Lothian NHS Board

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Date: 30/07/2026
Our Ref: 11490
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Dear

FREEDOM OF INFORMATION – NEONATAL PROCEDURES

I write in response to your request for information in relation to neonatal procedures in NHS Lothian.

Question:

We would be obliged if you could provide us with information in relation to any guidelines in place in July 2016 relating to neonatal cord gases, hypoxic ischemic encephalopathy and/or the requirement for resuscitation at the time of birth.

In particular, we would be obliged for a copy of any guidelines that were in place at the time showing what normal blood gas ranges would be, what monitoring ought to be undertaken if blood gases were abnormal, and when a patient should be referred to the neonatal unit/special care baby unit.

We would be obliged if this could cover both St John's Hospital and Royal Infirmary of Edinburgh if there were different guidelines in place for the two hospitals at that time.

Answer:

I have attached the relevant archived policies and procedures which were in use during 2016 and which are still available. Not all policies and procedures from 2016 have necessarily been retained, therefore this may not be a complete list of policies and procedures in place at the time.

Scottish Cooling Group Neuroprotection Care Pathway – both Royal Infirmary of Edinburgh and St John's Hospital, September 2015.

Cord PH Procedure – Royal Infirmary of Edinburgh, 2014.

Newborn Observation Chart – Royal Infirmary of Edinburgh, December 2014.

I hope the information provided helps with your request.

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Chair Professor John Connaghan CBE
Chief Executive Professor Caroline Hiscox
Lothian NHS Board is the common name of Lothian Health Board

If you are unhappy with our response to your request, you do have the right to request us to review it. Your request should be made within 40 working days of receipt of this letter, and we will reply within 20 working days of receipt. If our decision is unchanged following a review and you remain dissatisfied with this, you then have the right to make a formal complaint to the Scottish Information Commissioner within 6 months of receipt of our review response. You can do this by using the Scottish Information Commissioner's Office online appeals service at https://www.foi.scot/appeal. If you remain dissatisfied with the Commissioner's response you then have the option to appeal to the Court of Session on a point of law.

If you require a review of our decision to be carried out, please write to the reviewer at the address at the top of this letter. The review will be undertaken by a Reviewer who was not involved in the original decision-making process.

FOI responses (subject to redaction of personal information) may appear on NHS Lothian's Freedom of Information website at: https://org.nhslothian.scot/FOI

Yours sincerely

ALISON MACDONALD
Executive Director of Nursing Midwifery and AHPs
Cc: Chief Executive

Cord pH

- Labour ward staff now perform cord blood gas analysis on all newborn infants.
- Medical Paediatric staff called to deliveries, should document the cord pH of the babies with their resuscitation notes.
- If the cord pH is less than 7.0 and the baby required resuscitation at delivery, the baby should be admitted to the neonatal unit for observation. The Paediatric Registrar should review the baby and document their examination particularly CNS examination. These babies will require a repeat blood gas and blood sugar measurement. (Link to cooling guideline)
- A small number of infants will be born who appear completely well but have surprisingly low cord pH.
- If the cord pH is less than 7.0, and no resuscitation required at delivery, even if the infant appears completely well, the Paediatric Registrar should review the baby and document their examination particularly CNS examination within an hour after the delivery. These infants should get an early feed and should get a repeat blood gas and blood sugar measurement at around four hours of age. For the first four hours of life they should have hourly Nursing observations recorded (heart rate, respiratory rate, colour).
- If the cord pH is above 7.0 and the baby is completely well, no further action is required.
- Regardless of the cord pH, any infant who is causing clinical concern for any reason should be reviewed by the Paediatric Medical staff if requested and an appropriate plan made.
- Fill in a critical incident report form

SCG

SCOTTISH COOLING GROUP

Neuroprotection Care Pathway for the Management of Infants with Hypoxic-Ischaemic Encephalopathy

The Scottish Cooling Group

September 2015

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Disclaimer

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach.

Information in this guideline is current at time of publication.

The Scottish Cooling Group does not accept liability to any person for loss or damage incurred as a result of reliance upon the material contained in this guideline.

Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each specific patient case.

Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible to:

- Discuss care with parents in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct
- Apply standard precautions and additional precautions as necessary, when delivering care
- Document all care in accordance with mandatory and local requirements

Document Properties

Policy	**Care Pathway for Management of Infants with Hypoxic Ischaemic Encephalopathy (HIE)**
Document Purpose	For use in Scottish Maternity and Neonatal units and by the Scottish Neonatal Transport Team
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Superseded Docs	All current local, regional and transport guidelines for the management of HIE
Timing	With Immediate Effect
Contact details	Dr Julie-Clare Becher on behalf of the Scottish Cooling Group, Department of Neonatology, Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh Tel: 0131 536 1000 Email: julie-clare.becher@nhslothian.scot.nhs.uk

1. Neuroprotection Care Pathway for the Management of Infants with Hypoxic-Ischaemic Encephalopathy

1.1 Purpose of pathway

This pathway has been designed to inform the diagnosis, referral, transport and management of infants with moderate and severe hypoxic-ischaemic encephalopathy who are born and/or treated in Scotland.

This pathway has been devised to ensure safe, timely and high quality care is available to all infants who may be eligible for therapeutic hypothermia. Guidelines have been developed in accordance with the main treatment principles of the TOBY protocol (http://www.npeu.ox.ac.uk/toby) and with the East of England Perinatal Network Cooling Pathway. It has been endorsed from representatives in Cooling Centres, referring maternity units and the Scottish Neonatal Transport Service (Appendix 1).

The pathway gives guidance in the following areas:

1. Diagnosis and management of HIE
2. Referral and transport of infants with HIE
3. Ongoing management of infants with HIE undergoing therapeutic hypothermia

1.2 Audit standards

1. Infants identified as eligible should have access to therapeutic hypothermia
2. Infants reach target temperature (33-34˚C) within 6hrs of life
3. Infants receive continuous rectal temperature monitoring throughout servo-cooling and the re-warming process
4. Infants are not overcooled (below 33˚C)
5. Infants undergo MRI at 5-14 days of age, with image acquisition and reporting informed by current professional guidance (BAPM 2015)
6. Infants undergo neurodevelopmental follow up to the age of 2 years

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.

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)

HIE is the term used to describe babies who have a neonatal encephalopathy **AND** convincing evidence of antepartum or intrapartum hypoxia (criteria as outlined by the International Cerebral Palsy Taskforce, MacLennan A). HIE in the term infant results from an acute shortage of oxygen and blood flow in the perinatal period resulting in depression at birth and ongoing encephalopathy. HIE causing moderate or severe encephalopathy occurs in approximately 2/1000 births (Levene, MI) and the risk of death or cerebral palsy in survivors is around 60%: 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 mild hypothermia (33-34ºC) can improve neurological outcome at 2 years (Edwards AD) 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 tem follow-up of surviving infants (BAPM 2010, NICE).

This guideline will focus on the management of HIE and not the other causes of neonatal encephalopathy.

3. Early Clinical Management of the Infant with HIE

3.1. Resuscitation

Resuscitation should be carried out following the Newborn Life Support (NLS) or Newborn Resuscitation Programme (NRP) guidelines. Resuscitation should be initiated using room air. The 2010 International Liaison Committee on Resuscitation (ILCOR) consensus statement recognised 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.

In a resuscitation situation it may become apparent that a baby may eligible for cooling (see section 3.2.1), but priority must be given to effective resuscitation of the infant, not to passive cooling until physiological stability has been achieved. The decision to start passive cooling should always be made by a Consultant or senior Specialty Doctor (not a doctor in training) and if made in the resuscitation room then the overhead heat source should be switched off. At non cooling centres the decision to passively cool can be made by a local Consultant or senior Specialty Doctor in conjunction with early discussion with the Cooling Centre.

At all times during resuscitation of an asphyxiated infant and pending decision to cool, hyperthermia should be avoided. In clinical trials of hypothermia, hyperthermia ($\geq$ 38ºC) has been shown to be associated with adverse brain outcomes.

Principles

- Resuscitation should be carried out following Newborn Life Support (NLS) or Newborn resuscitation Programme (NRP) guidelines
- Decision to start passive cooling should always be made by a Consultant or senior Specialty Doctor in conjunction with the Cooling Centre

- Hyperthermia should be avoided

Note that the availability of cooling as a later treatment should not alter decisions made during initial resuscitation at birth and that to this end the usual criteria for discontinuing resuscitation still apply. The long-term outcome in surviving infants with an Apgar score of zero at 10 minutes of age is generally extremely poor and historically over 95% of such infants die or suffer severe disability (Harrington DJ). The influence of therapeutic hypothermia on outcome in these infants is not clear but in one large multicentre trial of normothermia vs hypothermia, a quarter of such infants who were successfully resuscitated, were alive and well at follow up (Laptook AR, Natarajan G). Although in the current ILCOR 2005 guidelines it is considered justifiable to stop resuscitation if there are no signs of life after 10 minutes of continuous and adequate resuscitation (ILCOR), this predates this new evidence which might suggest that a resuscitation time of greater than 10 min should be advised for infants going on to receive cooling.

3.2. Assessing eligibility for Therapeutic Hypothermia

3.2.1 Criteria for cooling

Infants with suspected HIE who meet the following criteria should be considered for treatment with cooling:

Criterion A. Infants ≥ 36 completed weeks' gestation and ≥ 1.8kg 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:

Any baby with a cord or initial pH of 6.7 or below should be cooled if they have required any resuscitation at birth, irrespective of early encephalopathy or CFM changes. This is because over 80% of such infants will go on to develop seizures and encephalopathy in the first day of life.

Criterion B: Moderate to severe encephalopathy, including ALL of the following features*:*

- Consciousness: Altered state of consciousness (reduced or absent response to stimulation)
- Reflexes: Abnormal primitive reflexes (weak or absent suck or Moro response)
- Tone: Abnormal tone (focal or general hypotonia, or flaccid)

All of the above and/or seizures (see below) should be present for the achievement of the encephalopathy criterion. Note that sedation, anticonvulsants and prematurity may alter consciousness, reflexes and tone.

The table below provides extended detail to the above criteria and defines the differences in symptoms between moderate or severe encephalopathy. It is a guide for recording the grade of

encephalopathy in the clinical record at the onset and throughout cooling, and for informing audit. It can be used in conjunction with or as an alternative to the Modified Thompson Encephalopathy Score, Table 2 (Thompson CM).

Table 1. Features of moderate and severe HI encephalopathy

Category	Moderate	Severe
Level of consciousness	Lethargic	Stupor/coma
Spontaneous activity	Reduced May be seizures	No activity May be intractable seizures
Posture	Distal flexion/complete extension	Decerebrate
Tone	Reduced	Reduced, flaccid hypotonia
Primitive reflexes:		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system:		
HR	Bradycardia	Variable
RR	Periodic	Apnoeic
Pupils	Constricted	Deviated/dilated/nonreactive

Seizures (clinical or sublclinical)

Seizures may be apparent on clinical examination (abnormal rhythmic movement of limbs, eye deviation, lip smacking etc) but can often be difficult to diagnose. The Cerebral Function Monitor (CFM) is able to detect most seizures including many seizures that are not apparent clinically – known as subclinical seizures. Although a CFM should ideally be performed on all infants with moderate-severe HIE, it is not mandatory prior to starting cooling and may not be available in all units. An initial tracing of around 30 minutes allows assessment of trend, and interpretation of artefactual features.

Where CFM is used, features supportive of initiating or continuing with cooling include:

- Normal background with some electrical seizure activity
- Moderately abnormal activity (upper margin of trace >10μV and lower margin of trace <5μV
- Suppressed activity (upper margin of trace <10μV and lower margin of trace <5μV)
- Continuous seizure activity

In the event of an infant **not meeting** the criteria for cooling but where the local clinicians feel cooling may benefit the infant, the Cooling Centre should be contacted for further advice. Please see Appendix 2 (Cooling Outside of Trial Criteria Guidelines).

