Therapeutic Hypothermia for Neonatal Encephalopathy - A Framework for Practice Consultation Responses

Submitted by Dr Ruth Allen, Consultant Paediatric Radiologist, Royal Hospital for Children, Glasgow ruth.allen@ggc.scot.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
General comments	general	The lack of involvement of radiologists in the production of these guidelines is disappointing. This is not a reflection on the ability or knowledge of those involved, but the reality is that the majority of studies will be performed with and reported by paediatric radiologists or neuro radiologists with a paediatric interest.
16	general	Earlier text in document suggests imaging days 5 to 7 – text here suggests second week of life. Risk of being too early in first 2 days accepted (most site will not image while cooling unless catastrophic / exceptional circumstances) however it is not clear why imaging cant commence after cooling – in second week you risk pseudonormalistion of diffusion, reduction in yeild of MRS and are too early for T1 changes to be reliably present – important if you are looking for subtle basal ganglia changes
17	Field strength	While 3T might be better for MRS the wording of this suggests it shouldn't be used – it is usable and achievable at 1.5T and may be more accessible for many units
17		As above DT-MRI can also be achieved at 1.5T – it has not be included in the 1.5 T sequences and there are no details on suggested number of directions
18		Comments on DT and FA maps but not on ADC maps
18		Use of Tarquin – this is opensource, not CE marked and therefore does not fall under MDR
18		Absolute quantification in MRS is not realistic or practicable in a clinical setting
18		Comment on use of centre specific normal ranges for MRS – is there consensus

18		Comment on use of MRS in periventricular white matter would be useful
Response		**The panel included a number of academic neonatologists who have extensive experience in the performance, interpretation and prognosis in relation to MRI and MRS. In terms of the timing we recommend between day 5 and 15 and acknowledge there are various pros and cons for different periods. We do recognise that MRS can provide useful prognostic information but appreciate there are currently some limitations to wider usage**

Submitted by Dr Anusha Arasu, Consultant Neonatologist, King's College Hospital anusha.arasu@nhs.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
Page 14	General	Apologies for the length of this comment- When you describe "Follow up" it currently implies sequential reviews. If you don't mean this, you may want to use just "outcomes at 2 years". Agree on Formal testing for ND at 2 years. Need adding a structured general and neurology examination. Good practice in my view, for babies with hypoxia ischaemia that have had TH, should include a structured follow up programme run by the neonatal service as recommended by NICE. These reviews aim at early intervention and informing aspects of neonatal care that could potentially be modified. General follow up 1- First review after discharge – parents would normally expect a summary and interpretation of events that happened in NICU. Most parents need psychological support for PTSD 2- At 3-6 months of age: Growth (mainly head circumference) and early identification of subcutaneous fat necrosis is warranted- the baby may need metabolic screening for hypercalciuria, kidney scans and referrals as appropriate. 3- 0-12 months- Growth and Feeding issues with sensory problems are commonplace and MDT approach with SALT and dietitian should be available. Behaviour problems may arise at 12 months and needs monitoring. Neurodevelopmental (ND) follow up 1- In the same way that neurology sequence is advised in NICU, ND follow up should be offered during the first two years- If possible all the way to 4-6 years- with reviews of at least 3-6 months intervals depending on the case 2- At the three months review- Prechtl General Movements are, in addition to the brain imaging, an excellent predictor of motor function. DVM (Delayed Visual Maturation) is also seen at this review in a fraction of babies that will need close monitoring with consideration for early referrals to ophthalmology and neuro-ophthalmology. 3- At the 3-6-12-18 months of age- transient dystonias are present in a good number of babies- Reviews at these ages will identify issues with tone and asymmetries and monitor their progression. Sensory issues are usually present and Early Intervention should be offered. Formal testing for development is warranted as it may be the only way of identifying subtle problems in specific areas- (visual impairments, hearing impairments, speech and communication in general) 4- At 2 and 4 years – Full neurodevelopmental assessment will notice problems with behaviour, attention, cognition, readiness for

		school should be assessed and appropriate referrals made.
Response		**We agree that follow up should involve sequential reviews with a multidisciplinary team . We did not feel that there was a clear evidence base to any particular pattern or frequency. The NICE guidance covers follow up of preterm infants**

Submitted by Dr Simon Clark, Neonatal Consultant, Sheffield Teaching Hospitals simon.clark4@nhs.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
9, infants<36 weeks	Line 5	Expecting a second opinion for cooling a baby of 33 to 35 weeks is unnecessary. Any neonatal consultant should be able to make this decision. Otherwise they should not be a neonatal consultant. Additionally, the vast majority of units do not have 2 consultants available 24 hours per day. It is likely that most will only have one consultant available for 128 hours per week, which is the most likely time when a baby requiring cooling would be born.
Response		**As we state this is currently an area of practice without a good evidence base. We maintain that a second opinion would be helpful in this situation**

Submitted by Dr Medhat Ezzat, Consultant Neonatologist and Honorary Senior Clinical Lecturer, Aberdeen University m.ezzat@nhs.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
8		Although the TC has changed the landscape of resuscitation and outcome of asphyxiated babies however adding some prognostic markers like Apgar score(e.g if 0 at 10 minutes is associated with mortality / ND abnormalities at 18-24 m in nearly ¾

		of cooled babies7 also pH of < 7 is associated with CP
		Having predictor markers can help during the consultation with parents and to make a better informed decision and management plan particularly for babies who are born in DGH and have severe encephalopathy ,and are transported to a regional centre where reorientation of care may be offered
Response		**We agree that a number of factors need to be considered in providing a prognosis and clearly where reorientation of care is being considered. However the sensitivity and specificity of early markers is not sufficient to give a definitive prognosis shortly after birth.**

Submitted by Dr Claudia Chetcuti Ganado, Neonatal Consultant, Luton & Dunstable Hospital claudia.chetcutiganado@ldh.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
page 6	Table	Eligibility criteria have to include CFM abnormalities worries me that some encephalopathic infants miss cooling. Some encephalopathic infants present with minimal encephalopathy and only develop seizures after 6 hours due to the evolutionary nature of HIE. If they had a normal EEG in first 6 hours these infants would not be cooled.
Page 9	Line 2	Evidence that starting cooling >12 hours of age harmful in animal models
		There should be formal logs of training and competence in the key skills of standardised neurological examination and its interpretation, and in aEEG interpretation. (*). Is it worth liaising with the training colleges to ensure competencies in these areas. We have created an e learning module which I shared with BAPM on CFM interpretation and training. I also worry about Level 1 and 2 units having the adequate training in neurological examination. There is a very good training video by Frances Cowan. If we were to include these training resources and make it part of paediatric training through liaison by the colleges it might be of benefit. I like the table on neurological examination. Is it worth supplementing it with some pictures such as the Dubowitz screening neurological examination chart?
Response		**We recommend selection of babies based on that used in the TOBY trial. We recognise there is one trial that shows potential benefit to infants where cooling was commenced between 6 and 24 hrs but our recommendations in this area reflect the limitations of the evidence. We recommend that training be coordinated at network level and that competent evaulaiton from birth and throughout a referral pathway is critical**

Submitted by Dr Rosaline Garr, Consultant Paediatrician, St Helens & Knowsley Teaching Hospitals rosaline.garr@sthk.nhs.uk

