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| Question | |
| **Should therapeutic hypothermia vs. standard care be used for late preterm and term infants (>34+0 or more weeks gestation) with moderate /severe hypoxic ischemic encephalopathy managed in low resource settings?** | |
| **Population:** | Late preterm and term infants (>34+0 or more weeks gestation) with moderate /severe hypoxic ischemic encephalopathy managed in low resource settings |
| **Intervention:** | Therapeutic hypothermia |
| **Comparison:** | Standard care (no therapeutic hypothermia) |
| **Main outcomes:** | Death or Neurodevelopmental Impairment at 18-24 months (critical); Death at Hospital Discharge (critical); Neurodevelopmental Impairment at 18-24 months (critical); Cerebral Palsy (critical); Blindness (critical); Deafness (critical); persistent pulmonary hypertension of newborn; adverse outcome as defined by authors. |
| **Setting:** | Neonatal intensive care unit |
| **Perspective:** | Population perspective |
| **Background:** | Therapeutic hypothermia is now considered standard care in high income countries for the treatment of moderate and severe hypoxic ischemic encephalopathy in term and near-term infants. There has been limited research studying the efficacy of therapeutic hypothermia in low resource settings or in middle/low-income countries. As asphyxia is a leading cause of neonatal mortality and morbidity, it is important to continue to study potential interventions to improve the important outcomes of mortality and neurodevelopmental outcome. |
| **Conflict of interests:** | No conflict of interest |

# Assessment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | Therapeutic hypothermia is now considered standard care in high income countries for the treatment of moderate and severe hypoxic ischemic encephalopathy in term or near-term infants. There is no consensus as yet, on the use of therapeutic hypothermia in low resource settings or in middle- and low-income countries. As asphyxia is a leading cause of neonatal mortality and morbidity, it is important to continue to study potential interventions to improve the critical outcomes of mortality and neurodevelopmental impairment. Other outcomes such as cerebral palsy, blindness, and deafness may be impacted. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know | Although death as an outcome was not shown to have clear benefit with the intervention, the critical outcomes of neurodevelopmental impairment, cerebral palsy, and deafness were found to have reduced incidence with the intervention of therapeutic hypothermia. The primary composite outcome of death or neurodevelopmental impairment favored the intervention. This systematic review found that for **therapeutic hypothermia when compared to no hypothermia (standard care)** for late preterm or term infants in middle- or low-income countries:   * For the critical primary composite outcome of **death or neurodevelopmental impairment at 18-24 months,** there was **probable clinical benefit** (relative risk (RR) 0.6663; 95% CI, 0.4505, 0.9855; p = 0.0420, absolute risk difference (ARD) 153 fewer infants per 1000 [95% confidence interval (CI) 252 fewer to 7 fewer]), **moderate certainty** evidence from five RCTs enrolling 813 participants. {Aker 2022 32, Li 2009 147, Thayyil 2021 e1273, Zhou 2010 367, Zou 2019 2332} * For the critical primary composite outcome of **death or neurodevelopmental impairment at follow up**, there was **possible clinical benefit** (RR 0.4973; 95% CI, 0.3497 to 0.7071; p = 0.0001, ARD 239 fewer infants per 1,000 [95% CI 309 fewer to 139 fewer]), **low certainty** evidence, downgraded for risk of bias and inconsistency, from nine RCTs enrolling 1168 participants. {Aker 2022 32, Bharadwaj 2012 382, Das 2017 157, Gane 2014 134, Li 2009 147, Sun 2012 e316, Thayyil 2021 e1273, Zhou 2010 367, Zou 2019 2332}   Among important secondary outcomes, **comparing therapeutic hypothermia to no therapeutic hypothermia**:   * For the critical outcome **death at 18-24 months**, there was **improbable clinical benefit** (RR, 0.8936; 95% CI 0.5495 to 1.4531; p = 0.6502, ARD 27 fewer infants per 1,000[95% CI113 fewer to 114 more]), **moderate certainty** evidence downgraded for risk of bias from five RCTs enrolling 827 participants. {Aker 2022 32, Li 2009 147, Thayyil 2021 e1273, Zhou 