California Perinatal Quality Care Collaborative

Early Screening and Identification of Candidates for Neonatal Therapeutic Hypothermia Toolkit

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Priya Jegatheesan, MD, Anna Morgan, MD, Thomas Shimotake, MD, Dongli Song, MD, PhD and Krisa Van Meurs, MD on behalf of the Perinatal Quality Improvement Panel (PQIP), California Perinatal Quality Care Collaborative (CPQCC)

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Introduction

Therapeutic hypothermia, when implemented within 6 hours of birth, has been shown to significantly improve survival and neurodevelopmental outcomes in neonates with moderate to severe hypoxic ischemic encephalopathy (HIE) [19]. Unfortunately, not every baby who might benefit from cooling therapy is identified or referred to a regional cooling center in a timely fashion. Early identification of the risk factors for perinatally-acquired asphyxia and recognition of the signs and symptoms of neonatal encephalopathy are challenging even for experienced neonatologists, let alone primary care providers at community delivery hospitals when significant HIE may occur in only 1-3/1000 live births. Accurate neurologic assessments and timely consultations with a regional cooling center should occur so that appropriate decisions can be made about initiating cooling and potentially transferring care.

Some neonates with only minimal or mild signs of encephalopathy, even with other risk factors, may appropriately be observed at delivery hospitals with good expectations for a favorable outcome. However, initial signs and symptoms of neonatal encephalopathy or seizures may be subtle or subclinical. Many providers at delivery hospitals may not be accustomed to conducting detailed neurologic assessments of encephalopathic newborns. Therefore, the use of reliable screening and assessment tools as well as early consultation with a neonatologist at a regional cooling center familiar with this patient population can greatly facilitate this critical decision-making process. If cooling therapy is determined to be indicated, prompt referrals can expedite safe transport to a tertiary care NICU appropriately equipped to provide the full course of therapeutic hypothermia and its associated specialized care. The sooner a baby with HIE is identified, the sooner the appropriate therapies can be initiated and outcomes optimized.

While each cooling center may have slightly different criteria for initiating cooling therapy, the overall goal of this toolkit is to improve early screening at all delivery hospitals so that thoughtful evaluations occur for each baby with significant risk factors for HIE. It is therefore important to recognize that these are **screening criteria only,** meant to improve early identification of at-risk babies who might warrant closer assessment. They are intentionally designed with more inclusive criteria and are **NOT by themselves qualifying criteria for cooling therapy**. It is therefore essential that these guidelines be coupled with ongoing staff education and training. We hope the strategies outlined in this toolkit will help ensure that no baby who might qualify for cooling therapy would miss the opportunity to benefit from it.

We would like to acknowledge the contribution of the members of the *Bay Area Cooling Summit,* a collaborative consortium of regional cooling centers with the common goal to improve outcomes of neonates at risk for brain injury from HIE, in developing this toolkit.

Background, Rationale, and Goals

A. Diagnosis of hypoxic ischemic encephalopathy (HIE)

Hypoxic ischemic encephalopathy (HIE) or birth asphyxia is estimated to be responsible for 23% of neonatal mortality worldwide.[1] Epidemiology studies have found the incidence of HIE to be 1.5 per 1000 live born infants.[2] Approximately 10-60% of newborns with HIE die and an additional 25% of survivors have lifelong neurodevelopmental sequelae.[3]

HIE is characterized by neonatal encephalopathy (NE), a "clinically defined syndrome of disturbed neurologic function in the earliest days of life in the full-term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures". The Sarnat exam is a widely used grading system for HIE and categorizes infants into mild, moderate, and severe categories.[4] The development of encephalopathy within hours after birth is considered to be essential in order to be confident that a perinatal insult has occurred. In addition, HIE is invariably associated with other clinical markers such as low Apgar scores, abnormal cord or postnatal gases, abnormal fetal heart rate tracings, and sentinel events during labor (i.e. abruption, cord prolapse, uterine rupture). NE can develop for reasons other than hypoxia ischemia and the differential diagnosis must be carefully considered to exclude infection, genetic and metabolic disorders.

Apart from supportive care, the only proven treatment for HIE is therapeutic hypothermia. Actively lowering body temperature has been shown to reduce the extent of brain injury after an ischemic event, and has a favorable effect on multiple biochemical pathways contributing to brain injury.[5-7] The pathophysiology of brain injury caused by hypoxia-ischemia has two phases; primary and secondary energy failure, based on studies in both animal models and human infants. The interval between primary and secondary energy failure represents the latent phase during which hypothermia can inhibit the excito-oxidative cascade, including secondary energy failure, increased brain lactate, glutamate, and nitric oxide concentrations as well as inhibiting mitochondrial failure, free radical damage, lipid peroxidation, inflammation, and injury triggered by NMDA receptor activation. This therapeutic window allows an opportunity for therapeutic intervention prior to the secondary phase of impaired energy metabolism and permanent injury.

B. Evidence for early initiation of therapeutic hypothermia

Initiation of hypothermia has been determined to be time sensitive in animal models. It is effective in reducing brain injury when started at 1.5 hours following ischemia, was less effective at 5.5 hours and was not effective at 8.5 hours.[8-10] Hypothermia may provide minimal or no benefit if initiated after secondary energy failure, while earlier intervention may maximize its beneficial effects.[11] Investigations have suggested that the latent phase may be even shorter and secondary energy failure more pronounced in severe insults.[11] In the Total Body Hypothermia (TOBY) trial, infants treated within 4 hours of delivery benefited most from hypothermia therapy.[12]

C. Randomized clinical trials of therapeutic hypothermia for HIE

In neonates with moderate or severe HIE, hypothermia within 6 hours of birth has been shown to reduce mortality and neurodevelopmental disability. Numerous randomized trials have confirmed this finding.[12-18] A recent Cochrane review of 11 randomized trials including over 1,505 newborns found a significant reduction in the risk of death or major neurodevelopmental disability from HIE among infants receiving hypothermia, with a relative risk of 0.75 (95% CI 0.68-0.83) and number needed to treat (NNT) of 7 (95% CI 5-10).[19] In other words, for every 7 infants that receive

active cooling for HIE, one infant will avoid death or severe/moderate disability, compared to those who receive no treatment. Cooling also resulted in statistically significant reductions in mortality (RR 0.75 (95% CI 0.64–0.88), and in neurodevelopmental disability in survivors (RR 0.77 (95% CI 0.63–0.94). In the overall Cochrane analysis, the effects on each component of the composite outcome (death, major neurodevelopmental disability, cerebral palsy, neuromotor delay, developmental delay) were also statistically significant and clinically important. Adverse effects of hypothermia have been limited to an increase in sinus bradycardia and a significant increase in thrombocytopenia.

