National Institute for Health and Clinical Excellence

552 – Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury

Consultation Comments table

IPAC date: 11 March 2010

Com no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS Professional	**1**	I agree Â with these recommendations. Â The TOBY management recommendation Â are good but not detailed enough for practical use when you start up cooling and Â do not have experience. I have made a detailed protocol based on the TOBY protocol called the "bristol protocol" which is freely available and the one I teach on on my course. I am , together Â with Professor Pierre Gressens the scientific advisor for the French neonatal Society. They Â decided on the 22/1 2010 that hypothermia was standard of care for the whole of France. They decided to centralise to Â few and large centres (20-25) for the whole of France (60 mill people). The Bristol Protocol is modified for France. The UK protocol needs to be more specific on the clinical mangement of these babies. This is not only about temperature but but about optimal neonatal intensive care.	Thank you for your comment.
2	Consultee 3 NHS Professional	**1**	I agree with this recommendation, particularly 1.2 as it is critical that staff understand the dangers and limitations of the treatment.	Thank you for your comment.

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3	Consultee 6 NHS Professional	**1**	Agree, particularly with 1.3 which is very important. Should specify that it is carried out in term babies with specific selection criteria	Thank you for your comment. Section 1.1 of the guidance supports use of the procedure in carefully selected neonates. Section 2.5.1 refers to and notes the difficulties of selecting suitable neonates for the procedure.
4	Consultee 9 NHS professional	**1**	I support these recommendations. However, I am honestly disappointed that at this time they are so lukewarm. As of today, I am aware of data from 1124 infants from formal, randomized trials, published or presented at international fora. The relative risk for death or severe disability is 0.73 (0.66, 0.82) from all trials, or for the 3 largest trials alone, 0.79 (0.7, 0.92). No clinically important adverse effects have been found. Although it is only to 18 m of age, we know that although moderate problems are not identified at 18m, severe disability is highly stable over time. This is a powerful, compelling outcome, that far exceeds that for the vast majority of treatments in routine use today, and provides a strong basis for further refinement. Surely this deserves more positive support! 8-).	Thank you for your comment. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. The Committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition. The recommendations place conditions for use of the procedure on a par with procedures in normal clinical practice. The Committee only considered evidence from peer-reviewed published data.
5	Consultee 10 NHS Professional	**1**	Having been local study coordinator for the TOBY trial and working in a unit that has continued to offer cooling as a therapy since that time I whole heartedly agree with the recommendations in this section. Even with our experience there have been instances where mistakes have been made. As the therapy is basically inocuous I feel there is a tendancy for some to think anyone can do this. These infants are still very sick and have the potential for multi-organ failure. Cooling should only be used in units where they have the resources to care for a potentially sick infant. I also feel contributing to the register vital in monitoring the effect of cooling.	Thank you for your comment.

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6	Consultee 11 NHS Professional	**1**	Can NICE do more than encourage. Data from these infants is essential for improvement in outcomes.	Thank you for your comment. The Committee encourages submission of data to the register but are unable to enforce mandatory submissions.
7	Consultee 12 NHS Professional	**1**	Re:1.2 Â Who can cool? I worked in the recruitment and management of infants while at Hammersmith and have met some resistance (PCT/ other tertiary centres) in introducing this treatment on site, when we are able to care for much sicker infants. I have sought a medico-legal opinion from MPS who clearly state that PCTs and NHS Trusts are wide open to litigation if they deprive infants of receiving this treatment as soon as possible after birth, in a hospital that possesses the minimum requirements for provision of hypothermia treatment. According to Denis Azzopardi these are: i)ability to do intensive care ii) MRI brain and neurodevelopmental follow-up facilities and iii) adequate training for staff (personal email to Trust). Â MPS also state that each level 2/3 centre in a Network must therefore decide, on an individual basis, whether to provide this service on site (the ideal), or whether to transfer and run the risk of treatment being initiated too late to be of any benefit, and the potential for litigation. The very least that a level 2/3 centre should do is to purchase a servo-controlled device and initiate treatment on site, when considering cost/benefit/risk.	Thank you for your comment. Sections 1.2 and 1.3 of the guideline outline the scenarios for use of this procedure. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. The Committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition.

