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

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Guidance specific to the care of neonatal patients.

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I confirm that the guideline "HIE" was approved at the COG on the date above and consequently ratified by the ODN Board on the date stated.
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AUDIT STANDARDS

1. Infants reach target temperature (33-34°C) within 6hrs of life
2. Infants receive continuous rectal temperature monitoring throughout cooling and re-warming process
3. Infants are not overcooled (below 33°C)
4. Infants undergo MRI at 5-14 days of age unless clinical indications require it to be performed sooner (Target 100%)
5. Neuroprotection Care Pathway completed in full (Target 90%)
6. All infants with moderate to severe HIE or received therapeutic hypothermia should have formal neurodevelopmental assessment at 2 years of age (target 100%)

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 Perinatal Networks.

CONTENTS

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 documents. The care pathway integrates a checklist of steps that should be undertaken to ensure that cooling is safely initiated and maintained.

There are three parts to the Neuroprotection Care Pathway documents:

- **NCP 1: Diagnosis and Initial Management of HIE**
- **NCP 2: Transport of Infants with HIE**
- **NCP 3: On-going Management of HIE**

To allow for the most appropriate medical management of infants and accurate data collection, all sections of this form should be completed. Where an infant is born within a Regional NICU the transport sections will not be applicable. **The Care Pathway should travel with the infant with copies to remain in local notes. Copies of the care pathway should then be sent back to the local hospital on repatriation.**

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 (NE) is a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, sub normal level of consciousness and often seizures.

There are many potential causes of neonatal encephalopathy, the commonest of which is 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
- inborn errors of metabolism
- 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 infant refers to acute brain dysfunction following critical lack of cerebral blood flow and oxygen delivery. HIE causing moderate or severe encephalopathy occurs in approximately 2-3/1000 births [1] and may account for up to 40% of cases of cerebral palsy [2] it is consequently a very significant health care and financial burden to the NHS.

Infants with HIE are often very sick with multi-organ failure requiring intensive care. Current evidence shows that moderate hypothermia (33-34^{o}C) started within 6 hours after birth can improve neurological outcome at 2 years and at 6 years of age [3, 4] and is now recommended as the standard of care. However, cooling is not performed in isolation and should be part of a package of neurointensive 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. The 2016 UK NLS guideline recognises that term or near term infants with evolving moderate to severe hypoxic-ischaemic encephalopathy should be offered therapeutic hypothermia, which should be initiated and conducted under clearly defined protocols [5].

If it is apparent whilst in a resuscitation situation that a baby may be eligible for cooling (see section 3.2.1) then the overhead heat source should be switched off, but priority must be given to effective resuscitation of the infant, not to passive cooling until physiological stability has been achieved.

3.2. Therapeutic Hypothermia – Cooling

3.2.1. Criteria for Cooling

Infants with suspected HIE who meet the following criteria A and B should be considered for treatment with cooling: (See appendix 1 for identification flowchart)

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.

Infants that meet these criteria should be assessed for whether they meet the neurological abnormality entry criteria. Infants must fulfil one or both of the following criteria:

Criteria B

Moderate to severe encephalopathy, consisting of:

- Consciousness: Altered state of consciousness (reduced or absent response to stimulation)

AND at least one of the following

- Reflexes: Abnormal primitive reflexes (weak or absent suck or Moro response)
- Tone: Hypotonia

OR, Seizures (clinical or subclinical).

Seizures may be apparent on clinical examination (abnormal rhythmic movement of limbs, lip smacking etc.) but can sometimes be difficult to diagnose. The amplitude integrated EEG (aEEG) as recorded by a Cerebral Function Monitor (CFM) is able to detect most seizures including many seizures not apparent clinically – known as subclinical seizures. Although aEEG recording is not necessary to decide whether an infant should be cooled, early assessment with the aEEG can be helpful in suspected cases of seizures and provides valuable information on baseline activity with encephalopathy. If possible aEEG assessment should be performed prior to transfer to the Regional Cooling Centre.

