. How long to cool?

72 hours from when temperature reaches 33.50C. Longer cooling for >72 hours has not shown to be beneficial and may infact be harmful and may increase the risk of arrhythmias, anuria and longer hospitalisations [11] .

3.2.7. Where should infants be treated with cooling?

- Cooling can be initiated in any hospital, however all infants who are eligible for cooling should be transferred to a Regional NICU [4]. These NICUs have facilities for providing full neuro-intensive care, recording the aEEG/EEG and carrying out appropriate investigations including neuroimaging.

- Cooling should not be initiated in stand-alone midwifery led units, instead early transfer should be initiated so that cooling can be initiated within 6 hours of age [4].

3.2.8. Referral to EBS/PaNDR

When an infant has been identified as suitable for cooling, there should be early discussion with the PaNDR and Regional NICU if appropriate. A referral should be made to:

EBS/PaNDR – 01223-274274

as soon as possible who will locate a cooling cot and provide ongoing advice regarding management of the infant whilst preparation for transfer is made. This should be recorded in the NCP 1. Management during transport will be according to the guidelines for cooling during transport and will be provided by the PaNDR Team.

3.2.9. Passive Cooling

For all infants born in units without active cooling available, passive cooling should be commenced and continued until the infant is transferred. Ensure that the Neuroprotection Care Pathway "NCP 1" is completed as fully as possible prior to transfer.

Practical Guide to Passive Cooling (see Appendix 3)

- Infants with suspected HIE should be assessed to determine whether the criteria for offering cooling are met
- Decision to start cooling should be in discussion with attending consultant
- Nurse the infant naked in an open cot, and switch off the incubator/radiant warmer heater - discontinue active warming
- A closed incubator may be used. Open all the portholes of the incubator for ventilation and switch off the incubator heater
- Consider changing the mattress for one that has not been in a preheated incubator
- Insert a rectal temperature probe. Cooling should not be started without intracorporeal temperature monitoring.
- Monitor core temperature (rectal) continuously aiming for a core temperature of 33.5^{o}C (range 33-34^{o}C - **do not** allow it to drop below this). Record rectal core temperature every 15 minutes on the NCP-1 temperature chart
- If necessary, a fan can help induce cooling, but do not place cold objects (e.g., ice packs) against the baby

- Infants with HIE frequently have thermal instability and spontaneously cool down considerably faster [12]. Care must be taken as the infant's temperature approaches 34°C. Cooling measures should be stopped at this point, as thermal inertia will mean the core temperature continues to drop. A hat should be placed on the infant and the incubator should be turned on to its lowest temperature setting to avoid over cooling.
- If the temperature is falling too rapidly, every effort should be made to avoid rapid cooling, as temperatures below 33°C can be detrimental

The infant's core temperature should reach the target of 33.5°C (33-34 °C) in an expedient, safe and controlled manner. Ideally this temperature should be achieved 2 hours from commencing cooling and within 6 hours of birth. Plotting core temperature on the NCP-1 temperature chart can give an indication as to whether the temperature is falling too rapidly or too slowly.

3.2.10. Active Cooling

While therapeutic hypothermia can be initiated with passive cooling methods, therapeutic hypothermia is best delivered using active cooling methods [4]. Servo-controlled systems have been shown to minimise temperature fluctuations and are less labour intensive on nursing staff [13].

If an infant is born in a unit with active cooling, this should be initiated as soon after birth as possible. For infants who have initially undergone passive cooling, active cooling will be initiated on transfer by PaNDR. Using a servo-controlled system active cooling to target temperature can be achieved safely within 30 minutes.

Practical Guide to Active Cooling

- Infants with suspected HIE should be assessed to determine whether the criteria for offering cooling are met and discussed with the attending consultant.
- Nurse infant naked in an open cot and switch off the incubator/radiant warmer heater - discontinue active warming.
- A closed incubator may be used. Open all the portholes of the incubator for ventilation and switch off the incubator heater.
- Insert a rectal temperature probe
- Monitor rectal temperature continuously aiming for a rectal temperature of 33.5°C (range **33-34°C**).

- Cooling should be maintained using appropriate cooling equipment. Only certified equipment should be used to provide treatment with cooling. The manufacturer's instructions should be followed when using the cooling equipment.
- Cooling should be continued for a total of 72 hours from the point at which the target temperature of 33.5°C (range **33-34°C**) has been achieved and maintained.

The 72 hours of cooling is considered to have commenced when a temperature of 33.5°C has been reached and maintained (irrespective of using active or passive cooling).

3.2.11. Complications associated with cooling

Both the clinical trials and TOBY register have shown that cooling infants to 33-34°C in an intensive care environment can be done safely. Cooling is associated with physiological changes such as fall in heart rate and prolongation of QT intervals. Cooling does not appear to have any direct effect on respiratory function. Immunosuppression, coagulopathy, increased insulin resistance, electrolyte alterations are more likely to occur when core temperature falls below 32°C and are unlikely to cause significant clinical abnormalities at the temperature range used for neural rescue therapy [14].

Subcutaneous fat necrosis (SCFN) is a recognised complication of both perinatal asphyxia and total body cooling [15]. This condition can lead to pain, scarring, and hypercalcaemia that may present after the infant has been discharged home from hospital. It is recommended that the infant's skin be closely observed for the development of SCFN. If it develops, weekly calcium levels should be monitored until the clinical resolution of the SCFN occurs and for up to 6 months to prevent the serious complications that can result from hypercalcaemia [16].

3.2.12. Rewarming

- Cooling should be stopped 72 hours from when a temperature of 33.5°C has been achieved and maintained.
- Re-warming should be gradual and no faster than 0.5°C/hour until 37.0°C (normothermia) is attained. Newer servo-controlled systems have automatic rewarming modes, which avoid stepwise increments in temperature.
- aEEG should be continued till rewarming is over.
- Monitor for hypotension, apnoea and seizures including continuing aEEG
- Rewarming can be delayed or slowed where seizures (re)emerge.

3.2.13. Alterations in the clinical condition of the infant

- **The infant whose clinical condition improves *within* 6 hours of birth**

Careful neurological assessment including clinical and aEEG is essential to demonstrate that the infant does not meet criteria B & C. If cooling has been commenced, it would be reasonable to continue.

- **The infant whose clinical condition improves *after* 6 hours of birth**

Infants whose clinical condition improves after 6 hours of birth and are already being cooled should continue cooling for 72 hours. If their clinical condition improves over the subsequent 72 hours, then they would be in a good prognostic group.