3.2.2. Exclusions

If an infant meets the inclusion criteria, but cooling is NOT offered due to also meeting the exclusion criteria, the reasons for this decision (including discussions with the Cooling Centre) should be clearly documented in the medical notes. It is highly recommended that where possible all such decisions involve the Cooling Centre.

Cooling is not appropriate if:
There are other abnormalities indicative of poor long term outcome eg trisomy 18.
Infants who are likely to require surgery during the first 3 days after birth should be discussed with the Cooling Centre and the Surgeon at an early stage as cooling may still be feasible whilst the infant undergoes surgery or the surgery may be delayed to accommodate neuroprotective interventions.

Cooling may not be appropriate if:
The infant appears 'moribund' (dying despite intensive care efforts) or has features indicating brain death in the absence of sedation or paralysis (including fixed dilated pupils and absent respiration, primitive reflexes, spontaneous movements and response to pain) such that further treatment is likely to be futile.

Cooling may be appropriate if:
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 2 (Cooling Outside of Trial Criteria Guidelines) and contact the Cooling Centre for further advice.

3.2.3. HIE Score

The severity of encephalopathy should be assessed at the beginning and throughout cooling using the criteria in Table 2, (Modified Thompson Encephalopathy Score, Thompson CM). There is no specific score threshold that indicates treatment with cooling, but by scoring the infant daily a clinical picture is built up. The initial score can be recorded prior to starting cooling and then 12-24hourly for the first four days after birth on Badgernet. 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 CFM monitoring is needed.

Table 2. Calculating the HIE score

HIE Score	0	1	2	3	Score
Alertness	Normal	Irritable	Poorly Responsive	Comatose	
Tone	Normal	Hypertonia	Hypotonia		
Respiratory Status	Normal	Resp distress (Apnoea/ needing O2)	CPAP or mechanical ventilation		
Reflexes	Normal	Hyperreflexia	Hyporeflexia	Absent Reflexes	
Seizure	None	Suspected	Confirmed clinical Seizure		
Feeding	Normal	Tube/nil by Mouth			

3.3 When to initiate cooling

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. Cooling is unlikely to be beneficial if started more than twelve hours after the insult. Please see Appendix 2 (Cooling Outside of Trial Criteria Guidelines) for guidance if the infant is older than 6 hours.

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 Cooling Centre (NICE, BAPM 2010). These NICUs have facilities for providing full neuro-intensive care, recording the aEEG, carrying out appropriate investigations including neuroimaging e.g. MRI and in the prognosis of brain injured infants and subsequent counselling (Appendix 3. Standards for Cooling Centres).

4. Referral of a baby to a Cooling Centre

When an infant has been identified as eligible for cooling, the local Regional NICU should be contacted as early as possible to provide advice regarding cooling. In the West of Scotland the Perinatal Advisory Service will advise the location of the nearest cooling cot. If the infant is accepted by the Cooling Centre, a referral should be made to the local transport team by the usual route. The Cooling Centre will provide ongoing advice to the referring unit regarding management whilst preparation for transfer is made. In the North of Scotland, urgency of transfer will be considered on a case by case basis. Management during transport will be according to the guidelines for cooling during transport and will be provided by the Transport Team (Section 9).

4.1 Principles

- All staff responsible for the resuscitation and ongoing care of newborn infants should be trained in the early assessment of asphyxiated infants for eligibility for therapeutic hypothermia. This training should be provided by the Cooling Centre and regional Transport Teams and supported by the Managed Clinical Networks and the Scottish Cooling Group.
- All infants who are potentially eligible for therapeutic hypothermia should be referred promptly for consideration by the Cooling Centre. Referral should not be delayed while central lines are sited unless essential for resuscitation and stabilisation.
- Non Cooling Centres (Inverness excepted) should not undertake passive or active cooling without discussion with the Cooling Centre and only then as part of an agreed and previously defined process following stabilisation of cardiorespiratory status. The decision to cool or otherwise is critical, and practically impossible to change as by the time the transport team arrives, the baby is likely to be over 6 hours old and may have received sedation which will alter neurological examination and CFM.
- Continuous rectal monitoring is the gold standard of temperature measurement in both passive and active cooling.
- All infants eligible for therapeutic hypothermia should reach target temperature within 6 hours of birth.
- Hyperthermia (>37.5C) and hypothermia (<33C) should always be avoided.

4.2 General advice

Assessment
Resuscitate and stabilise as per the Newborn Life Support or Newborn Resuscitation Programme algorithm, ensuring normoxia with a saturation monitor and avoidance of supplemental oxygen where not required.

Monitoring cardiovascular status continuously, including oxygen saturation and blood pressure if able. Record observations.

Secure venous access, and check blood sugar, replacing with intravenous glucose if there is hypoglycaemia.

Take a capillary blood gas. Consider whether manual/mechanical ventilation is required.

Assess perfusion and consider whether volume may be required.

Take blood cultures and start on first line antibiotics to cover congenital sepsis. Consider lumbar puncture. Give Vitamin K.

Umbilical arterial and venous lines may be inserted if expertise is available.

Other tests advised, if available, include baseline urea and electrolytes, full blood count, group and save plus coagulation screen. Placental histology should be requested. Urinalysis for blood and protein should be performed if urine is passed.

Temperature
Nurse baby in an open cot, with a radiant heater set to servocontrol and keep temperature in normal range. Nurse the infant naked, do not dress, use a hat or any form of cover. The infant

may lie on an open nappy. Do not nurse on a sheepskin or nested. Follow Cooling Flowchart C (Appendix 4) for the maintenance of normothermia.

Neurology
Assess neurological symptoms of HIE early and always within the first hour (Table 1). Early discussion with Cooling Centre should occur if criteria A and B in Section 3.2.1 are fulfilled or if there is any uncertainty about need for cooling.

If a decision is made by the Cooling Centre to initiate cooling, referring units will either follow Cooling Flowchart A or B (Appendix 4) to lower the temperature to a specified target or maintain normothermia according to Flowchart C while awaiting arrival of the transport team.

The temperature target for any particular unit and the appropriate flowchart to follow, should in all cases have been agreed in advance between the referring unit and the Cooling Centre following a site assessment of individual unit capabilities, expertise and equipment.

If servocontrol cooling is available and used for initiation of therapeutic hypothermia, target temperature should be set at 33.5C and management of the baby will proceed as under Sections 4 and 5 below until the Transport Team arrive.

Continuous rectal monitoring (gold standard) or interscapular monitoring will be used to monitor temperature. Where this is not available, axillary temperature will be measured every 15 minutes.

Transfer readiness
A letter containing comprehensive patient information should be prepared for the Transport Team and Cooling Centre. This will include details of maternal history, labour, delivery, cord pH, resuscitation of baby including response of heart rate, first gasp and need for cardiopulmonary resuscitation. Blood test results and timing of drugs and their dosages should be provided. Examination of the baby including head circumference and HIE score should be documented as well as the results of any imaging specifically cranial ultrasound and the position of central lines. Details of what information has been discussed with parents should be included as well as whether the Parent Information Leaflet has been issued (Table 5 and Appendix 5).

5. Inducing Therapeutic Hypothermia

Passive cooling refers to the passive drop in body temperature resulting from the removal of all extraneous heat sources, clothes and equipment which traditionally are used to maintain normothermia eg switching off incubator, removing hat or nappy.
Active cooling refers to the application of a source of cold in order to actively reduce body temperature eg gel packs, fans, cooling jackets or mats.

5.1 Passive cooling
For many infants born outside of a Cooling Centre, passive cooling can be commenced following stabilisation of cardiorespiratory status and assessment of eligibility, and continued until the infant is transferred.
In some units, local expertise may dictate that priority is given to maintaining normothermia rather than initating passive cooling. Each referring unit will either follow one of two Flowcharts for Passive Cooling which will have been agreed in advance with the Cooling Centre in relation to skills and equipment and expertise (Appendix 4 Flowchart A and B for Passive Cooling)

Principles:

- Passive cooling will always take place with the agreement of the Cooling Centre (or Inverness)
- Parents should be informed early in the process that cooling is being undertaken and why. Consent is not required. This discussion should be documented in the medical record (Table 5 and Appendix 5). The infant will be nursed naked preferably on an open cot, and all active heat sources will be switched off.
- Rectal temperature (gold standard) or interscapular temperature (with baby lying supine) will be monitored continuously and the temperature recorded every 15 minutes. Where these modalities are not available, axilla or rectal temperature will be measured intermittently every 15 minutes.
- Fans, cold gel packs or ice packs will not be used to decrease core temperature.
- The infant's core temperature should reach a predefined target (Appendix 4) in an expedient, safe and controlled manner, ideally achieved within 2 hours from commencing cooling and within 6 hours of birth.
- Core temperature will not be allowed to drop below 33ºC. Care must be taken as the infant's temperature approaches 34.0ºC as overcooling from this point is common and can be dangerous. 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 heater should be turned on to its lowest temperature setting to avoid over cooling.

The 72 hours of cooling is considered to have commenced when a temperature of 33-34ºC has been reached and maintained. The time that this occurs should be documented in the medical record.

5.2 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 teams.

If an infant who fulfils the criteria is born within a Cooling Centre or Inverness, active cooling should be initiated as soon after birth as possible. For infants who have initially undergone passive cooling, active cooling will be initiated upon transfer to the NICU from the place of birth.

Principles of Active Cooling

- All infants with suspected HIE should be assessed to determine whether the criteria for offering cooling are met, and the attending Consultant should be informed.
- The decision to initiate Therapeutic Hypothermia should be made by a Consultant or senior Specialty Doctor.
- Parents should be informed early in the process that cooling is being undertaken and why. Consent is not required. This discussion should be documented in the medical record. Parents should be given the National Parent Information Leaflet on Therapeutic Hypothermia (Appendix 5).
- Rectal temperature will be monitored continuously using a rectal probe aiming for a core temperature of 33.5ºC (range 33-34ºC)
- Cooling should be maintained using appropriate cooling equipment. Only CSE certified equipment should be used to provide treatment with servocooling. The manufacturer's instructions should be followed when using servocooling equipment.

- Cooling should be continued for a total of 72 hours from the point at which the target temperature of 33.5ºC (range 33-34ºC) has been achieved and maintained. Cooling may be discontinued before 72 hours if a decision to reorientate care is made or if the infant's neurological condition rapidly improves such that cooling is not believed to be beneficial.

5.3 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 including a rise in blood pressure and a fall in heart rate. Neutropenia, thrombocytopenia and hypokalaemia may also occur. All these abnormalities are more severe and more common when the core temperature is less than 32°C.

Subcutaneous fat necrosis (SCFN) is a recognised complication of perinatal asphyxia total body cooling (Strohm B). This condition can lead to pain, scarring, and hypercalcaemia that may present after the infant has been discharged home from hospital. This may occur in any area of the body containing subcutaneous fat and is not restricted to that in contact with cooling mats. It is recommended that the infant's skin is closely observed for the development of SCFN during neonatal stay. 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. It is recognised that the lesions of SCFN may be subtle. Parents should be alerted to the symptoms of hypercalcaemia whether or not SCFN is diagnosed during stay. Information is included in the National Parent Information Leaflet on Therapeutic Hypothermia (Appendix 5).

5.4. Re-warming

Active cooling should be stopped 72 hours from when a temperature of 33.5 has been achieved and maintained. Re-warming should be gradual and no faster than 0.5ºC /hour until 37ºC (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 vasodilatation resulting in hypotension and also the re-emergence of seizures. CFM is essential during re-warming. If the clinical condition deteriorates during re-warming, stop re-warming and discuss further with the Consultant.

The infant's temperature should be closely monitored for 24 hours after normothermia is achieved to prevent rebound hyperthermia. Temperature may be maintained in the normal range by servocontrol methods in the 24 hours following re-warming. Rebound hyperthermia should be treated with environmental measures and paracetamol.