If an infant **meets** these criteria, but cooling is NOT offered, the reasons for this decision including discussions with the Regional NICU 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, the Regional NICU should be contacted for further advice. Please see **Appendix 3** – Cooling Outside of Trial 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. There is limited evidence to support treatment with cooling in infants less than 36 weeks gestational age or with other conditions such as postnatal collapse or cerebral infarction. In the event of an infant falling outside published criteria for cooling, please see **Appendix 3**- Cooling Outside of Trial Criteria Guidelines and contact the Regional NICU 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 and the Regional NICU [6].

3.2.3. HIE Score

The severity of encephalopathy should be assessed using the criteria in **Table 1**. The initial score should be recorded on the NCP 1 (see Section 1) prior to starting cooling and then daily for the first four days after birth. All fields should be completed using the highest scoring option if a lower score cannot be elicited on examination (e.g. if ventilated and sedated).

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. Please see CFM Guidelines.

Table 1 - HIE Score (Modified Thompson Encephalopathy Score [7]

Sign	0	1	2	3	Score
Alertness	Alert	Irritable	Poorly Responsive	Comatose	
Tone	Normal	Hypertonia	Hypotonia		
Respiratory Status	Normal	Resp distress (Apnoea/ needing O_2)	CPAP or mechanical ventilation		
Reflexes	Normal	Hyperreflexia	Hyporeflexia	Absent Reflexes	
Seizure	None	Suspected	Confirmed electro-graphic Seizure		
Feeding	Normal (Breast/bottle)	Tube/nil by Mouth			

3.2.4. When to initiate cooling

Passive or active cooling should be started as soon as possible after resuscitation is completed and eligibility is confirmed (see section 3.2.1). Current evidence suggests that the maximum benefit can be derived from cooling when it is commenced within 6

hours of birth [8]. Currently there is no consensus regarding cooling beyond 6 hours and should be discussed case by case.

3.2.5. 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 (NICE/BAPM). These NICUs have facilities for providing full neuro-intensive care, recording the aEEG and carrying out appropriate investigations including neuroimaging.

3.2.6. Referral to EBS/ANTS

When an infant has been identified as suitable for cooling, the local Regional NICU may be contacted to provide advice regarding cooling. A referral should be made to:

EBS/ANTS – 01223-274274

as soon as possible who will locate a cooling cot and provide on-going 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 ANTS Team.

3.2.7. Passive Cooling

For all infants born in units without active cooling available, passive cooling should be commenced and continued until the infant is transferred. Please follow the Passive Cooling Flowchart, appendix 3 and the guidelines below*).* Ensure that the Neuroprotection Care Pathway "NCP 1" (see section 1) is completed as fully as possible prior to transfer.

Practical Guide to Passive Cooling (see Appendix 2)

- Infants with suspected HIE should be assessed to determine whether the criteria for offering cooling are met and the attending consultant should be informed.
- 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 (see Appendix 3)
- Monitor core temperature (rectal) continuously aiming for a core temperature of 33.5°C (range 33-34°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 [9]. 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 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.

The 72 hours of cooling is considered to have commenced when a temperature of 33-34°C has been reached and maintained.

3.2.8. Active Cooling

While it is relatively straightforward to achieve the target temperature using passive cooling techniques, active cooling methods are recommended for maintenance over 72 hours. Servo-controlled systems have been shown to minimise temperature fluctuations and are less labour intensive on nursing staff [10].

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 ANTS. Using a servo-controlled system active cooling to target temperature can be achieved safely within 30 minutes. Ensure that Neuroprotection Care Pathway NCP 1 is completed and that NCP 3 is commenced (see section 1).

Practical Guide to Active Cooling

- Infants with suspected HIE should be assessed to determine whether the criteria for offering cooling are met and the attending consultant should be informed.
- 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 (see Appendix 3)
- 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.

3.2.9. 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. Immunosuppression, coagulopathy, increased insulin resistance, electrolyte alterations are more likely to occur when core temperature falls below 31°C and are unlikely to cause significant clinical abnormalities at the temperature range used for neural rescue therapy [3].

Subcutaneous fat necrosis (SCFN) is a recognised complication of both perinatal asphyxia and total body cooling [11]. 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 [12].

3.2.10. Re-warming

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.

Re-warming may be associated both with peripheral vasodilation resulting in hypotension (see section 3.4) and also the re-emergence of seizures. aEEG should be continued till rewarming is over.