- **The infant who develops 'rebound' seizures following re-warming**

Prevention of delayed energy failure is thought to be the reason hypothermia is beneficial. Therefore, ongoing seizures during cooling are an indication of continuing delayed energy failure; similarly, the re-emergence of seizures during re-warming is a suggestion that delayed energy failure is 'reactivated'. Theoretically maintenance of cooling for a further 24 hours may limit further brain injury, however there is no clinical evidence that prolonging cooling improves neurodevelopmental outcome. In a RCT by Shankaran et al, cooling for 120 hours was stopped after 50% recruitment and strongly suggests that much longer or deeper cooling (to 32^0C) is at least futile and may be harmful [17].

3.3. Airway and Respiratory Support

- Aim for normal blood gas values and saturations- avoid hypocarbia/hyperoxia.
  PaO_2 should be maintained between 6-10kPa and $PaCO_2$ between 5-7kPa. PaO_2 > 27kPa and pCO_2 < 2.6kPa are associated with poor outcome [18].
- Blood gases should ideally be taken from invasive arterial lines, as with cool peripheries the pH will be low on a capillary sample.
- Correct blood gas for patient temperature.
- Intubation and ventilation should be considered to maintain adequate gas exchange depending on respiratory drive, need for sedation.
- Ensure regular repositioning and suction if secretions increase.
- Watch for stridor in extubated and non-ventilated patients.

Cooling does not appear to have any direct effect on the respiratory function. Persistent Pulmonary Hypertension of the Newborn or meconium aspiration may coexist with HIE and should be treated with the necessary ventilatory support (including HFOV and nitric oxide if necessary).

3.4. Cardiovascular Support

- Hypotension, metabolic acidosis and pulmonary hypertension are often noted in HIE.
- Achieve central venous and arterial access and monitor intra- arterial blood pressure continuously whenever possible.
- Give IV fluids/bolus cautiously as volume replacement may worsen myocardial dysfunction seen in HIE and consider early use of inotropes.
- Routine use of sodium bicarbonate is not recommended for correction of acidosis and may exacerbate intracellular acidosis.
- Bradycardia and prolonged QT interval is often seen during cooling. Rise in heart rate may be a sign of pain, distress, sepsis, seizures or inotropes or hypovolemia.
- Arrythmias can be seen on cooling and are rectified with rewarming.
- If temperature drops below 33 ^{0}C, ventricular fibrillations may be seen on ECG.
- Aim for blood pressure >45mm Hg and treat hypotension according to local guidelines.

3.5. Seizures *(see Seizure Guidelines)*

- Clinical seizures should only be treated if there is electrical correlation on aEEG [4].
- Consider treating seizures which are confirmed with aEEG, particularly if they are associated with physiological disturbance, are prolonged (>3 minutes) or frequent (>3 per hour).
- If aEEG is not available, then there should be a discussion with PaNDR and regional NICU if appropriate, prior to treatment, as antiepileptic treatment can affect neurological examination and aEEG and may therefore impair decision- making about eligibility for TH.
- In HIE, seizures usually occur on day 1, and those seen prior to 6 hours of age should raise suspicion of earlier in utero insult.

  Seizures have been shown to be an independent risk factor for more severe brain injury on MRI and poorer neurodevelopmental outcome [19-22].
- Detection of seizures is an indication for urgent review of blood sodium, glucose, calcium and magnesium.
- Accurate documentation of the timing of administered anticonvulsant in relation to aEEG should take place.
- Anticonvulsant therapy should be given intravenously to achieve a rapid onset of action and predictable blood levels. Slow elimination rates secondary to cooling, hepatic and/or renal injury may lead to drug accumulation. It is also important to remember the effect of anticonvulsant therapy on the aEEG/EEG, all of which can suppress the background activity.

- Use intravenous phenobarbital as first line treatment in babies undergoing TH, in a dose of 20 mg/kg given over 20 minutes. See EOE Seizure guideline for further management.
- While seizures are common in HIE, unremitting seizure activity should lead to urgent consideration of other causes of epileptic encephalopathy, including consideration of a trial of pyridoxine.
- A Cochrane review demonstrated that there is no evidence to support the use of prophylactic anticonvulsants after perinatal asphyxia. Anticonvulsants are usually only required in the first week because seizures are 'acute symptomatic' and burn out with time. Occasionally longer-term therapy is required in severely affected infants [23]. Drug levels are important when maintenance doses of these drugs are used.

Please see the East of England Neonatal Seizure Guideline for specific information on drug therapy.

3.6. Infection

- Take blood cultures and give antibiotics within 1 hour of birth.
- Consider lumbar puncture.
- Physiological drop in WBC and platelets is common in TH.
- CRP rise with TH is often seen and may not be a sensitive marker for infection.

3.7. Analgesic and sedative therapy

- Signs of distress include tachycardia, facial grimacing and irritability. A HR >110bpm consistently in a cooled infant is suggestive of either distress or persistent seizures. There is preclinical evidence that distress increases brain injury in neonatal encephalopathy. However, this needs to be weighed against concerns that analgesic agents are themselves potentially neurotoxic.
- It is important to assess whether the baby is irritable, shivering or has clonus. Shivering has been shown to reduce the neuroprotective effects of cooling and so sedation should be considered to minimise this.
- Ventilated infants should be sedated as per unit guidelines. If an infant is not ventilated, they may be given chloral hydrate (50mg/kg) and respiratory function should be closely monitored. If the infant appears distressed or in pain, then also consider paracetamol. If necessary, sedation with morphine and ventilation may be indicated.

3.8. Fluid & Electrolytes

- Initial maintenance fluids at 40-60ml/kg/d.
- Watch for SIADH and avoid severe hyponatraemia.
- Avoid hypoglycaemia maintaining glucose >=2.6mmol/L [24].
- Avoid fluid overload during oliguria and avoid hypovolemia once diuresis starts.
- Watch for accumulation of nephrotoxic drugs e.g., gentamicin.

3.9. Gastrointestinal and Liver

- Consider trophic breast milk if there is no ongoing organ dysfunction or poor perfusion [4].
- Give colostrum as mouth care where available.
- Beware accumulation of drugs metabolised by liver e.g., morphine, midazolam, phenobarbital.
- Coagulopathy is physiological in therapeutic hypothermia and only active bleeding and or platelet count < 25 needs treatment [4].
- Be alert for any evidence of intracranial bleeding particularly in babies where there may have been head trauma at birth and consider correcting coagulation accordingly.
- Give IM Vit K as standard.