7. Ongoing management of the cooled infant with HIE

All babies being cooled should be assigned 1:1 nursing and should receive regular, thorough Senior medical review. Umbilical venous access and arterial access should be secured.

6.1 Monitoring and data gathering

1. **Double continuous rectal temperature monitoring** with alarm limits set within 1°C of the target rectal temperature. Insert rectal probes to 6cm and secure firmly. One rectal probe is to allow the machine to servo-control and the other is connected to monitoring for continuous recording and alarming when out of the target range. Both should be checked for correct placement every hour and placement recorded. If the servocontrol probe is displaced, the cooling machine may start to rewarm the baby to the target temperature, although an alarm will also be activated in the case of a sudden change in temperature.
2. Continuous heart rate, oxygen saturation and invasive BP monitoring.
3. Regular blood gas and glucose analysis to assess metabolic acidosis, adequacy of ventilation and glucose requirements. Due to a lack of evidence a recommendation cannot be made as to whether non-temperature corrected blood gas values are superior to temperature corrected values.
4. Fluid balance 6 hourly- measure urine volume by catheter. Urinalysis for at least 24 hrs following birth.
5. At least daily FBC, daily urea and electrolytes, including Ca and Mg for the duration of cooling and 24 hours after re-warming commenced- more frequently if indicated. Initial coagulation screen on day of admission and as clinically indicated thereafter.

   Suggested target values during hypothermia
   - T rectal 33.5°C +/- 0.5°C
   - HR 80-100 bpm
   - O_2 sat 92- 98%
   - MABP 45- 65 mmHg
   - PO_2 6- 10 kPa
   - PCO_2 5- 7 kPa
   - Electrolytes, within normal range
   - Glucose, within normal range
   - Lactate, within range for condition

6. CFM should be continued throughout cooling and re-warming, particularly as non-clinical seizures may occur on re-warming.
7. Neurological examination and encephalopathy score- every 12-24 hours for the first 4 days of life.
8. Ultrasound scan on day of admission and as clinically indicated thereafter
9. Anticonvulsant and aminoglycoside levels as required- there may be delayed metabolism during hypothermia and doses may need to be adjusted on the basis of these results (Appendix 6).
10. The following table is a recommended schedule of investigations to be sought in infants undergoing therapeutic hypothermia:

Table 3. Recommended schedule of investigations in infants undergoing therapeutic hypothermia

Maternal data	First 24 hours	Days 1-3	Day 5-14
Microbiological results Cord gases Placental histology Full history incl family **Consider:** Kleihauer	Blood gas Glucose and lactate FBC, film and group Coagulation Urea and electrolytes, Ca, Mg Liver function Blood cultures- culture Urinalysis CFM/EEG Cranial USS Head circumference Neurological examination including HIE score **Consider:** CSF- microscopy/culture Cardiac Troponin Congenital viral screen Metabolic screen including ammonia, amino acids Urine for amino and organic acids, ketones, reducing substances Genetic investigations	Blood gas Glucose and lactate FBC Urea and electrolytes, Ca, Mg CFM/EEG CRP Liver function Head circumference Neurological examination including HIE score **Consider:** Coagulation Cranial USS Gentamicin level	MRI **At discharge:** Head circumference Neurological examination Examination of skin for subcutaneous fat necrosis

6.2 Ventilation

Cooling does not have any direct effect on respiratory function. Persistent pulmonary hypertension of the newborn or meconium aspiration may coexist with HIE and should be treated with the necessary ventilatory support, including HFOV and nitric oxide if necessary.

- Most babies will require ventilation. A hat should not be used to fixate the ETT.
- Some babies will be able to be extubated half way through cooling but may require noninvasive support due to sedation and respiratory pathology.
- Ventilator gases should be warmed and humidified in the normal way, according to unit policy.
- Avoid hyperoxaemia and hypocarbia (severe hyperoxaemia with PO2 greater than 27kPa and hypocarbia with PCO2 less than 2.6 kPa are associated with poor outcome (Klinger G)). Hypothermia will reduce respiratory rate as metabolism is reduced. If ventilated it is easy to overventilate as CO_2 production is reduced. Hypocarbia may induce seizures.

- More frequent suction and regular re-positioning might be necessary as secretions become more abundant as cooling duration continues. Decisions about whether to use saline during suction should be made on an individual basis.
- Stridor has been reported in the context of hypothermia with or without preceding intubation. Apnoea is more common particularly if sedation has accumulated or if there are seizures. Both are transient though may require temporary escalation of ventilatory support.

6.3 Positioning and skin care

- Vary the position 6 hourly during care – flat – slightly uptilted – supine, right or left side to avoid pressure sores
- Do not turn the head only but keep nose in body midline to avoid impairment of cerebral blood flow or return.
- Cyanosis of the hands and feet (but not of the central oral mucous membranes) is common initially but settles with time.
- Subcutaneous fat necrosis (SCFN) is a recognised complication of therapeutic hypothermia in asphyxiated infants. Monitor all skin for red painful nodules during the neonatal stay and if SCFN is diagnosed, ensure a plan for regular monitoring of calcium levels over coming weeks is made.

6.4. Cardiovascular Support

Cardiovascular instability is a frequent 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 initially and in the face of poor myocardial function, volume replacement may worsen cardiac function and inotropic support should be considered early. Cardiovascular support should be directed at improving cardiac contractility and systemic perfusion.

- Use clinical guidelines and assess cardiac function clinically (BP, heart rate) and/or by echocardiogram when choosing volume or drug.
- Electrocardiography and biochemical markers, such as troponin levels, may help in the assessment of myocardial dysfunction (Shastri AT).
- Dopamine and dobutamine can be used to treat hypotension before starting hydrocortisone. Noradrenaline may be required.
- Later in the cooling process infants can become hypovolemic as water is displaced to the tissue and because hypothermia can induce diuresis. This is particularly common where fluids have been restricted in the prior days and where renal function is not impaired. Volume replacement may be appropriate in this instance.
- During the rewarming process, a rise in body temperature may cause hypotension by inducing peripheral vasodilatation. If hypovolaemia is suspected an initial bolus of 10-20ml/kg of normal saline should be given and repeated if necessary.
- Bradycardia (<100bpm) is normal during cooling as is a prolonged QT interval. It is important to maintain the temperature above 33°C 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. Consider increasing sedation if the pain or distress suspected.

6.5 Fluid and electrolyte management

Renal function is commonly impaired after asphyxia and weight, creatinine, electrolytes and urine output will guide fluid management. However, be aware that hypothermic patients may need more volume due to redistribution of fluid to the tissue. Although babies may suffer acute renal failure due to the HI insult, cold induces diuresis, which is often seen after renal function resumes towards the end of cooling. As such babies often need more volume at this stage.

- Babies may require catheterisation to assess urine output accurately.
- Maintenance fluids should start at 40-60 ml/kg/day and fluid balance assessed 6 hourly, with increments in fluids when urine output is adequate.
- Maintain electrolytes in the normal range, including calcium and magnesium levels.
- If there is renal failure, maintenance fluid may be dropped to 30ml/kg/day plus any measured losses
- Ensure blood glucose is kept in the normal range which in the fluid restricted infant may require infusion of higher dextrose concentration (>10%) through central venous access.
- Care must be taken regarding the potential accumulation of nephrotoxic drugs such as aminoglycosides in the event of renal impairment. Consider withholding aminoglycosides until the blood level is known, or changing to a non-nephrotoxic alternative such as a cephalosporin (Appendix 6).

6.6 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 not be given in infants with significant multisystem derangement where gut perfusion may be compromised. Consideration of parenteral nutrition should be given in view of the initial catabolic state, although where there is significant electrolyte, fluid and glucose imbalance this may be complex.

Early trophic feeding may be beneficial and can be started during cooling but the evidence is limited in this population group. Feed intolerance is common even after re-warming as gut circulation may have been compromised and sedation may slow gut motility. There is an increased risk for necrotising enterocolitis (Zanelli S) and breast milk is preferable to formula milk. Advice and support for mothers regarding expressing breast milk should be provided early in the course of the infant's management appreciating the impact of acute stress on milk production.

Any baby in whom there are concerns with chest, swallow function or suck following rewarming should be assessed by a Speech and Language Therapist for suitability for oral feeding. For other babies with intact gag and suck reflex, oral feeds can be introduced by either breast or bottle.

6.7. Impaired synthetic liver function/consumptive coagulopathy

If a baby starts hypothermia treatment with normal clotting, a 3.5°C reduction in temperature will affect coagulation only moderately (~30% prolongation) and function should remain within normal limits. A reduction in the production of clotting factors and platelets is seen with hypothermia resulting in prolonged coagulation, this is physiological. In the absence of bleeding, mild derangement of coagulation can be tolerated without treatment.

It is likely that hypothermia has a significantly adverse effect on clotting if the patient starts out with abnormal coagulation. Be aggressive in checking coagulation and treating deranged clotting when there is a suspicion of increased bleeding or when there has been a large blood

loss (eg antepartum haemorrhage, subgaleal bleeds). FFP and/or other blood products should be ordered before clotting results are available where concern is present about active bleeding.

If active bleeding is present it is important to exclude intracranial haemorrhage as this may necessitate neurosurgical management.

Any drug metabolised by the liver has prolonged metabolism in hypothermia especially morphine and phenobarbitone. Avoid continuous infusions of paralytic agents or anticonvulsants where possible, using boluses as an alternative (Appendix 6).

6.8 Infection

Perinatal infection often co-exists with HIE. All babies who have been born after spontaneous onset of labour or who have other risk factors for infection should have a septic screen and be commenced on antibiotics (as per local policy) as soon as possible after birth. It is important to consider viral infections such as herpes simplex. A clear history should be taken and the use of antiviral medications considered.

Note that renal impairment may affect aminoglycoside clearance and that it is advisable to be cautious about toxicity if urine output is low (Appendix 6).

Note that it is normal to observe a fall in white cell and platelet counts during cooling.

Hypothermia is not known to be associated with an increased risk of infection in newborn infants. However ventilated babies do need regular ET suction to clear secretions and regular positioning to avoid skin breakdown. The presence of central venous and arterial lines increase the risk of bloodstream infection.

6.9 Seizure treatment

Clinical seizures following HIE can be difficult to diagnose and treat. 30-90% of seizures are subclinical and only 27% of suspected seizures have an electrical correlate On the other hand two thirds of electrographic seizures do not have overt clinical signs (Murray DM). It should be remembered that true seizures secondary to hypoxia-ischaemia are relatively uncommon in the first six hours of life and that the treatment of presumed seizures will alter the neurological examination and may impair robust decision-making about the suitability of a child for therapeutic hypothermia. On the other hand, other abnormalities of neurological behaviour such as tremulousness, cycling, paddling movements and oromotor dyskinesia are very common and do not require anticonvulsant treatment.

All infants undergoing cooling should have continuous CFM 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. Symptomatic seizures or where the total electrical seizure (aEEG/EEG) burden within 1 hour is 10 minutes or longer should be treated with anticonvulsants. Seizures may re-emerge on re-warming and CFM monitoring is advised until normothermia is reached. If seizures occur during re-warming, hypothermia to 33.5°C can be re-induced for a further 24 hours and a slower rate of re-warming commenced (<0.5°C/hour).

Ensure that ventilation and cardiovascular status are stable and monitored before giving anticonvulsant therapy. 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 (Appendix 6). It is also important to remember the effect of anticonvulsant therapy on the CFM/EEG, all of which can suppress the background activity.

Hypothermia has no effect on CFM background (unless temp is < 29°C), rate of recovery of background or time to onset of seizures. It may decrease the amplitude of seizures and seizure burden- possibly due to earlier detection and earlier treatment.

