Title:	**NWNODN Hypoxic Ischaemic Encephalopathy (HIE) Guideline**
Reference Number	**GL-ODN-03**
Main Author (s)	**Ian Dady and NWNODN Therapeutic Hypothermia SIG**
Target Audience	**NWNODN Neonatal Providers** **Connect NW/Cot Bureau**
Ratified by:	**TH SIG, SMT and NSG**
Date Ratified:	**26.01.22**
Review Date:	**26.01.25**
Version:	
Document status:	**Final**

Contents

Introduction

This clinical guideline has been developed to ensure appropriate evidence-based standards of care are achieved across the North West Neonatal Operational Delivery Network (NWNODN). Currently across the NWNODN all NICUs provide active Therapeutic Hypothermia (TH) as per service specification. A number of Local Neonatal Units (LNUs) are also accredited to initiate active TH prior to transfer to an appropriate NICU for on-going management and care.

This guideline has been developed and adapted based on previous TH guidelines in place across the NWNODN. We would like to acknowledge all the previous work that has been undertaken and thank everyone for their collaborative working in allowing this document to be developed. A list of all members of the TH Guideline subgroup and the wider TH Special interest group is available in Appendix 4. The expertise of all those within the group has enabled this guideline to be produced collaboratively.

Background

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

Therapeutic hypothermia (TH) is a treatment which aims to cool the brain to several degrees below the baseline temperature, to a target temperature between 33°C and 34°C, with the intention of preventing continued neuronal loss that occurs in the days after brain injury. Treatment is started as soon as possible after diagnosis, ideally within 3 hours of the insult, to optimise the neurological outcome. Therapeutic hypothermia is induced by whole body cooling using a cooling mattress. A rectal thermometer is used to measure the intracorporeal temperature as a proxy for brain temperature. The rectal temperature is measured continuously throughout the TH treatment. Treatment is usually undertaken for 72 hours after which point the infant is slowly rewarmed, over several hours, to normal body temperature.

Key Recommendations

Resuscitation:	•Cooling should only be considered once cardiorespiratory stability has been achieved including heart rate and oxygen saturation. Normothermia should be maintained during the resuscitation period whilst the assessment of HIE is taking place
Therapeutic Hypothermia:	•Babies with moderate to severe encephalopathy should be offered therapeutic hypothermia at the earliest opportunity, however babies with mild HIE should initially be maintained with normothermia but monitored carefully as the signs may evolve over the first few hours of life.
TH Assessment:	•In cases of mild HIE, TH assessment should include review by a senior clinician, regular neurological examination over at least the first hours of life and CFM monitoring with early discussion with a NICU/ Connect NW if features of moderate to severe HIE evolve as per the flow chart in Appendix 3
CFM Monitoring:	•All Neonatal Units should have or work towards obtaining CFM monitoring to support decision making for potential TH patients and corroborate the presence of seizures. The interpretation of this must be gestation specific when assessing any baby <36/40. CFM monitoring is encouraged and supported by the NWNODN.
Active Cooling:	•All Neonatal Units should have, or work towards, the capability of initiating active cooling using a servo - controlled system to provide a rapid and controlled means of achieving hypothermia. This will be encouraged and supported by the NWNODN using the agreed guideline.
Conference Calling:	•Connect North West (CNW) offer the opportunity for a conference call to be set up should a case need to be discussed in more detail, for example if the referring unit is unsure if the infant meets the criteria for treatment.
Parents:	•There should be early, regular and sensitive communication between a senior clinician and the family with the aim of minimising separation where possible

Therapeutic Hypothermia Referral Pathway

Infants who are ≥35^{+0} weeks gestation and demonstrate features of significant perinatal hypoxia ischaemia, but do not initially demonstrate any features of encephalopathy (see Appendix 1) may be observed on the NNU or the postnatal ward, depending on clinical condition, but MUST have regular neurological assessment. It is recommended that this assessment is undertaken on admission (or by 1 hour of age), and then repeated around 3,5 and 8 hours.

If there is any abnormality or evidence of encephalopathy the infant must be admitted promptly to a Neonatal Unit for further assessments. If this evolves into more definite HIE start CFM monitoring, if available, and passive or preferably active TH, if available.

All definite and suspected cases for TH should be referred *immediately* to Connect North West via the North West Cot Bureau. Clinical details will be taken with the option of a conference call, if necessary, to discuss, advise and develop a management plan for each baby on a case by case basis. Use the pathway in Appendix 3 to support actions.

NW Cot Bureau/ Connect North West Telephone number: 0300 330 9299

Decision to commence Therapeutic Hypothermia

Supportive decision-making tools for TH treatment are available in Appendix 1.

An assessment of HIE should be made for all infants of at least 35 weeks gestation who are admitted to the neonatal unit with features of significant perinatal hypoxia-ischaemia (Criteria A). This must include a full neurological examination and ideally the use of cerebral function monitoring to assess for Criteria B / C.

A TH referral should be made by an LNU/SCU or TH should be initiated in an NICU if an infant meets Criteria A and also exhibit a reduced conscious level and/or another neurological abnormality and/or CFM abnormalities (CRITERIA B/C).