3.2.11. Alterations in the clinical condition of the infant

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

Infants whose clinical condition improves within 6 hours of birth and is no longer encephalopathic would not have been entered into the RCT's on cooling. Careful neurological assessment is essential to demonstrate that the infant does not meet criteria B. If cooling has been commenced it would be reasonable to slowly rewarm the infant. These infants should be carefully observed over the next 24 hours. Cerebral function monitoring is useful in these infants.

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

Infants whose clinical condition improves after 6 hours of birth and is already being cooled should continue cooling for 72 hours. If the infant fits criteria A and B at 6 hours of age then by definition they have moderate to severe encephalopathy and would have been included in the RCT's. If their clinical condition improves over the subsequent 72 hours then they would be in a good prognostic group, but in the trials these infants remained cooled for 72 hours.

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

Seizures can be regarded as the clinical sign of delayed energy failure. It is prevention of delayed energy failure which is thought to be the reason hypothermia is beneficial. Therefore, on-going 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[39].

3.2.12. Other aspects of clinical care to be completed along with cooling

- Obtain central access (UVC/UAC).
- Perform cranial ultrasound (CUSS) to investigate for any other major structural causes of encephalopathy. Discuss any unexpected findings with regional NICU.
- If available start aEEG monitoring.

3.3. Ventilation

Most infants who require cooling will initially require ventilation as a consequence of their encephalopathy or anticonvulsant medication. PaO_2 should be maintained between 6-10kPa and $PaCO_2$ between 5-7kPa. Avoid hyperoxaemia and hypocapnia: !severe hyperoxaemia with PaO_2 greater than 27kPa and hypocapnia with pCO_2 less than 2.6kPa are associated with poor outcome [13]. Hypocarbia can be treated with a longer endotracheal tube, in ventilated infants. Ventilator gases should be warmed and humidified in the normal way, according to unit policy.

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

Blood gases should ideally be taken from invasive arterial lines, as with cool peripheries the pH will be low on a capillary sample. Ensure the baby's core temperature is entered into the blood gas machine when running the sample to ensure temperature correction is made.

3.4. Cardiovascular Support

Cardiovascular instability is a common finding as seen by the occurrence of hypotension, metabolic acidosis and pulmonary hypertension. Although some of the pathologic mechanisms associated with asphyxia involve a loss of volume (usually blood), hypovolaemia is not consistently associated with asphyxia and in the face of poor myocardial function, which in HIE is often due to direct myocardial injury, volume replacement may worsen cardiac function.

Bradycardia (<100bpm) is normal during cooling as is a prolonged QT interval. It is important to maintain the temperature above 33^0C as there is a risk of ventricular fibrillation at lower temperatures. Arrhythmias that can happen during cooling usually resolve with re-warming.
If there is a rise in heart rate the infant may be distressed, in pain or it may be a sign of sepsis.

Blood pressure is used as a marker for systemic perfusion, however it is a poor predictor of low cardiac output and should not be the only criterion by which systemic perfusion is monitored. Assessment of the baby should include assessment of peripheral perfusion (capillary refill time, urine output and lactate can all be measures of this), establishment of whether hypotension is symptomatic of another problem including hypovolaemia or blood loss, sepsis or high mean airway pressure on mechanical ventilation. Echocardiography is useful to determine filling and contractility. Electrocardiography and biochemical markers may help in the assessment of myocardial dysfunction: cardiac troponin I is a marker of myocardial injury and serum levels have been shown to correlate with the clinical severity of HIE and with the need for inotropic support [14]. Cardiovascular support should be directed at improving cardiac contractility and systemic perfusion.

During the rewarming process, a rise in body temperature may cause hypotension by inducing peripheral vasodilatation. However, whenever hypotension occurs the cause should be investigated. If hypovolaemia is suspected an initial bolus of 10ml/kg of normal saline should be given and repeated if necessary. However fluid boluses should be used with caution in infants with HIE as myocardial function is often compromised and inotropic support should be considered early.