The current state of evidence strongly supports the use of hypothermia therapy for infants of gestational age >35 weeks with HIE, if initiated within 6 hours of birth. All the major clinical trials randomized infants by 6 hours of age.[12-19] Only two trials enrolled infants at 35 weeks gestation so the benefit at this gestational age is not certain.[17,18] Trials of therapeutic hypothermia in more preterm infants 32-35 weeks gestation are planned (NCT 01793129). The benefit of therapeutic hypothermia initiated beyond 6 hours has not yet been demonstrated, but a randomized clinical trial in newborns presenting at 6 to 24 hours is currently underway (NCT00614744).

D. Challenges in providing therapeutic hypothermia as standard of care

There are significant challenges in the identification of newborns likely to benefit from therapeutic hypothermia as well as barriers in achieving neuroprotective core temperatures prior to 6 hours of age. The majority of infants enrolled in the therapeutic hypothermia RCTs are outborn.[19] Outborn infants have been shown to experience significant delays in initiation of therapy, take longer to attain target temperatures, and have more severe HIE.[20] These problems highlight the urgent need to disseminate educational materials and provide teaching in order to assist birth hospitals and their medical staff in identifying newborns that may potentially benefit from therapeutic hypothermia in the delivery room.

Initiation of cooling at the birth hospital and cooling during transport are necessary given the limited therapeutic window, travel distances between the birth hospital and cooling center, and in cases of late referral. The methods of providing therapeutic hypothermia available outside of cooling centers are currently limited to passive cooling that involves turning off all external heat sources such as the radiant warmer or transport isolette or active cooling with ice or gel packs. Fairchild et al used passive cooling at referral and active cooling by transport team. They reported that these practices resulted in the earlier application of hypothermia by 3 hours, however target temperatures were not achieved in the majority of transported infants.[21] Akula et al examined temperatures on admission to cooling centers in California during 2010 and found that only 44% of infants cooled in transport achieved a target temperature (33-34° C).[22] Several methods of transport cooling were studied by O'Reilly et al. They found that with passive and active cooling with adjuncts, 20% and 35% respectively had temperatures in the target range. In contrast, using two servo-regulated cooling devices, the Tecotherm Neo (Inspiration Healthcare, Leicester, UK) or the Criticool (MTRE, Southampton, PA, USA), 90% of infants transported were in the target range.[23] At this time, the only FDA approved servo-regulated cooling devices available in the U.S. are the Blanketrol III (Cincinnati Sub Zero, Cincinnati, Ohio) and Criticool. Both are large and heavy (131 and 77 pounds), making their use during transport challenging.

E. Objectives of the Toolkit

The objective of this CPQCC toolkit is to provide a strategic approach and reliable tools to assist birth hospitals in the timely identification of newborns that are potential candidates for therapeutic hypothermia. Simple screening criteria, if used in a consistent fashion, are likely to result in earlier identification of cooling candidates leading to prompt involvement of the cooling center. With input from the cooling center, timely decisions can be made regarding implementation of safe passive cooling techniques and the need for transfer to a cooling center for therapeutic hypothermia. Not all newborns that are identified in the screening process will ultimately require cooling or transport. Contact with a cooling center can assist birth hospitals in gathering the clinical information necessary to make these critical decisions in conjunction with neonatologists who are knowledgeable about this subject area.

Recommended Guidelines and Algorithms

Screening Algorithm and Criteria for Consultation with Cooling Center

Given that the therapeutic window for cooling is within the first 6 hours of life, prompt recognition of candidates for therapeutic hypothermia is crucial for its success. Therefore, any infant delivered with perinatal depression, or in the setting of an acute perinatal event, should be evaluated expeditiously for signs of hypoxic ischemic encephalopathy (HIE) after initial resuscitation and stabilization.

Although specific criteria for initiating therapeutic hypothermia vary between cooling centers, in general they are derived from entry criteria used in published multi-center randomized control trials evaluating hypothermia as a therapeutic intervention for term neonates with moderate/severe HIE.[12-18] In order to facilitate prompt recognition and referral of these infants, we have devised a standard algorithm for identification and evaluation of potential cooling candidates born at outside facilities. Our intent is to cast a wide net, capturing as many infants as possible who may benefit from cooling. Therefore, the screening criteria, as outlined in **Appendix A,** is generally more liberal than individual centers' actual cooling criteria. Similar workflows have been successfully implemented in several northern California centers including UCSF Benioff Children's Hospital Oakland, Kaiser Permanente, and Santa Clara Valley Medical Center, all of which participated in devising the criteria presented here.

As outlined in **Appendix A**, to be considered for closer evaluation by a regional cooling center, neonates must be:

≥ 35 weeks gestational age and ≤ 6 hours old

Any one of the following must also be present:

1) History of acute perinatal event

Placental abruption, cord prolapse, uterine rupture and fetal bradycardia are *sentinel events* known to significantly increase the risk of HIE. Other intrapartum risk factors may include prolonged rupture of membranes, abnormal fetal heart rate tracings, thick meconium stained fluid, tight nuchal cord, and failed vacuum delivery.

2) Apgar ≤ 6 at 10 minutes

3) Continued need for positive pressure ventilation (PPV) for 10 minutes or history of CPR

4) Venous or arterial cord gas or baby blood gas with pH ≤ 7 or BE ≤ -10

If any of the first three criteria are met, an attempt should be made to collect an umbilical cord blood gas as well as an infant blood gas at less than 1 hour of age. A targeted neurologic exam should also be performed once the infant has been stabilized (Appendix B is an example of a standardized neurologic exam checklist.)) The baby should be closely monitored for seizures.

According to the screening algorithm, the practitioner is then prompted to call the nearest cooling center to discuss the case and the potential need to transfer care for further evaluation and cooling. While most cooling criteria allow for identification and initiation of cooling therapy within 6 hours of birth, ideally the initial call to a regional cooling center is made within 2 hours of birth for all infants. In fact, in cases where there is clear evidence of HIE particularly when the infant has a severely abnormal neurologic exam or is critically ill, the call should be made within 1 hour of birth.

