NLS 5051 EVIDENCE TO DECISION TABLE FOR CORD MANAGEMENT AT BIRTH FOR PRETERM INFANTS

This evidence to decision (EtD) table will include evidence for three questions or comparisons in the pairwise IPD meta-analysis:

1) deferred cord clamping (DCC) compared to immediate cord clamping (ICC), 2) Umbilical cord milking (UCM) compared to ICC, and 3) UCM compared to DCC.

The ILCOR Adolopment process was used to guide the adaptation of the newly conducted 2 systematic reviews with individual participant data (IPD) on cord management at preterm birth (iCOMP study). {Seidler 2023 2209, Seidler 2023 2223} iCOMP is the latest and only IPD meta-analysis of cord-management of preterm infants at birth. By including the trials' original IPD rather than aggregate data, this meta-analysis provides the best estimates of treatment effects for the rare outcomes and enhances the subgroup analysis.

QUESTION #1

Should deferred cord clamping (DCC) vs. immediate cord clamping (ICC) be used for preterm infants?	
POPULATION:	Preterm infants <37 weeks' gestation
INTERVENTION:	Deferred cord clamping (DCC)
COMPARISON:	Immediate cord clamping (ICC)
MAIN OUTCOMES:	Infant outcomes: - Mortality before discharge - Severe intraventricular hemorrhage (IVH) for infants <32 weeks' gestation: ultrasound diagnosis grades III and/or IV - Chronic lung disease (CLD) for infants <32 weeks' gestation: oxygen at 36 weeks' postmenstrual age (PMA) - Late onset sepsis for infants <32 weeks' gestation - Necrotizing enterocolitis (≥ Bell's Stage II) for infants <32 weeks' gestation - Patent ductus arteriosus requiring medical/surgical treatment for infants <32 weeks' gestation - Hyperbilirubinemia (treated by phototherapy) - Receipt of blood transfusion - Hypothermia on admission (body temperature <36.5℃) - Hemoglobin/Hematocrit within the first 24 h after birth Maternal outcomes: - Mortality - Postpartum hemorrhage - Use of therapeutic uterotonic agents - Post partum blood transfusion - Manual removal of the placenta - Postpartum infection
SETTING:	Locations where infants are born
PERSPECTIVE:	Infants and their families Health Care Providers for newborn infants and their mothers
BACKGROUND:	Umbilical cord management affects every one of the 130 million infants born in the world each year. Cord management at birth impacts not only the volume of placental transfusion to the baby, but also the cardiovascular transition around the onset of breathing and/or ventilation. {Bhatt 2013 2113, Yao 1969 871} Placental transfusion at birth, through delayed cord