A neurological examination record is available for use in Appendix 2 or via the NWNODN website

Infants who are identified as having significant HIE at or around 6 hours of age may be considered for TH provided the target temperature is likely to be achieved by 12 hours. Realistically this means the latest a decision to cool should be agreed is by 9 hours. All clinicians are urged to seek support via NICU and Connect North West colleagues to support conversation in such cases.

Once an infant is identified for TH; this should be initiated using a servo controlled active cooling system. If this is not available, then passive TH may be commenced until the arrival of the transport service.

"Grey" Cases or Evolving Presentation:

For any infant born in an LNU that falls in the following categories the decision to initiate should only be reached following a discussion between a consultant from the referring unit, a consultant at the receiving NICU and / or a neonatal transport ANNP or consultant. When considering Offering TH to patients that fall within these categories within an LNU the referring clinician must request that the North-West Cot Bureau set up a conference call to discuss patients on a case by case basis.

In all grey cases or in cases of evolving presentation, parents must be fully informed of the limited evidence base supporting treatment.

Whilst this guideline allows for a case by case judgement to be made following the involvement of senior clinicians, parents should be aware that the evidence base is weak and that a decision to cool is not mandated

Appendix 3 sets out a pathway for these cases.

Near Term Admissions

Therapeutic hypothermia is a standard of care for infant's ≥36+0/40 weeks. There is no high-quality evidence currently available that offering TH below 36 weeks is beneficial and concerns exist about a potential increase in adverse effects.

Infants who are >35+0 - 35+6/40 GA and meet the eligibility criteria can be considered for TH if there is a clinical consensus that TH may benefit the patient.

In this cohort TH should only be considered where the interval between the birth or initial hypoxic insult is 6 hours or less.

Sudden Unexpected Postnatal Collapse (SUPC):

TH may be considered for those infants who suffer a collapse requiring significant resuscitation whilst on the post-natal ward or neonatal unit during the first 72 hours of life. Evidence of a significant hypoxic ischaemic event and neurological abnormality should be sought using the usual eligibility and assessment criteria for TH. It is important to consider differential diagnoses such as sepsis, cardiac and metabolic disorders alongside TH assessment.

In SUPC cases TH should only be considered where the interval between the initial hypoxic insult is 6 hours or less.

Evolving / delayed presentation:

Current evidence suggests that TH is most beneficial within three hours of the initial insult and has limited benefits when started beyond six hours (Thorsen et al, 2015). It is possible that there may be a small benefit from providing TH in this group of patients however there is a paucity of research evidence for this. Infants who are just above the 6-hour threshold who fully meet the eligibility criteria may be considered for TH, providing that target temperature can be realistically achieved by 12 hours of age. In practice this means a decision to cool must have been reached by 9 hours of age.

Diagnosing HIE

The following points are useful when making a diagnosis of HIE:

- History of a sentinel event such as abruption or uterine rupture.
- History of foetal /intrapartum distress or acidosis.
- Low Apgar scores and/or delayed onset of respiration requiring resuscitation.
- Symptoms or signs of encephalopathy.
    - A characteristic feature of many cases of HIE is an *evolving* encephalopathy – babies get worse and then get better - this will require regular assessment and documentation by an experienced practitioner using a standardised template – an example assessment is available in appendix 2.
- Signs of multi-organ involvement usually occurs in association with a moderate to severe encephalopathy
- Measurement of Lactate levels:
    - An initial cord or admission lactate of >= 12 mmol/L or persisting high Lactate levels on subsequent measurements correlates with the severity of HIE and may provide a useful adjunctive marker.
- Exclusion of other likely causes of encephalopathy

HIE - Grading of severity

Neurological examination should be undertaken at regular intervals during the first 6 -12 hours of life by an experienced, competent practitioner and documented in the medical notes. Practitioners should have their competency assessed and maintained annually via local or network-based training.

Table 1 sets out the grading system recommended for use nationally and should be used alongside the Neurological Examination Record.

Table 1: HIE Grading of Severity (adapted from Sarnat and Sarnat)

Domain	Stage1	Stage2	Stage3
Seizures	None	Common focal or multifocal seizures	Uncommon (excluding decerebration) Or frequent seizures
Level of consciousness	Normal hyper alert	Lethargic Decreased activity in an infant who is aroused and responsive Can be irritable to external stimuli	Stuperose/ comatose Not able to rouse and unresponsive to external stimuli
Spontaneous activity when awake or aroused	Active Vigorous does not stay in one position	Less than active Not vigorous	No activity whatsoever
posture	Moving around and 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 extension of limbs followed by flexion	Suck: weak Moro: incomplete	suck: completely absent Moro: completely absent
Autonomic system	Pupil – normal size Reactive to light Heart rate normal >100 Respirations - normal	Pupils – constricted <3mm but react to light Heart rate: bradycardia (<100 variable up to 120) Respirations: periodic irregular breathing effort	Pupils: fixed dilated, skew gaze not reactive to light Heart rate: variable inconsistent rate, irregular, may be bradycardic Respirations: completely apnoeic requiring positive pressure ventilation

When therapeutic hypothermia is not appropriate:

Initiating and/or continuing TH treatment may not be appropriate in certain circumstances. If any clinician is unclear regarding the need to initiate or continue TH for any patient within an LNU or Special Care Unit (SCU) please call the North-West cot bureau *immediately* who will set up a conference call to discuss the management of the patient. Please see pathway in Appendix 3.