This screening algorithm (Appendix A), with its associated focused neurological exam, can be printed, laminated, and posted in the delivery room and/or at physician workstations for quick

reference.

Throughout this phase of evaluation, the baby should continue to receive standard ongoing intensive care and referring hospitals should be prepared to provide early, yet safe initiation of passive cooling , once it is determined that the infant is a candidate for cooling, as described in **Appendix C**. This entails having the appropriate equipment, as well as properly trained staff, to monitor these infants. The radiant warmer should be turned off, with the infant remaining uncovered. The core temperature should be measured **at least every 15 minutes** by whatever means is considered safe and routine in the birth hospital. Ideally, continuous rectal temperature monitoring is initiated. If rectal monitoring is not available, then axillary temperatures should be measured. The goal core temperature is **33.5^{o}C** (equivalent to approximately 32.5^{o}C axillary). Of note, infants that are cooled to this temperature range can become relatively bradycardic with resting heart rates in the 80-100 bpm range. This is to be expected, and does not cause or worsen hemodynamic instability. However, if the core temperature drops below 33^{o}C (32 ^{o}C axillary), the heart rate may fall to dangerously low levels. It is recommended to turn the warmer back on its lowest setting or cover the patient loosely with a blanket, and continue to monitor core temperatures closely until the target temperature and baseline heart rates are restored. Just as overcooling can place the infant at significant risk, inadvertent over-heating a baby with HIE may also worsen brain injury. Therefore, continued vigilance by monitoring and maintaining core temperature in target range is of upmost importance.

Ongoing support for potential cooling candidates may also include measures to correct metabolic acidosis, appropriate respiratory support and vigilant surveillance and treatment of hypotension. Infants are often made NPO and started on intravenous fluids initially. Hypoglycemia may exacerbate hypoxic brain injury in these neonates. Therefore, glucose levels should be checked early and monitored frequently to maintain blood sugars >50mg/dl). In any infant accepted for evaluation at a cooling center, placement of umbilical catheters is helpful prior to transport, but may depend upon the comfort level and experience of the providers at the referring center. This can be discussed with the cooling center, but peripheral IV access should be obtained at a minimum. Pre- and postductal saturation measurements may also be helpful to identify possible pulmonary hypertension. Initial laboratory evaluation should include CBC, coagulation panel, Chem-10, LFTs, lactate, as well as blood cultures and repeated blood gases, as warranted.

Once a potential cooling candidate has been identified through the screening algorithm, it is vital that the nearest affiliated hypothermia/cooling center be notified expeditiously. Though most protocols provide for a 6 hour window before initiation of cooling therapy, ideally the call should be by no later than 2 hours of age. Infants with clear signs of encephalopathy (severely abnormal neurologic exam) and who are critically ill should be discussed with the cooling center as soon as possible after birth. As noted previously, the screening criteria in this toolkit are designed to be purposely broad so as to capture all infants who may be at risk for developing significant HIE. As a result, not all infants that meet screening criteria for consultation with a cooling center will ultimately qualify for therapeutic hypothermia. In this setting, the cooling center's role is to determine whether transfer for continued evaluation and possible therapeutic hypothermia is warranted, as well as to advise the referring hospital on ongoing care. If the infant has undergone passive cooling and is subsequently deemed not eligible or not requiring therapeutic hypothermia, careful re-warming per direction of the cooling center or by specific guidelines should ensue (**Appendix E**). Because these are often infants with complications at birth, they may be at risk for other co-morbidities which might require specialized intensive care, regardless of their cooling status.

Ultimately, the cooling center plays a central role in triaging potential cooling candidates and advising the referring hospital on appropriate management. The ability to do so, in turn, hinges on prompt identification and evaluation of these infants at the birth hospital, as well as streamlined communication between the birth hospital and the cooling center (**Appendix J**). It is vital that cooling centers take the lead in establishing educational outreach programs to ensure optimal identification and management of this vulnerable patient population.

As HIE often occurs unexpectedly, it places families in a stressful situation where decisions are being made quickly about the care of their child. To achieve the best possible outcome for the infant, therapeutic hypothermia needs to be initiated within 6 hours of birth. This requires the healthcare providers (at both the birthing hospital and the cooling center) and the parents to develop a rapport quickly in order to work in partnership to provide the best possible care for their child. Providing adequate information about HIE and hypothermia therapy is important because it helps them cope with the fear and uncertainty of their situation, gives them a sense of involvement and control, and re-affirms their role as parents (**Appendix F**).

Quality and Process Improvement

The criteria for hypothermia therapy for infants with HIE have been established by RCTs.[12-18] The National Institute of Child Health and Human Development and the American Academy of Pediatrics Committee on Fetus and Newborn recommend that clinicians should follow published trial protocols, ensure systematic follow-up of survivors, and submit patient data to registries when using hypothermia therapy outside of a trial.[25-26] Potential Better Practices for hypothermia therapy have been developed based on the evidence from RCTs and piloted by a national collaborative on neonatal encephalopathy.[27]

As hypothermia therapy has become a standard of care for term infants with HIE, it is important to establish benchmarks to monitor the adherence to the RCT efficacy standards, minimize variations in clinical practice, improve quality and safety, and assess both short- and long-term outcomes of infants treated with hypothermia therapy outside clinical trials.

In 2006, the Vermont Oxford Network (VON) established the Neonatal Encephalopathy Registry (NER). A subset of the registry data (2006 to 2010) was published.[28,29] Of the 95 participating centers, 51.6% are AAP Level IIIB and 34.7% are IIIC and IIID.[30] Thus, NER hospitals may be the best representation of those caring for encephalopathic infants in the "real world" and represent a generalizable view of hypothermia therapy as it occurs outside the academic sector or in a research setting. Of the 4232 eligible infants, the route for entry was seizure within the first 72 hours of life (59%), 5 minute Apgar score of 3 or less (50%), hypothermia therapy (38%), stupor/coma (18%), or neuromuscular blockade (2%). Only a small proportion of infants in the NER had documented exposure to acute intrapartum asphyxia ("sentinel events"). The VON NER data demonstrated significant practice variations and opportunities for improvement in early identification of eligible infants for hypothermia therapy. In the reported data set only about 60% of infants had either an umbilical cord blood gas and or a baby blood gas evaluation within one hour following birth. One third of infants receiving hypothermia therapy were admitted after 6 hours of life. Over 60% of infants were outborns, which may be a significant contributing factor in the observed delay in admission. Data from the 108 VON NER participating centers in 2012 showed much improvement on these benchmarks (VON 2012 Neonatal Encephalopathy Registry Report). Unfortunately, VON NER ended in December 2012.