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8	Consultee 1 NHS Professional	**2.1**	I disagree on 2.1.3. There is Â sufficient evidence to cool infnats that fulfil the entrycriteria. I also think one need to be specific on which babies Â could be cooled. Trials are designed to have clean groups and "difficult" patients are Â excluded. Also we did not know whether HT would Â be dangerous so only the very sickest were included. Today we know there are no serious adverse effects described. We therefore have implemented entrycriteria such that any term baby that woudl receive intnesive care to be kept alive woudl also be offered cooling if it happened to have perinatal asphyxia. parents woudl be informed that this treatment had not been tried in a trial for this gorup of infants. Examples are- postnatal collapse, surgical anomalies, chromosomal disorder and more. We do not cool premature babies but I know some do. Sometimes we start later than 6h but this is all protocolled.	Thank you for your comment. The Committee considered this comment and decided to change section 2.1.3. Section 2.1.4 will be added to the guidance to reflect the age of infants suitable for cooling, as most of the published literature specified gestational age ≥ 36 weeks in inclusion criteria..
9	Consultee 5 NHS Professional	**2.1**	paired umbilical arterial and venous blood gas analysis - is this referreing to cord blood samples? Not sure how useful this is and even if it was may not always practical. Note point 2.1.2. says MAY be associated with acidosis. Please state the gestational age range within which these babies should be	Thank you for your comment. Section 2.1.2 of the guidance will be changed and section 2.1.4 will be added to the guidance to reflect the age of infants suitable for cooling, as most of the published literature specified gestational age ≥ 36 weeks in inclusion criteria..
10	Consultee 6 NHS Professional	**2.1**	2.1.1 - not just reduced oxygen impaired perfusion also important	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
11	Consultee 7 Pharmaceutical Company	**2.1**	Term or near-term infants only	Thank you for your comment. Section 2.1.4 will be added to the guidance to reflect the age of infants suitable for cooling, as most of the published literature specified gestational age ≥ 36 weeks in inclusion criteria.

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12	Consultee 9 NHS professional	**2.1**	This description is OK, but muddling and imprecise. The great majority of infants experience fetal distress but without injury. Only a minority develop injury, in all cases because the period of fetal hypoxia is very severe or recurrent, leading to failure of fetal adaptation. Acidosis is not a possibility but rather by definition occurs in all cases. The correct framework is that used in all of the clinical trials: evidence of exposure to severe hypoxia (acidosis, need for prolonged resuscitation etc), followed by the early development of clinical and EEG defined encephalopathy shortly after birth.	Thank you for your comment. Section 2.1 of the guidance will be changed.
13	Consultee 10 NHS Professional	**2.1**	Nothing to add.	Thank you for your comment.
14	Consultee 11 NHS Professional	**2.1**	It should be made clear that the guidance is applicable to full term infants only as the studies included in the review have only studied full term infants and not preterm infants. A gestational age cut-off should be included.	Thank you for your comment. Section 2.1.4 will be added to the guidance to reflect the age of infants suitable for cooling, as most of the published literature specified gestational age ≥ 36 weeks in inclusion criteria.
15	Consultee 1 NHS Professional	**2.2**	Fine. I Â often rewarm very slowly in response to the bloodpressure and aEEG.	Thank you for your comment. Section 2.2.3 of the guidance states that infants should be warmed slowly back to normal body temperature.
16	Consultee 3 NHS Professional	**2.2**	Personally I would like to see some quantification of the rate of rewarming.	Thank you for your comment. The overview includes the rate of rewarming used in each study but this level of detail will not be included in the guidance.
17	Consultee 6 NHS Professional	**2.2**	ok	Thank you for your comment.
18	Consultee 7 Pharmaceutical Industry	**2.2**	This should include guidance on the gestational age. Treatment has only been evaluated in term or near-term infats	Thank you for your comment. Section 2.1.4 will be added to the guidance to reflect the age of infants suitable for cooling, as most of the published literature specified gestational age ≥ 36 weeks in inclusion criteria.