Page number/ heading /	Line number/ 'general' for	Comments

general comments	comments	Please insert each new comment in a new row.
Page 11	Second paragraph	'*Ongoing care of the cooled infant is an intensive care activity and should only be undertaken in NICUs'* In large LNU's with over 4000 births could therapeutic hypothermia not be provided to the infants locally as long as the relevant standards are adhered to, especially if the infant is not ventilated (no respiratory failure) in order to avoid separation of families?
Response		**In the opinion of the working party given the incidence of therapeutic hypothermia there is insufficient ongoing practice in any LNU or SCU**

Submitted by Dr Cath Harrison, Consultant Neonatologist, Leeds Teaching Hospitals cath.harrison@nhs.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
11	3rd paragraph 1st sentence	To be replaced with : *'Infants in whom TH has been initiated should be transferred to the appropriate NICU by an established transport service with ongoing servo controlled cooling using central temperature monitoring, in addition to all other necessary intensive care therapy and monitoring.* Comments from NTG- At present technology does not permit reliable aEEG monitoring DURING transfer and this needs to be removed from the guidance
11	After 3rd paragraph	Insert: *Where local units do not have access to aEEG, transport services should consider taking portable CFM with them to facilitate decision making.* *Suitable platforms for sharing data from CFM need to be in place to allow data from referring hospitals, and/or transport teams, to be shared with tertiary cooling centres to allow correct interpretation and ongoing management. Approaches to this may differ between regions.*
Response		**We would recommend that transport teams have access to portible aEEG equipment but recognise the limitations of this while the baby is in transit.**

Submitted by Kelly Harvey, Quality Improvement Lead Nurse, North West Neonatal Operational Delivery Network kelly.harvey@alderhey.nhs.uk

"I just wanted to note as part of the cooling group my details are not correct on the framework. I am an ANNP which I am happy to be on there but my current role is lead nurse for the North West Neonatal Network and NNA (Neonatal Nurses Association) representative for the group – could these be added, I am based at Alder Hey Foundation Trust too. Thanks."

So… Ms Kelly Harvey, ANNP, Lead Nurse for the North West Neonatal Network and NNA (Neonatal Nurses Association) representative, Alder Hey Foundation Trust.

Submitted by Dr Nicholas Lipscomb, Consultant Paediatrician, Western Health and Social Care Trust nicholas.lipscomb@westerntrust.hscni.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
11	General	The practicality of all SCBU having staff trained to do and interpret aEEG is unrealistic as frequency of managing such patients mean skills will not be maintained. Far better to highlight the need for any baby meeting criteria A and B to be urgently discussed with a NICU with regard to transfer for cooling.
Response		**We recognise the difficulty of gaining and maintaining skills, which is why we recommend this is supported by collaboration at network level.**

Submitted by Dr Naaz Merchant, Consultant Neonatologist, West Hertfordshire NHS Trust nazakat.merchant@nhs.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
Pg 3	Reference to local cooling centre	This might read better as local cooling centre or regional transport team – with the proposal for decision support in ANTS (and in other retrieval services) the decisions rest with the transport team which has a number of benefits including reducing the confusion around referral pathways (grey case/direct referral,) single contact number and single point of referral, minimising the number of times information is shared between teams and allowing teams to focus on the clinical care, overview of activity across a region impacting on decision making around prioritisation and preparation and stabilisation for transfer
Pg 6	Criteria A for eligibility	Toby criteria was >=36 weeks, APGAR <=5, Base deficit >=16. If the BAPM framework criteria is revised to >36 weeks etc, this needs further explanation
dPg 6	Criteria B for eligibility	Why are abnormal reflexes and weak and absent suck on different bullet points. It should be abnormal reflexes including weak or absent suck

Pg 7	"Infants starting any form of TH, including switching the resuscitaire heater off"	NLS guidance clearly states that resuscitation takes priority and resuscitaire heater should not be switched off. This has also been raised in a recent HSIB investigation as a concern if cooling was started during resuscitation. Also the baby will not have completed criteria C
Pg 7	Clinical seizures should only be treated if there is electrical correlation on aEEG-	Sometimes it may be difficult e.g.lack of trained personnel for correct placement of EEG leads and interpretation. If well documented seizures are seen clinically with senior input these should be treated if there is delay in aEEG acquisition. On the other hand not all seizures have aEEG correlates and again if senior input present anticonvulsants can be given. It may be justified to wait for aEEG confirmation for subtle seizures with no haemodynamic or respiratory effects or when uncertain but not clear seizures that are having haemodynamic or respiratory consequences
Pg 7	paragraph 2 when the document is referring to the treatment of clinical seizures it says that teams should discuss this with the network NICU	Page 7 paragraph 2 when the document is referring to the treatment of clinical seizures it says that teams should discuss this with the network NICU consultant but in fact in many of these cases the baby may already be under the care of the retrieval team as the seizures may not be present at the time of a decision to cool and transfer and referral to an additional team within the Network may in fact be an additional and potentially unnecessary step could we advocate that this reads network NICU Consultant or if appropriate regional neonatal transport Consultant
Pg 7		Add- Accurate documentation of the timing of administered anticonvulsant in relation to aEEG should take place
Pg 7	prevented from cooling below 33.5 C	Please give a range (between 33-34C) ideally at 33.5C
Pg 9	Cooling in 33-36 weeks' gestation	BAPM suggests an ambivalent approach. Should we be taking a stance that cooling in premature infants should be done only in research settings (Laptook 2017).
Pg 9	Cooling between 6-24 hours	There may be evidence of harm when cooling after 12 hours in rats - Thorensen
Pg 10	All infants undergoing TH should have an MRI scan undertaken between 5 and 15 days	If the baby is preterm or less than 38 weeks, ideally the MRI scan should be postponed till 40-42 weeks so that appropriate myelination can be documented aiding prognostication (Prof Rutherford personal communication)
Pg 10	This (MRI) would best be performed in the treating NICU	Do not agree with this statement as some level 2 may be well placed to do the scans and discussing these results, rather than bed blocking level 3 units.
Pg 10	MRS Lactate/N acetyl aspartate (Lac/NAA) of the basal ganglia and thalamus should be performed with the MRI at 5-10 days after birth	Discrepancy in dates: MRS at 5-10 days while MRI is 5-14 days Pg 16 says 5-15 days for MRS
	Add comment on rewarming early	Does not address rewarming early. Agree ideally there should be completion of Criteria a, b, c before cooling is commenced but this does may not happen at a SCBU or a LNU and if cooling has been started and CFM and neurological status is normal even by 6 hours- should cooling be continued. – Need a consensus. This was discussed in the EOE neuroprotection group and it was felt that if TH has been commenced it should continue for 72 hrs as standard.