2010 367, Zou 2019 2332} * For the critical outcome **death at follow up**, **clinical benefit or harm cannot be excluded** (RR, 0.6188; 95% CI, 0.3798-1.0083; P = 0.054, ARD 90 fewer infants per 1,000[95% CI146 fewer to 2 more]), **low certainty** evidence downgraded for risk of bias and inconsistency from nine RCTS enrolling 1182 participants. {Aker 2022 32, Bharadwaj 2012 382, Das 2017 157, Gane 2014 134, Li 2009 147, Sun 2012 e316, Thayyil 2021 e1273, Zhou 2010 367, Zou 2019 2332} * For the critical outcome **death at hospital discharge**, there was **possible clinical benefit** (RR, 0.70; 95% CI, 0.47, 1.02; P = 0.06; I2 = 54%; ARD 64 fewer infants per 1000 [95% CI, 112 fewer to 5 more]), **moderate certainty evidence** from fifteen RCTs enrolling 1488 participants. {Aker 2022 32, Akisu 2003 45, Bharadwaj 2012 382, Catherine 2021 fmaa073, Chen 2018 1046, Joy 2013 17, Liao 2018 64, Lin 2006 180, Rakesh 2018 2418, Robertson 2008 801, Sun 2012 e316, Tanigasalam 2016 2545, Thayyil 2021 e1273, Yang 2020 300060520943770, Zou 2019 2332} * For the critical outcome **neurodevelopmental impairment at 18-24 months**, there was **possible clinical benefit** (RR, 0.5129; 95% CI, 0.3941 to 0.6674; P = < 0.0001; ARD 154 fewer infants per 1000 [95% CI, 178 fewer to 124 fewer]), l**ow certainty** evidence from six RCTS enrolling 929 participants. {Aker 2022 32, Joy 2013 17, Li 2009 147, Thayyil 2021 e1273, Zhou 2010 367, Zou 2019 2332} * For the critical outcome **neurodevelopmental impairment at follow up**, there was **possible clinical benefit** (RR, 0.43; 95% CI, 0.34, 0.54; P < 0.0001; ARD 154 fewer infants per 1000 [95% CI, 178 fewer to 124 fewer]), **low certainty evidence**, downgraded for risk of bias and inconsistency, from twelve RCTs enrolling 1482 participants. {Aker 2022 32, Bharadwaj 2012 382, Catherine 2021 fmaa073, Chen 2018 1046, Das 2017 157, Gane 2014 134, Joy 2013 17, Li 2009 147, Sun 2012 e316, Thayyil 2021 e1273, Zhou 2010 367, Zou 2019 2332} * For the critical outcome **cerebral palsy**, there was **clinical benefit** (RR, 0.52; 95% CI, 0.37 to 0.72; P ≤ 0.0001; ARD 89 fewer infants per 1000 [95% CI from 117 fewer to 52 fewer]), **high certainty** evidence from six RCTs enrolling 919 participants {Aker 2022 32, Jose 2017 86, Li 2009 147, Sun 2012 e316, Thayyil 2021 e1273, Zhou 2010 367} * For the critical outcome **blindness at follow up**, there was **improbable benefit** (RR, 0.4767; 95% CI, 0.2203 to 1.0317; P = 0.06; ARD 28 fewer infants per 1000 [95% CI 41 fewer to 2 more]), **moderate certainty** evidence, downgraded for risk of bias, from four RCTs enrolling 718 participants. {Das 2017 157, Gane 2014 134, Jose 2017 86, Thayyil 2021 e1273} * For the critical outcome **deafness at follow up**, there For the critical outcome **deafness at follow up**, there was **probable clinical benefit** (RR, 0.42; 95% CI, 0.21, 0.82; P = 0.01; ARD 42 fewer infants per 1000 [95% CI 57 fewer to 13 fewer]), **moderate certainty evidence**, downgraded for risk of bias, from four RCTs enrolling 718 participants. {Das 2017 157, Gane 2014 134, Jose 2017 86, Thayyil 2021 e1273} * For the critical outcome **persistent pulmonary hypertension of the newborn (PPHN)**, **clinical benefit or harm could not be excluded** for the use of therapeutic hypothermia vs no therapeutic hypothermia in infants with HIE (RR, 1.31; 95% CI, 0.76 to 2.25; P = 0.33; I2 = 32%; 23 more patients/1000 [95% CI 18 fewer/1000 to 92 more/1000]), **high certainty evidence** from three RCTs, enrolling 564 participants. {Aker 2020 405, Tanigasalam 2016 2545, Thayyil 2021 e1273} | For neurodevelopmental impairment, the assessment method differed amongst studies.  The timing of assessment of death or neurodevelopmental impairment was inconsistent amongst some studies. For the primary outcome of death or neurodevelopment assessment at 18-24 months, studies were included only if the assessments occurred during that time period.  Other studies were included even when the period of assessment was not 18-24 months in the outcome of death or neurodevelopmental impairment at follow up (without specification of time period). This was considered as a different variable in order to include those other studies when the timing was not 18-24 months. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know | There was no increase in death or other adverse outcomes observed with the intervention. While a meta-analysis of adverse outcomes was not possible due to heterogeneity, the individual studies also did not point to harm from the intervention. | While some studies reported adverse outcomes, the elements that characterized this variable was inconsistent amongst studies and could not be combined. For the studies reporting on adverse outcomes, there were no significant differences in the individual studies in the groups. It would be important to continue to study the potential for undesirable effects with the therapies directly and indirectly related to implementing therapeutic hypothermia in these settings. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ● Moderate ○ High ○ No included studies | The certainty of evidence for the primary outcome, death or neurodevelopmental impairment at 18-24 months, was moderate.  Certainty for the secondary outcomes varied from low (death or neurodevelopmental impairment at follow up, neurodevelopmental impairment at 18-24 months) to high (PPHN, cerebral palsy).  Limitations of the analysis include the lack of a standardized timing and assessment across all studies for neurodevelopmental impairment. |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability | There may be different perspectives on the desirable outcomes in settings where individuals who have disability may be cared for differently. Some settings may not have the capability to care for individuals with more profound disabilities. However, improvements in rates of disability would be favorable in both high and low resource settings. | While death was not found to be different amongst the intervention and control groups, the rates of other outcomes such as neurodevelopmental impairment in survivors was not worse in the intervention group. |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know | The largest included study found increased risk of mortality. {Thayyil 2017 432} Nevertheless, the balance of results shows a benefit for the intervention in some outcomes, including the critical outcome of neurodevelopmental impairment. Adverse effects were not consistently seen for the intervention. It is also helpful to know that the intervention of therapeutic hypothermia has been extensively studied and found effective in high resource settings. Although those studies are not part of the current analysis, the recognition that physiology would be applicable across settings would increase confidence in the effectiveness of the intervention. | Many of the studies included were either in middle income countries and/or NICU settings that had higher resources. Not all NICUs even in higher income countries provide therapeutic hypothermia. Therefore, further considerations as to generalizability and applicability will depend on local context. |
| Resources required How large are the resource requirements (costs)?" | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | No studies reported provided a detailed report of resources. Some studies used technology (e.g. servo-controlled cooling devices) that would increase costs of neonatal care. While some studies used lower cost technology, there will ultimately be increased costs of NICU care and neonatal and developmental care and expertise. Implementing therapeutic hypothermia protocols would require adequate other resources which include both personnel and other equipment to ensure a successful therapeutic hypothermia program.  There may be increased burden in training personnel and providing other NICU resources when implementing protocols for therapeutic hypothermia. | It would be important to characterize the costs, resources required for NICU care, and personnel needed to implement programs of therapeutic hypothermia in low resource settings. Improvement in disability may lead to changes in resources required for follow-up care after hospital discharge and into school age. |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | No included studies reported data on costs or similar variables. Further research on cost and resource allocation for this intervention in limited resource settings are warranted. |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | Cost effectiveness in low-resource settings has not adequately studied. In high-income countries, therapeutic hypothermia leads to increased short-term costs at the hospital level but is likely to be cost effectiveness over an extended time horizon. {Regier 2010 695} |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know | Hypoxic ischemic encephalopathy and associated poor outcomes disproportionately affect newborns in low- and middle-income countries. Therefore, interventions to improve outcomes in these countries will advance health equity.  