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19	Consultee 8 NHS Professional	**2.2**	Current evidence on clinical efficacy (ie improving intact survival) Â of whole body cooling is based on a reduction of core temperature to 33-34 C (TOBY, NICHD). Brain temperature in selective head cooling is unclear more over less than 3% of units use selective head cooling in the UK. I feel that until more evidence is available, core temp of 33-34 should be used for whole body cooling.	Thank you for your comment. The guidance is not restricted to whole body cooling. Evidence on selective head cooling is also included.
20	Consultee 9 NHS professional	**2.2**	2.2.2. Where used, head cooling in all cases has been titrated to achieve mild systemic hypothermia i.e. it is not absolutely selective. Cooling may also be achieved by other, low tech approaches including cold packs and cold water bottles.	Thank you for your comment. Section 2.2.2 of the guidance will be changed.
21	Consultee 10 NHS Professional	**2.2**	In our unit we now offer cooling up to 12 hours after birth, based on our experiences of the difficulty (sometimes) in getting an infant cooled within 6 hours and the number of infants we have obesrved that have become symptomatic shortly after the 6 hour cut-off. I feel the current recommendation (2.2.3) is appropriate.	Thank you for your comment.
22	Consultee 11 NHS Professional	**2.2**	Why head cooling also - the data are much weaker in regard to this. And the phase or sometimes by cooling the head only is non-commital and potentially confusing. Parents will ask why are you just cooling the head?	Thank you for your comment. The Committee considered data on both whole body cooling and selective head cooling.
23	Consultee 1 NHS Professional	**2.3**	I am an author on 2 of the 3 large trials. I am also well informed on other cooling trials being Â the chair on the datamonitoring com. for the ICE trial and reviewing the Chines head cooling trial (which I think is actually not Â a head cooling Â but a total body cooling trial). I think the current evidence is Â strong in favor of cooling and the NICE recommendations are rather late in reviewing this. I presume the BAPM recommendations are out any minute.	Thank you for your comment. The publication of the TOBY trial was viewed by the Committee as key to a NICE evaluation of cooling, hence the perceived delay in guidance production.

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24	Consultee 2 NHS professional	**2.3**	I think it would be really helpful to have a number needed to treat for normal neurological survival in here (from memory i think it is around 8), in order to help contextualise this treatment in comparison to other treatments for other conditions.	Thank you for your comment. An NNT statistic would be included in the overview if available in the published literature. Only prevalence, incidence, relative risks and odds ratios are generally included in the guidance. .
25	Consultee 3 NHS Professional	**2.3**	Agreed	Thank you for your comment.
26	Consultee 6 NHS Professional	**2.3**	Need to be clear about gestational age of these babies - it is not an intervention in preterm babies	Thank you for your comment. Section 2.1.4 will be added to the guidance to reflect the age of infants suitable for cooling, as most of the published literature specified gestational age ≥ 36 weeks in inclusion criteria.
27	Consultee 8 NHS Professional	**2.3**	I am surprised why TOBY trial results are not included and meta-analysis not restricted to the three high quality cooling trials	Thank you for your comment. The TOBY trial results are included in the overview and guidance.
28	Consultee 9 NHS professional	**2.3**	This is a very confusing and fragmented summary. The detailed analysis is very comprehensive, whereas this short version only includes the trials available last year, when it was first drafted e.g. it omits data from TOBY but doesnt make it clear that the meta-analysis includes the two major RCTs in 2.3.2 and 2.3.3. I wonder if it would be less confusing to present the summary data from a current meta-analysis of neurological outcome in press with the BMJ (contact denis azzopardi [redacted] for a pre-print). Further complete data have been presented for two additional trials (from Shanghai and from the european neonatal network I have included those data in the full meta-analysis above), and partial data on early survival from the ICE trial from Australia, all of which indicate favorable effects of hypothermia.	Thank you for your comment. The TOBY trial results are included in the overview and guidance.

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29	Consultee 10 NHS Professional	**2.3**	Efficacy would appear to support the use of cooling.	Thank you for your comment.
30	Consultee 1 NHS Professional	**2.4**	Now that we have more knowledge of the how to apply use hypothermia I am not worried about these sideeffects which are all preventable. We know which electrolyte disturbances to expect and how to treat it- it is not the fault of hypothermia but of the doctors not being educated. that is why a detailed Â treatment protocol is needed for new users like the one we provide in our network and on our cooling course.	Thank you for your comment. The Committee considered these comments and decided not to change the guidance. The safety outcomes included in the guidance relate specifically to cooling.
31	Consultee 3 NHS Professional	**2.3**	Agreed	Thank you for your comment.
32	Consultee 3 NHS Professional	**2.4**	Although I dont have the facts to hand it is understood that TH prolongs the half life of many of the medications used in the care of babies with NE, which could be very dangerous if dose and dose interval are not adjusted	Thank you for your comment. Section 2.4.4 will be changed to include metabolic effects as a theoretical adverse event.
33	Consultee 6 NHS Professional	**2.4**	Anecdotally, have also seen fat necrosis due to contact with cooling packs. Important that the method of cooling and related complications are recorded in any register	Thank you for your comment.
34	Consultee 8 NHS Professional	**2.4**	Safety and efficacy of cooling in less well resourced settings of low income and transitional countries is not known. However, many neonatal units in such places are already cooling babies and this may be re-in forced by NICE guidelines. A caution note that the the cooling studies have been performed in developed countries only and may not appropriate to developing country settings may be useful.(Robertson NJ. Lancet 2008)	Thank you for your comment. Section 1.2 of the guidance states that this procedure should only be carried out in units experienced in the care of severely ill neonates, by staff who have been specifically trained in the use of therapeutic hypothermia.