	clamping and cord milking, improves cardio-respiratory post-natal adaptation of preterm infants, hemoglobin concentration, and cerebral oxygenation. {Bhatt 2013 2113, Hooper 2015 147, Kluckow 2015 225, Niermeyer 2013 385} There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. Long-term neurodevelopmental outcomes in preterm infants are being investigated. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Meta-analyses to date have suggested that placental transfusion at birth significantly reduces mortality in preterm infants as well as improving cardiovascular and hematological parameters. A recent systematic review found that delayed cord clamping at birth for >30s reduced mortality in preterm infants <28 weeks' gestation with number needed to treat for benefit (NNTB) of 20 infants, with a high GRADE level of evidence. {Fogarty 2018 1} In addition to examining timing of cord there has also been exploration of whether some or all of the benefits of delayed cord clamping, especially those attributable to placental transfusion may be achieved by milking the intact cord or a segment of cut cord. The optimal cord management at birth for preterm infants remains unclear. Cord management and resuscitation interventions may be simultaneous or sequential in time, and each may impact the performance and outcomes of the other. History, values, and preferences significantly impact interpretation of cord management studies. So-called "natural" cord management is based on the supposition that historically, immediate cord clamping has been an unusual practice and there have been natural delays between delivery and cord separation. As a result, early clamping and milking may be considered "medical interventions" that were increasingly practiced since the middle of the 20th century. This systematic review, however, chose early clamping as the control based on the (recent) commonest practice, and also because early cord clamping was the control condition in a large number of randomized trials of other methods.
CONFLICT OF INTERESTS:	Walid El-Naggar is a member of the iCOMP collaborative group, received NICHD grant as a co-investigator of the Umbilical Cord Milking in Non-Vigorous Infants (MiNVI Trial), received a grant from IWK Research as the principal investigator of the MoCC trial, received a grant from Nova Scotia Health Research Foundation (NSHRF) as a principal investigator of the study: The effect of umbilical cord milking on hemodynamic status of preterm infants: a randomized controlled trial, received a grant from National Health and Medical Research Council (NHMRC) as a co-investigator of the Australian Placental Transfusion study (APTS). Peter Davis is a member of the iCOMP collaborative group and received NHMRC funding for BabyDUCC trial, Justin Josephsen is a member of the iCOMP collaborative group, published an UCM trial that could be included in this analysis, and received NICHD funding as co-investigator of the VentFirst trial. Lene Seidler is the lead of iCOMP collaborative group, received a grant from the National Health and Medical Research Council (NHMRC) to support iCOMP. Daniela Costa-Nobre, Tetsuya Isayama, Roger Soll and Keith Couper have no relevant COI. Measures to manage conflicts of interest are described in the accompanying CoSTR statement.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Management of the umbilical cord at birth needs to be considered in the context of other resuscitation interventions. It may also alter responses to resuscitation and outcomes.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies	1) The pairwise IPD metanalysis identified 21 trials including 3292 preterm infants. *For the critical outcome of* ***death before discharge,*** there was **clinical benefit** for DCC compared to ICC (odds ratio (OR) 0.68,	

○ Don't know	95% confidence interval (CI) 0.51 to 0.91; number needed to treat for benefit (NNTB) 40, 95% CI 143 to 26; I^2 = 0%; 25 fewer infants per 1000 died before discharge [95% CI, 38 to 7 fewer per 1000]), **high certainty evidence** from 20 trials including 3,263 infants. {Backes 2016 35, Chu 2011 S502, Datta 2017 418, Duley 2018 F6, Finn 2019 121, García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 307, Liu 2018 , Oh 2011 S68, Okulu 2022 838444, Rana 2019 36, Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Salae 2016 S159, Tarnow-Mordi 2017 2445, Yunis 2021 157} **For infants < 32 weeks' gestation:** f*or the important outcome of* ***receiving transfusion of red blood cells***, there is **probable clinical benefit** (OR 0.59, 95% CI 0.47 to 0.73; I^2 = 0%; NNTB=7, 95% CI 5 to 12; 131 fewer infants per 1000 received blood transfusion after DCC than after ICC, [95% CI, 186 fewer to 78 fewer]), **Moderate certainty evidence** (downgraded for serious risk of bias) from 13 trials including 1929 infants. {Chu 2011 S502, Duley 2018 F6, Finn 2019 121, García 2023 , Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 307, Oh 2011 S68, Rana 2018 655, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157} For the important outcomes of ***hemoglobin concentrations (g/dL) and hematocrit values (%)*** *within the first 24 hours after birth*, hemoglobin concentrations and hematocrit values are **probably higher** after DCC compared to ICC (mean difference (MD)= 0.88 g/dL, 95% CI 0.52 to 1.24 (corresponds to MD of 8.8 mg/L, 95% CI 5.2 to 12.4), I^2= 0% and MD= 2.69%, 95% CI 1.43 to 3.95%; I^2 = 0% respectively), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 523 infants reporting ***hemoglobin concentrations*** {Chu 2011 S502, Finn 2019 121, García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}and 8 trials including 260 infants reporting ***hematocrit values*** {Backes 2016 35, García 2023 , Gharehbaghi 2020 11095, Kugelman 2007 307, Oh 2011 S68, Ranjit 2015 29, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.* **For infants ≥32 weeks' gestation** ***Hemoglobin concentrations*** within the first 24 hours after birth *(important outcome),* are **probably higher** after DCC compared to ICC (MD 1.26 g/dL, 95% CI 0.72 to 1.80 (corresponds to MD of 12.6 mg/L, 95% CI 7.2 to 18.2), I^2= 0%, **low certainty evidence** (downgraded for risk of bias and inconsistency) from 7 trials including 302 infants. {García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Liu 2018 , Okulu 2022 838444, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.* ***Hematocrit values*** within the first 24 hours after birth are **probably higher** after DCC compared to ICC (MD 3.69%, 95% CI 2.43 to 4.95%; I^2 = 0%), **moderate certainty evidence** (downgraded for risk of inconsistency) from 8 trials including 420 infants {García 2023 , Gharehbaghi 2020 11095, Kugelman 2007 307, Liu 2018 , Okulu 2022 838444, Ranjit 2015 29, Ruangkit 2019	