3.5. Seizures (see Seizure Guidelines)

Clinical seizures following HIE can be difficult to diagnose and treat. Seizures have been shown to be an independent risk factor for worse prognosis [15] and a recent study of infants undergoing therapeutic hypothermia found that seizure burden was associated with poor outcome [16].
All infants undergoing cooling should have continuous aEEG monitoring as subclinical seizures are common and may be the only evidence of abnormal electrical activity if the baby is muscle relaxed, or even following anticonvulsant therapy. Seizures should be treated if symptomatic i.e. associated with cardiovascular/respiratory instability, prolonged (>3mins) or frequent (3/hr). Accurate documentation of the timing in relation to aEEG trace of administered anticonvulsant drugs should take place.
Anticonvulsant therapy should be given intravenously to achieve a rapid onset of action and predictable blood levels. Drug levels are important when maintenance doses of these drugs are used. 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.

Standard first line therapy is phenobarbital followed by either phenytoin or a benzodiazepine. Prolonged or difficult to control seizures may respond to lidocaine or levetiracetam, however it is recommended that advice is sought from a paediatric neurologist in these cases. Other causes of intractable seizures in neonates should be considered, e.g. Pyridoxine deficiency and other inborn errors of metabolism.

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

3.6. Infection

Perinatal infection often co-exists with HIE. All babies should have a septic screen and be commenced on antibiotics (as per local policy) as soon as possible after birth until the results from blood cultures are available. It is important to consider viral infections such as herpes simplex. A clear history should be taken and the use of antiviral medications considered.

3.7. Impaired synthetic liver function/consumptive coagulopathy

Disseminated intravascular coagulopathy (DIC) is a significant risk after hypoxic injury to the liver. Liver function tests, clotting and platelets should be monitored regularly. Standard treatments (e.g. FFP, cryoprecipitate, platelets, vitamin K) should be given to treat disturbances in clotting or low platelets. If the infant already has DIC, cooling may increase the risk of thrombocytopenia. In these infants platelet count will decrease rapidly (within 24-48h) after platelet transfusion, suggesting increased destruction and intravascular sequestration.

In the event of clinically significant bleeding despite active management, aggressive correction of coagulopathy should ensue. If active bleeding is present it is important to exclude intracranial haemorrhage as this may necessitate neurosurgical management. In these instances it may be appropriate to re-warm the infant to prevent further deterioration in coagulopathy until the bleeding has stopped and/or diagnosis intracranial haemorrhage confirmed.

3.8. 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. 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.

3.9. Fluid Management

Renal function is likely to be impaired following severe perinatal asphyxia. The infant's weight, creatinine and electrolyte levels with urine output should guide fluid management. 40ml/kg/day is usually adequate intake for these infants. If they are in oliguric renal failure this may be dropped to 30ml/kg/day plus any measured losses, while maintaining adequate glucose intake (see below). Bolus infusions of saline may be required to avoid hypovolaemia if diuresis occurs or vasodilation occurs during re-warming.

Hypoglycaemia can be a considerable issue with infants with HIE. With fluid restricted to 40mls/kg/day of 10% dextrose, a total of 2.8mg/kg/min of glucose is administered. In view of this, higher dextrose concentrations are frequently needed. Central access should be obtained early to allow for this (a maximum of 12.5% dextrose can be delivered peripherally). Blood glucose must be regularly monitored and normoglycaemia maintained.

Care must be taken regarding the potential accumulation of nephrotoxic drugs such as aminoglycosides in the event of renal impairment.

3.10. Gastrointestinal

Commencing enteral feeds in infants during therapeutic hypothermia should be considered on an individualised basis taking into account the overall clinical status. Enteral feeds should be withheld in infants with significant multisystem involvement. Feeds should initially be increased according to the regional guidelines for high-risk infants. Early consideration of parenteral nutrition should be given in view of their initial catabolic state.

Advice and support for mothers regarding expressing and the impact of acute stress on milk production should be provided early in the course of the infant's management. Skin to skin contact should be initiated as soon as possible, even if the baby is nil by mouth or on trophic feeds. Ideally all babies with moderate to severe encephalopathy should be assessed before discharge by a Speech and Language Therapist (SLT) regarding oral feeding and assessing suck quality. For the babies in whom there are no concerns with chest, swallow function or suck following rewarming, oral feeds can be introduced by either breast or bottle (not cup/ syringe). If feasible, a SLT assessment should be undertaken in all infants where there have been concerns regarding chest status, secretion management, absent or minimal sucking or swallow behaviours noted.