Babies with evidence of perinatal hypoxic ischaemia and either no or mild encephalopathy should not be considered for therapeutic hypothermia (except in the context of a clinical trial).

Examples of cases where TH may not be appropriate:

- up a conference call to discuss the management of any surgical infant that fulfils the TH criteria.
- Confirmed major congenital or chromosomal abnormalities or syndromes with long term poor prognosis. Infants with suspected or confirmed Trisomy 21 *should not* be excluded from TH treatment.
- Moribund infants with severe HIE not responding to resuscitation or intensive care.
- Babies with severe coagulopathy or PPHN unresponsive to full intensive care measures, including nitric oxide, may be considered for controlled rewarming
- Babies where perinatal brain trauma is strongly suspected as the cause of encephalopathy

Centres where Therapeutic Hypothermia should take place

Passive TH can be initiated in any neonatal unit and active TH in all NICUs and accredited LNUs, however all infants eligible for TH should be transferred to a regional Neonatal Intensive care unit (NICU) for ongoing care and treatment[7,12] NICUs have the facilities for providing full neuro-intensive care, recording aEEG and carrying out appropriate investigations including neuroimaging.

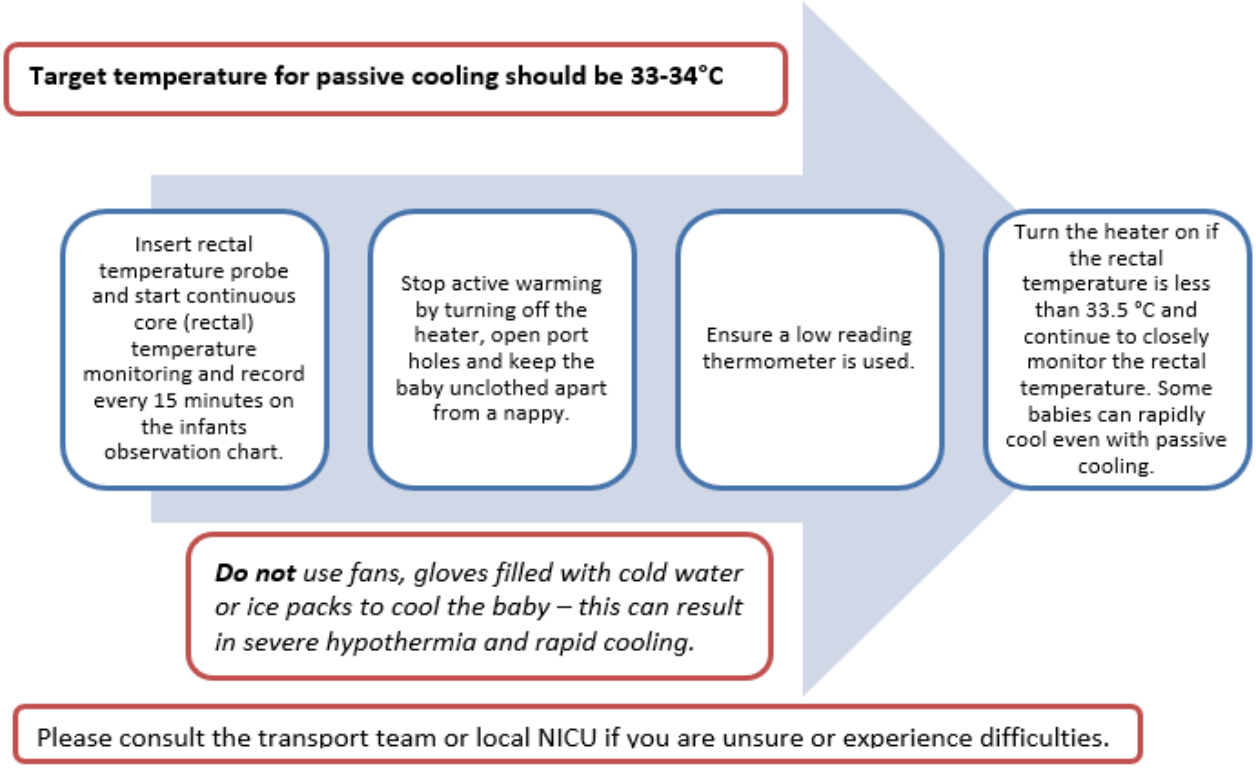
Babies born in poor condition outside of a hospital setting or within a setting without neonatal services on site, should be assessed early and identified as potentially in need of TH. They should be managed in a normothermic environment with attention to stabilising the airway and breathing whilst being transferred as an emergency to the nearest neonatal unit, where further assessment can be carried out.

Passive Cooling

Servo controlled active cooling provides a quicker, more predictable and controlled method of initiating TH. It is recommended that all neonatal units provide or work towards the provision of active TH with the support of the NWNODN.

For infants that fulfil the criteria for TH born in units that do not yet provide active cooling, passive cooling should be initiated and continued until the infant is transferred.