The subgroup analysis showed that for non-servo-controlled methods of cooling (e.g., refrigerated gel packs, cold water bottles, etc.) there was a probable clinical benefit for the primary outcome of **death or neurodevelopmental impairment at 18-24 months** (RR, 0.333; 95% CI, 0.1243 to 0.8939; P = 0.0291). There was additional probable clinical benefit for the secondary outcomes of **death at hospital discharge** (RR, 0.6621; 95% CI, 0.4990 to 0.8784; P = 0.0043), **death at follow up** (RR, 0.3415; 95% CI, 0.1934 to 0.6093; P = 0.0002), **neurodevelopmental impairment at follow up** (RR, 0.3873; 95% CI, 0.2758 to 0.5438; P = <0.0001), **neurodevelopmental impairment at 18-24 months** (RR, 0.5227; 95% CI, 0.3566 to 0.7662; P = 0.0009), **death or neurodevelopmental impairment at follow up** (RR, 0.3023; 95% CI, 0.2057 to 0.4444; P = <0.0001), and **deafness** (RR, 0.3333; 95% CI, 0.1145 to 0.9704; P = 0.0439).  These methods of cooling, which are more easily accessible, show probable clinical benefit and could be easily implemented in low-resource or high-resource settings. |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | No studies in this review included information about acceptability of therapeutic hypothermia. However, as the studies were performed in low- and middle-income country settings, there is likelihood that stakeholders in those settings will welcome advancements in treatment that improve outcomes. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | The studies were conducted in low- and middle-income countries and therefore, the feasibility and generalizability are increased compared to applying protocols conducted in high-resource settings. However, there is a presumption that the NICUs providing therapeutic hypothermia will be able to provide other components of advanced NICU care. As hypoxic ischemic encephalopathy is often associated with multi-organ failure, NICUs would need to provide support for other organ systems including respiratory, cardiovascular, and renal. These aspects of care were generally not addressed in these studies. | The centers in which the studies were conducted are likely to be relatively higher resourced than other centers in the same countries. Large multicenter trials and further research into the requirements for implementation is needed in order to assess generalizability of findings within each middle- or low-income country. |

# Summary of judgements

|  | **Judgement** | | | | | | |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Trivial | Small | Moderate | **Large** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | **Favors the intervention** | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | **Increased** | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | **Strong recommendation for the intervention** |
| ○ | ○ | ○ | ○ | **●** |

# Conclusions

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| Recommendation |
| We suggest the use of therapeutic hypothermia in comparison with standard care alone for term (≥37+0 weeks gestational age) newborn infants with evolving moderate-to-severe hypoxic-ischemic encephalopathy in low- and middle-income countries in settings where a suitable level of supportive neonatal care is available (weak recommendation, low-certainty evidence).  For late preterm infants, 34+0 to 36+6 weeks gestational age infants, a recommendation cannot be made due to insufficient evidence.  Cooling should only be considered, initiated, and conducted under clearly defined protocols with treatment in neonatal care facilities with the capabilities for multidisciplinary care and availability of adequate resources to offer intravenous therapy, respiratory support, pulse oximetry, antibiotics, anticonvulsants, transfusion services, radiology including ultrasound, and pathology testing. Treatment should be consistent with the protocols used in randomized clinical trials. Most protocols included commencement of cooling within 6 hours after birth, strict temperature control to specified range (typically 33°C to 34°C) and most commonly for a duration of 72 hours with rewarming over at least 4 hours. Adoption of hypothermia techniques without close monitoring, protocols, or without availability of comprehensive neonatal intensive care may lead to harm. (Good practice statement) |