3.11. Investigations

Table 2 – schedule for investigations

DAY ONE		**SUBSEQUENT DAYS**
1st line On admission	**2nd line Same day**	**Daily bloods**
Blood glucose		Daily FBC
Blood cultures	Troponin I* (peaks 6-12 hours post insult)	Coagulation if abnormal on day or clinical indication
Coagulation (PT/APPT/TT/Fibrinogen)		U&Es and LFTs Calcium and Magnesium
Arterial blood gas	Maternal Kleihauer if anaemic or history of APH	
Lactate	**To exclude other causes of neonatal encephalopathy consider:** Congenital infection screen •Lumbar puncture •Metabolic screen including ammonia, amino acids Urine for amino and organic acids, ketones, reducing substances •Genetic investigations *Placental histology can be very useful in aiding diagnosis and every effort should be made that this is sent off*	
FBC/film/platelets		
Hb/PCV		
U&Es and LFTs Calcium and Magnesium		
CRP		

4. Neurophysiology

4.1. Cerebral Function Monitoring (see CFM Guidelines)

The amplitude-integrated EEG (aEEG) is a single or dual channel time-compressed and filtered EEG, which is recorded on a cerebral function monitor (CFM). The aEEG provides useful information on overall global or hemispheric electrical activity. aEEG monitoring should ideally be commenced in the local unit. 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.

Continuous aEEG recording during the treatment period 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.

The decision to commence cooling should be made on the basis of criteria A and B (section 3.2.1). 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 which 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 provides information on regional background cerebral activity and can detect some seizures and other abnormalities not seen using aEEG. Severe hypoxia ischemia is typically associated with disruption of the 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.

Access to neurophysiology services both to perform and interpret the examination can be limited however. 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. The diagnosis of HIE can be complicated, and other disease processes, such as neonatal stroke may present in a similar way to HIE. CUS may help in diagnosis of a large intracranial bleed. For these reasons an infant with suspected HIE should ideally have a CUS prior to their transfer to a Regional Cooling Centre. Scans should be performed, including assessment of the resistance index, on admission, D1, D4 (post rewarming) and later if needed (depending on the MRI).

5.1.1. Resistance Index

During normothermia a reduced resistance index (<0.55) after 24 hours was associated with cerebrovascular vasodilatation and is linked with an increased risk of adverse outcome [17] The positive predictive value of the resistance index was just 60% (95% CI 45-74%) in infants treated with hypothermia for HIE, considerably less than that reported in normothermic infants [18]. The negative predictive value of the cerebral resistance index in the cooled infants was 78% (95% CI 67-86%) similar to that reported in non-cooled infants with HIE [18].

5.1.2. Possible CUS Findings in HIE

- Early cerebral oedema – generalised 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 echodensities.
- After day 7 cystic degeneration of the white matter.

5.2. Magnetic Resonance Imaging (MRI) (See MRI Guidelines)

MRI is the imaging modality of choice for assessing the distribution of injury and likely prognosis and to support a diagnosis of hypoxic-ischaemic encephalopathy.

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 may be being considered or where the clinical, neurophysiological, or ultrasound assessment is suggestive of another causes of encephalopathy (e.g. subdural haemorrhage or perinatal arterial ischaemic stroke).

The most accurate prognostic information can be obtained at 5-14 days of age. 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 [19]. More chronic hypoxia-ischaemia is associated with cortical and subcortical abnormalities. Further information on MRI scanning can be found in the MRI guidelines.

6. Withdrawal of intensive support

If a decision is made to withdraw intensive support, cooling should be discontinued and, if time allows, the baby re-warmed before intensive care is withdrawn. The discussions with parents preceding intensive support withdrawal should include the uncommon but possible outcome of long-term on-going survival after intensive support withdrawal in babies with grade 3 HIE.

Involving teams from a local children's hospice may be very beneficial to both the infant and their family. The ANTS 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 on-going 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 ANTS team and Regional NICU.

See **Appendix 2** for useful contacts for families.