Practical Guide to Passive Cooling:



Risks and Precautions

- If axilla thermometers are being used in addition to rectal temperature monitoring, ensure a low reading thermometer is used to check axilla temperatures - some will have a lower limit which can potentially lead to false readings.
- Every effort should be made to avoid rapid cooling as a temperature below 33°C can be detrimental.

Active Cooling

If an infant is born in an LNU or SCU which provides active TH this should be initiated once the baby clearly meets the criteria and has been discussed with either an NICU or Connect NW. For those infants without active cooling available they will initially undergo passive cooling, active cooling will be initiated on transfer by Connect North-West, using a servo-controlled system.

TH equipment used across the NWNODN may be different and for this reason please follow your unit's own Active Cooling Guideline. It is recommended units download the temperature log from the active cooling equipment where possible to provide an accurate record of temperature management throughout the active cooling period.

LNUs and SCUs wishing to undertake active cooling will be supported to do so by the NWNODN and they will be required to demonstrate a robust education and training policy to support its use. Full details are available within the NWNODN guideline on LNU initiated Active Cooling.

Cerebral Function Monitoring (CFM)

It is recommended that all neonatal units have or work towards the provision of cerebral function monitoring. This will aid in decision making regarding whether to initiate TH treatment and provides corroboratory evidence to support the use of anticonvulsants in babies with suspected clinical seizures. CFM monitoring should be initiated before the onset of TH, for the duration of the cooling episode and up to 24 hours after re-warming where clinically appropriate.

Please refer to your local unit guidelines for use and interpretation of CFM monitoring. Local guidance should acknowledge the need for CFM interpretation in infants <36/40 to be gestation specific and interpreted with caution.

CFM recordings should be archived in a secure manner for future governance and medicolegal reviews. If possible live CFM recordings or snapshots should be made available for a second opinion via a secure IT portal.

Supportive Management

Monitoring

Monitoring throughout the TH and rewarming period should include:

- Continuous invasive blood pressure monitoring
- Continuous oxygen saturation monitoring
- Continuous respiratory monitoring
- Continuous electrocardiograph (ECG)
- Documented hourly observations including:
    - oxygen saturation
    - temperature (skin & rectal)
    - heart rate and blood pressure
    - respiration rate
    - urine output

Respiratory Support

Ventilate if poor respiratory effort, frequent apnoea, respiratory acidosis or severe hypoxaemia. If transferring a baby for TH, intubation to secure the airway during transfer may be necessary, however many babies will have normal lung function and can be readily overventilated.

The aim during ventilation is to maintain a normal pH Oxygenation and Co2, whilst avoiding hyperventilation and alkalosis. Infants can be extubated whilst being cooled if their respiratory drive is sufficient. Ensure that blood gas measurements are corrected for core body temperature by adjusting the blood gas analyser

Cardiovascular Support

Most cooled infants will have a resting heart rate of approximately 100 bpm or less.

Gain and secure central vascular access, both venous and arterial umbilical lines, ideally with a double lumen Umbilical Venous Catheter. Intra-arterial access is required to continually monitor systemic blood pressure. Once cooled it becomes difficult to insert peripheral lines and capillary blood gas analysis becomes unreliable

Hypotension is usually secondary to myocardial compromise from hypoxic-ischaemic damage rather than hypovolaemia and therefore volume expansion should be used cautiously. For management of hypotension please refer to local hypotension guidelines.

Investigations

Collect samples for Full Blood Count (including the nucleated red cell count) C Reactive Protein (CRP), Urea & Electrolytes, Ca, Mg, Liver Function Tests, group & save, cultures & clotting. Lumbar Puncture need only be considered if there is a suspicion of meningitis and is not a routine investigation in the management of TH. Cranial Ultrasound Scan should be undertaken within the first 24 hours if possible as the RI index can be used to prognosticate

Seizure management:

Please follow local seizure management guidelines.
Early use of amplitude integrated EEG (aEEG) with two or more channels to establish severity of encephalopathy is seen as best practice. If this is not available, then a discussion with the consultant prior to commencing anti-seizure medication should be undertaken as it may affect both the neurological examination and aEEG. TH may affect the metabolism of several drugs, including anticonvulsants and sedatives, and toxic drug levels may occur even with normal doses.

Clinical Practice Points – Seizure Management

- 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). There is no evidence that prophylactic anticonvulsants are of benefit and they should not be given.
- Detection of seizures is an indication for urgent review of blood sodium, glucose, calcium and magnesium.
- Use intravenous phenobarbital as first line treatment in babies undergoing TH, in a dose of 20 mg/kg given over 20 minutes. Repeat in a dose of 10-20 mg/kg to a maximum of 40 mg/kg if seizures continue. Note that in babies who are not ventilated respiratory depression can occur at these high doses
- In babies who do not respond to phenobarbital consider phenytoin IV 20 mg/kg over 30 minutes, Levetiracetam 20mg/kg IV over 15 minutes with repeat doses to a maximum of 40 mg/kg, or midazolam 150 micrograms/kg over 5 minutes followed by a continuous infusion of 60 micrograms/kg/hour (max 300 microgram/kg/h) being aware that midazolam levels will accumulate. Lidocaine has also been shown to be effective, but dosing should be modified in TH and avoided if phenytoin has already been given.
- 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.