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| Justification |
| Although the outcome of death was not significantly different between the intervention and control groups, the critical outcomes of neurodevelopmental impairment and cerebral palsy were decreased with the intervention. The primary outcome of death or neurodevelopmental impairment at 18-24 months was shown to favor the intervention of therapeutic hypothermia. The intervention has already been established as standard care in high resource settings. As the burden of hypoxic ischemic encephalopathy is higher in low- and middle-income countries, implementing treatments to reduce this burden is a high priority. |

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| Subgroup considerations |
| There were insufficient data to conduct the planned subgroup analysis. It was difficult to distinguish studies that used solely “passive” methods of cooling (removal of heat sources, clothing and coverings) from those that may have also used manually controlled “active” methods such as refrigerated gel packs and those that used both. Furthermore, both these methods may result in wider variation of core temperature than servo-controlled devices. The task force concluded that a more meaningful distinction was between studies that used servo-controlled vs non-servo-controlled methods of therapeutic hypothermia, and so this post-hoc subgroup analysis was conducted. The subgroup analysis demonstrated improvement in outcomes for both subgroups of studies.  For subgroup analysis by servo-controlled vs non-servo-controlled methods, for the critical outcome death or neurodevelopmental impairment at follow up, the non-servo-controlled methods were more efficacious than servo-controlled (test for subgroup differences (random effects): χ2 = 22.43, df =1 (p < 0.0001)). For the critical outcome of death at follow up, the non-servo-controlled methods were more efficacious than servo-controlled (test for subgroup differences (random effects): χ2 = 14.80, df =1 (p = 0.0001)). For the critical outcome of death at hospital discharge, the non-servo-controlled methods were more efficacious than servo-controlled (test for subgroup differences (random effects): χ2 = 7.39, df =1 (p = 0.0065)). For all other outcomes, results of tests for subgroup differences were not statistically significant. However, heterogeneity in study design, meaning that factors other than method of cooling may have made a major contribution to the effect sizes for each subgroup.  Other subgroup analyses were not feasible due to lack of data.  The servo-controlled studies **could** **not exclude clinical benefit or harm** for the critical primary combined outcome of **death or neurodevelopmental impairment at 18-24 months** (RR, 0.73; 95% CI, 0.50 to 1.07; P = 0.11; I2 = 74.40%), and the outcomes of **death at hospital discharge** (RR, 1.17; 95% CI, 0.89 to 1.54; P = 0.26; I2 = 41.40%), **death at any follow-up** (RR, 1.12; 95% CI, 0.90 to 1.07; P = 0.31; I2 = 35.30%), **death at 18-24 months** (RR, 1.13; 95% CI, 0.91 to 1.07; P = 1.42; I2 = 47.8%), **blindness** (RR, 0.51; 95% CI, 0.18 to 1.4656; P = 0.2112; I2 = n/a), **deafness** (RR, 0.51; 95% CI, 0.13 to 2.01; P = 0.34; I2 = n/a), and **PPHN** (RR, 1.53; 95% CI, 0.84 to 2.79; P = 0.17; I2 = n/a).  There was **probable clinical benefit** for the outcomes of **neurodevelopmental impairment at any follow-up** (RR, 0.48; 95% CI, 0.35 to 0.65; P = <0.0001; I2 = 0.0%) , **neurodevelopmental impairment at 18-24 months** (RR, 0.51; 95% CI, 0.36 to 0.72; P = 0.0002; I2 = 0.0%), **death or neurodevelopmental impairment at any follow-up** (RR, 0.68; 95% CI, 0.48 to 0.98; P = 0.04; I2 = 73.00%), and **cerebral palsy** (RR, 0.46; 95% CI, 0.29 to 0.71; P = 0.0004; I2 = 0.0%).  