3.10. Investigations

Table 1 – schedule for investigations

<table>
<tr><th colspan="2">DAY ONE</th><th>SUBSEQUENT DAYS</th></tr>
<tr><td>1st line
On admission</td><td>2nd line
Same day</td><td>Daily bloods</td></tr>
<tr><td>Blood glucose</td><td></td><td>Daily FBC</td></tr>
<tr><td>Blood cultures</td><td>Troponin I* (peaks 6-12 hours post insult)</td><td>Coagulation if abnormal on day 1 or clinical indication</td></tr>
<tr><td>Coagulation (PT/APPT/TT/Fibrinogen)</td><td></td><td>U&Es and LFTs Calcium and Magnesium</td></tr>
<tr><td>Arterial blood gas (correct for temperature)</td><td>Maternal Kleihauer if anaemic or history of APH</td><td></td></tr>
<tr><td>Lactate
FBC/film/platelets
Hb/PCV
U&Es and LFTs Calcium and Magnesium
CRP</td><td colspan="2">To exclude other causes of neonatal encephalopathy, consider:
• Congenital infection screen
• Lumbar puncture for bacteria and viral PCR
• Metabolic screen including ammonia, amino acids
• Plasma amino acid and urine organic acids, ketones
• Genetic investigations
• Investigations to exclude folinic acid, biotin and pyridoxine dependent seizures especially if uncontrolled seizures

Placental histology can be very useful in aiding diagnosis and every effort should be made that this is sent for histological examination and culture</td></tr>
</table>

4. Neurophysiology

4.1. Amplitude-integrated EEG (aEEG) (see aEEG Guidelines)

aEEG provides useful information for obtaining evidence of cerebral depression and in the ongoing management of these infants including prognostication and recognition of seizures [25]. aEEG monitoring should ideally be commenced in the local unit and used as part of assessing eligibility to reduce the number of babies cooled unnecessarily. If aEEG monitoring is not available cooling should be commenced and the aEEG will be started when the infant reaches the Regional NICU. If possible, a copy of the aEEG trace should be sent to the regional NICU with the infant with clear documentation of any medications that may have affected the aEEG trace particularly sedatives and anticonvulsant medication. Electronic aEEG files should be stored in compliance with Data Protection act and should be easily retrievable for later case review if needed.

Continuous aEEG recording during the treatment period and rewarming is helpful clinically to assess the occurrence of seizures and monitor the severity of encephalopathy. Anticonvulsant therapy and sedative drugs may cause reversible suppression of EEG activity. Ideally the aEEG should be commenced before administering anticonvulsant therapy, although if not available treatment of seizures should not be delayed until an aEEG is performed.

A normal aEEG record (confirmed by assessing the underlying EEG and excluding artefact distortion of aEEG) in the first 6 hours of life indicates a high probability of normal outcome. Apparent improvement of the aEEG *after* 6 hours of age (e.g., increasing baseline aEEG activity) is not an indication for discontinuing cooling. aEEG that continues to be abnormal at 48-72 hours is predictive of poor prognosis. Further information on the prognostic value of the aEEG can be found in the CFM guideline.

4.2. Electroencephalography (EEG)

A formal EEG can provide useful information on regional background cerebral activity and seizure detection. Severe hypoxia ischaemia is typically associated with disruption of the Sleep Wake Cycling (SWC), low amplitude recordings <30uV, discontinuous recordings with interburst intervals >30s asymmetry and electrographic seizures, all providing important prognostic information in the first few days of life, even in infants being treated with therapeutic hypothermia. However, access to neurophysiology services both to perform and interpret the examination can be limited.

4.3. Near Infrared Spectroscopy (NIRS) Monitoring

There is good evidence that NIRS along with aEEG is more sensitive prognostication marker than aEEG alone and should be considered.

However, access to neurophysiology services both to perform and interpret the examination can be limited. The most useful prognostic information can be obtained once the infant has been rewarmed and off anticonvulsant medication, although it is not as sensitive as MRI.

5. Imaging

5.1. Cranial ultrasound Scans (CUS)

Cranial ultrasound scans can provide valuable information on infants with HIE and to exclude other causes of encephalopathy. Scans should be performed, including assessment of the resistance index, on admission (atleast within 12 hours [4], D1, D4 (post rewarming) and later if needed (depending on the MRI).

5.1.1. Resistance Index

A reduction in RI to ≤0.55 is associated with poor outcome after HIE however the sensitivity and specificity as a prognostic indicator is low.

5.1.2. Possible CUS Findings in HIE

- Early cerebral oedema – generalized increase in echogenicity, indistinct sulci and narrow ventricles.
- Intracranial bleed (e.g., IVH, extradural hematoma).
- Cortical highlighting.
- After 2-3 days of age, increased echogenicity of thalami and parenchymal echo densities.
- After day 7 cystic degeneration of the white matter.

5.2. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) (See MRI Guidelines)

MRI is the imaging modality of choice for assessment of injury and prognostication of neurological outcome and exclude other causes of neonatal encephalopathy [26, 27]. Neonatal units should ensure access to appropriate facilities. MRI should be reported by a consultant radiologist with expertise in neonatal brain MRI interpretation. MRI scans should be stored in compliance with Data Protection act and should be easily retrievable for later case review if needed.

All infants undergoing therapeutic hypothermia should have an MRI scan undertaken between 5 and 15 days, preferably between 5 and 7 days of birth [4]. The scan should be delayed until term corrected age if less than 38 weeks' gestation to ensure myelination is noted.
Proton (1H) MRS Lactate/N acetyl aspartate (Lac/NAA) of the basal ganglia and thalamus can also be performed with the MRI if there is local expertise available to undertake and interpret the scan. In research settings this has been shown to be the most accurate predictor of outcome in babies who have undergone therapeutic hypothermia [26, 28].

Early conventional MR imaging (within the first 4 days of life) may not reflect the true extent of the injury, although abnormalities may be seen on diffusion-weighted imaging. Early MR imaging may be considered in very sick infants where discontinuation of intensive support is being considered or where the clinical, neurophysiological, or ultrasound assessment is suggestive of other causes of encephalopathy (e.g., subdural haemorrhage or perinatal arterial ischaemic stroke).