Pg 11	Training in aEEG interpretation	Ideally this should form part of training and ideally coordinated by the deanery with a competency package
Pg 12	aEEG	Nurses need to know when to escalate concerns on the aEEG to the medical team. There should be appropriate monitoring and documentation
Pg 14	appropriate tests should be undertaken to ensure that the assessment of prognosis has not been confused by drug effects	What tests? Please expand
Pg 14	In infants in whom it is possible to deliver TH with physiological stability, it is recommended that such consideration be delayed for 48 hours to assess any recovery before considering reorientation of care	48 hours from starting cooling or from birth or from anticonvulsant medication? please be more specific.
Pg 20	Breast milk	If breast milk not available donor milk should be used
Pg 20	Coagulopathy is physiological	Clotting profile should not be done unless active bleeding
Pg 21	Lidocaine	Lidocaine should not be given following phenytoin
	In babies who do not respond to phenobarbital consider phenytoin IV 20 mg/kg over 30 minutes. Levetiracetam 20mg/kg IV over 15 minutes with repeat doses to a maximum of 40 mg/kg, or midazolam 150 micrograms/kg over 5 minutes followed by a continuous infusion of 60 micrograms/kg/hour (max 300 microgram/kg/h) being aware that midazolam levels will accumulate. Lidocaine has also been shown to be effective but dosing should be modified in TH (35).	Needs more clarity as to which is recommended as second and third line and referenced
Pg 21	Add: Prophylactic	Please incorporate re prophylactic anticonvulsants

	anticonvulsants	A Cochrane review demonstrated that there is no evidence to support the use of prophylactic anticonvulsants after perinatal asphyxia. (Evans D, Levene M, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. Cochrane Database Syst Rev 2007;18:CD001240)
Pg 22	If repeated examination within the 6 hours after birth suggests deterioration to stage 2 or 3, apply aEEG if not already in place and cool if meet criterion C.	This will necessitate that all infants who meet criteria A should be admitted to NICU for observation an CFM monitoring for the first 6 hours of life. This is not clear in the text should we specifically recommend this? I don't think we imply that all babies meeting criterion A should be admitted. Just that they get examined. I don't think we need to change this.
Pg 22	Modified Sarnat and Sarnat Score	Why other scores not used eg. Thompson, Modified Thompson not considered which are easier to do. Is this for standardisation? Explanation would be useful. Also timepoints of examination: 6, 12, 24, 48 hrs would be useful. No change
Pg 24	Ref 5	5 Reference- Please included 2013 Cochrane review
Pg 24	Ref 31	Not complete
Scenario		Term baby abnormal CTG, required resuscitation, intubation, ventilation, poor cord gases pH <7, BE-16, floppy, no suck, neurologically abnormal, normal CFM throughout According to BAPM framework the baby would not meet the criteria for cooling. EOE neuroprotection group had a discussion and it was felt that it would need senior and possibly 2 consultant input (local and tertiary) but we would be inclined to cool this baby. Sarkar 2008. Including aEEG as absolute measure would miss infants who are clearly encephalopathic. aEEG should be used in decision making in infants where we are not sure about criteria B.
Response		**This document is a framework document and seeks to base its recommendations on evidence. It recognises there may be some variation in guidelines generated from it. It also recognises that there is clinical uncertainty in some areas and suggests that such areas can be reasonably approached using an individualised approach employing a second opinion where necessary. It does recommend that availability of aEEG be extended to all paediatric units where babies are born.** **NLS says: The temperature must be actively maintained between 36.5°C and 37.5°C after birth unless a decision has been taken to start therapeutic hypothermia.** **We recommend where infants have met criteria a, b and cooling should continue for 72 hours**

Submitted by Zoë Moulton, Policy Manager, Royal College of Obstetricians and Gynaecologists zmoulton@rcog.org.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
General comment	General	The Royal College of Obstetricians and Gynaecologists (RCOG) welcomes this framework and particularly the recommendation that a consistent definition of hypoxic-ischaemic encephalopathy is used for diagnostic, treatment, documentation and audit

		purposes.
General comment	General	There does not appear to be any recognition that the threshold for TH varies across the UK. This is important as it may lead to confusion when TH rates are used as a marker of intrapartum care. This may mean that some babies are given TH when they do not meet the criteria. Sometimes they do well from the treatment, but it can lead to prolonged investigations. This can be distressing for the mother and her family as well as the staff involved. NHS Resolution and HSIB have now moved away from TH as an entry criterion to their investigations, at least partly because of this issue of lack of thresholds and criteria. The RCOG recommends that, as suggested in the paper, all babies who do not meet the standard entry criteria for TH should be part of a controlled research study. Furthermore, there should be some coordinated follow up.
Page 3 Page 8 And general	Line 15-16 and 20 General	'Parents' should be changed to 'parent/parents' so that the document does not assume two parents will be present. It could also be changed to 'the mother and her family'. The two sentences should therefore be changed to the something along the following lines: "Early open and honest communication by senior members of the neonatal team with the parent/parents is essential. There should be no barriers to the parent/parents visiting and caring for their baby." Similarly, this should be changed on line 20 and throughout the document where this occurs.
Page 6	Lines 31-35 (paragraph 2 under heading 'Notes on the practical application of TOBY criteria')	The following paragraph is important and therefore requires highlighting, for example, by putting it in a box or making it bold. Currently the text is lost within the other bits of text. "Neonatal encephalopathy evolves with time. Therefore, infants who meet at least one A criterion but on initial examination are neurologically normal should be reviewed several times in the first 6 hours of life by a trained practitioner who is competent in neonatal neurological examination. (*) It is also recognised that aEEG may not be available in all circumstances, and failure to obtain aEEG should not prevent or delay treatment if there is evidence from A and B criteria."
Pages 6-7	Section entitled: "Notes on the practical application of TOBY criteria"	Perhaps an interactive diagram supporting this text would be useful here as a visual aid for practitioners.
Page 7	Line 34	Reiterate that transfers and treatment should start as soon as possible by editing the sentence to say: "This transfer should be undertaken as an emergency so that treatment can be started <u>as soon as possible,</u> within 6 hours."
Page 15	Lines 24-26	This is an important sentence and we would recommend reminding clinicians that listening is key. The sentence could be amended to the following:

		"Given the proven benefit of TH and its safety, formal written parental consent is not considered necessary, but it is important that parents are as fully informed as possible and their views are listened to and fully taken into account when making clinical decisions."
Pages 20-21	All text	Full stops should be removed from all bullet points to make it unified across the points and pages. ….
Response		**As a framework document this sets the basis for guidelines that will follow it. We agree that involvement , communication listening and talking into account the views of parents as a group is very important.**

Submitted by Louise Page, Clinical Leadership, Healthcare Safety Investigation Branch louise.page@hsib.org.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
P3 And P6	11 9	**'should be reviewed several times in the first 6 hours of life by a trained practitioner who is competent in neonatal neurological examination.'** We welcome this advice as our investigations have observed this is not always undertaken. Staff would benefit from additional guidance as to what **'several times'** means in practical terms – how many times, at what time interval?
P5	10	**'handicap'** We would ask BAPM to reconsider the use of this term, which we believe to be outdated terminology. We would suggest that 'a child with a severe disability' might be a suitable alternative.
P7		**'Infants starting any form of TH, including switching the resuscitaire heater off, should have their temperature continuously monitored ideally using an intracorporeal (e.g. rectal) temperature probe. Cooling should only be considered once cardiorespiratory stability has been achieved including heart rate and oxygen saturation. (*) If infants are maintained with passive hypothermia (removal of external heat sources and clothing) while full assessment is undertaken , they must be continuously monitored with rectal temperature, and prevented from cooling below 33.5 C using a servo-controlled system if necessary. Alternatively, if the aim is normothermia but that requires an incubator then continuous rectal temperature should be used to prevent overheating. (*)'**