For treatment of seizures, refer to local guidelines on seizure management.
Note that Lidocaine should not be given if Phenytoin has already been given due to similar arrhythmogenic effects and that specific dosing schedules have been published for infants undergoing therapeutic hypothermia (Appendix 6). Other causes of intractable seizures in neonates should be considered, e.g. Pyridoxine deficiency and other inborn errors of metabolism.

6.10 Analgesic and sedative therapy

The large majority of babies will require sedation as being cold is stressful and unpleasant. There is experimental evidence that hypothermia may not be neuroprotective in the absence of sedation (Thoresen MJ). A persistently high heart rate, shivering and facial grimacing may all indicate that a baby is experiencing discomfort and it is not unusual for babies to require an increase in sedation dose. It is important to assess regularly 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.

Sedation should not be withheld to avoid respiratory depression which can be easily supported with ventilatory adjuncts. Morphine may not be required in the most severely affected babies who show no signs of consciousness and have severely suppressed CFM if there is concern around impairing clinical evaluation. This must be kept under frequent review with a low threshold maintained for commencing morphine from a standpoint of avoidance of unnecessary discomfort and improving the efficacy of the therapeutic hypothermia.

Sedation should be provided with morphine prior to inducing hypothermia and continuing thereafter. Consider whether infusion rate should be reduced after 24-48hours to lessen the risk of toxicity and accumulation as the metabolism of morphine is reduced during hypothermia (Appendix 6). At 48 hours, discontinuation of morphine should be considered. Morphine should be made up in 10% dextrose to avoid hypoglycaemia.

Chloral hydrate may also be given as an adjunct to morphine or as an alternative in non-ventilated babies. There is also a risk of over-sedation due to accumulation. Infants may need ventilatory support even following sedation (Appendix 6).

Monitoring of pain and distress

Heart rate is a good proxy marker for adequate sedation. At 33.5°C, the average heart rate is around 80-100 bpm. The heart rate changes by 14 beats per minute per 1°C change in temperature over a wide range.

If HR is high (>120bpm) despite hypothermia, the reasons may be:

- Distress and/or pain
- Hypovolaemia
- Hypotension
- Inotrope use
- Seizures
- Other reasons for pain

NB if the heart rate is lower than 80bpm, this suggests the baby may be overcooled and the position of the temperature probes should be checked immediately. It may also mean that the baby is overly sedated with morphine or anticonvulsants and the doses of these should be reduced.

7. Neurophysiology and neuroimaging for assessment and prognostication

7.1 Cerebral Function Monitoring (CFM)

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. Although this is a useful monitoring tool, many units do not yet have access to CFM. Cooling should be commenced and the CFM will be started when the infant reaches the Cooling Centre.

Continuous CFM 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 CFM should be commenced before administering anticonvulsant therapy, although if not available, treatment of seizures should not be delayed until a CFM is performed.

The decision to commence cooling should be made on the basis of criteria A and B detailed in section 3.2.1. While a normal CFM 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, the results should be interpreted with caution as they can still be associated with poor outcome if there are clinical signs of encephalopathy. Apparent improvement of the aEEG after 6 hours of age, however, is not an indication for discontinuing cooling. Refer to local guidance about CFM monitoring and interpretation.

7.2 Electroencephalography (EEG)

A formal EEG provides information on regional background cerebral activity and can detect some seizures and other abnormalities not seen using aEEG. However access to neurophysiology services both to perform and interpret the examination can be limited. The most useful prognostic information can be obtained once the infant has been rewarmed and off anticonvulsant medication.

EEG may also be important in the following circumstances:

- If needed clinically to confirm or exclude electrical seizures
- Where aEEG background has not returned to normal at end of cooling
- Continuing clinical concern about encephalopathy after the period of cooling

7.3 Cranial ultrasound Scans (CUSS)

Cranial ultrasound scans can provide vital information on infants with HIE. The diagnosis of HIE can be complicated, and other disease processes may present in a similar way such as neonatal stroke. For this reason, a cranial USS should be preformed in any infant with suspected HIE, ideally prior to their transfer to a Cooling Centre. Refer to local guidance for image acquisition and interpretation.
Scans should be performed on admission and then daily for the first three days of life.

Possible USS Findings in HIE

- Early cerebral oedema – generalised increase in echogenicity, indistinct sulci and narrow ventricles, loss of normal tissue differentiation
- After 2-3 days of age, increased echogenicity of thalami and parenchymal echodensities
- Haemorrhage
- Relative increase of end-diastolic blood flow velocity compared to peak systolic blood flow velocity (Resistive Index <0.55) in anterior cerebral artery predicts poor outcome.

7.4 Magnetic Resonance Imaging (MRI)

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 imaging (within the first 5 days of life) may not reflect the true extent of the injury, although abnormalities may be seen on diffusion weighted imaging. Early imaging may be considered in very sick infants where discontinuation of intensive support may be being considered or where the clinical assessment is suggestive of other causes of encephalopathy (e.g. subdural haemorrhage).

The most accurate prognostic information can be obtained at 10 days of age and should take place before repatriation to the referring hospital. Infants who develop signs of HIE following an acute severe 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 (Srinivasan L). More chronic subtotal hypoxia-ischaemia is associated with cortical and subcortical abnormalities. National guidance is pending to support optimal acquisition and interpretation of images (BAPM 2015).

7.5 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, can provide valuable early prognostic information. Table 4 provides a guide to the prognostic value of early clinical, electrophysiological and imaging examination.

Where infants are repatriated to their referring hospital, the following best practice should apply:

1. The referring hospital should be provided with a detailed discharge summary
2. There should be a Consultant to Consultant referral with exchange of information relating to parental communication, parental expectations and current neurological status including prognostic information where available.
3. Where MRI report becomes available following repatriation, there should be either
    a. a Consultant to Consultant exchange of information
    b. a follow up consultation after discharge at the Cooling Centre
4. For all babies born out with a Cooling Centre, consideration should be given to the initial follow up appointment taking place at the Cooling Centre so that parents' questions can best be answered by the clinical team undertaking cooling.

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 2010) currently recommends that a formal neurological examination and a psychomotor assessment should be carried out at approximately 2 years of age. A study of longer term outcomes indicates that the neuroprotective effect of hypothermia persists at school age (Azzopardi D 2014).

Table 4. Information for Prognosis in HIE (Updated and adapted from Statewide Maternity and Neonatal Clinical Guideline: Hypoxic-ischaemic encephalopathy, Queensland, Australia May 2010)

	Test	Timing	Outcome
Clinical	**Sarnat and Sarnat**	Early onset neonatal encephalopathy is the best single predictor of long-term outcome (Low JA) Quick recovery is associated with a better outcome (Carli G)	**Normothermia** Severity of the acute encephalopathy predicts the overall risk of death and severe handicap (Murray DM) Stage 1 HIE – normal neurologic outcome in greater than 90% of cases (Murray DM) Stage 2 HIE – incidence of poor outcomes ranges from 30- 60% (Murray DM) Stage 3 HIE – poor neurologic outcome (death or severe disability in almost all cases) (Murray DM) **Hypothermia** Clinical assessment is less predictive. May be more likely to have depressed neurology because of sedation (Gunn AJ) and many cooled infants remain stiff for some weeks after discharge. Cooling also affects the encephalopathy score in some infants resulting in more rapid normalisation (Azzopardi D) Severe encephalopathy persisting 72 hours after birth was associated with death or severe disability, 25/28 (89%) of infants (Gunn AJ)
	Seizures	Early onset of seizures	**Hypothermia** May predict a poorer neurodevelopmental outcome, independent of the severity of hypoxic-ischaemic brain injury on MRI (Glass HC) Seizures <6 hours predicts adverse outcome (OR 6) (Thoresen M) High seizure burden associated with greater injury on MRI independent of background or Apgar (OR 5) (Shah DK)
	Apgar score	0 at 10 minutes when surviving to admission	**Normothermia** (Harrington DJ) 90/94 (95%) of infants died or had mod/sev disability **Normothermia/Hypothermia** NICHD RCT (Laptook AR, Natarajan G) 19/25 (76%) of infants died or had mod/sev disability at 18-22 months and 19/24 (79%) of infants died or had mod/sev disability at 6-7years. No correlation between Apgar scores and cooling. **Hypothermia** (Shah P)

			4/13 (30%) of infants survived and were normal at 2 years.
		0-2 at 10 minutes when surviving to admission	**Normothermia/Hypothermia** NICHD RCT (Laptook AR) 40/51 (78%) of infants died or had mod/sev disability at 18-22 months.
		0-3 at 10 minutes when surviving to admission	**Normothermia/Hypothermia** NICHD RCT (Natarajan G) 64/85 (75%) of infants died or had mod/sev disability at 6-7 years.
	Time to spontaneous respiration	Greater than 30 minutes	**Normothermia** Overall risk of death or severe handicap 72% (Perlman JM)
Biochemistry	**Lactate dehydro-genase**	<6h of birth (survivors studied only)	Hypothermia (Thoresen M) <2085U/L- all had normal outcome ≥2085U/L- 6/11 had poor outcome Cut off of 2085U/L identifies all with poor outcome and 81% of those with good outcome.
Electrophysiology	**EEG**	First few days of life	Background EEG abnormalities, detected in the first few days of life after HIE can provide prognostic information even in babies treated with hypothermia. **Normothermia**: Grade of abnormality predicts the rate of death or severe handicap (Perlman JM) Severe abnormality (burst suppression, low voltage or isoelectric) - 95% (Perlman JM) Moderate abnormality (slow wave activity) - 64% (Perlman JM) Mild or no abnormality - 3.5% (Perlman JM) Persistence of EEG abnormalities at 1 month of age is associated with a higher risk of neurologic sequelae (Mariani E) Normal/mildly abnormal EEG results at 6, 12, or 24 hours had 100% positive predictive values for normal outcomes and negative predictive values of 67% to 76% (Murray 2009) A moderately abnormal EEG trace was associated with a normal outcome in 100% of neonates if recorded at 6 h, 43% at 12 h, 33% at 24 h, and 0% at 48 h (Murray 2009)

Electrophysiology	**aEEG**	aEEG <6 hours	PPV of an abnormal trace for adverse outcome is altered by cooling (Thoresen M) Normothermia 86% Hypothermia 59%
		aEEG 24-36 hours	**Normothermia** Continuous/discontinuous normal voltage by 36 hours associated with normal development at 12 months (Hallberg B) **Hypothermia** The PPV of an abnormal trace at 24-36 hours is over 90% (Thoresen M).
		aEEG 48 hours	**Hypothermia** Continuous/discontinuous normal voltage by 48 hours associated with normal development at 12 months. Isoelectric EEG at 48 hours assoc with poor outcome (Mariani E) All infants who develop SWC (sleep wake cycling) have a good outcome (Cseko AJ) Background is affected by several medications and must be considered when interpreting the aEEG trace (Hellstrom-Westas L)
	Cerebral artery Doppler	From 24h of age	PPV of Resistance index (RI) ≤0.55 for severe adverse outcome (Elstad M) **Normothermia** 84% **Hypothermia** 60% NPV of Resistance index (RI) >0.55 for normal outcome (Elstad M) **Normothermia** 76% **Hypothermia** 78% Predictive value increases to that seen in normomthermic infants after rewarming (Skranes): PPV for ≤0.55: 100% NPV for >0.55: 89%
Radiology	**MRI/MRS**	Median 6-8d	PPV of abnormal T1/T2 MR scan for adverse outcome (Rutherford MA 2010) Normothermia: 83% Hypothermia: 85%
		1-30d	Normothermia Proton MR spectroscopy deep gray matter lactate/N-acetyl aspartate (Lac/NAA) peak-area ratio (days 1- 30): 82% sensitivity and 95% specificity (Thayyil S)

7.6 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.

Involving teams from a local children's hospice may be very beneficial to both the infant and their family. The SNTS (transport) 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 died before the hospice team was contacted, the hospice may still be able to offer help and support to the family.