Infants who develop signs of HIE following an acute sentinel event (e.g., placental abruption) often sustain bilateral and usually symmetrical lesions within the basal ganglia and thalami, and exhibit an abnormal appearance in the posterior limb of the internal capsule (PLIC). Abnormality seen in the PLIC is an excellent predictor of abnormal neuromotor outcome [27]. More chronic hypoxia-ischaemia is associated with cortical and subcortical abnormalities. Further information on MRI scanning can be found in the MRI guidelines. See Table 4 for further discussion on prognostication.

6. Reorientation of care

Given the nature of severe neonatal encephalopathy and associated multi-organ pathology there will be some infants for whom the reorientation of care to a palliative pathway is appropriate.

In infants in whom it is possible to deliver therapeutic hypothermia with physiological stability, it is recommended that such consideration be delayed for 48 hours to assess any recovery before considering reorientation of care [4].

Consideration should be given to the drugs that have been administered and appropriate tests should be undertaken to ensure that the assessment of prognosis has not been confused by drug effects.

The discussions with parents preceding reorientation of intensive support should include the uncommon but possible outcome of long-term ongoing survival after intensive support withdrawal in babies with severe HIE.

Involving teams from a local children's hospice may be very beneficial to both the infant and their family. The PaNDR team can arrange transport of an infant planned for palliative care to a hospice or a unit closer to the infant's home. In the event that the infant has passed away before the hospice team was contacted, the hospice may still be able to offer help and support to the family.

In some cases, it may also be apparent soon after delivery that the prognosis of a baby is so poor that ongoing intensive care is likely to be futile. In these circumstances the baby should not be cooled, and it is usually inappropriate to separate the mother and baby by transferring to a regional NICU. These cases should be discussed with the PaNDR team and Regional NICU.

All parents whose child has died following neonatal encephalopathy should be offered a postmortem examination.

See **Appendix 4** for useful contacts for families.

7. Communication with Families

When a baby with HIE is admitted to the Neonatal Unit the parents must be fully updated by the most senior clinician available sensitively and openly. BLISS and PEEPS for HIE have suggested information that clinicians may wish to use when discussing aspects of HIE and therapeutic hypothermia with parents (Appendix 4). The decision to treat with cooling should be explained to the parents and the BLISS Parent Information Leaflet should be provided. All discussions with the parents about their infant's treatment should be documented clearly in the infant's notes.

Parents should be updated regularly and signposted to available information and support networks (see appendix 4). There is a whole section devoted for families on the neuroprotection website (**www.bebop.nhs.uk**).

There should also be no barriers to parents being with and caring for their baby, aiming for a culture of minimal separation. This will involve timely transfer of mothers after birth. Mothers should be encouraged and supported to express breast milk.

Every hospital should have their own risk pathways and review process followed. These babies are often reviewed under the HSIB. All parents whose baby has undergone therapeutic hypothermia should be offered follow up to reflect care (antenatal, intrapartum and postnatal care) and have opportunities to ask questions within the review process.

All parents whose child has died following neonatal encephalopathy should be offered a postmortem examination.

8. Prognosis

An assessment should be made of the likely prognosis into high, moderate and low risk of significant neurodevelopmental impairment, based on the baby's neonatal condition, the evolution of neurological examination, aEEG, MRI and where available, MRS.

If there is overwhelming clinical evidence of very poor prognosis before day 5, an MRI may not be required to support clinical judgement when counselling parents. Where MRI and 1H MRS are used for prognostication, clinicians should be aware of the confidence limits around point estimates of predictive values, and efforts made to translate uncertainties in appropriate ways for parents

Prognosis should be discussed with parents in a timely manner before discharge from the NICU and summarised in a written communication to parents and other health professionals.

Appendix 5 provides a guide to the prognostic value of early clinical, electrophysiological and imaging examination.

9. Follow up

The British Association of Perinatal Medicine (BAPM) and National Institute of Clinical Excellence (NICE) currently recommends that a standardised neurodevelopmental assessment such as Bayleys assessment should be carried out at approximately 2 years of age.

Babies in high and medium risk groups should have early assessments with experienced medical and/or Paediatric Allied Health Practitioners. This should be aimed at early detection of developmental problems with early intervention, to optimise outcomes.

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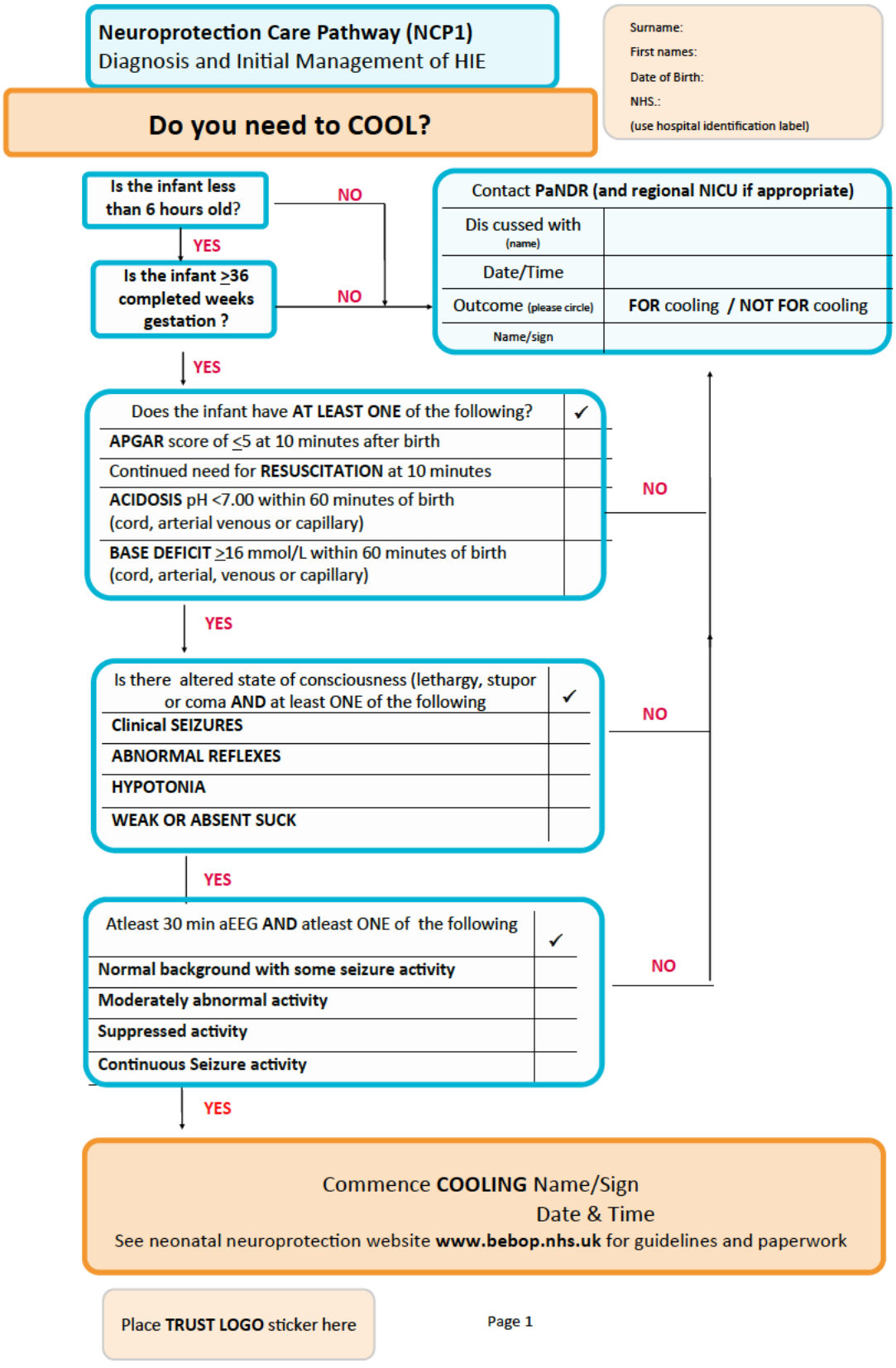
Appendix 1 – Neuroprotection Care Pathway (NCP1)