Analgesia/Sedation:

TH is potentially distressing. Stress may have adverse effects in asphyxiated infants and may influence the therapeutic effect of hypothermia. Infants receiving TH should be commenced on morphine regardless of their ventilatory status to reduce shivering and any pain or discomfort experienced due to TH. Respiratory function must be monitored. Please refer to

local guidelines for neonatal pain assessment to support ongoing monitoring of infant's stress and pain during TH.

Fluid Therapy:
Infants should initially be commenced on 40-60ml/kg/day with this being reviewed daily on the consultant ward round. Fluid balance must be assessed on at least a 12 hourly basis and adjusted according to blood glucose measurement, serum sodium levels, daily weights and urine output. Regular blood glucose monitoring (at least 4 hourly in the first 24 hours) should be performed and blood glucose should be maintain >2.5mmols.

Anti-cerebral oedema therapy:
Infants should not be treated with steroids (other than for treatment of hypotension), or mannitol.

Nutrition:
Asphyxiated infants are at increased risk of Necrotising EnteroColitis (NEC), aspiration secondary to pharyngeal incoordination and transient milk intolerance due to reduced small intestinal motility. Minimal enteral feeds (MEN) or comfort feeds using breast milk via naso/orogastric tube may be commenced in infants receiving TH. Enteral feeds can be cautiously increased every 24 hours during TH if MEN was tolerated well. Once the infant is rewarmed, enteral feeding can be cautiously introduced once the initial biochemical and metabolic disturbances are corrected, bowel sounds are present and the gastric aspirates are minimal.

The decision to commence enteral feeding should be made by a consultant.

Coagulopathy:
Disseminated intravascular coagulation can occur in HIE and therefore clotting studies must be performed on day one in all babies. If normal no further samples will be required. If abnormal treat and repeat until normalised.

Infection:
A full septic screen including Lumbar Puncture should be considered and antibiotics commenced as meningitis may have similar presenting features and infection can be the underlying aetiological factor for HIE. Whilst there is little published evidence, CRP can be elevated in HIE without infection and must be interpreted with caution. Equally there may be a lag period in the rise of CRP levels in babies who are cooled.

Parent Communication

Early open and honest communication by senior members of the neonatal team with parents is an essential part of neonatal care, and there should be no barriers to this.

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.

Sensitive and open communication needs to be repeated throughout the patient pathway, with care being Family Integrated within the NWNODN Fi Care offer. The clinical team should be responsive to parents concerns and questions, and to the well- being of siblings and the wider family.

There should be timely multidisciplinary and multispecialty review of the perinatal care of the mother and baby of any infant who undergoes TH with a particular focus on avoidable factors. This should be discussed with parents in a timely open and honest way, meeting standards of GMC/NMC duty of candour

All parents whose baby has undergone TH should be offered follow up to reflect on antenatal, intrapartum and neonatal care, and the opportunity to ask questions within the review process. All parents whose child has died following intrapartum hypoxia-ischaemia should be offered a post-mortem examination.

Families should be offered support from local and national charitable organisations such as the NWNODN affiliated PEEPS-HIE as well as being offered links to BeBoP, and Hope for HIE where needed.
https://www.peeps-hie.org/
https://bebop.nhs.uk
https://www.hopeforhie.org/
https://spoons.org.uk/

The content of discussions with parents should be recorded accurately in the patient notes and this should be supplemented with an offer of written information. The results of prognostic investigations, such as MRI, should be shared with parents by the staff at the hospital undertaking this test, considering information from the local hospital. This may be facilitated using a secure healthcare videoconferencing system.

Neuroimaging:

Cranial ultrasound scanning should be undertaken ideally within 12 hours of birth or the hypoxic ischaemic insult. If there is a suspicion of traumatic brain injury then cranial CT also may be indicated.

There is strong evidence that magnetic resonance imaging (MRI) and spectroscopy (MRS) are reliable predictors of neurological outcomes in infants treated with therapeutic hypothermia, and provide parents and follow-on services with information to help plan ongoing care .The use and interpretation of both MRI and MRS requires specialist equipment and skills, and NICU units undertaking TH should ensure access to appropriate facilities and expertise. MRS is not currently available in the NWNODN.

All infants undergoing TH should have an MRI scan undertaken between 5 and 15 days, preferably between 5 and 7 days after birth. This would best be performed in the treating NICU and should be reported by a consultant radiologist with expertise in neonatal brain MRI interpretation.

Duration of Cooling

Infants should be maintained at the target temperature for 72 hours – this period is considered to have commenced when a rectal temperature of 33-34C has been attained.
In a few cases Cooling therapy maybe stopped prior to the 72h treatment time. The decision to terminate Cooling early must be made by a Consultant Neonatologist and the rationale for doing so must be clearly documented in the medical notes and discussed with the infant's family.

Follow up

All infants who receive cooling treatment should receive a 6-8-week clinic appointment at the local neonatal unit. Babies should be followed up in neonatal clinic for at least 2 years and receive a formal 2 year neurodevelopmental follow up. Further information regarding neonatal neurodevelopmental follow up can be found here: https://www.bapm.org/pages/146-bapm-special-interest-group-bannfu

Follow up MRI appointments should be arranged by the neonatal unit undertaking the follow up care.