	156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	***For the important outcome of hypothermia on admission*** (body temperature <36·5°C), there is **probable clinical harm** as more infants developed hypothermia after DCC compared to ICC (OR 1.28, 95% CI 1.06 to 1.56; I^2 = 0%; NNTH 16, 95% CI 9 to 71; 62 more infants per 1000 were hypothermic on admission, [95% CI, 14 more to 111 more]), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 1995 infants. {Duley 2018 F6, Finn 2019 121, García 2023 , Kugelman 2007 307, Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157} ***For the important outcome of body temperature on admission,*** the **temperature is possibly lower** after DCC compared to ICC clamping (MD -0.13, 95% CI -0.20 to -0.06; I^2 =58.4), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 8 trials including 1995 infants.{Duley F6, Finn 121, García , Kugelman 307, Rana 655, Ruangkit 156, Tarnow-Mordi 2445, Yunis 157}. Note that the GRADE certainty of evidence was assessed post-hoc. - This finding was not replicated in infants ≥32 weeks' gestation. - No evidence of harm was identified in any other clinical outcomes for the infants or mothers related to deferred cord clamping compared to immediate cord clamping.	
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 is high for the critical outcome of infant's mortality before discharge and moderate for the important outcomes of receiving blood transfusion, hemoglobin and hematocrit levels within 24 hours of age and hypothermia on admission for infants <32 weeks' gestation. - The certainty of evidence was low for most of the other outcomes.	
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	The main outcomes are highly valued by health care providers and parents– they are critical outcomes. {Strand 2020 F328, Webbe 2020 425}	

● No important uncertainty or variability		
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	- Deferred cord clamping for 30- ≥180 compared to immediate cord clamping reduces infants' mortality before discharge (high quality evidence), reduces the receipt of blood transfusion (moderate quality evidence) and improves the hematologic status (Hemoglobin/hematocrit levels in the first 24 hours of age- moderate quality evidence). - The only undesired effect found for deferred cord clamping compared to immediate cord clamping is increased hypothermia (body temperature <36·5°C) on admission in infants <32 weeks' gestation (moderate certainty evidence).	
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 study evaluated required resources; however direct costs are expected to be similar regardless of method of umbilical cord management .	- For preterm infants requiring resuscitation at birth, additional equipment and additional training may be needed.
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 direct data available.	Although there are no published cost data, it is unlikely that deferred cord clamping compared to immediate cord clamping will add costs for infants not requiring resuscitation. However, for infants requiring resuscitation additional equipment and additional training may be needed.
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	- No studies evaluated cost-effectiveness. - Although there are no published cost-effectiveness studies, it is likely that deferring cord clamping for 30-180 seconds compared to immediate clamping favors the intervention because of the following reasons: A- There is high quality evidence that it reduces mortality before discharge in preterm infants <37 weeks' gestation. B- There is moderate quality evidence that it reduces the receipt of blood transfusion in infants <32 weeks' gestation. C- There is moderate quality evidence that it improves the hematologic status of preterm infants <37 weeks' gestation within the first 24 hours of age.	