The non-servo-controlled studies showed **probable clinical benefit** for the critical primary outcome of **death or neurodevelopmental impairment at 18-24 months** (RR, 0.333; 95% CI, 0.1243 to 0.8939; P = 0.0291; I2 = n/a) **,** and the outcomes of **death at hospital discharge** (RR, 0.66; 95% CI, 0.50 to 0.88; P = 0.004; I2 = 14.9%), **death at any follow-up** (RR, 0.34; 95% CI, 0.19 to 0.61; P = 0.0002; I2 = 0.0%), **neurodevelopmental impairment at any follow-up** (RR, 0.39; 95% CI, 0.28 to 0.54; P = <0.0001; I2 = 0.0%), **neurodevelopmental impairment at 18-24 months** (RR, 0.52; 95% CI, 0.36 to 0.77; P = 0.0009; I2 = 0.0%), **death or neurodevelopmental impairment at any follow-up** (RR, 0.30; 95% CI, 0.21 to 0.44; P = <0.0001; I2 = 0.0%), and **deafness** (RR, 0.33; 95% CI, 0.11 to 0.97; P = 0.04; I2 = 0.0%).  The non-servo-controlled studies **could not exclude clinical benefit or harm** for **death at 18-24 months** (RR, 0.33; 95% CI, 0.07 to 1.50; P = 0.15; I2 = n/a), **cerebral palsy** (RR, 0.33; 95% CI, 0.04 to 2.99; P = 0.33; I2 = n/a), **blindness** (RR, 0.38; 95% CI, 0.11 to 1.33; P = 0.13; I2 = 0.0%), and **PPHN** (RR, 0.60; 95% CI, 0.15 to 2.40; P = 0.47; I2 = n/a). |

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| Implementation considerations |
| It is critically important that the implementation of therapeutic hypothermia in low resource settings and in low- and middle-income countries, that appropriate protocols are followed that align with those that are described in published clinical trials. The protocols in the studies in low- and middle-income countries generally followed those that were described in earlier clinical trials in high-income countries. Key aspects of these protocols are timing of the intervention, starting as early as possible after birth, generally before 6 hours, and with a duration of 72 hours. Another aspect of these protocols is close targeting of goal temperature range during the intervention. Applying the intervention in ways that do not conform to published protocols is unlikely to lead to benefit and may potentially cause harm. It is also important to have adequate other NICU resources that can support other organ systems such as respiratory, cardiovascular, and renal, as patients with moderate or severe hypoxic ischemic encephalopathy are likely to have derangements in those systems. It is also important that appropriate resources and provisions are made for follow-up care beyond the neonatal intensive care unit, to provide early intervention services as appropriate, and ongoing assessment of development. |

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| Monitoring and evaluation |
| It will be important to monitor the use of therapeutic hypothermia and its impact in low- and middle-income countries. It may be beneficial to limit the application of therapeutic hypothermia initially to centers that specialize in this intervention. |

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| Research priorities |
| Therapeutic hypothermia has been found as an effective intervention in high resource settings and has been accepted as the optimal treatment for moderate to severe hypoxic ischemic encephalopathy. Some, but not all studies in low- and middle-income countries have shown benefit. As the physiologic basis for the intervention has been established along with its clinical benefit in some settings, the lack of benefit in other settings may point to other aspects of NICU care or other risk factors inherent to the patient that may not lead to a favorable outcome. Research in which patients and which settings may be most amenable to therapeutic hypothermia may allow for appropriate patient selection and allocation of resources to optimize outcomes. Cost analyses may inform the feasibility and resource allocation priorities.  Key gaps in knowledge include:   * minimum intensive care resources required for safety and effectiveness of therapeutic hypothermia in low- and middle-income countries. * cost effectiveness of therapeutic hypothermia (using various methods and devices) in low- and middle-income countries. * resource implications (including equipment, monitoring, nursing care and outcome measurement) for safe and effective care of infants receiving therapeutic hypothermia in low- and middle-income countries. * strategies for optimal case recognition of infants who may benefit or may be harmed from therapeutic hypothermia in countries at all income levels. |

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