		We appreciate this clear message as we have noted wide variation in practice during our investigations. We consider this recommended care will have equipment and training implications for SCUs and some LNUs that will require investment.
P8	General	We consider it would be helpful for the need to use interpretation services for some families to be more explicitly mentioned in this section.
P8	General	We would be grateful if BAPM might consider mentioning a referral to the HSIB maternity programme would be indicated for those babies that meet the referral criteria and were born in England.
P10		**'All infants undergoing TH should have a MRI scan undertaken between 5 and 15 days, preferably between 5 and 7 days of birth. This would best be performed in the treating NICU and should be reported by a consultant radiologist with expertise in neonatal brain MRI interpretation (29).'** We welcome this clarity. We have observed that some babies are transferred back to their 'home' SCU or LNU prior to day 5 and additional guidance in that situation would be welcomed. Should they be transferred to the NICU site for the MRI?
P10		**'Where possible, Proton (1H) MRS Lactate/N acetyl aspartate (Lac/NAA) of the basal ganglia and thalamus should be performed with the MRI at 5-10 days after birth. This is the most accurate predictor of outcome in babies who have undergone TH'** We have observed this is not currently being done for many babies in England that have undergone TH. We would suggest that a comment about the availability of this resource is mentioned alongside this recommendation.
P13		**'Prognosis should be discussed with parents in a timely manner before discharge from the NICU and summarised in a written communication to parents and other health professionals in the referring unit and primary care'** We consider it would be helpful for the need to use interpretation services for some families to be more explicitly mentioned in this section.
P15		**'There should be timely multidisciplinary and multispecialty review, following standardised Trust risk management procedures, of the perinatal care of any infant who undergoes TH with a particular focus on avoidable factors. This should be discussed with parents in a timely open and honest way, meeting standards of GMC/NMC duty of candour'** This is another potential opportunity to mention the role of HSIB for term cooled babies in England.
Response		**'There should be formal logs of training and competence in the key skills of standardised neurological examination and its interpretation, and in aEEG interpretation. (*) There should be clear, contemporaneous and complete documentation of decision making and management of cases where TH has been considered and initiated or not initiated including regular review of neurology and aEEG in the patient record. This should include documentation of discussions with parents. Given the proven benefit of TH and its safety, formal written parental consent is not considered necessary, but it is important that parents are as fully informed as possible and their views taken into account. (*)'**

		We are supportive of this statement. We have noticed variation in the training and confidence of staff to interpret aEEG monitoring.
P20-21	Appendix 2 General Care	This section does not mention the importance of regular checking of skin integrity, in terms of cold burn necrosis from the cooling mattress. We consider skin integrity checks and repositioning are important during TH.
Response		**As a framework document covering the whole UK we chose not to highlight differences in NHS structure between the home nations. We recognise that there are service, education and training changes that will be needed to fully implement these recommendations. The need for clear understandable two way communication with parents is critical and obviously involves the use of interpreters where necessary.**

Submitted by Catherine Pain, Consultant Neonatologist, Royal Hampshire County Hospital katherine.pain@hhft.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
6	Criteria A	Has there been consideration of including raised lactate in the criteria for acidosis?
6	general	Worth a caveat of not due to opiate/drug effect? Could cause need for ongoing respiratory support and ongoing neurological depression
6	Criteria C	CFAM in SCBU or LNU – if this is recommended it will be a big change of practice. There will need to be very clear guidelines either regionally or nationally regarding which kit is required and how to use it with relevant support for staff training as it is not something which is familiar to most medical/nursing teams currently. I also think interpretation can be hard if not done regularly so there will need to be the facility for local NICU to see the CFAM trace and comment in a timely manner. Telemedicine could work but the onus should be on networks to find a system which works not on each individual unit.
7	Paragraph 2	Only treat clinical seizures when correlated with aEEG or after discussion with NICU consultant. Is this really what the panel think is best? Given aEEG will take time to set up (especially in the context of a team who are less familiar with doing so) or discussing with a consultant will take time, this could significantly delay treating a seizure and my understanding is that prolonged seizures are detrimental to outcome. This is a TH guide but I suspect will catch on and no neonatal seizures will then be treated without CFAM.
11	First paragraph	TH in SCBU and LNU - if this is recommended it will be a big change of practice. There will need to be very clear guidelines either regionally or nationally regarding which kit is required and how to use it with relevant support for staff training as it is not something which is familiar to most medical/nursing teams currently. Getting it wrong and therefore having a baby who is cooled too far or not cooled effectively (and transfer delayed due to false reassurance that TH is underway) could be detrimental.

Feedback form	Second column	There are no line numbers in the document so this form is somewhat hard to use! Also had to copy into word as no way to save to then email.
Response		**The framework recommends using the criteria of the TOBY study. This did not use lactate. The working group recognise that new equipment, training and maintenance of skills will be necessary to fully implement this framework. The working group recognised there is a tension between diagnostic accuracy, over and under treatment of seizures which we have tried to balance.**

Submitted by Dr Balamurugan Palanisami, Consultant Neonatologist, Liverpool Women's Hospital balamurugan.palanisami@lwh.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
Page 7, second paragraph, general comment	Line 1, general comment	Clinical seizures should only be treated if there is electrical correlation on aEEG. There could be circumstances of brain stem seizures resulting in cardiorespiratory instability without aEEG changes.
Page 9, Infants less than 36 weeks gestation, general comment	Line 5, general comment	In our hospital, we offer Therapeutic Hypothermia for babies more than 34 weeks gestation. Parents are counselled about therapeutic hypothermia in 34-36 weeks about the existing evidence. Getting second opinion during out off hours within 6 hours of age is going to be challenging. Clarification about accepting local guidelines in 34 – 36 weeks gestation age group is needed.
Page 16, Magnetic Resonance Imaging, general comment	Line 1, Timing of imaging / general comment	Timing is always best in the 1st week after Therapeutic Hypothermia. Milder injuries may be challenging to appreciate during the 2nd week of life.
Page 17, Table	Line 1 / Sequence type, TR (ms)	As suggested we always use higher echo times for the T2 sequences but our (Alderhey, Liverpool) times are different from those mentioned.
Page 18, Optimizing MRS General comment	Line 1 -6, general	We agree MRS has been shown to be a very good predictor of outcome, but the sequences used in the MARBLE trial is long. 6 minute sequence, is still long so has practical challenges. The other issue is that the MRS has been processed by special software (Tarquin) which are not available to all and one of the studies talk about absolute concentration of NAA which not be possible to calculate from standard MRS software provided by the vendors. The papers talk about various threshold values of normal and abnormal but there needs to be set guidance on what metabolite and metabolite ratios need to be looked at and what values are regarded as abnormal. We would appreciate specific guidance with which metabolite, area for measurement and normal values.
Response		**As a framework document this document is designed to help the formation of local or ideally network wide guidelines. In some areas the poor evidence base may generate small variation between network guidelines.**

Submitted by Angela Philipson, Maternity Investigator, Healthcare Safety Investigation Branch angela.philipson@hsib.org.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
3		If neurological examinations are normal Is a standardised approach suggested for "several times in the first 6 hours" – would this be on an individual basis or hourly perhaps- just thinking of limiting variation and the documentation used to record these several reviews – is there a suggested template likely.
7		Cooling therapy starting after resuscitation - happy with this guidance as many cases where cooling has been started during resuscitation as there has been appreciation that cooling should be started as soon as possible
7		Happy to see guidance that rectal temperature monitoring should be used from the off set
Response		**As a framework document this document is designed to help the formation of local or ideally network wide guidelines and documentation.**