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	The improvement in the main outcomes using an intervention that doesn't need additional resources, probably improves equity.	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Deferred cord clamping for most preterm infants has been recommended by different governing bodies including WHO and has been practiced for many years in both high and low resources settings.	For preterm infants requiring resuscitation at birth, additional equipment and additional training may be needed.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Deferred cord clamping for most preterm infants has been recommended by different governing bodies including WHO and has been practiced for many years now in both high and low resources settings.	For preterm infants requiring resuscitation at birth, additional equipment and additional training may be needed.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
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

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**
○	○	○	○	●

QUESTION #2

Should umbilical cord milking (UCM) vs. immediate cord clamping (ICC) be used for preterm infants?	
POPULATION:	preterm infants
INTERVENTION:	Umbilical cord milking (UCM)
COMPARISON:	Immediate cord clamping (ICC)
MAIN OUTCOMES:	Infant outcomes: - Mortality before discharge - Severe intraventricular hemorrhage (IVH) for infants <32 weeks' gestation: ultrasound diagnosis grades III and/or IV - Chronic lung disease (CLD) for infants <32 weeks' gestation: oxygen at 36 weeks' postmenstrual age (PMA) - Late onset sepsis for infants <32 weeks' gestation - Necrotizing enterocolitis (≥ Bell's Stage II) for infants <32 weeks' gestation - Patent ductus arteriosus requiring medical/surgical treatment for infants <32 weeks' gestation - Hyperbilirubinemia (treated by phototherapy) - Blood transfusion - Hypothermia on admission (body temperature <36.5℃) - Hemoglobin/Hematocrit within the first 24 h after birth Maternal: - Mortality - Postpartum hemorrhage - Use of therapeutic uterotonic agents - Post partum blood transfusion - Manual removal of the placenta
SETTING:	Locations where infants are born
PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
BACKGROUND:	As for question #1
CONFLICT OF INTERESTS:	Walid El-Naggar is a member of the iCOMP collaborative group, received NICHD grant as a co-investigator of the Umbilical Cord Milking in Non-Vigorous Infants (MiNVI Trial), received a grant from IWK Research as the principal investigator of the MoCC trial, received a grant from Nova Scotia Health Research Foundation (NSHRF) as a principal investigator of the study: The effect of umbilical cord milking on hemodynamic status of preterm infants: a randomized controlled trial, received a grant from National Health and Medical Research Council (NHMRC) as a co-investigator of the Australian Placental Transfusion study (APTS). Peter Davis is a member of the iCOMP collaborative group and received NHMRC funding for BabyDUCC trial, Justin Josephsen is a member of the iCOMP collaborative group, published an UCM trial that could be included in this analysis, and received NICHD funding as co-investigator of the VentFirst trial. Lene Seidler is the lead of iCOMP collaborative group, received a grant from the National Health and Medical Research Council (NHMRC) to support iCOMP. Daniela Costa-Nobre, Tetsuya Isayama, Roger Soll and Keith Couper have no relevant COI. Measures to manage conflicts of interest are described in the accompanying CoSTR statement.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Management of the umbilical cord at birth needs to be considered in the context of other resuscitation interventions. It may also alter responses to resuscitation and outcomes.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	- The pairwise IPD MA identified **18 trials** (1565 infants). The cord was milked intact (2–4 times) in 12 trials (n=866 infants), whereas in four trials (n=340 infants) the cut-cord was milked once and in two trials (n=359) there was a delay before intact-cord milking. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31} *For the critical outcome of **death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.73, 95% CI 0.44 to 1.20; I^2 = 7.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 18 trials including 1565 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31} *For the important outcome of **receiving red blood cell transfusions,*** there is **probable clinical benefit** for UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I^2 = 20%; NNTB 10, 95% CI 5 to 55; 92/1000 fewer infants received red cell transfusion after UCM compared to ICC, 95% CI 167 fewer to 18 fewer), **moderate certainty evidence** (downgraded for serious risk of bias) from 15 trials including 1163 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763,	

	Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31} ***Hemoglobin concentrations (g/dL)*** within the first 24 hours after birth (*important outcome)* **were possibly higher** after UCM compared to ICC (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL; I^2 = 66.6%), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 12 trials including 944 infants. {Alan 2014 e493, El-Naggar 2019 F145, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat } *Note that the GRADE certainty of evidence was assessed post-hoc.* ***Hematocrit values (%)*** within the first 24 hours after birth **were possibly higher** after UCM compared to ICC (MD 1.71%, 95% CI 0.78 to 2.64%; I^2 = 36.9%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 12 trials including 900 infants. {Alan 2014 e493, Chellappan 2022 A178, Gharehbaghi 2020 11095, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Yadav 2015 720} *Note that the GRADE certainty of evidence was assessed post-hoc.*	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	• No important undesirable effects were noted in the analyses except for a small decrease of body temperature of infants ≥32 weeks' gestation, on admission to NICU. • For the important outcome of **temperature on admission for infants ≥32 weeks' gestation**, there is **possible clinical harm** from UCM compared to ICC (MD -0.20, 95% CI -0.35 to -0.05; I2 = 81.4%; evidence of **low** certainty (downgraded for serious risk of bias and inconsistency) from 2 trials including 190 infants. {Ram Mohan 2018 88, Xie 2022 31} • However, the small decrease in temperature on admission was not associated with any increase in the rates of hypothermia on admission in either gestational age group, and is judged unlikely to be clinically important. • Compared to ICC, there is no clinical benefit or harm from UCM for any IVH or severe IVH in infants <32 weeks' gestation. • Maternal outcomes OR were not estimable or showed no difference with wide confidence intervals, due to few trials collecting maternal outcomes and low event rates.	
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	Evidence of critical outcomes of death at discharge was of low certainty, it was of moderate certainty for any IVH and receipt of blood transfusion and for all the other outcomes it ranged from low to very low.	
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	The main outcomes are highly valued as they are critical outcomes. {Strand 2020 F328, Webbe 2020 425}	
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	• There are no important differences in the rates of critical outcomes between UCM and ICC. • *For the important outcome of* ***hemoglobin concentrations (g/dL)*** within the first 24 hours after birth, **there is possibly higher** hemoglobin concentrations after UCM compared to ICC (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL; I^2 = 66.6%), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 12 trials including 944 infants. • *For the important outcome of* ***receiving red blood cell transfusions,*** there is **probable clinical benefit** for UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I^2 = 20%; NNTB 10, 95% CI 5 to 55; 92/1000 fewer infants received red cell transfusion after UCM compared to ICC, 95% CI 167 fewer to 18 fewer), **moderate certainty evidence** (downgraded for serious risk of bias) from 15 trials including 1163 infants. • The only undesirable effect found was lower temperature on admission, which was statistically significant. However, the effect was small and was considered unlikely to be clinically important.	
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	There are no published cost data.	- Cord clamping strategies in infants who do not require resuscitation need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. - Training is required. - Although there are no published cost data, the intervention is of no cost and possibly improves hematological status and probably reduces blood transfusion and therefore may reduce cost indirectly.
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	There are no data available.	We perceive the additional resource requirements and costs to be low for both this intervention and its comparison.
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	There are no data available.	Umbilical cord milking probably reduces blood transfusions and possibly improves hematologic status which may lead to potential savings.
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	Improvement of hematologic status and reduced receipt of red cell transfusions may result in improved equity in low-resource settings where resources may not be readily available.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A retrospective multicenter study implies that this is an accepted practice among healthcare practitioners. {Kumbhat 2021 S0022}	There are no clear disadvantages to the caregiver or client with respect to the intervention.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The intervention is feasible. {Kumbhat 2021 S0022}	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
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

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 ○

QUESTION #3

Should umbilical cord milking (UCM) vs. deferred cord clamping (DCC) be used for preterm infants?	
POPULATION:	Preterm infants
INTERVENTION:	Umbilical cord milking (UCM)
COMPARISON:	Deferred cord clamping (DCC)
MAIN OUTCOMES:	Infant outcomes: - Mortality before discharge - Severe intraventricular hemorrhage (IVH) for infants <32 weeks' gestation: ultrasound diagnosis grades III and/or IV - Chronic lung disease (CLD) for infants <32 weeks' gestation: oxygen at 36 weeks' postmenstrual age (PMA) - Late onset sepsis for infants <32 weeks' gestation - Necrotizing enterocolitis (≥ Bell's Stage II) for infants <32 weeks' gestation - Patent ductus arteriosus requiring medical/surgical treatment for infants <32 weeks' gestation - Hyperbilirubinemia (treated by phototherapy) - Blood transfusion - Hypothermia on admission (body temperature <36.5°C) - Hemoglobin/Hematocrit within the first 24 h after birth Maternal outcomes: - Mortality - Postpartum hemorrhage - Use of therapeutic uterotonic agents - Post partum blood transfusion - Manual removal of the placenta - Postpartum infection