Allied Health Professional Input

Babies and families experiencing HIE and TH are likely to need input from Allied Health Professional services including Dietetics, Speech & Language Therapy, Occupational Therapy, Physiotherapy and Psychology. It is essential that long term follow up is considered throughout the neonatal stay as both infants & families benefit from the support that this multidisciplinary team can provide in line with NICE guidelines.

References

1. Abbot R. Laptook, Seetha Shankaran, Namasivayam Ambalavanan et al. Prediction of Early Childhood Outcome of Term Infants using Apgar Scores at 10 Minutes following Hypoxic-Ischemic Encephalopathy. Pediatrics. Dec 2009; 124(6): 1619.
2. Allanson ER, et al (2016) Umbilical lactate as a measure of acidosis and predictor of neonatal risk: a systematic review. Available at:
3. *https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/1471-0528.14306*
4. Agut T, et al. Early identification of brain injury in infants with hypoxic ischemic encephalopathy at high risk for severe impairments: accuracy of MRI performed in the first days of life. BMC Pediatrics. 2014; 14(1):177.
5. Azzopardi D, Strohm B, Edwards AD et al. Moderate hypothermia to treat perinatal asphyxia encephalopathy. N Engl J Med 2009; 361:1349-58.
6. Azzopardi D et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ. 2010 Feb 9;340:c363
7. Balamurugan Thyagarajan. Minimal enteral nutrition during neonatal hypothermia treatment for perinatal hypoxic-ischaemic encephalopathy is safe and feasible. Acta Paediatrica 2015 Feb;104(2):146-51
8. BAPM (2020), Therapeutic hypothermia for Neonatal Encephalopathy: A BAPM Framework for Practice https://www.bapm.org/resources/237-therapeutic-hypothermia-for-neonatal-encephalopathy
9. Boudes E, et al. MRI obtained during versus after hypothermia in asphyxiated newborns. Archives of Disease in Childhood – Fetal and Neonatal Edition. 2015;100(3):F238-F42.
10. Heljic S (2018) Serial measurements of blood lactate and early outcome of neonatal hypoxic ischemic encephalopathy after therapeutic hypothermia, Clinical Research Trials, 2018 doi: 10.15761/CRT.1000223
11. Karlsson, M et al (2010) Lactate dehydrogenase predicts hypoxic ischaemic encephalopathy in newborn infants: a preliminary study. Available at: First published: 01 July 2010 https://doi.org/10.1111/j.1651-2227.2010.01802.x
12. Lomax R, Zipitis C, Dady I (2015) Cool & Transfer – the way forward. Journal of neonatal Nursing 21, pp114-120
13. Martinez-Biarge M, et al, Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy, Early Hum Dev (2010). doi:10.1016/j.earlhumdev.2010.08.013
14. National Institute for Health and Care Excellence, (2010), Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury, https://www.nice.org.uk/guidance/ipg347/chapter/1-Guidance
15. Shah DK, Wusthoff CJ, Clarke P, et al. Arch Dis Child Fetal Neonatal Ed 2014; 99: F219–F224.
16. Shah s, Tracey M, Smyth J (2004) Postnatal lactate as an early predictor of short-term outcome after intrapartum asphyxia. Journal of Perinatology . 2004 Jan;24(1):16-20.available at: https://www.ncbi.nlm.nih.gov/pubmed/14726932
17. Smit E, Liu X, Jary S, Cowan F, Thoresen M. (2015) Cooling neonates who do not fulfil the standard cooling criteria–short-and long-term outcomes. Acta paediatrica. Feb 1;104(2):138-45.
18. Skranes JH, et al. (2015) Brain imaging in cooled encephalopathic neonates does not differ between four and 11 days after birth. Acta Paediatrica.

19. Thorensen M. Effect of hypothermia on amplitude integrated Electroencephalogram in Infants with Asphyxia Paediatrics 2010 *126:* e130
20. Thoresen M. Who should we cool after perinatal asphyxia? (2015) Seminars in Fetal and Neonatal Medicine; *20:*66-71
21. UK TOBY Cooling Register Clinician's Handbook. Version 4, May 2010
22. UK Toby Cooling Register Clinician's handbook. V 4 May 2010. https://www.npeu.ox.ac.uk/toby/protocol
23. TOBY study protocol. https://www.npeu.ox.ac.uk/toby/protocol

Appendix 1 – Criteria Assessment

Criteria A:

CRITERIA A

Infants >36 completed weeks gestation[#] (with no exclusion criteria) admitted with at least one of the following features of perinatal hypoxia / ischaemia:

- Apgar score of <5 at 10 minutes after birth
- Continued need for resuscitation*, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis defined as an occurrence of **one or more** of the following:
    - pH <7.00
    - Base deficit >16mmol/l
    - Lactate >12 mmol/L

  in any cord or baby gas sample within 60 minutes of birth

Normothermia must be maintained throughout resuscitation

***Continued resuscitation = continued need for resuscitation including mask or endotracheal ventilation excluding infants who are receiving PEEP or CPAP alone.**
 # infants with gestational age between 35 and 36 weeks should be managed using the same initial steps but should be discussed on a conference call before any TH treatment is commenced.