In some cases, it may also be apparent soon after delivery that the prognosis of a baby is so poor that ongoing intensive care is likely to be futile. In these circumstances the baby should not be cooled and it is usually inappropriate to separate the mother and baby by transferring to a Cooling Centre. These cases should be discussed with the SNTS team and Cooling Centre. When a baby dies, the parents should be counselled by a Consultant paediatrician about the value of post mortem examination.

8. 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. The decision to treat with cooling should be explained to the parents and the Parent Information Leaflet should be provided (Appendix 5). Table 5 suggests information that clinicians may wish to use when discussing aspects of HIE and therapeutic hypothermia with parents. Avoid giving opinion about any potential breach of duty by caregivers.

Table 5. Suggested information to use in parental discussions about HIE and Therapeutic Hypothermia

Criteria	Advice to parent(s)
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 complications within the brain from the direct effects at the time, and also from ongoing changes that begin around six hours after the event. These secondary changes are known to increase the amount of brain damage which occurs
Prognosis	Approximately 30 to 60% of those babies who survive after this type of event 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 complications in these newborn babies Recent research has shown that cooling these babies can reduce the secondary brain damage, increase the chances of survival and reduce the severity of possible long-term disability. Cooling does not help all babies and will only benefit one baby out of every 7 treated.
What does the treatment entail	Your baby will receive cooling therapy in addition to standard intensive care support. This may require transfer to a centre who is able to provide this specialised care. Your baby's temperature will be slowly lowered and kept between 33 to 34°C for 72 hours. Cooling will be achieved by exposing your baby to the ambient air temperature and if needed to be transferred to a Cooling Centre, cooling will be achieved using a special machine. 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 a temperature of 37°C

Parents should be updated regularly and at least daily by a senior member of the medical team. All discussions with the parents about their infant's treatment should be documented clearly in the infant's notes. On discharge from the Cooling Centre, professionals with ongoing involvement in the infant's care should receive clear information about what discussions have taken place with parents including those relating to the expected prognosis for the baby and the MRI result (see section 7.5)

A list of organisations and websites is given in Appendix 7 which may be helpful in supporting families.

9. Cooling on transport

9.1 Principles

- Therapeutic Hypothermia will be provided on transport by skilled teams who have received training in the transfer and management of asphyxiated babies including those undergoing cooling.
- Continuous rectal temperature monitoring will be used in all transports involving infants undergoing therapeutic hypothermia.
- Servocontrolled cooling will be used to maintain hypothermia unless transport is by air, or there is equipment malfunction. In these cases hypothermia will be maintained by gel packs.
- In each case, the Transport Team will liaise with a Consultant in the Cooling Centre as to the appropriateness of hypothermia prior to initiating active cooling

9.2 Management

The initial role of the Transport Team on reaching the referring unit is to ensure that the infant's condition is stable and then to assess eligibility for cooling. It is recognised that the neurological condition of many infants evolves with time and that it may be possible on arrival of the Transport Team that the infant is making a good recovery and no longer fulfils cooling criteria or may indeed be so severely ill that cooling is no longer considered beneficial. The decision to cool should only be made by a Consultant either as a member of the Transport Team or within the Cooling Centre. The HIE score should be calculated and documented prior to cooling and 12 hourly thereafter (Table 2).

Two rectal probes should be inserted prior to the initiation of cooling.

The time at decision to cool should be recorded and the baby's temperature rapidly cooled to ensure that target temperature is reached as soon as possible after birth and ideally within 6 hours.

Servocontrolled cooling should proceed according to manufacturer's guidelines and those of the Transport Team.

Temperature should be monitored continuously and documented every 15 minutes. Alarm limits should be set 0.2°C above and below target temperature. Probe placement should be checked every hour to ensure the probes have not become displaced. Continuous heart rate, oxygen saturation and invasive BP monitoring should occur.

Seizures should be treated only after discussion with a Consultant. Most observed seizures are not true seizures and treatment may alter both neurological examination and EEG such that ability to accurately assess these may be impaired on arrival at the Cooling Centre.

Consider ETCO2 measurement to avoid hypocarbia on transport.

All other management should be undertaken as in Section 5 and as per Transport Team guidelines.

9.3 Back transfer

Receiving units and parents should be made aware that:

1. Temperature instability may occur in the days after back transfer and should be treated with environmental measures and paracetamol
2. Subcutaneous fat necrosis is a complication that requires investigation and follow up.
3. Neurodevelopmental follow up will be required and a 2 year formal assessment will be undertaken by the Cooling Centre or the local hospital.

On discharge from the Cooling Centre, the referral centre as well as those professionals with ongoing involvement in the infant's care should receive clear information about what discussions have taken place with parents including those relating to the expected prognosis for the baby and the MRI result (see section 7.5).

10. Data Collection

It is recommended that Cooling Centres collect data on process and outcomes and share these nationally. A suggested national dataset for every infant with hypoxic-ischaemic encephalopathy or who is treated with hypothermia is provided in Appendix 8 and is consistent with that required for Badgernet.

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12. Appendices

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Appendix 1. Individuals and organisations involved in the production and endorsement of this document

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Appendix 2. Cooling Outside of Trial Criteria Guidelines

1. Cooling Outside Trial Criteria

There are several clinical circumstances where it may be appropriate to offer therapeutic hypothermia, despite the lack of clinical evidence in the form of randomised controlled trials (RCT). These include:

- 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 Consultant in the Cooling Centre BEFORE cooling is started.

The BAPM position statement 2010 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 judgement where any potential benefits of hypothermia outweighs any risks. As outlined in the BAPM 2010 position 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 not experimental nor part of a clinical trial/research study.

1.1 Infants <36 weeks gestation

Infants between 34+0 and 35+6 weighing more than 1.8kg should be considered for cooling if the infant fits criteria A and B detailed in section 3.2.1.

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. 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 33.5C-36.5°C (Silverman WA). There is some evidence from the CoolCap trial that smaller infants benefitted less than larger infants, but the relationship between weight and gestational age was unclear (ie whether it was related to growth retardation) (Gluckman P). There is emerging data from the TOBY register as to the safety of cooling infants <36 weeks (Azzopardi D). Therefore it would seem reasonable to consider infants between 34 and 36 weeks and infants >1.8kg for cooling if they otherwise fitted criteria A and B detailed in section 3.2.1.

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 (Thoresen M). Experimental studies have shown a lack of benefit from delayed cooling (Sabir H). Training and education should be focussed 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.

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 detailed in section 3.2.1 should be cooled the following should be considered:

- Is the condition life-limiting? ie would cooling actually alter the long term outcome?
- Would cooling impact on the anomaly? For example cooling may compromise blood flow to the gut in an infant with gastroschisis.
- Would the condition make it harder to assess neurological examination? 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 Sudden Unexpected Postnatal Collapse

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

Although there is no clinical trial specifically looking at hypothermia following postnatal collapse, one trial did include some such infants (Eicher DJ). These babies often have good evidence of hypoxic-ischaemic brain injury on neuroimaging and so it is likely that they could benefit from cooling if initiated within the 6 hours following the point of their collapse. Although around half of infants presenting with postnatal collapse appear to have suffered simple asphyxiation, the other half had an underlying pathological condition such as infection, cardiac abnormality, brain haemorrhage or inborn error of metabolism (Becher JC). In such cases therapeutic hypothermia may be detrimental. As with any case of neonatal encephalopathy an underlying cause must be sought and care taken that the risks of treatment do not outweigh the benefits (Guidelines for the Investigation of Infants suffering an Unexpected Postnatal Collapse 2010). If a baby dies in the days following unexpected or unexplained postnatal collapse, the death *must* be reported to the Procurator Fiscal.

1.5 Infants presenting with neonatal stroke

Infants presenting with neonatal stroke should be considered for cooling only if the diagnosis is made within 6 hours of birth.

Many of the experimental studies used a stroke model to study the efficacy of cooling and there is recent interest in cooling adult patients following stroke (Harris B). However the main problem in the neonate is making an early diagnosis – these infants often present after 24 hours of age with seizures, are not encephalopathic and early ultrasound imaging can be difficult to detect the stroke. The presumed onset of focal brain ischaemia in stroke is shortly before or around the time of birth. Therefore it is possible that by the time the diagnosis is made the 'therapeutic window' has been missed.

2. Other Clinical Situations

2.1 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 RCTs on cooling. Careful neurological assessment is essential to demonstrate that the infant does not meet criteria based on neurological examination. 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.

2.2 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 detailed in section 3.2.1 at 6 hours of age then by definition they have moderate to severe encephalopathy and would have been included in the RCTs. 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.

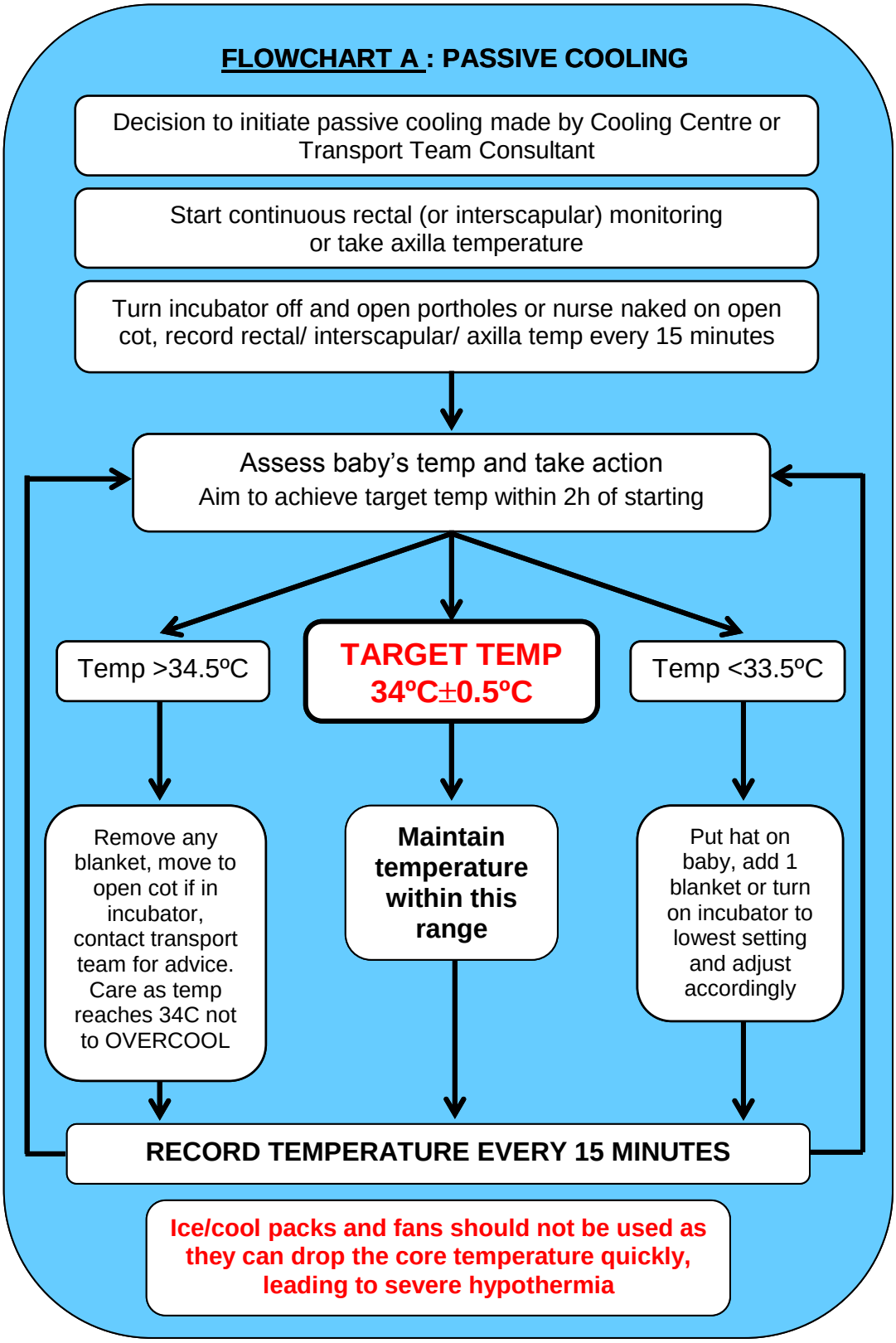
2.3 The infant who develops 'rebound' seizures following re-warming