The UK national TOBY Cooling Register,[31-32] begun after completion of the TOBY trial, collects data on infants who are treated with hypothermia therapy outside of any trial. A recent data analysis of this registry demonstrated that therapeutic hypothermia was implemented appropriately within the UK.[33]

Currently, the CPQCC data collection in 2013 includes infants with perinatal asphyxia defined as pH<7, Apgar score of $\leq$ 3 at 5 minutes and $\leq$ 4 at 10 minutes, and those who receive therapeutic hypothermia.[34] All cooling centers in California are CPQCC members. This will provide the opportunity to benchmark both the short-term neonatal outcomes from CPQCC database and long-term neurodevelopmental outcomes from the CCS-HRIF database.

Ongoing benchmarking using registries and network data is necessary to ensure safe and effective implementation of hypothermia therapy in routine clinical practice. We recommend that all referral centers collect at least minimal data in order to monitor the process of screening for therapeutic hypothermia as a Quality Improvement effort (**Appendix J**). This data is meant to evaluate the process and efficacy of the screening criteria and to identify any unintended consequence.

Summary of Key Points and Implementation

This toolkit suggests some simple strategies, screening criteria and assessment tools to help delivery hospitals more effectively identify babies with risks for perinatally-acquired hypoxic ischemic brain injury. The overall aim of the toolkit is to improve identification rates of neonates who might qualify and benefit from a course of therapeutic hypothermia.

The objective of this toolkit is to improve identification rates and reduce referral times for babies who might benefit from neonatal cooling therapy. The attached algorithm (**Appendix A**) includes **screening criteria only** and is **NOT intended as qualifying criteria for cooling therapy** per se. In this regard, the screening criteria can be used similar to "panic values" for clinical labs. They do not replace clinical judgment but may help alert providers of certain high-risk situations that might warrant timely and closer evaluation.

- Screening criteria are intended for neonates who are:
  - **≥ 35 weeks and ≤ 6 hours old**
- Evaluate risk for neonatal encephalopathy if any of the following risk factors are present:
  - **History of acute perinatal event** *(See Appendix A)*
  - **Apgar ≤ 6 at 10 minutes**
  - **Continued need for positive pressure ventilation (PPV) for 10 minutes or history of CPR**
  - **Venous or arterial cord gas or baby blood gas with pH ≤ 7 or BE ≤ -10**
- Screening criteria should be coupled with ongoing staff education and training.
- *Toolkit* includes Appendices with guidelines and templates to help educate staff and standardize care.
- Recommendation that all referral centers collect data and track benchmarks using registries or network datasets (e.g., CPQCC and Vermont Oxford) to minimize variation, improve quality and safety, and assess both short- and long-term outcomes of infants treated with hypothermia therapy.

We hope the strategies outlined in this *toolkit*, coupled with ongoing staff training, educational outreach programs and close communication with regional cooling centers, will help improve the timely identification of these neonates so that no baby who might benefit from cooling therapy ever misses the opportunity to receive it.

References

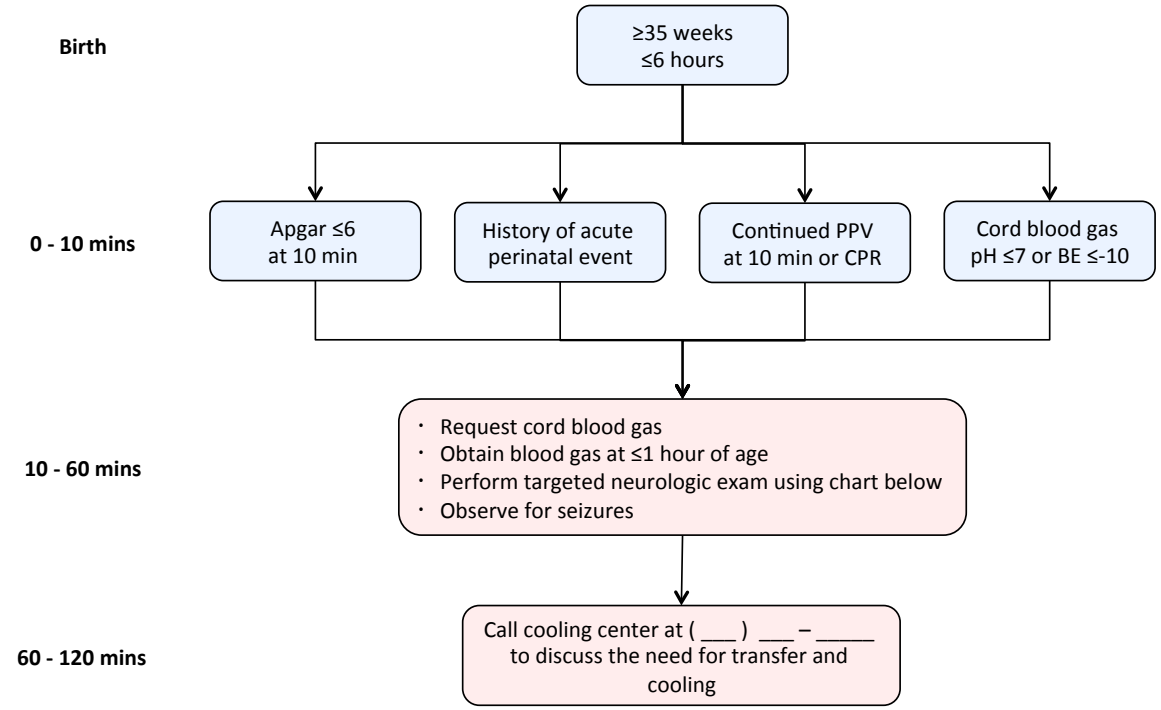
1. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet 2005;365: 891-900.
2. Kurinczuk JJ, White-Koning M, Badawin N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev* 2010;86:329-38.
3. Vannucci RC. Current and potential new management strategies for perinatal hypoxic ischemic encephalopathy. Pediatrics 1990; 85:961-8.
4. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol* 1976;33:696-705.
5. Thoresen M, Penrice J, Lorek A, et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cere- bral energy failure in the newborn piglet. *Pediatr Res* 1995;37:667-70.
6. Baldwin WA, Kirsch JR, Hurn PD, Toung WSP, Traystman RJ. Hypothermic cerebral reperfusion and recovery from ischemia. *Am J Physiol* 1991;261:H774-H781.
7. Edwards AD, Yue X, Squier MT, et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. *Biochem Biophys Res Commun* 1995;217:1193-9.
8. Gunn AJ, Bennet L, Gunning MI, Gluckman PD, Gunn TR. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. *Pediatr Res* Sep 1999;46(3):274-280.
9. Gunn AJ, Gunn TR, de Haan HH, Williams CE, Gluckman PD. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest* 1997;99(2):248-256.
10. Gunn AJ, Gunn TR, Gunning MI, Williams CE, Gluckman PD. Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. *Pediatrics* 1998;102(5):1098-1106.
11. Iwata O, Iwata S, Thornton JS, et al. "Therapeutic time window" duration decreases with increasing severity of cerebral hypoxia-ischaemia under normothermia and delayed hypothermia in newborn piglets. *Brain Res* 2007;1154:173-180.
12. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *NEJM* 2009;361(14):1349-1358.
13. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *NEJM* 2005;353(15):1574-1584.
14. Zhou WH, Cheng GQ, Shao XM, Liu XZ, Shan RB, Zhuang DY, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: a multicenter randomized controlled trial in China. *J Pediatrics* 2010;157(3):367-372.
15. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics* 2010;126(4):e771-778.
16. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;365(9460):663-670.
17. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Arch Pediatr Adolesc Med*. 2011;165(8):692-700.
18. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal

encephalopathy: efficacy outcomes. *Pediatr Neurol* 2005;32(1):11-17.
19. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2013;1:CD003311.
20. Natarajan G, Pappas A, Shankaran S, et al. Effect of inborn vs. outborn delivery on neurodevelopmental outcomes in infants with hypoxic-ischemic encephalopathy: secondary analyses of the NICHD whole-body cooling trial. *Pediatr Res* 2012;72(4):414-419.
21. Fairchild K, Sokora D, Scott J, Zanelli S. Therapeutic hypothermia on neonatal transport: 4-year experience in a single NICU. *J Perinatol* 2010;30(5):324-329.
22. Akula VP, Gould JB, Davis AS, Hackel A, Oehlert J, Van Meurs KP. Therapeutic hypothermia during neonatal transport: data from the California Perinatal Quality Care Collaborative (CPQCC) and California Perinatal Transport System (CPeTS) for 2010. *J Perinatol* 2013;33(3):194-197.
23. O'Reilly KM, Tooley J, Winterbottom S. Therapeutic hypothermia during neonatal transport. *Acta Paediatr* 2011;100(8):1084-1086; discussion e1049.
24. Kendall GS, Kapetanakis A, Ratnavel N, Azzopardi D, Robertson NJ, on behalf of the Cooling on Retrieval Study Group. Passive cooling for initiation of therapeutic hypothermia in neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 2010;95:F408-F412.
25. Higgins RD, Raju TN, Perlman J et al: Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. *J Pediatr* 2006, 148(2):170–175.
26. Higgins RD, Raju T, Edwards AD, et al. Hypothermia and other treatment options for neonatal encephalopathy: an executive summary of the Eunice Kennedy Shriver NICHD workshop. *J Pediatr. 2011 Nov;159(5):851-858.e1. doi: 10.1016/j.jpeds.2011.08.004. Epub 2011 Aug 27*
27. Olsen SL, Dejonge M, Kline A, Liptsen E, Song D, Anderson B, Mathur A. Optimizing therapeutic hypothermia for neonatal encephalopathy. *Pediatrics*. 2013 Feb;131(2):e591-603. *doi: 10.1542/peds.2012-0891.*
28. Pfister RH, Bingham P, Edwards EM, Horbar JD, Kenny MJ, Inder T, Nelson KB, Raju T, Soll RF. The Vermont Oxford Neonatal Encephalopathy Registry: rationale, methods, and initial results. *BMC Pediatr* 2012 Jun 22;12:84. *doi: 10.1186/1471-2431-12-84.*
29. Nelson KB, Bingham P, Edwards EM, Horbar JD, Kenny MJ, Inder T, Pfister RH, Raju T, Soll RF. Antecedents of neonatal encephalopathy in the Vermont Oxford Network Encephalopathy Registry. *Pediatrics 2012* Nov;130(5):878-86. *doi: 10.1542/peds.2012-0714.*
30. Stark AR: Levels of neonatal care. Pediatrics 2004,114(5):1341–1347.
31. The TOBY Register. www.npeu.ox.ac.uk/tobyregister.
32. Azzopardi D, Strohm B, Edwards AD, Halliday H, Juszczak E, Levene M, Thoresen M, Whitelaw A, Brocklehurst P: Treatment of asphyxiated newborns with moderate hypothermia in routine clinical practice: how cooling is managed in the UK outside a clinical trial. *Arch Dis Child* 2009, 94(4):F260–F264.
33. Azzopardi D, Strohm B, Linsell L, Hobson A, Juszczak E, et al. (2012) Implementation and Conduct of Therapeutic Hypothermia for Perinatal Asphyxial Encephalopathy in the UK – Analysis of National Data. PLoS ONE 7(6): e38504.
34. CPQCC. www.cpqcc.org/quality/improvement/collaborative

Appendix A

Screening Criteria for Evaluation of Risk for Neonatal Encephalopathy (NE)

Goal timeline



Level of encephalopathy

	Mild	Moderate	Severe
Level of consciousness	Irritable / hyperalert	Lethargic / obtunded	Stupor / coma
Spontaneous activity	Normal / increased	Decreased	No activity
Posture	Normal	Distal flexion / Complete extension	Decerebrate
Tone	Normal / increased	Hypotonic	Flaccid
Primitive reflexes			
Suck	Normal	Weak	Absent
Moro	Normal	Incomplete	Absent
Deep tendon reflexes	Mildly brisk	Brisk	Suppressed
Autonomic system			
Pupils	Normal	Constricted	Deviated, dilated, non-reactive
Heart rate	Increased	Bradycardic	Variable
Seizures	None	Common	Common

Appendix B

Standardized Neurologic Exam Checklist

Patient Name_____ **Date of examination**_____
Date/time of birth_____/_____ **Time of examination**_____