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35	Consultee 9 NHS professional	**2.4**	This summary is not a reasonable representation of the literature. Even the detailed summary is a little misleading. Safety was a major, well documented focus of every trial to date. To my personal surprise, no clinically significant adverse effects have been reported. There is a increase in mild thrombocytopenia, but not of bleeding, and a consistent fall in mean heart rate, without either hypotension or change in mean arterial blood pressure. There is a borderline increase in inotrope usage. Our secondary analysis of the coolcap trial (Battin Pediatrics 2009) indicates that this is due to altered practice, _not_ to compromised blood pressure. All of the other risks remain theoretical, and not supported by the multicentre trials. The risk of cold/pressure sores and of infection are both, I believe, real, but have been effectively mitigated by good practice.	Thank you for your comment. The Battin et al (2009) paper is included in the overview appendix A. The safety outcomes included in the guidance relate specifically to cooling and the guidance will not be changed.
36	Consultee 10 NHS Professional	**2.4**	Cooling has fewer safety issues than many procedures used in neonatology and provided it is used by experienced staff the risks are minimal and, in my opinion, are far out-weighed by the benifits.	Thank you for your comment.

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37	Consultee 1 NHS Professional	**2.5**	This is important. Some, but not all clinical predictors are affected by hypothermia. There is active research in this are among those cooling babies. I have a review in press in J pediatrics discussing this issue. Several papers are published Â from the CC cohort (Wyatt et al (pediatrics 2007) Â Gunn et al (J Pediatrics 2008) showing that clinical predictors (Sarnat) is not valid in cooled babies, drug levels are influcenced by temperature (Thoresen (Phenobarb), Azzopardi (Morphine) Liu(gentamicin) etc. MRI is still valid as a predicotr , cooled or not (Rutherford from the TOBY cohort) aEEG recovers more slowy and you can still be normal (changing cut-off point) Hallberg Acata paed 2010 , Thoresen 2010. In summary, it needs new "rules" when assessing a baby being cooled. I do not feel confident until 48 hours after birth where previously one could give a clinical prediction at 24h (we thought). Our own mortality in cooled babies have gone straight down from 34% to 17% and we Â do not have more sevevere survivors. In fact we have in Â my hsopital in Bristol Â since all were cooled (n80) had poor outcome of 40%. We use TOBY entrycriteria and Bayley follow + MRI+ clin	Thank you for your comment.
38	Consultee 3 NHS Professional	**2.5**	Agree	Thank you for your comment.

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39	Consultee 10 NHS Professional	**2.5**	It would be useful to have some guidance on withdrawing intensive care (including cooling)on infants who after being commenced on the therapy are then considered to have a poor prognosis, in relation to how soon this should be considered. From experience and feedback from other professionals this should perhaps not be considered before 24 hours of age. Guidance on the usefulness and need for MRIs during cooling would also be helpful.	Thank you for your comment. The Interventional Procedures programme assesses the safety and efficacy of new interventional procedures. The Committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition. It is anticipated that data submitted to the UK TOBY cooling register (section 1.3 of the guidance) may lead to improvements in management of these neonates.