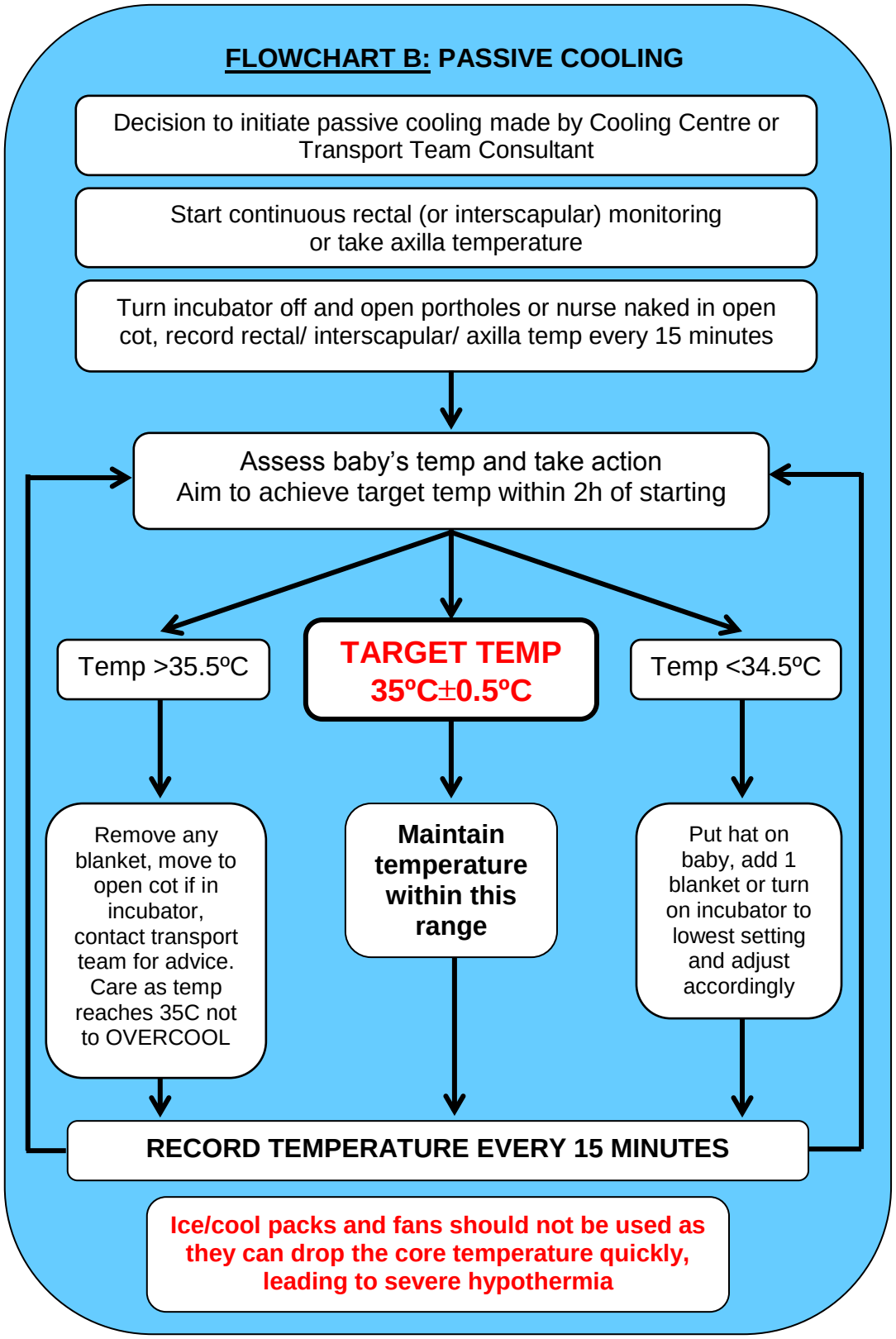
Seizures can be regarded as the clinical sign of delayed energy failure. It is the prevention of delayed energy failure which is thought to be the reason hypothermia is beneficial. Therefore ongoing seizures during cooling are an indication of continuing delayed energy failure; similarly the re-emergence of seizures during re-warming is a suggestion that delayed energy failure is 'reactivated'. Theoretically maintenance of cooling for a further 24 hours may limit further brain injury, however there is no clinical evidence that prolonging cooling to 96 hours improves neurodevelopmental outcome.

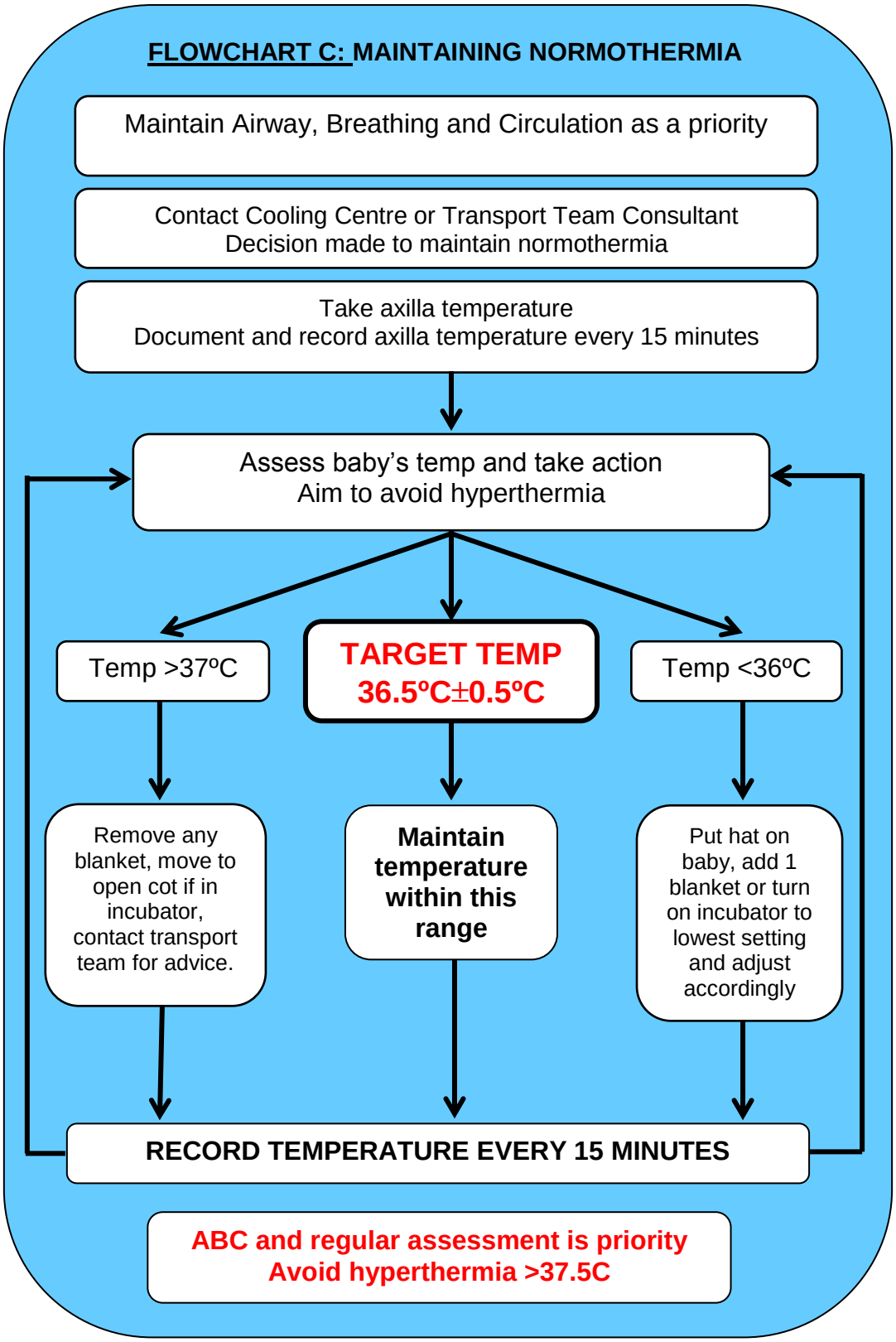
Appendix 3. Standards for Cooling Centres

- Within Cooling Centres, therapeutic hypothermia should be undertaken according to nationally developed guidelines and pathways.
- Cooling Centres should ensure there is an established pathway within networks for referral of infants and that frontline staff are trained to identify infants who are eligible for therapeutic hypothermia.
- Therapeutic hypothermia should only be undertaken in centres which are experienced in the care of severely ill neonates and which are supported by a multidisciplinary team experienced in neonatal electrophysiology and neuroimaging. Care of such infants should be directed by clinicians experienced in the diagnosis and prognosis of perinatal brain injury.
- There will be a named Lead Neonatologist and Lead Nurse in each Cooling Centre who has expertise in cooling and who remains abreast of professional recommendations and current literature.
- Cooling Centres should ensure that all in-house staff undergo training in the process and its effects.
- Cooling Centres should ensure that all infants undergoing cooling have access to a standardised developmental assessment at two years of age.
- Cooling Centres will ensure that all relevant professionals receive information on discharge about cooled infants, specifically with regard to parental communication about prognosis and the need for regular follow up.
- Cooling Centres should collect data on process and outcomes and be encouraged to share nationally.
- Individuals from Cooling Centres should contribute at least annually to teaching on National Hypothermia Training days.
- Cooling Centres should engage in annual meetings and other communications of the Scottish Cooling Group and be responsible for dissemination of information where appropriate through their network.

Appendix 4. Flowcharts A and B for Passive Cooling, C for Maintaining Normothermia




FLOWCHART B: PASSIVE COOLING
Decision to initiate passive cooling made by Cooling Centre or Transport Team Consultant
Start continuous rectal (or interscapular) monitoring or take axilla temperature
Turn incubator off and open portholes or nurse naked in open cot, record rectal/ interscapular/ axilla temp every 15 minutes
Assess baby's temp and take action
Aim to achieve target temp within 2h of starting
Temp >35.5ºC
TARGET TEMP 35ºC±0.5ºC
Temp <34.5ºC
Remove any blanket, move to open cot if in incubator, contact transport team for advice. Care as temp reaches 35C not to OVERCOOL
Maintain temperature within this range
Put hat on baby, add 1 blanket or turn on incubator to lowest setting and adjust accordingly
RECORD TEMPERATURE EVERY 15 MINUTES
Ice/cool packs and fans should not be used as they can drop the core temperature quickly, leading to severe hypothermia


FLOWCHART C: MAINTAINING NORMOTHERMIA
Maintain Airway, Breathing and Circulation as a priority
Contact Cooling Centre or Transport Team Consultant
Decision made to maintain normothermia
Take axilla temperature
Document and record axilla temperature every 15 minutes
Assess baby's temp and take action
Aim to avoid hyperthermia
Temp >37ºC
TARGET TEMP
36.5ºC±0.5ºC
Temp <36ºC
Remove any blanket, move to open cot if in incubator, contact transport team for advice.
Maintain temperature within this range
Put hat on baby, add 1 blanket or turn on incubator to lowest setting and adjust accordingly
RECORD TEMPERATURE EVERY 15 MINUTES
ABC and regular assessment is priority
Avoid hyperthermia >37.5C

Appendix 5. Parent Information Leaflet. Hypoxic Ischaemic Encephalopathy in the Newborn.