Neuroprotection Care Pathway (NCP1)
Diagnosis and Initial Management of HIE

Surname:
First names:
Date of Birth:
NHS.:
(use hospital identification label)

ADMISSION DETAILS

Time of Birth h h : m m
Gestation w w d d
Sex M F
Birth weight gm
Head circumference cm
Admission temp C

Resuscitated >10 minutes Yes No
First gasp (minutes)
Apgar Score (please write X if unknown)
1 min 5 min
10 min 20 min
Blood gas results *(worst set of results within 60 mins incl. cord blood)*
pH . pO_2 . kPa
pCO_2 . kPa Base deficit

Pregnancy complications: None or please give details Attach separate sheet if necessary

Mode of delivery: Pre-labour CS In labour CS SVD cephalic SVD breech Instrumental

Delivery complications: None or please give details Attach separate sheet if necessary

Congenital abnormalities apparent at birth: None or please give details Attach separate sheet if nec.

NEUROLOGICAL STATUS

Neurological Examination Time h h : m m

Domain	Stage 1 (mild)	Stage 2 (moderate)	Stage 3 (severe)
Conscious-ness	Normal Hyperalert	Lethargic Decreased activity in an infant who is aroused and responsive Irritable to external stimuli	Stuperose/ comatose Not able to rouse Unresponsive to exter-nal stimuli
Spontaneous activity	Active Vigorous does not stay in one position	Less than active Not vigorous	No activity whatsoever
Posture	Moving around Does not maintain only one position	Distal flexion, complete extension or frog – legged position	Decerebrate with or without stimulation (all extremities extended)
Tone	Normal – resists passive motion Hypertonic, jittery	Hypotonic or floppy, either focal or general	Completely flaccid like a rag doll
Primitive reflexes	Suck: vigorously sucks finger or ET tube Moro – Normal exten-sion of limbs followed by flexion	Suck: weak Moro: incomplete	suck: completely absent Moro: completely ab-sent
Autonomic system	Pupil – normal size Reactive to light Heart rate normal Respirations - normal	Pupils – constricted <3mm but react to light Heart rate: bradycardia (<100) Respirations: periodic irregular breathing effort	Pupils: fixed dilated, not reactive to light Heart rate: variable Respirations: apnoeic requiring IPPV
Seizure	none	Common focal or multifocal sei-zures	Uncommon (excluding decerebration) Or frequent seizures

Time Cranial USS done h h . m m

Resistance Index

US showed

Time CFM started h h m m

CFM showed

Place **TRUST LOGO** sticker here

Page 2

Neuroprotection Care Pathway (NCP1)
Diagnosis and Initial Management of HIE

Surname:
First names:
Date of Birth:
NHS.:
(use hospital identification label)

CLINICAL MANAGEMENT

CLINICAL MANAGEMENT CHECKLIST	✓	Sign/date/time
Actively manage blood pressure to maintain within normal range		ONGOING
Avoid hyper/hypocapnoea		ONGOING
Restricted fluids (unless clinically indicated)		
Maintain blood sugar within normal range		ONGOING

TRANSFER REFERRAL (IF REQUIRED)

TRANSFER CHECKLIST (for infants born outside of Regional NICU)	✓	Sign/date/time
Refer to PaNDR for transfer to Regional NICU ASAP		
Full handover to PaNDR including this form (original in local notes)		

PARENTAL INVOLVEMENT

PARENTAL INVOLVEMENT CHECKLIST	✓	Sign/date/time
Parents spoken to by the most senior member of the medical staff on site (information in HIE Guidelines)		
Parents given the opportunity to see the baby		
Parents given a Parental Information leaflet		
Parents receive a picture of their baby		

TEMPERATURE CONTROL

TEMPERATURE CONTROL CHECKLIST	✓	Sign/date/time
Continuous rectal temperature monitoring started		
Rectal temperature documented every 15 minutes (chart overleaf)		ONGOING

	Time	Team (Referring Unit / ANTS /Receiving Unit)
Passive Cooling: (time started)	h h : m m	
Active Cooling: (time started)	h h : m m	
Time TARGET TEMPERATURE consistently maintained (33.0°C-34.0°C)	h h : m m	