Dr David Quine, Neonatal Consultant, Simpson's Centre for Reproductive Health, Royal Infirmary Edinburgh david.quine@nhslothian.scot.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
General		Congratulations on another helpful framework document. Below are only respectful suggestions from a non TH expert, which would help me apply the framework.
General		Would it be possible to publish a standard structured BAPM framework approach to how: panels are selected, frameworks are structured, evidence review is structured, consensus is achieved, recommendation strength is graded (suggesting how strongly each should be followed) and what are the most pressing research questions to be answered? I think this is an absolutely essential action for BAPM for transparency purposes Compared to NICE guidance I am personally concerned about the apparent lack of transparency of BAPM framework review methods many recommendations are not clearly referenced with structured evidence reviews and strength of evidence graded. While I accept that there is not always clear evidence for a lot of area's we practice and consensus guidance can be helpful, the lack of evidence for a recommendation should also be acknowledged so clinicians can act without fear of litigation and research can be promoted where evidence is lacking.
Page 2	(*)	(*)- I was not aware this meant consensus view until I contacted BAPM to ask about all the missing references – consider making explanation more prominent ?
Page 3	12	"should be reviewed several times" –Can be difficult for busy staff to achieve reviews more than 2 hourly ?-open to interpretation but sounds like > 3 ? Would a more specific set suggestion be less open to interpretation ? Timing also important,

		paeds are commonly retrospectively called when pH is unexpectedly poor, first exam may be over 1 hour of age, so exam done then (~2hours of age) repeated at 5 hours is this enough reviews ? certainly not what I would have felt several means. "Ideally within the hour and then every 2 hours with last between 5-6 hours ? "
Page 6	General	Normal aEEG not clearly defined in this document as far as I can see, would be helpful to define what is normal so could avoid cooling unnecessarily. Think this is especially relevant if as this document appears to be suggesting LNU and SCBU units should be using CFAM/initiating cooling. Examples would also be helpful.
	Top paragraph	Ref 13 –Toby trial link broken
	Second para from bottom	-same expression as above on page 3.
	Criteria-right side box	I would value a definition of lethargy in the box Google/Oxford dictionary: "a lack of energy and enthusiasm" "a pathological state of sleepiness or deep unresponsiveness and inactivity" Stanford children's: **"Lethargic** or listless babies appear to have little or no energy. They are drowsy or sluggish. They may also sleep longer than usual. They may be hard to wake for feedings and even when awake, are not alert or attentive to sounds and visual cues." I note your modified Sarnat scoring system suggests stage 2 encephalopathy is associated with: Decreased activity in an infant who is aroused and responsive Less than active Not vigorous Also note the Toby register handbook (2010) includes the following and another table describing moderate/severe encephalopathy: Altered state of consciousness (reduced response to stimulation or absent response to stimulation) https://npeu.ox.ac.uk/downloads/files/tobyregister/Register-Clinicans-Handbook1-v4-07-06-10.pdf
Page 20	Airway/breathing section	Second-fifth bullet points are one sentence but has three bullet points. amend
	General	Consideration for UVC or central access ?
	Fluids and electrolytes	Suggests maintaining glucose more than or equal to 2.6 mmol/l. Although suggesting it is outside its scope the BAPM-hypoglycaemia 2017 document suggests glucose should be at least 2.5 mmol/l (bottom of page 15). https://hubble-live-assets.s3.amazonaws.com/bapm/attachment/file/53/Identification_and_Management_of_Neonatal_Hypoglycaemia_in_the_full_term_infant_-_A_Framework_for_Practice_revised_Oct_2017.pdf I spoke with David about this and in fact the hypoglycaemia FfP is inconsistent. In flowchart C it says to wean drip and stop

		monitoring when BG are > 2.5 not 'at least 2.5'. Having spoken to James Boardman he feels it is not necessary to change his document but while it is likely to have any impact on causation, I feel it is anunnecessary inconsistency which probably has implciations for mother-baby separation and testing.
Page 22		Reference 38 appears to be an abstract ? but the link has no abstract when searched by me, an abstract was published in ADC would the following be a better ref ? https://adc.bmj.com/content/archdischild/104/Suppl_3/A228.2.full.pdf Your Encephalopathy scoring chart: appears different to toby register link above/unreferenced ?? Not sure where this is from ?
Page 23	Ref13 General	Appears to be missing some of the reference and link does not work. Appears to be some further formatting issues.
General		I note the acknowledgment that cooling may have been used in some infants with less severe brain injury and use should only be used in moderate to severe encephalopathy. Clearly there is a trend to consider cooling more mild cases, research is ongoing and you have stipulated this is essentially experimental. I wonder if this document could clearly say when cooling could be avoided, for less experienced (me) it is often hard to avoid or stop cooling even where an infant no longer fits criteria, or in infants transferred for further assessment. Examples or clear statement on when not to cool would be helpful, to reduce a trend to treat mild encephalopathy until more research is known. In my experience clinicians may also continue cooling where neurology continues to be abnormal but CFAM is normal. Or where CFAM is abnormal (possibly from sedation) but neurology no longer fits criteria. Difficult to know what to do in these situations and guidance would be welcome.
Response		**This framework document covers areas of practice where there is a good evidence base together with areas where the evidence basis is weaker. We sought to identify when the recommendation was based on the consensus of the group which we maintain is clear. As a framework it seeks to provide a basis for network and local guidelines and teaching and training material. In the BAPM document there is reference to blood sugar. 2.5 which is the same as 2.6 or higher**

Submitted by Dr Ghada Ramadan, Associate Medical Director, Medway NHS Foundation Trust gramadan@nhs.net

Page number/ heading / general comments	**Line number/ 'general' for comments**	**Comments** **Please insert each new comment in a new row.**

P20/Appendix 2 general care	Line number 5 starting with airway and respiratory	It will be useful to indicate if appropriate to provide TH for a baby who is in need of high oxygen requirements. This is an ongoing debate about the risks and benefits in such cases to avoid further respiratory deterioration, surfactant deactivation and possible need for ECMO. It may be that TH can be deferred until respiratory status is table to Fio2 <0.8 as a ball park figure.
P20/Appendix 2 general care	Fluids and electrolytes	It will be useful to indicate if babies can be fed during cooling to full enteral feeds or if they should be kept on trophic feeds during cooling and start going up on feeds after rewarming commences.
Response		**We recommend initial trophic feeding if there is no organ dysfunction or poor perfusion. This framework document seeks to provide an evidence based foundation for UK practice in this area. The groups recognise this is a complex group of patients in whom there are many unresolved tensions such as that between severe respiratory failure and therapeutic hypothermia. These are best resolved on an individualised basis by teams who are experienced in these areas which adds to the argument regarding a centralised approach.**

Submitted by Prof David Rowitch, Professor of Paediatrics and Head of Department, Wellcome Trust Investigator, Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge, Honorary Consultant Neonatologist, NHS Cambridge University Hospitals dhr25@medschl.cam.ac.uk