7. Information for Families

When a baby with HIE is admitted to the Neonatal Unit the parents must be fully updated by the most senior clinician available. Please see **Table 3** for suggested

information that clinicians may wish to use when discussing aspects of HIE and therapeutic hypothermia with parents. The decision to treat with cooling should be explained to the parents and the 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**).

8. Prognosis and Follow up

The prognosis for infants with HIE depends on the evolution of encephalopathy over the first 72 hours and it can be difficult to assign prognosis until this time. Careful neurological examination is important and together with information from neurophysiology and imaging investigations can provide valuable early prognostic information. **Table 4** provides a guide to the prognostic value of early clinical, electrophysiological and imaging examination.

When counselling parents it is important to emphasise that it is never possible to be entirely confident regarding long term neurodevelopmental outcome based on early findings and to this end long term follow up is important to ensure that problems, if apparent, are identified early and appropriate referral to specialist services are made in an expedient manner. The British Association of Perinatal Medicine (BAPM) and NICE currently recommends that a formal neurodevelopmental examination should be carried out at approximately 2 years of age. It is possible that more subtle problems may emerge later in childhood.

Table 3 - Suggested information that clinicians may wish to use when discussing aspects of HIE and therapeutic hypothermia with parents. (Adapted from Statewide Maternity and Neonatal Clinical Guideline: Hypoxic-ischaemic encephalopathy, Queensland, Australia May 2010).

Criteria	Advice to parents
Resuscitation	Your baby needed significant resuscitation at birth to help him/her breathe. He/she appears to have suffered from the effects of lack of oxygen and blood supply to the brain
Incidence	About 2 in 1000 newborn babies suffer from the effects of reduced blood flow or oxygen supply to their brain around the time of birth
Consequences	This can result in brain damage from direct injury and also from on-going changes that begin around six hours after the injury. These secondary changes are known to increase the amount of brain injury that occurs
Prognosis	Approximately 30 to 60% of those babies who survive after this degree of damage to their brain may develop long-term disabilities. These disabilities include cerebral palsy and severe learning difficulties
Treatment	In the past there were no treatments to reduce the severity of brain injury in these newborn babies Research has shown that cooling these babies reduces the secondary brain injury, increases the chances of survival and reduces the severity of possible long-term disability

What does the treatment entail	Your baby will receive cooling therapy in addition to standard intensive care support. Your baby's temperature will be lowered and kept between 33 to 34°C for 72 hours. Cooling is achieved by exposing your baby to the ambient air temperature and/or subsequently by specialised cooling equipment Your baby's temperature and other vital signs will be closely monitored throughout the process. If your baby shows any signs of discomfort during cooling he/she will be prescribed medication to reduce this After 72 hours of cooling, your baby will be gradually rewarmed to the normal body temperature of 37°C

Table 4 - 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 [20] 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 NIHCD [21] 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.
Clinical assessment of hypoxic– ischaemic encephalopathy	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) [22]. 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 [23, 24].
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%) [25]. Evolution of the aEEG following asphyxia. aEEG changes during the first few days following asphyxia depending on the duration and severity of the insult. The duration of aEEG abnormalities correlates with neurological outcome: in mild cases, there is a rapid recovery of aEEG within 6 to 12 hours, and the prognosis is excellent. Most infants with continuing severe suppression of the aEEG beyond 24 hours (low voltage/flat trace patterns) ultimately have a very poor prognosis, with a high rate of death or severe neurodevelopmental abnormalities in survivors. Infants with prolonged intermediate abnormalities (moderately abnormal voltage or burst suppression pattern) have a more variable outcome. Treatment with hypothermia alters the prognostic value of aEEG within 72 hours of birth: All infants with continuing abnormal aEEG at 48 hours had a poor outcome, despite cooling [26, 27].