SETTING:	Locations where infants are born
PERSPECTIVE:	Infants and their families Health Care Providers for newborn infants and their mothers
BACKGROUND:	As in question #1
CONFLICT OF INTERESTS:	Walid El-Naggar is a member of the iCOMP collaborative group, received NICHD grant as a co-investigator of the Umbilical Cord Milking in Non-Vigorous Infants (MiNVI Trial), received a grant from IWK Research as the principal investigator of the MoCC trial, received a grant from Nova Scotia Health Research Foundation (NSHRF) as a principal investigator of the study: The effect of umbilical cord milking on hemodynamic status of preterm infants: a randomized controlled trial, received a grant from National Health and Medical Research Council (NHMRC) as a co-investigator of the Australian Placental Transfusion study (APTS). Peter Davis is a member of the iCOMP collaborative group and received NHMRC funding for BabyDUCC trial, Justin Josephsen is a member of the iCOMP collaborative group, published an UCM trial that could be included in this analysis, and received NICHD funding as co-investigator of the VentFirst trial. Lene Seidler is the lead of iCOMP collaborative group, received a grant from the National Health and Medical Research Council (NHMRC) to support iCOMP. Daniela Costa-Nobre, Tetsuya Isayama, Roger Soll and Keith Couper have no relevant COI. Measures to manage conflicts of interest are described in the accompanying CoSTR statement.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Management of the umbilical cord at birth needs to be considered in the context of other resuscitation interventions. It may also alter responses to resuscitation and outcomes.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	- The pairwise IPD MA identified 15 trials (1655 infants). One trial with six infants milked the cut cord once, whereas 14 studies with 1649 infants milked the intact cord (2-4 times). Deferral times in the DCC group ranged from 30 to 120 seconds. *For the critical outcome of **death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.95, 95% CI 0.59 to 1.53; I^2 = 0.0%), **low certainty evidence** (downgraded for very serious imprecision) from **12 trials** including 1303 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}	

	- For the outcomes of ***chronic lung disease, necrotizing enterocolitis, Patent ductus arteriosus receiving medical or surgical treatment, late-onset sepsis, retinopathy of prematurity, hemoglobin concentrations (g/dL) for infants, receiving transfusion of packed red blood cells, hypothermia*** on admission for infants <32 weeks´ gestation, **clinical benefit or harm cannot be determined** for UCM compared to DCC. - For the outcomes of ***hemoglobin concentrations (g/dL), hematocrit (%), receiving transfusion of red blood cells, hypothermia on admission*** for infants ≥32 weeks' gestation, **clinical benefit or harm cannot be determined** for UCM compared to DCC.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*For the critical outcome of **severe intraventricular hemorrhage,*** there is **possible clinical harm** after UCM compared to DCC (OR 2.20, 95% CI 1.13 to 4.31; I^2 = 0.0%) NNTH 24 (95% CI 9 to 200 infants more have severe IVH after UCM compared to DCC), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 860 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22} *For the critical maternal outcome of **post-partum receipt of blood transfusion**, there is **possible clinical harm** after UCM compared to DCC (OR 2.72, 95% CI 1.11 to 6.65; I^2 = 0.0%; NNTH 26 (95% CI 8 to 333) 39 more/1000 (95% CI from 3 more to 118 more), **low certainty evidence** from 4 trials including 653 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2015 61}*	A new RCT published after the NMA was completed, showed no significant difference in the rates of severe intraventricular hemorrhage between preterm infants born at 28-32 weeks' gestation who received umbilical cord milking compared to those who received deferred cord clamping. {Katheria 2023 217.e1}
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	In general, the evidence was low for the critical and important infant and maternal outcomes.	
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	The main outcomes are highly valued as they are critical outcomes. {Strand 2020 F328, Webbe 2020 425}	
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	- Overall, clinical benefit or harm cannot be determined for UCM compared to DCC except for 2 outcomes: *For the critical outcome of **severe intraventricular hemorrhage,*** there is **possible clinical harm** after UCM compared to DCC (OR 2.20, 95% CI 1.13 to 4.31; I^2 = 0.0%) NNTH 24 (95% CI 9 to 200 infants more have severe IVH after UCM compared to DCC), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 860 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22} *For the critical maternal outcome of **post-partum receipt of blood transfusion**, there is **possible clinical harm** after UCM compared to DCC (OR 2.72, 95% CI 1.11 to 6.65; I^2 = 0.0%; NNTH 26 (95% CI 8 to 333) 39 more/1000 (95% CI from 3 more to 118 more), **low certainty evidence** from 4 trials including 653 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2015 61}*	
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	- There are no published cost data. However, for infants who do not require resuscitation, it is likely that umbilical cord milking and deferred cord clamping do not add cost. - For infants requiring resuscitation, additional equipment and additional training may be needed.	- Cord clamping strategies in infants need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. - Training is required.
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 data available.	We perceive the additional cost and resource requirements to be low for both this intervention and its comparison.