Page number/ heading / general comments	**Line number/ 'general' for comments**	**Comments** **Please insert each new comment in a new row.**
Page 6	In sentence: **B.** Moderate to severe encephalopathy, consisting of altered state of consciousness (lethargy, stupor or coma)	Add: "hyperalert" as altered state
Page 7	2nd paragraph	State: The gold standard is continuous video EEG and should always be preferred over aEEG. aEEG is satisfactory if EEG is not feasible.
Page 20	Sentence: Rise in heart rate may be due to distress, hypovolaemia, hypotension, seizures or inotropes	Change to Rise in heart rate may be due to respiratory distress, pain, hypovolaemia, hypotension, tachyarryhmia, seizures or inotropes

Page 20	Sentence that reads: Consider treating seizures which are confirmed with aEEG	Add: 'continuous video EEG or aEEG' to end of sentence.
Page 21	After sentence: Use intravenous phenobarbital as first line treatment in babies undergoing TH, in a dose of 20 mg/kg given over 20 minutes	Add sentence: In those without IV access, consider midazolam 0.1 mg/kg IN.
Response		**The group did not think that the evidence base and experience with video EEG made it a technique we could recommend for routine practice across the UK. aEEG is a technique which is useful for patient selection as well as seizure detection, which formed the basis of our recommendation. The hyper alert state is not included in the definition of moderate or severe encephalopathy as defined in the TOBY trial**

Submitted by Dr Cathryn Seagrave, Paediatric Consultant and Neonatal Lead, Hereford County Hospital Seagrave, cathryn.seagrave@wvt.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
11		**Network and transport implications** All Special Care Units (SCUs), Local Neonatal Units (LNUs) and NICUs should be able to assess infants and instigate TH using aEEG and servo controlled cooling equipment as outlined above. Staff in all units should be trained and competent in the neurological assessment of infants, as well as in aEEG monitoring and interpretation. This should be coordinated at Network level (*). I can't see any SCU representation in the author list. I wonder how many SCU have aEEG and servo controlled cooling equipment? I know when I came to my SCU I looked into getting a basic aEEG but these were 40k+ price tags and for 1-2 babies a year who in the vast majority were also needing ITU for ventilation/multi-organ involvement and would be transferred anyway for NICU it did not seem this would have made any difference to the decision to start TH. I think a survey into this aspect for SCU may be needed to look at this statement as I don't think we are the only unit without this, but admit I don't know. Maybe out of date now but when I was on the transport team 6 years ago there were very few LNUs who had this equipment as well.
11		Infants in whom TH has been initiated should be transferred to the appropriate NICU by an established transport service with

		ongoing servo controlled cooling, ongoing intensive care monitoring including rectal temperature and aEEG monitoring. These uplift transfers should be prioritised according to clinical need and follow local and national transport service guidance regarding timeliness of transfer (30). Is aEEG possible in transport? I don't think our local transport team have this
Response		**The working group included LNU consultants and network lead clinicians and considered this issue at length. There are networks in which all the scus and LNUs have aEEG and cooling equipment to establish the need for and initiate therapeutic hypothermia. We appreciate this will take further investment and training/ governance that we recommend is co ordinated and potentially delivered at network level. Portable aEEG is available and again may require investment to be applicable to all transport teams.**

Submitted by Dr Sunita Seal, Consultant Neonatologist, Bradford Teaching Hospitals sunita.seal@bthft.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
6 Criteria A		Shouldn't it be ≥36 weeks (ie include babies who are 36+0)
General	General	Could there be some advice on Early discontinuation of cooling – for eg in situations where (a) cooling has been started in a local hospital but baby does not appear to meet the criteria on review + aEEG is normal on arrival at cooling unit or (b) baby appears to meet the criteria for cooling soon after birth and aEEG is depressed so active cooling is started immediately, but recovers rapidly (including normalisation of aEEG) within an hour or two
20 Seizures		Should aEEG only seizures be treated with anticonvulsants
Response		**This framework encourages all units to make an accurate rapid assessment of whether the baby meets the threshold of moderate or severe encephalopathy. We would recommend that in cases where this has not been possible cases are reviewed on their individual merits by consultants in NICUS who are experienced in these assessments and where necessary seek a second opinion.**

Submitted by Sophia Smith, Neonatal Sister, Queen Elizabeth Hospital, King's Lynn sophia.smith@qehkl.nhs.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
6	Last sentence of penultimate	… and FAILURE to obtain aEEG… "Failure" implies that the NICU have neglected to take action. Maybe "inability" would be a better way of phrasing this?

	paragraph	
7	10	"Initiation of cooling in infants who are clearly neurologically abnormal should not be delayed awaiting aEEG" Maybe this should be mentioned in the Criteria C box on p6
22	Modified Sarnat scoring system	I really like this! It is descriptive and therefore more objective. Easy to use for those less experienced in neurological assessment, and should enable greater consistency across neonatal units.
Response		**This framework bases the selection of patients with moderate or severe encephalopathy on that of the TOBY trial. The framework provides further clarification for some practical situations**

Submitted by Prof Sudhin Thayyil, Professor of Perinatal Neuroscience and Hon Consultant Neonatologist, Imperial College London s.thayyil@imperial.ac.uk

(Professor Sudhin Thayyil (Imperial College London); Professor Seetha Shankaran (Wayne State University, USA); Dr Aung Soe (Medway Hospital); Dr Santosh Patnayak (Medway Hospital) Dr Bala Palanimurugan (Liverpool Women's Hospital); and Dr Sundeep Harigopal (Royal Victoria Infirmary, Newcastle) on the behalf of MARBLE consortium)

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
Page 6:	Last paragraph	**"It is also recognised that aEEG may not be available in all circumstances, and failure to obtain aEEG should not prevent or delay treatment if there is evidence from A and B criteria."** What do the authors suggest if the aEEG is performed within six hours and is completely normal or shows normal voltage with loss of sleep wave cycling and no seizures? A normal aEEG at 6 hrs has a very high negative predictive value for adverse outcomes, hence most 'apparently' encephalopathic infants with normal aEEG are likely to have mild neonatal encephalopathy. We believe such infants should not be cooled until there is more evidence on cooling in mild encephalopathy. We acknowledge this point. However, there is no robust electroencephalographic signature of mild encephalopathy established yet. It is of-course, appropriate to cool a baby who has clearly moderate or severe encephalopathy if a standardised modified Sarnat examination used and aEEG may not be required in such cases. However, the TOBY neurological examination was not standardised and requires only two neurological abnormalities than three as in the NICHD examination. This situation has led to cooling of many babies with mild encephalopathy in the UK. This is partly due to the inconsistent administration and neurological assessment and may not be related to the scale as such. They have a valid argument. TOBY or CoolCap used neurological examination more of a screener and confirmed with aEEG. My feeling is that if cooling is offered without aEEG, we could recommend using the NICHD neurological examination.
Page 18	Optimising MRS	Authors claim that Mitra ADC 2019 et al used "threonine (Thr) and N-acetylaspartylglutamate (NaaG) in the fitting function, and hence had higher prognostic accuracy than the MARBLE study (Lally et al Lancet Neurology 2019). They also claim that TARQUIN software has a better prognostic accuracy. These statements are factually incorrect for the following reasons. • Mitra et al ADC 2019 is a small single centre retrospective study and there are a number of issues with these data. The