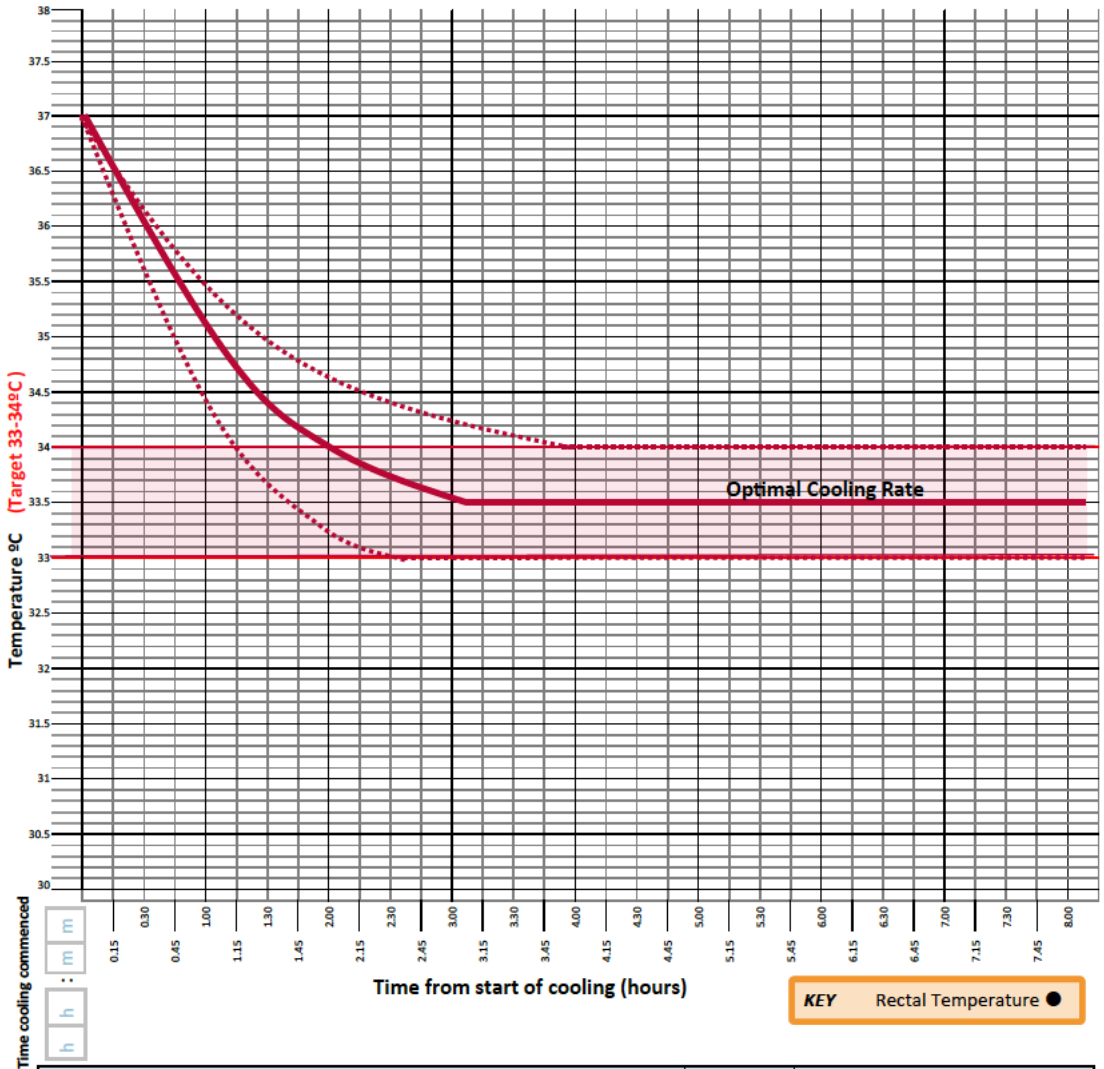
Place **TRUST LOGO** sticker here

Page 3

Neuroprotection Care Pathway (NCP1)
Diagnosis and Initial Management of HIE

Surname:
First names:
Date of Birth:
NHS.:
(use hospital identification label)

RECTAL TEMPERATURE MONITORING CHART IF PASSIVE COOLING USED



ACTIONS TAKEN TO ACHIEVE TEMPERATURE CONTROL	TIME	Sign/date
CAUTION from **34ºC** to avoid hypothermia (hat on, incubator to minimum)		

Place **TRUST LOGO** sticker here

Appendix 2 – Cooling Outside of Trial Criteria Guidelines

1. Cooling Outside Trial Criteria

There are several clinical circumstances where it may be appropriate to offer therapeutic hypothermia, despite the lack of clinical evidence in the form of RCT.

In all cases, the patient should be discussed with the PaNDR and regional NICU if appropriate BEFORE cooling is started.

The decision to offer cooling should be based on senior clinical judgment where any potential benefits of hypothermia outweigh any risks.

As outlined in the BAPM framework [4] parents should be informed about the risks and benefits of treatment along with the limitations of evidence, before it is started and the discussion documented in the clinical notes. However, it is not necessary to obtain written consent and it should be explained to the parents that it is neither 'experimental' nor part of a 'clinical trial/research study'.

1.1 Infants with mild HIE

Therapeutic hypothermia is NOT recommended outside clinical trials for treatment of mild HIE
There is no clear agreed definition of mild neonatal encephalopathy. There is some evidence that there may be increased neurological morbidity in this group of patients [29]. However, in the absence of any evidence of benefit, TH for the treatment of mild HIE is not recommended outside clinical trials [30].

1.2 Infants <36 weeks' gestation

Infants between 33+0- and 35+6-weeks' gestation may be considered for cooling after careful consideration and often seeking second opinion from an experienced consultant. There should be detailed documentation and discussion with parents explaining the risks of therapeutic hypothermia which may be increased in such late preterm infants and the limitations of evidence suggesting benefit [4].

There are currently no randomised clinical trials to support use of therapeutic hypothermia in infants less than 36 weeks. The mechanism of brain injury in infants >33 weeks' gestation following a period of hypoxia-ischaemia is likely to be similar to that of a later gestation, however the confounding factors of prematurity and infection may create a predisposition of features suggestive of HIE. Although the safety profile of hypothermia is relatively well established in term infants, this is not the case in late preterm infants [31]. A retrospective cohort study [32] found more deaths and potentially adverse events and trends for more brain injury detected by MRI among preterm infants who were cooled.

There is currently an ongoing RCT (NCT01793129) cooling preterm infants due to be completed in 2022.

1.3 Infants between 6 and 24 hours

Every effort should be made to identify and diagnose infants as soon as possible, but in rare cases where this does not happen within 6 hours, in the absence of evidence of harm or other available treatments, clinicians may decide to administer hypothermia in infants 6-24 hours of age [4].

NICHD trial on late hypothermia initiated between 6 and 24 hours after birth failed to complete and an interim analysis of data did not reach statistical significance [33].

1.4 Infants with congenital anomalies

Cooling should be considered on a case by case basis depending on underlying anomaly.