Intubated ❒ Yes ❒ No **Medication:** _____
Temperature _____ºC
Source: _____ (e.g., axillary/rectal/skin)

MENTAL STATUS:

1. Does the baby cry?

Vocalization ❒ Normal ❒ High-pitched, irritable ❒ Weak ❒ No cry

2. Does the baby open his/her eyes?

Eye opening ❒ Spontaneous, sustained ❒ Brief or to stimulus ❒ No eye opening

3. Does the baby move?

Motor response ❒Yes, spontaneous, smooth, coordinated ❒ Yes, spontaneous but jittery
❒ Yes, to pain only ❒ No movement

TONE: *(i.e., Resistance to passive movement)*

Truncal	❒ Normal	❒ Decreased	❒ Increased	❒ Cannot determine
Extremities	❒ Normal	❒ Decreased	❒ Increased	❒ Cannot determine

PRIMITIVE REFLEXES:

Palmar grasp	❒ Present	❒ Weak	❒ Absent	❒ Cannot determine
Moro	❒ Present	❒ Weak	❒ Absent	❒ Cannot determine
Suck	❒ Present	❒ Weak	❒ Absent	❒ Cannot determine

OTHER:

SUMMARY:
❒ ***Normal*** – consolable, active, normal exam
❒ ***Abnormal hyperalert*** - jittery, irritable, agitated
❒ ***Abnormal mildly depressed*** – decreased or no eye opening, weak cry, movements only with stimulation, depressed primitive reflexes

By Hannah C.Glass, based on Sarnat, HB and Sarnat, MS, Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976 Oct;33(10):696-705, and Volpe's "Neurology of the Newborn'.

Appendix C

Management of Screened Neonates Who Qualify for Possible Cooling

1. **Identify patients to discuss with regional cooling center within 1 hour of birth.**
    a. After initial resuscitation and stabilization, perform screening evaluation (*Appendix A*).
    b. If screening criteria met, call neonatologist at regional cooling center.
    c. Discuss if patient is appropriate to remain for observation vs. transport for cooling.
    d. If determined to be a candidate for cooling by regional cooling center, begin passive cooling (see also *Appendix D*)
2. **Turn down/off external heat sources and avoid hyperthermia**
    a. Document time and **do not actively cool patients**. (See *Appendix D*).

3. **Monitor core (rectal) temperature closely**
    a. Target rectal temp = 33-34°C (91.4 – 93.2°F) or **Axillary temp = 32-33°C** (89.6 – 91.4).
    b. Check temp continuously/frequently (q15 min)**.** Complete flow sheet (*Appendix H*).
    c. Core temp may still fall <33.5C with passive cooling. Be prepared to respond

    (Appendix D).

4. **Secure vascular access** - Before peripheral vasoconstriction occurs with cooling.
    a. Umbilical venous and arterial access, if possible.
    b. Peripheral IV at a minimum.

5. **Maintain adequate sedation** - Keep comfortable/minimize cold stress and avoid shivering during passive cooling.
    a. **e.g., Morphine IV –** consider prn dosing or continuous infusions as indicated in discussion with cooling center.

6. **Treat only clinical seizures –** No prophylactic antiepileptic treatments.
    a. Lorazepam (Ativan): 0.1mg/kg/dose IV, repeat once prn for suspected seizures.
    b. Phenobarbital: *20mg/kg IV load, for obvious clinical seizures.*

7. **Expect these physiologic states in cooled infants**
    a. Expect low baseline heart rates (80-100bpm) as patient approaches target temp.
    b. Manage blood pressure and oxygenation as usual. Maintain normal values (see #10).
    c. Consider volume bolus (e.g., normal saline) if perfusion compromised.

8. **Monitor electrolytes closely** - maintain normal ranges.
    a. Fluctuations often seen in ***Ca, K, Mg*** levels with cooling.

9. **Avoid hypoglycemia -** maintain within high normal ranges.
    a. Maintain ***Glucose*** levels > 50mg/dl.

10. Avoid iatrogenic **hyperventilation** and **hyperoxygenation.**
    a. Target **pCO2= 40-50** (patients may have compensatory hyperventilation).
    b. Target **PaO2 = 60-100mmHg** and keep **oxygen saturations = 94-98%**

11. Send **Blood cultures** and consider **IV antibiotics as indicated**

12. Send **other baseline labs** if indicated, but don't delay transport for routine labs.
    a. CBC, differential and platelets
    b. Coagulation panel (INR, PT/PTT), LFT, BUN/Cr.

Appendix D

Guidelines for Passive Cooling

1. Document Regional Cooling Center contacted and decision made to initiate passive cooling for those determined to be a candidate for cooling.
2. Turn radiant warmer off and leave infant uncovered, except diapers.
3. Monitor core/rectal temperature continuously (if equipped) or every 15 minutes using a lubricated digital thermometer carefully inserted 2 cm into rectum. If core temperature monitoring cannot be done safely or is not available, monitor axillary temperatures every 15 minutes. Record temperatures on flow sheet (see Appendix H).
4. Allow temperature to fall to target temperature ranges:
    1. Target rectal temperature is **33-34°C or 91.4-93.2°F** .
    2. Target axillary temperature is **32-33°C or 89.6-91.4F**.
5. Avoid overcooling. When the rectal temp reaches **33 °C (91.4 °F)** or axillary temp **32 °C (89.6 °F)**, turn warmer back on to lowest setting or covering patient with clear plastic (avoid face).
6. If rectal temp continues to fall quickly or remains **< 33 °C** (91.4 °F) or axillary temp **< 32 °C** (89.6 °F), increase warmer setting. Recheck temperature until recovered.
7. Avoid overheating. Minimize big changes in heater settings that may result in overcorrections.
8. Monitor vital signs, electrolytes and glucose levels closely.
9. If administering respiratory support, avoid hyperoxia and iatrogenic hyperventilation.
10. Keep patient comfortable and adequately sedated (i.e., avoid shivering).

Appendix E

Management of Screened Neonates Who Do Not Qualify for Cooling

Not all neonates who meet screening criteria will require or qualify for cooling therapy. However, they may still have significant risks factors that warrant special consideration. These risks may range from mild acidosis to multi-organ dysfunction. In addition, initial signs of neonatal encephalopathy may be subtle and neurologic symptoms may evolve over time. In some cases, passive cooling may already have been initiated. Patients without clinical evidence of perinatal brain injury should be rewarmed only after a thorough evaluation and consultation (phone/video) with a neonatologist at a regional cooling center. Levels of concern and need for observation or other interventions/therapies may be appropriate depending upon the clinical presentation.