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40	Consultee 4 NHS Professional	**2.5**	1. The NICE document does not highlight the urgency required if therapeutic hypothermia is to be effective. The high quality animal model evidence (not reviewed by NICE) indicates that efficacy declines with time. The major RCTs all had a time limit of around 6 hours after birth for starting hypothermia. In view of the progressive nature of the cellular damage after re-oxygenation (not reviewed by NICE), hypothermia needs to be applied as quickly as possible. 2. Whether to withdraw life support in a baby with hypoxic-ischaemic injury may be made more difficult by therapeutic hypothermia after 48 – 72 hours because the effect of sedation and anticonvulsant drugs is more prolonged (RÃ³ka et al Pediatrics. 2008, Gunn et al J Pediatr 2008). However, the decision to initiate life support is independent of the availability of hypothermia. 3. NICE cannot recommend hypothermia for infants with lesser grades of hypoxic-ischaemic injury than the entry criteria for the trials. In view of the considerable evidence of safety and the lack of alternative therapy, Â hypothermia could be discussed with parents but making it clear there was uncertainty as to benefit.	Thank you for your comment. The IP programme does not look at animal model evidence. Section 2.5.1 of the guidance notes the uncertainties and difficulties in selecting neonates for this procedure.
41	Consultee 6 NHS Professional	**2.5**	Agree, this can be an issue in practice	Thank you for your comment.
42	Consultee 8 NHS Professional	**2.5**	Efficacy of low tech cooling equipments is not proven (eg ice, fan). Many of these equipments may cause shivering which may adversely affect outcome	Thank you for your comment. The guidance will not be changed.

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43	Consultee 9 NHS professional	**2.5**	This is a fair comment. Might I suggest augmenting it by specifying first that infants with mild encephalopathy appear to an excellent outcome without treatment, and therefore there would appear to be limited benefit from treatment? Conversely, clearly there are infants whose injuries are too severe or too far advanced for effective treatment, but at present it is not yet possible to rigorously identify them in a timely manner.	Thank you for your comment. The guidance will not be changed.
44	Consultee 11 NHS Professional	**2.5**	Can specific criteria be established?	Thank you for your comment. Section 1.1 of the guidance supports use of the procedure in carefully selected neonates. Section 2.5.1 refers to and notes the difficulties of selecting suitable neonates for the procedure.
45	Consultee 1 NHS Professional	**general**	I have published a series of animal experiments on rats and pigs leading up to the clinical trials. I piloted the coolcap equipment and trial entrycriteria in a feasibility study in bristol (Thoresen and Whitelaw, pediatrics 2000. Bristol recruited 80% of the UK infants entered into the CC trial and we have carried out the long term follow up for the UK survivors. I am an author on all the papers published from the CC trial. I am one of 6 PI and grant holder for the TOBY trial and was heavily involved in the planning and the carrying out of this trial. I am an author on the outcome papers from this trial. Bristol is a large recruiting centre for cooling in the South and West where we have centralised this treatment to the 2 NICUs in Bristol. I am running only CPD approved cooling course in the UK , this is a one day course with an MCQ, exam and a Â certificate and it runs 3 times per year (4th year is 2010). It has participant, doctors and nurses from the UK , Europe as well as overseas.	Thank you for your comment. The Committee does not consider evidence from animal models. The guidance will not be changed.

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46	Consultee 3 NHS Professional	**General**	I was a collaborator on the TOBY study and an a PI on the subsequent TOBY Children Study	Thank you for your comment.
47	Consultee 6 NHS Professional	**General**	Took part in the TOBY trial	Thank you for your comment.
48	Consultee 7 Pharmaceutical Company	**general**	Should there be a minimum number of infants cooled in centres per year to demonstrate continuing experience and skills? Is the presumption of care being coordinated from units xperienced in care of severely ill infantsthat cooling only occurs in level 3 units	Thank you for your comment. This falls outside the remit of the IP programme.
49	Consultee 8 NHS Professional	**General**	I have been involved in conducting cooling trials, particularly in low resource settings	Thank you for your comment.
50	Consultee 9 NHS professional	**General**	Contributed to preclinical development and clinical testing of therapeutic hypothermia.	Thank you for your comment.
51	Consultee 12 NHS professional	**General**	I think that the evidence for cooling is firm. However: 1. The benefits are not massive as yet 2. There may be more advantage to be had with earlier cooling given the relatively late average time of enrolment in the studies so there should be a registry for any cooling in the UK which should be compulsory. 3. We do not know which temperature is best. 4. We do not know how long we should cool for the best result. These matters should be addressed with further information/research.	Thank you for your comment. The Committee considered these comments and decided not to change the guidance. The TOBY cooling register may help to address these uncertainties.