For obvious reasons this broad patient group was excluded from the clinical trials. When deciding whether an infant born with congenital anomalies who fit criteria A and B should be cooled the following should be considered:

- Is the condition life-limiting? ie would cooling actually alter the long term outcome?
- Would cooling impact on the anomaly? For example cooling may compromise blood flow to the gut in an infant with gastroschisis.
- Would the condition make it harder to assess criteria B? For example a baby with Down's syndrome may be hypotonic as a result of the underlying condition (this does not mean that a baby with Down's syndrome should not be cooled, just careful neurological assessment is necessary).

1.5 Infants presenting with sudden onset postnatal collapse (SUPC)

Infants presenting with postnatal collapse in the first 48 hours may be considered for cooling after ruling out any other cause of postnatal collapse and following a second senior opinion and discussion with parents explaining the potential risks and benefits [4].

There are currently no randomised control trials to support the use of TH in infants who have signs of moderate or severe encephalopathy following a postnatal collapse, and given the rarity of this condition high-quality trial data is unlikely to become available. However, many animal models of neonatal hypoxic-ischaemic encephalopathy that demonstrate the effectiveness of TH involve a postnatal insult. Moreover a cohort study indicated that the outcomes of infants cooled following postnatal collapse are similar to that of infants cooled for presumed HIE, providing circumstantial evidence that TH might be of benefit [34]. As the underlying conditions leading to SUPC are varied, including conditions in which TH may carry adverse risks, it is recommended that every effort is taken to understand any underlying reasons for collapse preferably before TH is initiated.

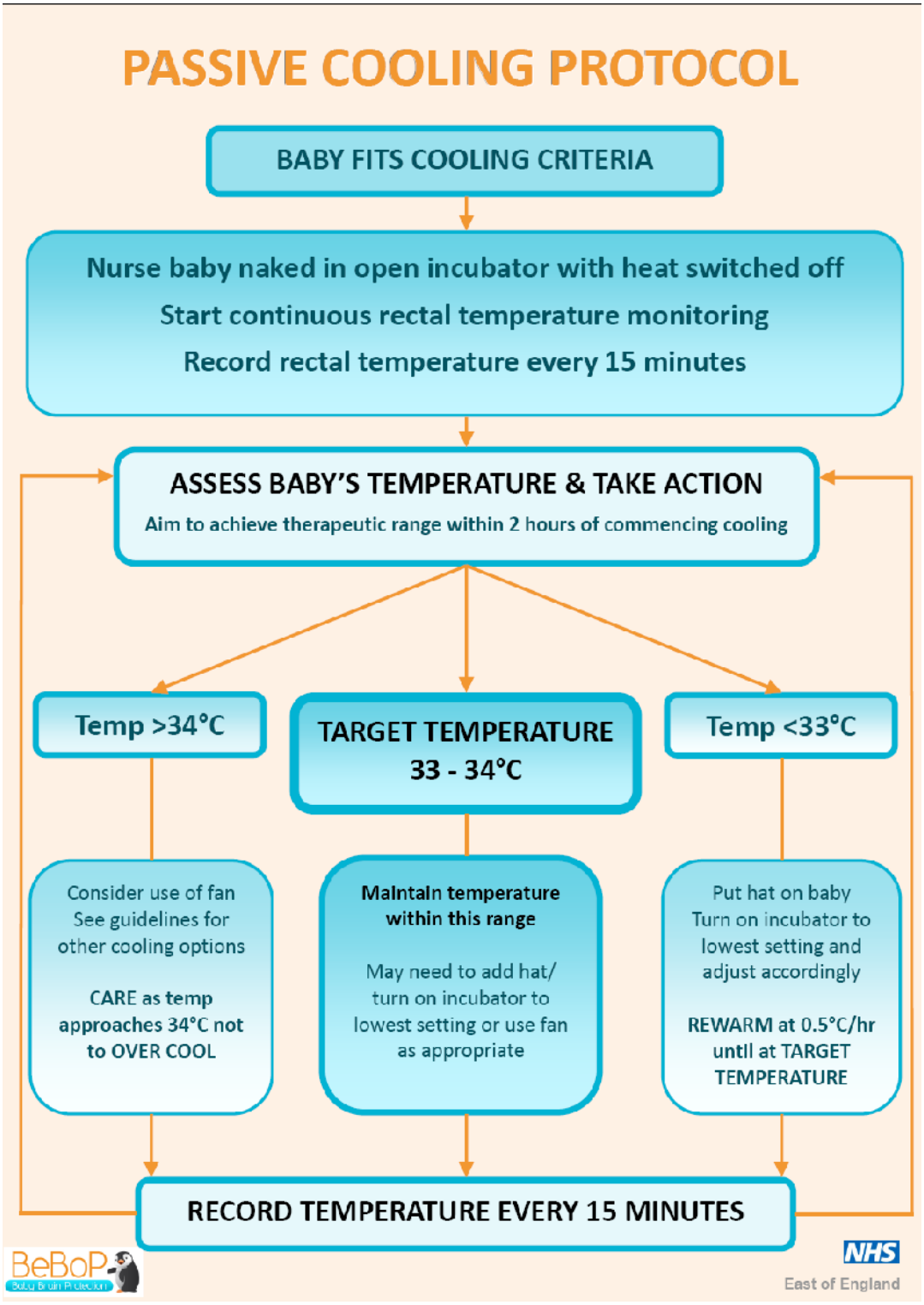
1.6 Infants presenting with neonatal stroke

Infants presenting with neonatal stroke should be considered for cooling only if the diagnosis is made early.

Animal studies have shown that cooling improves outcome after focal cerebral ischaemia and reduced the infarct size by 44% (95% CI: 40–47%).

The timing of cooling is important, in that hypothermia should be implemented within 2–3 h of ischaemia onset [35]. Recent evidence suggests that hypothermia is associated with a decrease in seizures and better language and cognitive outcome in newborns with encephalopathy and a focal infarct [36]. The main problem in the neonate is making an early diagnosis – these infants often present after 24 hours of age with seizures and are not encephalopathic and early ultrasound imaging can be difficult to detect the stroke. Therefore, it is possible that by the time the diagnosis is made the 'therapeutic window' has been missed.