		authors had defined adverse outcomes were defined as motor, cognitive or language scores of less than 85 in this study. This will include babies with mild disability or even normal infants with mild language or motor delays and is not clinically useful. This definition of adverse outcome is very different to the major cooling trials that used Bayley II or III and the MARBLE study which defined adverse outcomes as moderate or severe disability. • Adding NAAG and Threonine to NAA and Lactate fitting is a standard practice and was done in the MARBLE study as well. Please read the methods section of the paper in the supplementary appendix (Lally et al Lancet Neurology 2019) • The values of metabolites will vary with the sequences used and the post-processing program. The MARBLE study is the only prospective multicentre study to date that has used a cross platform (Siemens, GE and Philips) sequence.
Page 22	Appendix 3	The neurological examination details are not same as modified Sarnat stage used in all major NICHD cooling trials (Please see Shankaran et al NEJM 2005, Shankaran et al NEJM 2009, Shankaran et al JAMA 2014, Shankaran et al JAMA 2016, Laptook et al JAMA 2017, Lally et al Lancet Neurology 2019). While no neurological examination would be prefect, the modified Sarnat staging is one of the most used and validated neurological examination for neonatal encephalopathy. When used by trained examiners it has the same prognostic accuracy as aEEG. The NICHD Neonatal Research Network training slides can be downloaded from the following link: https://neonatal.rti.org/index.cfm?fuseaction=tools.main. This is listed under Tools on the public side of the NRN website (neonatal.rti.org). We suggest that the authors stick to this validated examination and not alter the scoring system as this would create further confusion. Thanks. The neurological examination in Lally 2019 is not validated and is similar to the appendix 3 and does not corroborate with other publications mentioned by the group. Appendix 3 will help to delineate mild encephalopathy from moderate to severe.
Response		**This framework document seeks to define best practice and encourage developments such as access to a EEG and servo controlled cooling equipment in all units with paediatric support. However currently this is not the case so some recognition of situations where aEEG is not available was also suggested. The group suggests basing patient selection on that of the TOBY study and sought to provide some practical guidance on neurological examination**

Submitted by Dr Wendy Tyler, Consultant Neonatologist, Shrewsbury & Telford NHS Trust wtyler@nhs.net

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
Page 3	Next to Eleri Adams	representing the GIFT neonatology - ? should be GIRFT
Page 3		Dr Jane Hawdon, Neonatologist London representing NMPA (until 12:15) – do you need the "until 12:15"
Page 10	Investigations, 2nd paragraph	"All infants undergoing TH should have a cranial ultrasound within 12 hours to exclude some other causes of encephalopathy other than intrapartum hypoxia-ischaemia. (*) Cranial ultrasound is less sensitive than MRI for the detection of small or subtle

		problems (e.g. focal arterial infarction)." Could you please provide the rationale for within 12 hours – could 24 hours be considered please? This is to allow LNU and SCU clinicians to achieve this standard for those few babies that are not transferred in a timely manner due to lack of cot availability or severity of illness I think the treatable condition here is subdural haematoma that might improve with draining. May be we can further qualify this by saying in circumstances where intracranial bleed is suspected early cranial ultrasound within 12hours of age is recommended.
Page 15	Governance, 2nd paragraph	"There should be peer review of all cases that are assessed for possible TH," - please can you stipulate joint reviews for those babies referred in to NICUs from LNUs and SCUs, with the NICUs?
Page 15	Governance, para 5	"There should be formal logs of training and competence in the key skills of standardised neurological examination and its interpretation, and in aEEG interpretation. (*)" - do you mean in addition to SPIN module and GRID training? Is this something the working group would recommend every nurse, ANNP, middle-grade Tier 2 trainee and consultant performs every year please? Clarification will help as if this is in the document a FOI could come asking for this information and clarity would be helpful. Do you wish for consultants to be observed performing neurological examinations by their colleagues for example, and if so how often? Is there to be an e-learning module for aEEG that we can all take every 1-2 years for our mandatory training?
Page 20	Airway & respiratory – 2nd-4th bullet points	• Aim for normal blood gas values and saturations- avoid hypocarbia /hyperoxia – correct blood gas for patient temperature. Should the 2nd-3rd bullet point be one sentence? • Intubation and ventilation should be considered to maintain adequate gas exchange depending on the respiratory drive, need for sedation and the ventilatory status
Page 20	Gastroenterology and Liver	"Coagulopathy is physiological in TH but only active bleeding needs treatment. Be alert for any evidence of intracranial bleeding particularly in babies where there may have been head trauma at birth and consider correcting coagulation accordingly." Could you please state that coagulopathy is not an indication to delay or even to not transfer a baby, as our transport team have done so on occasion and this delays the transfer to the NICU as they desire full correction before moving and this is not always possible?

Page 20-21	Paralysis	Would the working group consider a statement regarding paralysis please? We have had paralysis recommended to permit a transfer even in a neurologically depressed and sedated baby which has led to severe hypotension as the babies seem to be very sensitive to paralysing agents given their multi-organ involvement including cardiac dysfunction?
Page 20-21	Bicarbonate & acidosis	Did the working group consider the use of bicarbonate for correction of acidosis perhaps to manage hyperventilation to avoid/limit hypocarbia, rather than the use of paralysing agents which drop the BP?
Response		**This framework document seeks to provide an evidence based resource for the creation of network based guidelines. The appendix on general care seeks to provide some general practical considerations on care. It does not seek to be a detailed review of neonatal intensive care. The group recommends that training and competence in this area be refreshed and recorded and that this is co ordinated at network level.**

Submitted by Dr Brigitte Vollmer and Dr Anthony Hart, British Paediatric Neurology Association b.vollmer@soton.ac.uk

Page number/ heading / general comments	Line number/ 'general' for comments	Comments Please insert each new comment in a new row.
		Comments by Dr Anthony Hart, Dr Brigitte Vollmer **BAPM Members and BPNA Fetal and Neonatal Neurology Special Interest Group**
Page 3 Executive summary		The term ***significant*** in ("significant perinatal hypoxia" and "significant encephalopathy") might appear ambiguous to the reader. It would be helpful to include a link or footnote that defines "significant" in this context. Significant perinatal hypoxia: evidence of perinatal acidosis (pH <7 or BE ≥16) impacting onset of breathing Significant encephalopathy: moderate to severe encephalopathy
Page 3 Executive summary		Neonatal encephalopathy has many aetiologies. Whilst it is reasonable to start TH where hypoxic ischaemic encephalopathy is the likely cause, therapeutic hypothermia should not stop clinicians from considering differential diagnoses later, especially if the clinical course is not typical. Collaboration with other specialities, including neurologists, should be encouraged for difficult cases, such as where the aetiology or prognostication are not clear, or where refractory seizures occur.
Page 3 Executive summary		Prognosis should be made after repeated neurological examinations using standardised tools, alongside clinical information on the neonatal course, amplitude integrated EEG results, and magnetic resonance imaging appearances of the brain.
Page 3 Executive summary		It would be helpful to add to the summary that all infants who undergo hypothermia treatment should be enrolled into a neurodevelopmental follow-up programme.