Prognostic Indicator	
EEG	Background EEG abnormalities, detected in the first few days of life after HIE can help provide further prognostic information Grade of abnormality predicts the rate of death or severe handicap [28] 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
Cranial Ultrasound	A normal cranial ultrasound scan can be reassuring whilst abnormalities in the thalamus and basal ganglia or evidence of cerebral oedema 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) [29]. Doppler cerebral flow velocity indices are commonly used as markers of cerebral perfusion. The PPV of the resistance index was just 60% (95% confidence intervals 45-74%) and the NPV was 78% (95% CI 67-86%) in infants treated with hypothermia for HIE [18].
MRI	The timing of scanning is important since the characteristic abnormalities detected by conventional MRI occur progressively over several days, and the severity of injury may be underestimated during the first few days after birth [30]. 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 [3, 6]. MRI within the first 2 weeks had a higher sensitivity of 98% (80-100%) and a lower specificity of 76% (36%-94%). Proton MR spectroscopy deep grey matter lactate/N-acetyl aspartate (Lac/NAA) peak-area ratio in the first 2 weeks had a pooled sensitivity of 73% (95% CI: 24-96% and 95% specificity (95% CI: 27-99%) [31].

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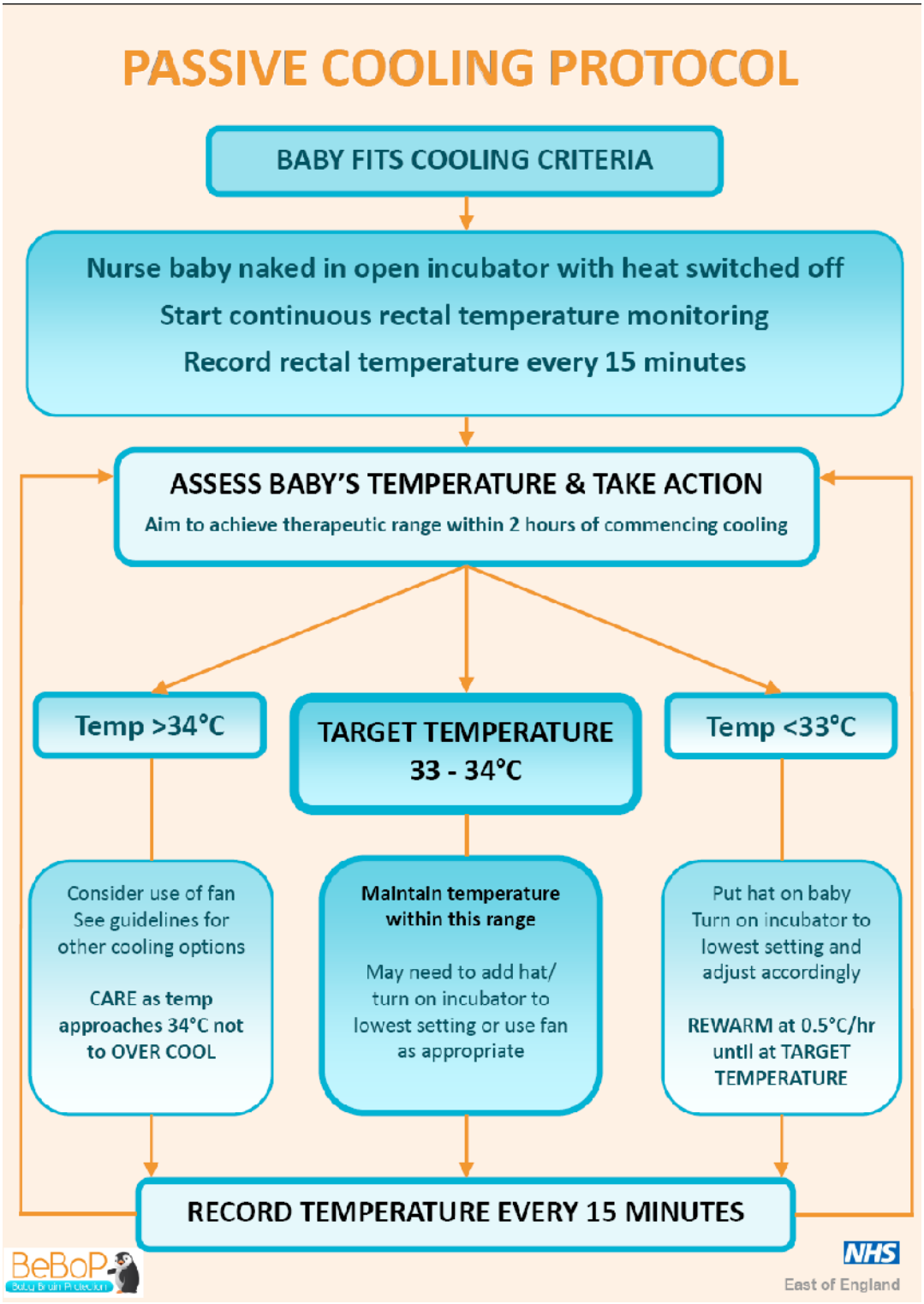
Appendix 1 – Passive Cooling Protocol