Appendix 3 – Passive Cooling Protocol



Appendix 4 – Useful contacts and information when discussing about HIE/NE

Organisation	Description
PEEPS for HIE	UK wide charity, providing support to parent and families of those affected by HIE. Provide information, buddy support, counselling and funding for equipment. Email: info@peeps-hie.org Web: https://www.peeps-hie.org
ACT	UK wide charity working to achieve the best possible quality of life and care for every child and young person who is not expected to reach adulthood Helpline: 0845 108 2201 Web: www.act.org.uk
Bliss	For baby born too soon, too small, too sick – the special care baby charity, provides vital support and care to premature and sick babies across the UK. Helpline: 0500 618 140 Web: www.bliss.org.uk
Child Bereavement Trust	Provide specialised support, information and training to all those affected when a baby or child dies, or when a child is bereaved. Phone: 01494 568 900 Web: www.childbereavement.org.uk
Hospice	Children's hospices in the UK want the best possible care for children and young people who are not expected to live to reach adulthood and their families. Phone: 0117 989 7820 Web: www.childhospice.org.uk
Newlife	Provides practical support for disabled children throughout the UK, cares for the carers, funds medical research, creates awareness and campaigns for change. Phone: 01543 462 777 Web: www.newlifecharity.co.uk
SANDS	Stillbirth and neonatal death charity – supporting anyone affected by the death of a baby and promoting research to reduce the loss of babies' lives Helpline 020 7436 5881 Web: www.uk-sands.org
Scope	Support disabled people and their families through practical information and support, particularly at the time of diagnosis. Phone: 0808 800 3333 Web: www.scope.org.uk

Appendix 5 - Information for prognosis with HIE

Prognostic Indicator	
Response to resuscitation at birth	A number of clinical parameters reflecting the condition of the neonate at delivery are closely associated with subsequent outcome but individually they have poor predictive accuracy. A combination of clinical variables is more predictive of subsequent outcome than individual analyses. Shah et al [37] showed that inclusion of variables- (1) administration of chest compressions >1 minute; (2) onset of breathing > 30 minutes after birth; and (3) a base deficit value of >16 improved the predictive power of poor prognosis of the variables with PPVs, increasing linearly with each additional prognostic indicator reaching to 80%. Absence of all three of these prognostic indicators reduced the probability of severe adverse outcome to 20%. Data from NICHD [38] showed that the rate of death and/or disability at 6 to 7 years of age was 75% in those with 10-minute Apgar scores of 0 to 3 and 45% in children with scores of more than 3. However, one-fifth of the infants with Apgar score of 0 survived to school age without disability.
Clinical assessment of HIE	The presence of moderate or severe encephalopathy, however graded or scored, has a strong association with an adverse clinical neurological outcome (e.g. odds ratios for death or disability of > 20) [39]. However, the level of HIE may change over the first few days after birth and is affected by medication and biochemical abnormalities; therefore, the predictive accuracy of encephalopathy for subsequent neurological outcomes is variable. In the NICHD and cool cap study the best time for predicting death or disability was the grade of encephalopathy at 72 hours and at discharge. Severe encephalopathy persisting 72 hours after birth was associated with death or severe disability in 89% in the cooled group [40, 41].
aEEG	aEEG recorded within 6 hours of birth In the TOBY trial, the predictive value of aEEG within 6 hours of birth was lower in the cooled group than in the non-cooled group, (PPV of 55% vs 63%) [42]. Evolution of the aEEG following HIE aEEG changes during the first few days following asphyxia depending on the duration and severity of the insult. With therapeutic hypothermia, the optimal time to assess aEEG for prognosis is 48 hours, with the return to a discontinuous normal voltage, or a continuous normal voltage being associated with good outcome, particularly if sleep wake cycling is present. All infants with continuing abnormal aEEG at 48 hours had a poor outcome, despite cooling [43, 44].
EEG	Background EEG abnormalities, detected in the first few days of life after HIE can help provide further prognostic information Grade of abnormality predicts death/disability [45] Severe abnormality (burst suppression, low voltage or isoelectric) - 95% Moderate abnormality (slow wave activity) - 64% Mild or no abnormality - 3.5% Persistence of EEG abnormalities at 1 month of age is associated with a higher risk of neurologic sequelae
CUS	A normal cranial ultrasound scan can be reassuring whilst abnormalities in the thalamus and basal ganglia or evidence of cerebral edema are associated with abnormalities on magnetic resonance imaging (MRI) and abnormal neurodevelopmental outcome, but predictive accuracy is poor, with specificity of 0.55 (0.39-0.7) [46].

	Cr US is a poor prognostic indicator, with only a 79% (95% CI 37% to 97%) sensitivity and 55% (95% CI 35% to 70%) specificity for abnormal outcome [47] In healthy term infants in the first 24 hours, the average resistance index (RI) is 0.726 (SD 0.057). A reduction in RI to ≤0.55 is associated with poor outcome after HIE, although with cooling the positive predictive value falls from 84% to only 60% (95% CI 45% to 74%) and the NPV was 78% (95% CI 67-86%) [48]
MRI	Major MRI abnormalities were defined as moderate or severe basal ganglia or thalamic lesions, severe white matter lesions, or an abnormal posterior limb of the internal capsule [27]. In the randomised trials of therapeutic hypothermia the predictive accuracy of T1/T2 MRI in the cooled groups did not differ from that in the non-cooled groups suggesting that MRI can be used for assessing prognosis even following treatment with hypothermia [8, 14]. MRI within the first 2 weeks had a higher sensitivity of 88% (79-97%) and a lower specificity of 82% (72-92%) to predict long term outcome [27]. MRI obtained during TH has a sensitivity of 100% (95% CI 84% to 100%) to identify the presence and extent of later brain injury [49]. Proton MRS deep gray matter lactate/N-acetyl aspartate (Lac/NAA) peak-area ratio between 5-15 days after birth is a good indicator of severe deep gray matter injury and accurately predicts neurodevelopmental outcome at 18-24 months with specificity (90% (95% CI 84% to 94%) and sensitivity (87% (95% CI 70% to 98%) [28]

AUDIT STANDARDS

1. Therapeutic cooling within criteria (A, B, C)
2. Infants reach target temperature (33-34˚C) within 6hrs of life
3. Infants receive continuous rectal temperature monitoring throughout cooling (passive and active) and re-warming process
4. Infants are not overcooled (below 33˚C) or undercooled (>34C) by 6 hrs of age
5. Infants cooled using active cooling methods.
6. Infants undergo MRI at 5-14 days of age unless (Target 100%)
7. Neuroprotection Care Pathway completed in full (Target 90%)
8. All infants with moderate to severe HIE or received therapeutic hypothermia receiving formal neurodevelopmental assessment at 2 years of age and documentation on Badgenernet (target 100%)
9. Training- neurological examination, aEEG interpretation