Parent Information leaflet
Hypoxic Ischaemic Encephalopathy in the Newborn

Introduction
Having a baby affected by Hypoxic Ischaemic Encephalopathy is very stressful for families. The team looking after your baby will keep you up to date with your baby's condition and explain what is happening. This leaflet gives you some background information but will not be able to say what will happen with your baby in detail. The medical and nursing teams will answer any questions so please ask.

What is Hypoxic Ischaemic Encephalopathy?
This is a term that we use to describe the way a baby behaves (encephalopathy) caused by a lack of oxygen (hypoxic) and blood flow (ischaemic) to a baby's brain. It is known as HIE for short.

HIE can affect newborn behaviour in many ways. A baby may be floppy and less alert than normal. They may need help with their breathing and seizures (also known as fits) may occur. Other babies can be jumpy or restless and appear more alert then usual.

As well as the brain, other organs such as the kidneys, liver and heart can be affected by the lack of oxygen. These organs will also be monitored carefully.

Why has this happened?
In the womb, oxygen reaches your baby through the placenta (afterbirth) and umbilical cord. HIE can occur if there has been a major problem with this oxygen supply in the womb. This might happen if the placenta comes away from the wall of the womb or the umbilical cord becomes entangled. Often the problem is not clear at the time of birth. Sometimes there is more information from having the placenta examined by a specialist in the coming weeks. The team looking after your baby will keep you informed about this. It may also help to discuss your labour and delivery with your obstetrician.

What treatment will be required?
Babies with HIE are cared for in the Neonatal Intensive Care Unit. This allows close monitoring of heart, lung, kidney and brain function, and supporting these where needed. This may involve your baby being on a ventilator, having "lines" (thin tubes) into their umbilicus (belly button) and bladder, and being attached to a brain monitor.

Babies with HIE are often cooled for the first three days of life. This involves carefully lowering a baby's temperature from the normal temperature of 37ºC (98.6ºF) to a temperature of 33.5ºC (92.3ºF). A normal body temperature is 37 ºC. Cooling is started as early as possible after birth. Pain relief will be given to prevent your baby feeling discomfort during cooling. At the end of the treatment the baby's temperature is slowly returned to normal. This period of cooling gives the brain a chance to recover from the injury. This is effective in some but not all babies. It has been shown to be a safe treatment with very few side effects.

During the first few days you may not be able to hold your baby because of the amount of monitoring equipment and the need to keep the body temperature very stable. You will still be able to touch and talk to your baby

and take part in cares, such as nappy changing and washing. If you are planning to breast feed you can express your milk and this can be given to your baby once they are well enough to digest it.

Will my baby be OK?
This is the most important question for families and often the hardest to answer. We know that each baby is different and predicting how any one baby may get on can be difficult.

Some babies do go on to make a full recovery. Other babies may develop disability as they grow up, which can range from very mild to severe. Some babies show such severe injury after birth that they do not survive.

We understand that families want to know as much as they can, and as we gather information we will discuss this with you.

The information that we collect includes monitoring of your baby's behaviour and brain waves, and if and how both of these recover. An MRI scan is usually done in the second week of life but even a scan will not be able to give an accurate prediction. Any baby affected with HIE who has received cooling treatment will be seen regularly in clinic over the first two years of life, where we will monitor your baby's progress and make sure that any extra help required is available as soon as possible.

What happens afterwards?
Once the cooling is over, the lines and monitoring can be removed, and your baby will be nursed in a normal cot, depending on how well your baby is.

Your baby will then need some time to learn to feed and continue recovery in hospital. Your baby will be discharged home when you and the staff think that your baby is ready. Once you are home you will be seen regularly by the team from your local hospital who will be able to answer any questions about your baby's progress.

Is there anything I should look out for?
Your baby's feeding and weight gain will be monitored as is usual with any newborn baby.

One rare complication of cooling that can occur is injury to the fat tissue in the skin. This causes red painful lumps in the skin in the first two months after cooling. These lumps will go away without lasting damage to the skin, but may result in high levels of calcium in the blood. High calcium levels can cause dehydration and sometimes injure the kidneys, so this will need correction.

The skin changes may not be seen straight away. Your baby may be more sleepy or floppy or restless. Your baby may not feed as well and lose weight or not gain weight as quickly as expected. There may be vomiting or constipation. If you are concerned that your baby may be affected by any of these problems you should contact the team that are caring for your baby.

Further information
If you wish to discuss anything about your baby's treatment, please speak to the doctor or nurse on the neonatal unit.

Appendix 6. Effect of hypothermia on medications (modified from Neonatal Formulary 2014)

Neonatal units should follow their local guidance/monographs pertaining to specific drug dosages. The following table delineates the known or expected effects of hypothermia on medications and as such, neonatal units may wish to modify local guidance taking the following information into account.

Drug	Effect of Therapeutic Hypothermia (TH)	Suggested dose adjustments during hypothermia
Antibiotics		
Beta-lactams	Pharmacokinetics not studied. Unlikely that TH has any effect.	No adjustment necessary.
Gentamicin	Unclear as coexisting renal injury may be present. Hearing impairment is present in 10% of infants who have undergone TH. Newborn data suggests there may be a 25-33% reduction in clearance.	Consider decreasing dosing frequency to once every 36 hours. Measure levels and consider withholding dose until level is known if renal impairment is present.
Vancomycin	No data in infants. No effect in adults.	No adjustment necessary.
Sedatives		
Morphine	The affinity of morphine for the opioid receptors is reduced in hypothermia rendering it less effective, and secondly, clearance is reduced.	50 micrograms/kg loading dose followed by an infusion started at 10-20 micrograms/kg/hour, titrating rate to the response of the infant. If adequately sedated, the dose should be reduced after 24–48 hours to lessen risk of accumulation and toxicity.
Fentanyl	Hypothermia can lead to a 25% increase in plasma fentanyl concentrations. There are insufficient data from hypothermic newborns to recommend any specific schedule; however, it would seem prudent to begin by halving the 'normothermic' dose.	Give loading dose of 5microgram/kg and then infuse at 0.75microgram/kg/h. Titrate according to the response of the infant. Consider reducing at 24–48 hours to lessen the risk of accumulation and toxicity.
Chloral hydrate	No data. Metabolised by liver. Potential risk of accumulation with repeated doses.	Consider starting at lower recommended dose. Ensure monitoring and access to respiratory support in non-ventilated patients.

<table>
<tr><th>Drug</th><th>Effect of Hypothermia</th><th>Suggested dose adjustments during hypothermia</th></tr>
<tr><td colspan="3">Anticonvulsants</td></tr>
<tr><td>Phenobarbital</td><td>Reduced metabolism by liver enzymes in TH may prolong half life two fold. Suppresses EEG and indices of neurological examination.</td><td>Give loading dose of 20mg/kg, and if required a further loading dose of 10-20mg/kg. Avoid maintenance.</td></tr>
<tr><td>Phenytoin</td><td>Levels higher in adults during TH due to reduced liver enzyme activity.</td><td>Give loading dose of 20mg/kg and monitor levels. Avoid maintenance dosing.</td></tr>
<tr><td>Midazolam</td><td>Levels higher during TH due to reduced liver enzyme activity. In cooled adults, levels are 5 fold higher. Cleared quickly during re-warming.</td><td>Dosing not established in neonates. Ensure monitoring and access to respiratory support in non-ventilated patients.</td></tr>
<tr><td>Clonazepam</td><td>No data. It is likely that levels will be higher during TH due to reduced liver enzyme activity.</td><td>Dosing not established in neonates. Ensure monitoring and access to respiratory support in non-ventilated patients.</td></tr>
<tr><td>Lidocaine</td><td>Lidocaine is metabolised by liver enzymes and during hypothermia clearance is reduced by 24%. Main adverse effects relate to arrhythmias which have been reported in neonatal TH. A modified regimen has been suggested.</td><td>
<table>
<tr><th></th><th colspan="2">Loading phase</th><th>Maintenance phase #1</th><th>Maintenance phase #2</th></tr>
<tr><td>Duration</td><td>10m</td><td>3.5h</td><td>12h</td><td>12h</td></tr>
<tr><td>Wt 2-2.5kg</td><td rowspan="2">2.5mg/kg</td><td>6mg/kg/h</td><td>3mg/kg/h</td><td>1.5mg/kg/h</td></tr>
<tr><td>Wt≥2.5kg</td><td>7mg/kg/h</td><td>3.5mg/kg/h</td><td>1.75mg/kg/h</td></tr>
</table>
</td></tr>
<tr><td colspan="3">Topiramate and Levetiracetam are included in this monograph as they have been reported to be among the drugs more commonly used off-label in neonates with seizures; inclusion should not be taken to imply that these drugs are now recommended.</td></tr>
<tr><td>Topiramate</td><td>Very limited data from infants undergoing hypothermia suggest a slower absorption and elimination. Oral preparation only.</td><td>5 mg/kg on the first day and then a lower dose (3 mg/kg daily) for the next 2 days</td></tr>
<tr><td>Levetiracetam</td><td>Predominantly renal excretion of levetiracetum means that TH should not impact on dosing; excretion may be affected by renal impairment.</td><td>40mg/kg loading dose followed by 10mg/kg once daily.</td></tr>
</table>

Drug	Effect of Therapeutic Hypothermia (TH)	Suggested dose adjustments during hypothermia
Neuromuscular blockers		
Pancuronium	Primarily excreted by the kidneys, with some biliary excretion. Studies in hypothermic adults show an initial increased requirement during early stages of hypothermia and then, when hypothermia is established, increased plasma concentrations. No data in neonates.	No dose adjustment necessary. The baby may seem to require more frequent dosing initially but once hypothermic the duration of action may be longer.
Vecuronium	Primarily eliminated via liver metabolism. Risks of accumulation increase during hypothermia particularly with infusions.	No initial dose adjustment is necessary but titrate the dose after 6–12 hours according to the need. Avoid infusion if possible.
Inotropes		
Adrenaline	There is no evidence to suggest that a different dosing strategy for inotropic support is needed during neonatal therapeutic hypothermia.	No dose adjustment necessary. Titrate according to response
Dopamine	As above	No dose adjustment necessary. Titrate according to response
Dobutamine	As above	No dose adjustment necessary. Titrate according to response
Milrinone	Limited data. Largely excreted unchanged in urine and is not likely to be affected by cooling but renal impairment reduce clearance.	No dose adjustment thought to be necessary. Titrate according to response.