1. **Maintain communication with regional cooling center**
    a. Discuss management and plan if significant clinical changes develop.

2. **If heat sources were removed/cooling was initiated, slowly begin rewarming**
    a. Document time of lowest temperature and source (e.g., axillary vs. rectal).
    b. Rewarm with target rate of approximately **0.5 °C /hour.** **Avoid overheating.**

3. **Monitor temperature periodically**
    a. **Target rectal/core temp = 36.5°C** (97.7°F) or **axillary/skin temp = 36.0°C** (96.8°F).
    b. Check temperature periodically (e.g., hourly for first 6 hours).

4. **Check glucose and electrolyte levels.**
    a. Fluctuations may be seen - check ***Glucose*** levels. **Avoid hypoglycemia**
    b. Consider maintaining higher normal target glucose levels (e.g., **>50mg/dl**)
    c. Consider checking ***Ca, K, Mg*** levels. Maintain within normal ranges.

5. **Obtain follow-up blood gases to confirm acidosis resolving**
    a. If acidosis persists, work-up other causes or discuss with neonatologist.

6. **Repeat neurologic examination** *(see appendix B)*
    a. Document initial neurologic exam.
    b. Repeat neurologic exam (e.g., after 1-3 hours) if clinically indicated.
    c. Document neurologic exam at time of discharge.

7. **If initial acidosis severe, consider delaying enteral feeds (NPO) until improved**
    a. Depends upon severity of clinical presentation. Discuss with neonatologist.
    b. May require initiation of maintenance IVF fluids.

8. **Avoid iatrogenic hyperventilation and hyperoxygenation**
    a. Normal **pCO2** levels **(35-45 mmHg) –** compensatory hyperventilation may be seen.
    b. Normal **PaO2** levels **(60-100mmHg)** and **oxygen saturations (<94-98%).**

9. **Consider ordering baseline labs:**
    a. CBC, platelets and Blood cultures.
    b. Start antibiotics if appropriate.

Appendix F

Family Information Sheet (example)

Access our patient education library online at www.ucsfhealth.org/childrens

Your Child's Health

Hypothermia Treatment for Hypoxic Ischemic Encephalopathy

Information for Parents

Terminology

Hypoxic = not enough oxygen

Ischemic = not enough blood flow

Encephalopathy = brain injury

Hypothermia = cooling

Introduction

Your baby might have Hypoxic Ischemic Encephalopathy (HIE). This means the baby is sick because the brain may not have gotten enough oxygen or blood flow for a period of time. There could be many reasons why this has happened. Your baby's doctor will talk with you about what those reasons might be.

A lack of oxygen before and during birth can injure cells in a newborn baby's brain. How long the brain was without oxygen can impact how serious the problems will be. The damage caused by the lack of oxygen can continue for some time after birth.

What can be done to treat HIE?

One way to reduce this damage is to cool the baby for hours to days. For babies with HIE, research has shown that if the brain is cooled just a few degrees below normal body temperature soon after birth, there may be less brain damage. Your baby will be placed on a cooling blanket (hypothermia blanket) for up to three days. After this time, your baby will be slowly re-warmed to normal body temperature.

UCSF Children's Hospital at UCSF Medical Center

Physician Referral Service: 888/689-UCSF

How will my baby be monitored during the cooling treatment?

While caring for your baby, we will monitor your baby's heart rate, breathing patterns and temperature. We will also be checking your baby's brain activity with a cerebral function monitor (CFM). Three tiny probes are placed just under the skin of your baby's scalp. These probes are connected to the CFM and will help show us if there are any changes in brain activity. Another way we will look at brain activity is with an electroencephalogram (EEG) and a video camera. Blood tests will also be sent to evaluate other aspects of your baby's health such as infections or metabolic problems.

Does the cooling blanket affect any other parts of the body besides the brain?

It is normal for your baby to have a slower heart rate and breathing rate during the cooling treatment. It is also normal for your baby to be quiet and sleepy.

How will my baby be kept comfortable while on the cooling blanket?

We will be giving medicines to help your baby rest comfortably and will be monitoring your baby closely for any signs of discomfort.

What can I do to help my baby during the treatment?

You are welcome to visit your baby anytime in the Intensive Care Nursery (ICN) according to the ICN guidelines. For the first few days, it is important that your baby rests. Your baby's nurse can show you ways to participate in your baby's care.

How will my baby receive nutrition during the cooling treatment?

Your baby will be getting nutrition through intravenous (IV) therapy. After cooling, and when your baby is ready to eat, breast milk or formula will be given. For breastfeeding mothers, please pump and store your milk. We will provide accommodations for you to do this and assist you with using the breast pump.

We realize this is a difficult time for you and your family. The stress of having a baby in the ICN, along with seeing unfamiliar machines and procedures, might be frightening. We encourage you, as the parents, to please ask questions about your baby's care or concerns you have. For additional information on your baby's care please ask your baby's nurse or doctor.