An initial cord or admission lactate of >= 12 mmol/L or persisting high Lactate levels on subsequent measurements correlates with the severity of HIE and may provide a useful adjunctive marker[10,16].

A cooling referral should be considered if a baby also exhibits a reduced conscious level, and/or another neurological abnormality and / or CFM abnormality (CRITERIA B/C).

Initial Management for Baby meeting Criteria A:

Timeline	Assessment	Actions
0-1 hour age	Admit to Neonatal Unit Assess conscious level & neurology on admission / by 1 hour of age (Criteria B) Place CFM and assess for Criteria C after 30 mins Continue stabilisation Avoidance of pyrexia	Assess
1-6 hours age Reassess at 3 and 5 hours with Neuro exam	Persistently Reduced conscious level Another Neurological Abnormality ** CFM changes ***	Refer for cooling
	Normal conscious level without CFM changes or other Neurological	Observe

Criteria B/C:

Assessment of criteria B must be documented on a neurological examination assessment form and stored within the noted. An example of such a record is available in Appendix 2. Assessment of criteria C must be clearly documented within the medical notes and CFM trace information should be downloaded and stored.

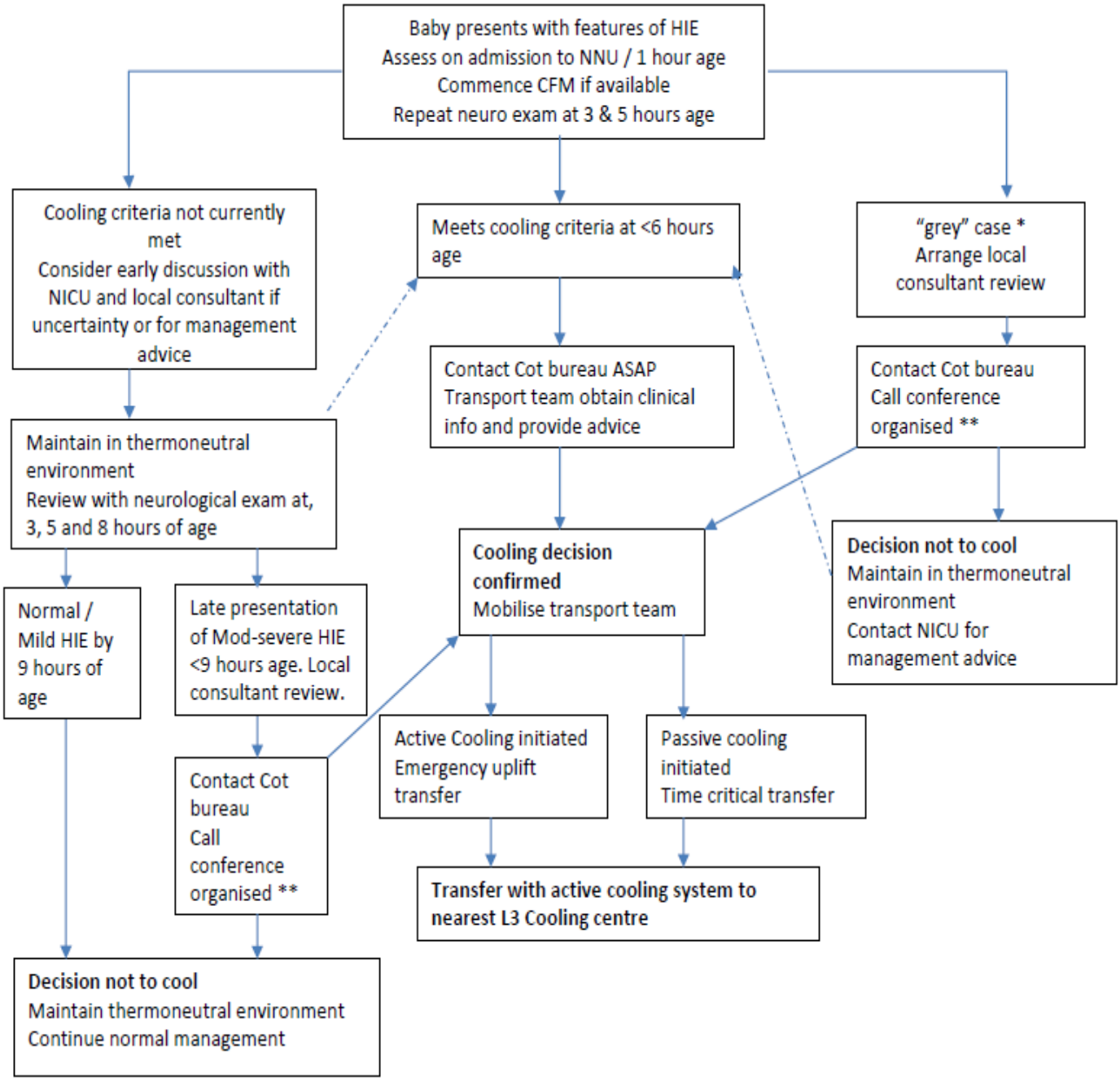
	Definitions
Criteria B	Reduced conscious level = Lethargy, Stupor or Coma **AND/OR** **<u>Another neurological abnormality</u> • Hypotonia • Abnormal reflexes including oculomotor or pupillary abnormalities • Absent or weak suck • Clinical seizures
Criteria C	***Gestation appropriate CFM changes **At least 30 minutes of CFM monitoring demonstrating any of the following:** • Normal background with some seizure activity • Moderately abnormal activity • Suppressed activity • Continuous seizure activity