Appendix 2 – Useful contacts

Organisation	Description
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 Please see "ACT's neonatal care pathway for babies with palliative care needs" -
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 3 – 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. This includes:

- Infants <36 weeks gestation
- Infants > 6 hours old
- Infants with congenital anomalies
- Infants presenting as postnatal collapse
- Infants presenting with neonatal stroke

In all cases, the patient should be discussed with the regional cooling centre BEFORE cooling is started.

The BAPM position statement included a general point regarding the use of therapeutic hypothermia in infants who did not fit the clinical trial criteria:

'No data currently supports the use of cooling for neuroprotection in infants of lower gestational age or for other conditions such as sudden postnatal collapse or seizures thought to be due to acute cerebral infarction. Clinicians who choose to cool in these situations should be aware of the weak evidence basis for treatment in these circumstances and parents should be informed of this before treatment is started.'

In the discussions around the position statement it was acknowledged that there are many practices in neonatal medicine which also have a similarly weak evidence base and that in certain clinical circumstances and patient groups it will always be difficult to obtain a high level of evidence.

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

As outlined in the BAPM statement parents should be informed about the treatment 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 <36 weeks gestation

Infants between 34+0 and 36+0 weighing more than 1.8kg should be considered for cooling if the infant fits criteria A and B above.

The main clinical trials included term and 'near term' infants (36-37 weeks gestation). The mechanism of brain injury in infants >34 weeks gestation following a period of hypoxia-ischaemia is likely to be similar 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 [32]. A pilot study of hypothermia (33.5^{o}C-

35.5 °C) for 48 hours, on preterm infants with advanced necrotising enterocolitis showed no increase in mortality or morbidity [33]. In one of the original studies on the effects of hypothermia in preterm infants, the 'warm' infants, with lower mortality, in fact had axillary temperatures from 33.5°C-36.5 °C [34]. There is currently an on-going RCT (NCT01793129) cooling preterm infants between 32-36 weeks gestation with the standard HIE criteria due to be completed in 2020.

1.2 Infants >6 hours old

Infants between 6 and 12 hours of age should be considered for cooling; however beyond 12 hours of age there is little evidence of benefit from hypothermia.

The experimental studies tended to cool immediately after the hypoxic-ischaemic insult. For practical purposes the clinical trials had a 6 hour cut off. Although there was no significant difference in neurodevelopmental outcome between those cooled early and those cooled late there was a trend to favour those cooled earlier [40]. Experimental studies have shown a lack of benefit from delayed cooling [41]. Training and education should focus on early identification of infants who may benefit from cooling, however it would be reasonable to still offer this treatment to infants between 6 and 12 hours of age. The NICHD is currently undertaking a RCT on therapeutic hypothermia in infants aged 6-24 hours of age (NCT00614744) and is due to be completed in 2016.

1.3 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? i.e. 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).

1.4 Infants presenting with postnatal collapse

Infants presenting with postnatal collapse in the first 48 hours should be considered for cooling.

No clinical trials of therapeutic hypothermia have specifically addressed PNC. Nevertheless, we can anticipate beneficial effect of brain cooling, and some newborns have been treated, but the results have not been reported [35].

Small observational studies have shown that complication rates and long term outcomes do not differ significantly between the groups [36].

As with any case of neonatal encephalopathy an underlying cause must be sought (e.g. inborn error of metabolism).

1.5 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 [37]. 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 [38]. 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.

References

Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead: Date:	Signature of Trust Nursing / Medical Director: Date:
Hard Copy Received by ODN (date and sign):	Date acknowledgement receipt sent out:

Please email form to: mandybaker6@nhs.net requesting receipt.

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