SDICN0435 • Rev. 7/08

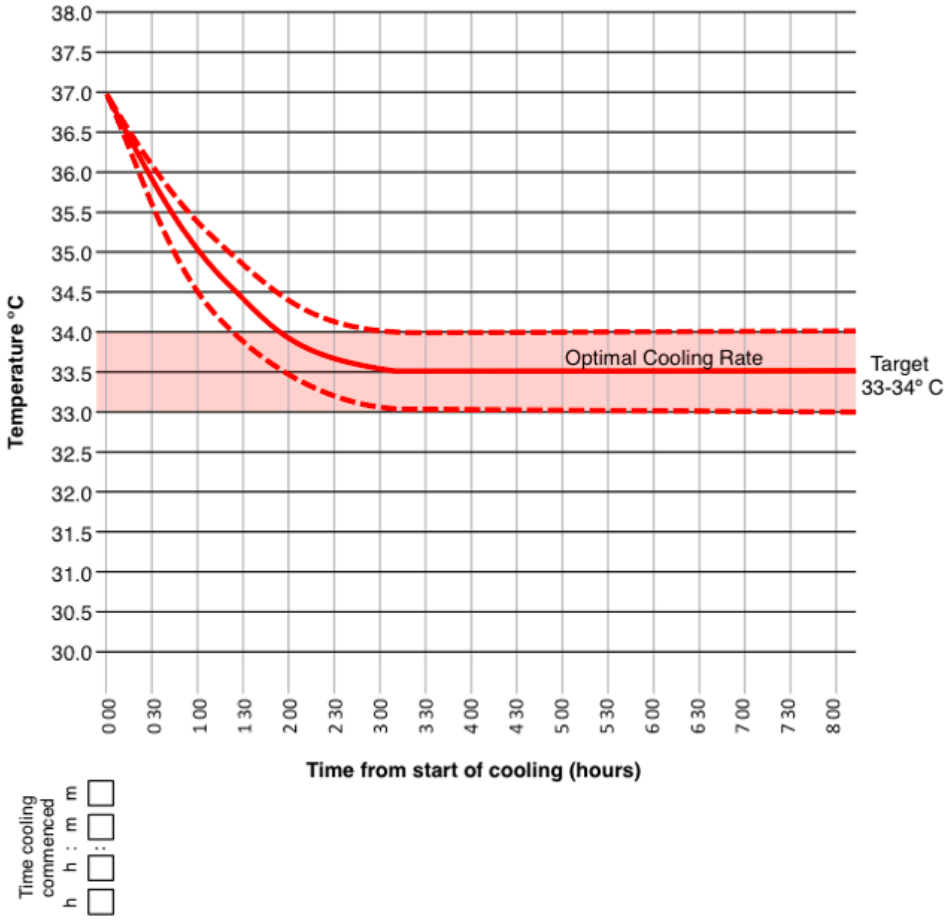
Appendix G

Recommended Rectal Temperature Trajectory for Cooling

Name: _____

DOB: _____

TOB: _____



Time cooling commenced h h : m m

Actions taken to achieve temperature control	Time	Sign/Date
Passive cooling started with turning off radiant warmer and removing blankets		

Active Versus Passive Cooling During Neonatal Transport. Rajiv Chaudhary, Kate Farrer, Susan Broster, Louise McRitchie and Topun Austin *Pediatrics* 2013;132;841; originally published online October 21, 2013; DOI: 10.1542/peds

Appendix H

Temperature Record for Passive Cooling at Referring Hospital

Passive Cooling at Referral Hospital

Vital Signs Record

DOB:___ ___ ___ **Time**: ___ : ___ 1ST Temperature after Birth: Date: ___ ___ ___ Time:___ : ___

Radiant Warmer turned off : ☐ No ☐ Yes: Date: ___ ___ ___ Time: ___: ___

Ordered By Doctor: _____MD

	Baseline	**15”**	**30”**	**45”**	**1 hr**	**1hr 15”**	**1hr 30”**	**1hr 45”**	**2 hrs**	**2hrs 15”**	**2hrs 30”**
Date											
Time											
Axillary	°C	°C	°C	°C	°C	°C	°C	°C	°C	°C	°C
HR											
RR											
BP											
Glucose											

Goal: Maintain baby’s Temperature between 34ºC-36ºC (93.2 ºF-96.8ºF)
Temperature: Every 15 minutes. HR, BP every 30 minutes
Glucose: on admission than every hour if stable.

Comment:

Date/Time	**RN Signature**	**Date/Time**	**RN Signature**
_____	_____	_____	_____
_____	_____	_____	_____

Appendix I

Temperature Record for Passive Cooling and Rewarming in NICU

Passive Cooling Temperature Record at SCVMC NICU

Admit Date: ___ ___ ___ **Time**: ____ : ____ **Admit Temp**: _____ **Time**:____ : ____

	15"	30"	45"	1 hr	1hr 15"	1hr 30"	1hr 45"	2 hrs	2hrs 15"	2hr 30"	2hr 45"
Date											
Time											
Axillary	°C	°C	°C	°C	°C	°C	°C	°C	°C	°C	°C
Rectal	°C	°C	°C	°C	°C	°C	°C	°C	°C	°C	°C
Intervention											

Goal: Maintain baby's Temperature between 34 ºC-35ºC (93.2 ºF-95ºF)

Total Body Cooling (TBC):

YES – Continue recording temperature on **NICU Induced Hypothermia Temperature Record**

NO ---Continue recording temperature using the log below

Passive Re-warming Temperature Record

Time: ____ : ____

	30"	1 hr	1hr 30"	2 hrs	2hr 30"	3hrs	4hrs
Time							
Axillary	°C	°C	°C	°C	°C	°C	°C
Rectal	°C	°C	°C	°C	°C	°C	°C
Intervention							

Date/Time **RN Signature** **Date/Time** **RN Signature**

_____ _____ _____ _____

_____ _____ _____ _____

Appendix J

Screening for Hypothermia Therapy for Infants with HIE

QI Form

Birthing Hospital: _____ Patient ID: _____

DOB/TOB: _____GA_____BW _____Apgar@1____Apgar@5_____

Criteria for screening: ☐ Apgar <6 at 10 minute ☐ pH<7 ☐ BD >10 ☐ PPV at 10minutes of life ☐ CPR ☐ use of epi/resuscitation drugs/blood?
☐ Perinatal event (Abruption, Fetal distress, Cord prolapse, Uterine rupture, maternal trauma)

Cord gas UA/unmarked: pH _____ pCO_2 _____ Base deficit _____

Cord gas UV/unmarked: pH _____ pCO_2 _____ Base deficit _____

1st Baby gas: date/time: _____ pH _____ pCO_2 _____ Base deficit _____

Heat sources removed: date/time: _____ **Temp monitoring began:** date/time:_____

Lowest temp: °C/F rectal / axilla / skin (*please circle one*) date/time: _____

Highest temp: °C/F rectal / axilla / skin (*please circle one*) date/time: _____

Time to reach temp 33-34°C: _____

Seizure: ☐ Yes ☐ No ☐ suspected/unsure If yes, date/time: _____

Lowest Glucose value in the 1st 6 hours of life: _____ date/time:_____

Called cooling center? ☐ Yes ☐ No If yes, date/time: _____

Cooling center: _____

Advice given about cooling: observe / passive / active / intermediate (explain):

Transferred? ☐ Yes ☐ No If yes, date/time: _____

Cooled on transport? ☐ Yes ☐ No ☐ intermediate (explain)

Cooled at the cooling center? ☐ Yes ☐ No If yes, date/time: _____