Appendix 7. Useful Links

CFM:
http://cfmusers.wikispaces.com/

TOBY tecotherm guide:
http://www.npeu.ox.ac.uk/downloads/toby/TOBYTecotherm.pdf

Olympic CFM 6000 guide:
http://www.npeu.ox.ac.uk/downloads/toby/TOBY-CFMManual-6000.pdf

Criticool guides:
http://www.mtre.com/apage/115203.php

http://www.adhb.govt.nz/newborn/guidelines/neurology/CritiCoolQuickReferenceGuide_new.pdf

Brainz guide:
http://nervecenter.natus.com/index.cfm?page=clinicalArea_1&crid=173

BeBop:
http://bebop.nhs.uk

TOBY documents:
https://www.npeu.ox.ac.uk/tobyregister/docs

Resuscitation Council- Newborn Life support:
http://www.resus.org.uk/pages/nls.pdf

Appendix 8. Support for families

Organisation	Description
BeBop	A resource for parents about HIE, hypothermia and neuroprotection Web: http://bebop.nhs.uk/families
Birth Trauma Association	Helping people who are finding it hard to cope with their childbirth experience. Web: www.birthtraumaassociation.org.uk
Bliss	For babies born too soon, too small, too sick –providing vital support and advice to families of premature and sick babies across the UK. Helpline: 0500 618 140 Web: www.bliss.org.uk
Child Bereavement Trust	They 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
Newlife	Offers 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	A 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	A charity that supports 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
Together for Short Lives	Charity working to ensure that all children and young people, unlikely to live to reach adulthood, and their families get the best possible care and support whenever and wherever they need it. Helpline: 0845 108 2201 Web: www.togetherforshortlives.org.uk

Appendix 9. Dataset for Infants with Moderate and Severe Hypoxic-Ischaemic Encephalopathy or others infants treated with Hypothermia

Clinical dataset

Hospital number	
Hospital of birth	
Gestation (weeks)	
Birthweight (g)	
10 minute Apgar score:	
Time to heart rate >100 (m):	min
Lowest pH (cord in first hour):	
Decision taken to actively cool?	Y / N
If yes:	
Time to target temp (33-34C)	h min
Adverse events of cooling process	
Lowest temperature recorded (C)	
Adverse events relating to equipment	
Worst grade of HIE documented*	
Seizures documented	□ Clinical □ Electrical □ Both
Died	Y / N
If cooling discontinued <72h, reason	
MRI result* At age	 ……days
If no:	
Reason why not cooled	
Worst grade of HIE documented*	
Seizures	
Died	Y / N
Age at final follow up (mo)	months
Standardised assessment performed?	□ Bayleys □ Griffiths □ Other: □ None
Outcome at 2 years*:	□ Died □ Disability: □ mild / □ moderate / □ severe □ Cerebral palsy

* see notes overleaf

Transport dataset

Referring hospital number	
Name of referring unit	
Age when Cooling Centre contacted	h min
Age on arrival of team at referring hospital	h min
Temperature on arrival at referring unit (C)	
Method of temperature measurement prior to team arrival	□ Rectal □ Axilla □ Interscapular □ None
Temperature on departure (C)	
Type of transport	□ Road □ Air
Method of cooling on transport	
Age on arrival at Cooling Centre	h min
Temperature on arrival at Cooling Centre (C)	
Adverse events on retrieval	
Name of Cooling Centre	

Guidance for completion of dataset

Criteria for defining moderate and severe HI encephalopathy		
Category	**Moderate**	**Severe**
Level of consciousness	Lethargic	Stupor/coma
Spontaneous activity	Reduced May be seizures	None May be intractable seizures
Posture	Distal flexion/complete extension	Decerebrate
Tone	Reduced	Reduced, flaccid hypotonia
Primitive reflexes: **Suck** **Moro**	 Weak Incomplete	 Absent Absent
Autonomic system: **HR** **RR** **Pupils**	 Bradycardia Periodic Constricted	 Variable Apnoeic Deviated/dilated/nonreactive

MRI report (suggested outputs)		
Age at scan (d)		
Region of the brain	**Normal**	**Altered**
Cortex		
White matter		
Basal ganglia		
Thalami		
Internal capsule		
Corpus callosum		
Cerebellum		
Brainstem		
Extracerebral space		
Ventricles		
Myelin		

Criteria for defining mild, moderate and severe disability at 2 years			
	Mild disability	**Moderate disability**	**Severe disability**
Definition	Some loss of function but able to function independently	Aids or assistance needed for some tasks. Moderate difficulty in doing some activities	Unable to undertake activity without aids or assistance most of the time or completely dependent on carer
Cognitive	MDI 70-84	MDI 55-69	MDI <55
Neuromotor	GMFCS level 1 Arms: clumsiness of fine movements but independent	GMFCS level 2-3 Arms: able to feed or self-dress but needs aids, or has some difficulty	GMFCS level 4-5 Arms: unable to undertake activity without aids/assistance most of the time or completely dependent on carer
Vision	Blind in one eye with good vision in the contralateral eye	Moderately reduced vision but better than severe visual impairment	Blind or can only perceive light/light reflecting objects
Other **eg medical**	Chronic medical condition requiring >1 admission per 6months or causing growth problems, or requiring special diet; epilepsy with >1fit per month	Medical condition needs supervision most of the time or meeting definition of moderate disability	Condition needs constant supervision/aid-includes home oxygen, suction, communication severely limited

Newborn Observation Chart

NHS Lothian

Consultant Neonatologist:	Name:
Date chart commenced:	DOB:
Birth weight: ____kgs Time of birth:	UHPI:
	CHI No:

Contents:

All babies identified with risk factors should have a full set of observations within 1 hour of identification.
A blood glucose should only be recorded if there is a clinical need – see separate hypogycaemia protocol.

Babies at risk of hypoglycaemia:

- ☐ Infant of diabetic mother
- ☐ BWt <3kg, **AND** <2nd centile (see centiles below)
- ☐ 35^{+0} - 36^{+6} weeks
- ☐ Mother on beta blockers
- ☐ Cord pH <7.0 (see separate guideline)

Other 'at risk' babies identified after birth:

- ☐ Poor tone, excess lethargy or unwell (do BG, observations and ask paediatrician to attend)
- ☐ Sodium ≥150mmol/l and/or >12% Weight loss

Identification of a baby with risk factors that requires postnatal observations. A baby can have risk factors due to maternal antenatal, intrapartum and postnatal conditions and/or the fetal and postnatal condition of the baby.

ANTENATAL

Maternal condition

- ☐ Maternal illness including: Maternal diabetes, hypertension requiring treatment, maternal thyroid disease
- ☐ Maternal drug use
- ☐ Prolonged rupture of membranes ≥ 24 hrs
- ☐ Chorioamnionitis
- ☐ GBS positive mothers
- ☐ Previous infant with invasive early onset GBS sepsis
- ☐ Other specified conditions on TRAK requiring postnatal observations of the baby

INTRAPARTUM

- ☐ Baby born through meconium stained liquor AND required resuscitation at delivery (including aeration/inflation breaths)
- ☐ Maternal intrapartum pyrexia of ≥ 38°C
- ☐ Antibiotic treatment given to the mother for confirmed/suspected infection 24 hrs before or after birth, and during labour
- ☐ Cord pH of < 7.0

POSTNATAL

- ☐ Gestation <37 weeks
- ☐ Suspected or confirmed infection in a co-twin

Signs at postnatal stage

- ☐ Abnormal movements
- ☐ Altered behaviour or responsiveness; lethargy/irritability
- ☐ Respiratory distress
- ☐ Central cyanosis
- ☐ Jaundice within 24 hrs
- ☐ Hypo/hyperglycaemia
- ☐ Temperature instability
- ☐ Local signs of infection
- ☐ Feeding intolerance
- ☐ Swelling of the abdomen
- ☐ Baby clinically unwell
- ☐ Nursery nurse/midwife instinctively concerned

CENTILES 2nd Centile for weight (g) by gestation (weeks)

	MALE	FEMALE
37	2100	2000
38	2300	2200
39	2500	2400
40	2700	2600
41	2850	2700
42	3000	2800

Signature: **Date/Time:**

NEWS Observation chart

Feeding behaviour	Normal												
	Abnormal												
Date (DD/MM/YY)													
Time (24hr)													
Temperature Ranges (°C)	38												
	37.5												
	37												
	36.5												
	36												
Respiratory Rate Ranges (breaths per minute)	80												
	75												
	70												
	65												
	60												
	55												
	50												
	45												
	40												
	35												
	30												
	25												
Heart Rate Ranges (beats per minute)	190												
	180												
	170												
	160												
	150												
	140												
	130												
	120												
	110												
	100												
	90												
Work of Breathing	Increased*												
	Normal												
Colour	Pale/Mottled/Dusky												
	Normal												
	Jaundiced at <24hrs of life												
Behaviour/ Tone	Settled, normal												
	Jittery, excessive crying												
	Floppy, unresponsive												
Action - please sign/initial													

***Signs of Increased Work of Breathing:**
Grunting; Wheeze or stridor; Chest recession

Guidance on observation frequency

0 hrs	You have identified a baby with one or more risk factors. Update parents.			**A**
1 hrs	Perform a NEWS set of observations and assessment within 1 hour. Identify category of care for baby and update parents.			**B**
	Green risk	**Amber risk**	**Red risk**	**C**
	Continue care	Following initial observations agree a plan of care with the shift coordinator and document in the baby's notes.	If any baby falls into the red category on NEWS chart, a paediatrician should examine and review the baby and formulate a care plan.	**D**
2 hrs	Repeat observation after 1 hour. Review category of care and update parents.			**E**
	Well + risk factors	**Borderline**	**Unwell**	**F**
	Continue care	If baby remains amber, contact the paediatrician to assess the baby, categorise care and formulate a plan of care.	If baby's category of care becomes amber or red at any time repeat steps from D.	**G**
4 hrs	Repeat observations and review category of care.			**H**
	Well + risk factors	**Borderline**	**Unwell**	**I**
	Discuss baby and observations with paediatrician. Formulate observation and management plan for next 8 hours. Maximum 2 hourly. Minimum to stop. **Babies with risk factors for infection, Group B strep and/or PROM must continue 2 hourly observations for a further 8 hours.**	If baby's category of care becomes amber or red at any time repeat steps from D.	If baby's category of care becomes amber or red at any time repeat steps from D.	**J**
12 hrs	If baby's observations are stable at 12 hours and remain in the **green category** no further observations required.			**K**

1 NEWS methodology

1.1 Initial assessment

The midwife/nursery nurse should screen all babies (not admitted to the neonatal unit) to identify those who fulfil the at risk criteria. All infants identified as at risk should have a full set of observations recorded within 1 hour.

1.2 Observations

Observations should include:

- temperature
- respiratory rate
- heart rate
- work of breathing
- colour
- behaviour
- feeding behaviour

These observation should be recorded on the *Neonatal Early Warning System (NEWS) chart.*
Blood glucose should only be recorded if there is a clinical need (see clinical guidelines for full protocol).
Babies at risk of hypoglycaemia are:

- infants of a diabetic mother
- birth weight <3kg, **AND** <2nd centile (see centiles on clinical guideline)
- 35+0 - 36+6 weeks gestation
- mother on beta blockers
- Cord pH <7.0

If the need for a blood glucose is not clear, advice should be sought from the midwife-in-charge, neonatal junior doctor or ANNP.

1.3 Categorisation of the infant

Following the observations the infant should be categorised as 'green', 'amber' or 'red'. Babies classified as 'green' should have all their observations in the green category; if any of the observations on the chart fall into the amber category then the baby should be classified as 'amber' and if any are red then the baby is in the 'red' category.

1. green
2. amber
3. red

1.3.1 Action to take for infants in green category

Continue with normal postnatal care. If remains 'green' at 4 hours, discuss observations with paediatrician. Formulate observation and management plan for next 8 hours. Maximum 2 hourly. Minimum to stop. Babies with risk factors for infection, Group B strep and PROM must continue 2 hourly observations for a further 8 hours.

1.3.2 Action to for infants in amber category

Inform shift lead of any infant in the amber category. A plan of care should be agreed and documented and observations should be repeated after 1 hour, or more frequently if the midwife/nursery nurse is concerned, or the infant's condition changes. The parent(s) should be informed of the concerns and the plan of care. Following the repeat set of observations, the plan of care should be evaluated and if the infant is now classed as 'green' the actions described in section 1.3.1 followed.

1.3.3 Action to take for infants in red category

The neonatal junior doctor/ANNP should examine and assess each infant in the red category. A plan of care should be agreed and documented by the neonatal junior doctor/ANNP and observations then recorded at the desired frequency. The parent(s) should be informed of the concerns and the plan of care.
The plan of care should be documented in the baby's hospital notes and communicated to the midwife/ nursery nurse caring for the baby. The plan of care should include frequency of observations, frequency of feed, volume of feed interventions and review period. The plan of care should be signed by the neonatal junior doctor/ANNP.

1.4 Escalation protocol

Once a plan of care has been agreed and documented, observations should continue at the desired frequency. If the midwife/nursery nurse has any further concerns a full set of observations should be taken immediately and the neonatal junior doctor/ANNP should be contacted again. Following this further review, a new plan of care should be agreed and documented.