Appendix 2 – Record of Neurological Examination

Patient Name		DOB		Birth Time		Time of Admission			
NHS Number			Exam 1	Exam 2	Exam 3		Exam 4	Exam 5	Exam 6
Assessment times:									
Age									
Anti-convulsant or sedative treatment commenced (please document in notes)									
Domain	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)	Please indicate severity of encephalopathy by denoting 1, 2 or 3 at each time point in the boxes below for each domain					
Seizures									
	None	Common. Focal or Multifocal	Uncommon, or frequent seizures						
Level of Consciousness									
	Normal or hyperalert	Lethargic. Decreased activity, irritability	Stupourose or Comatose. Unable to rouse, unresponsive to external stimuli						
Spontaneous activity when aroused									
	Active & vigorous	Less than active. Not vigorous	No activity						
Posture									
	Moves & doesn't stay in one position	Distal Flexion, complete extension or Frog leg position	Decerebrate (all extremities extended)						

Tone									
	Normal or hypertonic & jittery	Hypotonic & floppy, focal or generalised	Completely flaccid						
Primitive reflexes									
	Normal suck & Moro	Weak suck, incomplete Moro	Absent suck & Moro						
Autonomic system									
Pupils	Normal size, reactive	Small pupils, reactive	Fixed, dilated, not reactive or skew gaze						
Heart rate	Normal > 100	Bradycardia but variable	Variable rate, severe fixed bradycardia						
Breathing	Normal	Periodic breathing	Apnoeic - needs ventilation						
			Assessed By:						
			Role						
			Registration Number						

Appendix 3: Overview of pathway for complex or evolving cases



****Conference call to include**
Referring unit consultant
Cooling centre consultant
Transport ANNP / Consultant

***Grey cases may include:**
Gestation 35-36 weeks
Sudden unexpected postnatal collapse

Appendix 4:

Guideline Subgroup Membership:

Name	Trust	Role
Ros Garr	Whiston	Consultant
Sajit Nedungadi	St Marys	Consultant
Manigandan Chandrasekaran	LWH	Consultant Neonatologist
Ginny Wallace	LWH	Senior Sister
Christos Zipitis	WWL	Consultant
Holly Knapp	MFT	Senior Sister
Sarah Land	Peeps HIE	Parent

Cooling Special Interest Group Membership:

Name	Trust	Designation	Role
Ajit Mahaveer	NWNODN		Clinical Lead
Sarah Land	Parent		Parent representative
Shri Babarao	APH	NICU	Consultant
Ian Dady	CNW	Transport	Clinical Lead
Rachel Lomax	CNW	Transport	ANNP/Governance Lead
Jo Dangerfield	COCH	LNU	Consultant Paediatrician/Neonatal Lead
Kristi Penney	COCH	LNU	Nurse
Ruksana Patel	ELHT	NICU	ANNP
Charlotte Johnson	FGH	SCU	Sister
Mani Chandrasekaran	LWH	NICU	Consultant Neonatologist
Ginny Wallace	LWH	NICU	Nursing team Leader
Sajit Nedungadi	MFT - ORC	NICU	Consultant Neonatologist
Holly Knapp	MFT - Wyth	LNU	Sister
Beverley Knight	NMGH	LNU	Nurse - Educator
Clare Whitehead	NMGH	LNU	Nurse
Bivan Saha	NMGH	LNU	Consultant Paediatrician/Neonatal Lead
Michaela Halfhead	NWNODN		Education Lead
Lorraine Pilkington	ORMS	LNU	Sister
Archana Mishra	RBH	NICU	Clinical Lead
Chloe Walsh	RBH	NICU	Nurse team lead
Rubin Michael	RLI	LNU	Band 6 Nurse
Natasha Maddock	ROH	NICU	Consultant Neonatologist
Sarah McCullough	ROH	NICU	Consultant Neonatologist
Vicki Wheeler	ROH	NICU	Nurse Educator
Fazal Ur Rehman	ROH	NICU	Consultant Neonatologist
Laura Iley	WARR	LNU	ANNP
Ros Garr	WHIS	LNU	Consultant Paediatrician/Neonatal Lead
Christos Zipitis	WWL	LNU	Consultant Paediatrician/ Neonatal Lead
Sandeep Dharmaraj	RPH	NICU	Consultant Neonatologist
Sanjeev Rath	APH	NICU	Consultant Neonatologist
Angela Albiston	APH	NICU	ANNP
Helen Ewbank-Smith	APH	NICU	
Joanne White	RPH	NICU	Neonatal Nurse
Ranga Ranganna	MFT / CNW	NICU	Consultant
Francesca Patino	COCH	LNU	paediatric trainee
Emma Liggett	RBH	NICU	ANNP

Michael Rubin	MBHT	SCU	Neonatal Nurse
Kalwa Munthali	CNW	Transport	Consultant