Page 5 Introduction		The term "handicap" is no longer used. It would be preferable to use terminology from the WHO ICF framework for health and disability (https://www.who.int/classifications/icf/en/).We recommend the term disability, amongst others from the WHO ICF.
Page 6 Case selection		The guideline uses the old classification for interpreting aEEG. Whilst this is commonly used, it is a poor classification system and some of the trainees will be more aware of the modern classification, as promoted by Lena Hellstrom-Westas. If the committee are not sure that everyone knows this classification, then both should be included: Normal background (Continuous normal voltage) with seizures Moderately abnormal (Discontinuous normal voltage) with or without seizures Suppressed activity, which could be either: • Burst suppression + or – • Continuous low voltage with or without seizures • Isoelectric trace Continuous seizures (Status epilepticus or recurrent isolated seizures) It is our experience that many neonates with HIE have a relatively good / normal aEEG, which deteriorates to DNV, BS or isoelectric over the first few hours. If you are also saying that the absence of aEEG should not stop you starting TH, why have criteria C at all? They clearly have NE because of criteria B and you are potentially introducing a bias here, where a child in a tertiary centre would not be started until quite late when the aEEG deteriorates (or may even miss the window for TH), whilst a child who is less well in a DGH who starts passive cooling prior to transfer, is cooled on transfer, and is then continued on TH when they arrive at the NICU because no one wants to stop it. This is not equitable. Similarly, we see neonates who must have been neurological abnormal in a DGH in whom TH is not considered because they think the baby is normal, when clearly the aEEG would not have been. By the time they reach a tertiary centre (if they ever do), it is too late for TH. Can we suggest the most sensible way forward to resolve this paradox is a bold statement suggesting that "DGHs should have an aEEG monitor to help assess whether neonates would be eligible for TH"? This would ensure the assessment process is equitable for all. Certainly, in our areas, we know of DGHs who want to purchase aEEG monitors to improve the assessment of neonates, but can't owing to financial considerations. A bold statement in a guideline would enable them to persuade their managers that they need to fund one, and this would support your DGH colleagues.
Page 6 Case selection		How do you define "***competent in neonatal neurological examination***"? In our experience, very few people are competent in the neonatal neurological examination.
Page 9 Sudden unexpected postnatal collapse		This section would benefit from a statement that, whilst a chronic partial hypoxic ischaemic insult can lead to SUPC, there needs to be rigorous examination for other aetiologies in these babies, even where TH has been commenced.

Page 10 and Appendix 1, pp16-19 Neuroimaging (MRI and MRS)		We are pleased the guidelines recommend early MRI between days 5-7, where DWI information will be useful. We would recommend that if MRI is not possible in that time frame, it is delayed until day 12 or later to allow for evolution of brain injury on T1w and T2w sequences. Whilst we acknowledge some members of the faculty writing this guideline have experience in MRI from a research setting, it would be wise to actively seek the opinions of consultant neuroradiologists with expertise in neonates (not paediatricians or standard radiologists who report imaging). **Appendix 1** Sensitivities and Specificities etc are given for MR imaging and MR spectroscopy; however, information is missing on what outcomes are relating to these specificity and sensitivity data. It is important to add this information. You are overstating the role of MRS in clinical settings. It is certainly true that the MARBLE study and other smaller cohorts suggest MRS is a useful marker, but there is little data on how useful the generated cut-off points are. For example, we don't know what inter and intraobserver agreement is between different scanners, field strength, or sequence parameters. We have evidence (currently unpublished) that actually agreement on MRS values in this way may not be good. Radiologists will tell you the absolute quantification of chemicals using MRS if fraught with problems, which is why they use ratios. All of this has implications if you're trying to introduce MRS nationally across different scanners. If you are insistent on being so directive about MRS, then best to quote the cut-off figures for the relevant ratios that you consider significant from a neurodevelopmental perspective for all to see and use, so we can audit their effectiveness later to show whether you are right or not.
Page 13 Prognostication		It is stated that an assessment should be made with regards to prognosis of a newborn being at high, moderate, low risk of significant neurodevelopmental impairment. Here, the term "significant" should be defined, and the risk categories should also be defined. agree We also would recommend that the prognostication should be tailored to the imaging findings, i.e. the outcomes of "acute partial" HIE with basal ganglia changes are quite different from "chronic partial" where there is watershed injury, unless both insults are widespread and essentially affect the whole of the supratentorial brain. Prognostication should not only be low, moderate or high – this is a poor way of doing it. Parents want to know the functional outcome – i.e., not whether their child with have CP or epilepsy, but an estimation of whether they will walk, talk, feed themselves, go to special or mainstream school. Whilst doctors may be wrong, they should at least paint the best and worst case scenarios with a best estimate of the child's likely outcome. Where they don't know this, ask for neurology involvement, who are likely to see children with brain injuries for longer than is typical in neonatology. (Please also see above; Neuroimaging, comment on Appendix1; and below, Follow-up)
Page 14 Follow-up		It is stated that all infants undergoing TH should be offered a developmental assessment at age 2 years. We feel that this is too late to identify and act on evolving neurodevelopmental impairments. It is stated that babies in medium and high risk groups should have "early assessments". Here, it would be helpful to define "medium" and "high" risk, and also "early assessments". As above Cerebral Palsy (CP) is still an important outcome after neonatal moderate-severe HIE, in about 14 % of infants who undergo TH.

		It is important to identify early signs of CP so that appropriate counselling and early intervention can be provided. There is strong evidence that, together with neonatal MRI, standardised neurological examination and/or Prechtl's General Movement observation at **age 3 months** provides good predictive value of CP (Novak et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. .JAMA Pediatr. 2017 Sep 1;171(9):897-907. doi: 10.1001/jamapediatrics.2017.1689.PMID: 28715518 Review). T**herefore, early assessments at age 3 months should be offered as a minimum to all infants who undergo TH**. Screening for several developmental domains (communication, motor development, problem-solving, and personal-social development) **at age 12 months** should be offered for early identification of developmental impairment and to facilitate appropriate referrals for more detailed assessment. The Ages and Stages Questionnaire 3, used in many centres, and also often established in the community and used by health visitors, available in a web-based format in addition to paper form, would be a user friendly, reliable and valid tool for this. At **age 24 months**, for infants with CP, classification of functional level should be done by using the Gross Motor Function Classification System E&R, the Mini-MACS (for upper limb function), and, if possible, the Mini-EDACS (for eating and drinking abilities). These are easy to apply tools that can be done in a follow-up clinic or even over the telephone by parent interview. For those who are unable to do the Griffiths, Mullen, or Bayley Scales, because their motor impairment prevents them from completing some of the tasks, it should be avoided to assign arbitrary scores but rather, assessment of development should consider use of tools that are not as heavily motor based as the above mentioned scales. It is appreciated that this not be within the scope neonatal follow-up, but it is important to avoid underestimating the development of an infant with CP by using the practice of assigning minimum scores
Page 2/21 Appendix 2 Seizures		Your dose of levetiracetam is wrong. The loading dose should now be 40mg/kg. There is evidence that higher doses are more effective with little or no increase in side effects. The second (half) loading dose should be 20mg/kg. "Unremitting seizure activity". Here, refractory seizures is a better phrase. You should add a sentence to consult with neurological colleagues in this situation. Vitamin responsive seizures and metabolic-related seizures, and genetic epilepsies lie outside the expertise of neonatologists. Collaboration should be encouraged.
Response		**This is a framework document which seeks to report the evidence basis of management in this area. It seeks to provide some practical guidance in this management . It does not seek to be a didactic protocol. The group fully support the involvement of relevant specialities and disciplines in the management of these patients. We agree that prognostication needs to be presented clearly in ways parents can understand and with acknowledgement of uncertainty and an exploration of parents understanding of risk**