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	No data available	Although there are no published cost data, it is unlikely that umbilical cord milking compared to deferred cord clamping will add costs for infants not requiring resuscitation.

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	No data available.	Both the intervention and the comparison are widely available in all settings.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	- In preterm infants <32 weeks' gestation, who don't require resuscitation at birth, umbilical cord milking may not be accepted for practice over deferred cord clamping because of the evidence of increased severe IVH. - In preterm infants ≥32 weeks' gestation, umbilical cord milking may be acceptable for practice.	In preterm infants requiring resuscitation at birth, the evidence is insufficient to judge whether umbilical cord milking should/could be practiced.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The intervention is feasible. {Kumbhat 2021 S0022} Umbilical cord milking appeared to be feasible in the context of the included trials.	Current standard of care in some centers.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
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

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
○	●	○	○	○

OVERALL CONCLUSIONS

Recommendation

A- In preterm infants born at less than 37 weeks' gestational age who are deemed not to require immediate resuscitation at birth, we recommend deferring clamping of the umbilical cord for at least 60 seconds. (Strong recommendation, high-certainty evidence).

B- In preterm infants born at 28^{+0} to 36^{+6} weeks' gestational age who do not receive deferred cord clamping, we suggest umbilical cord milking as a reasonable alternative to immediate cord clamping to improve infant haematologic outcomes. Individual maternal and infant circumstances should be taken into account. (Conditional recommendation, low certainty evidence).

C- We suggest against intact cord milking for infants born at less than 28 weeks' gestation. (Weak recommendation; low certainty of evidence). There is insufficient evidence to make a recommendation regarding cut-cord milking in this gestational age group.

D- In preterm infants born at less than 37 weeks' gestational age who are deemed to require immediate resuscitation at birth, there is insufficient evidence to make a recommendation with respect to cord management. (Weak recommendation; low certainty of evidence).

E- There is insufficient evidence to make recommendations on cord management for maternal, fetal, or placental conditions that were considered exclusion criteria in many studies (monochorionic multiple fetuses, congenital anomalies, placental abnormalities, alloimmunization and/or fetal anemia, fetal compromise, and maternal illness). In these situations, we suggest individualized decisions based on severity of the condition and assessment of maternal and neonatal risk. (Weak recommendation; very low certainty of evidence).

F- Whenever circumstances allow, the plan for umbilical cord management should be discussed between maternity and neonatal providers and parents before delivery, and should take into account individual maternal and infant circumstances. (Good practice point).

Justification

A- Justification: In making a strong recommendation for deferring cord clamping for at least 60 seconds in preterm infants <37 weeks' gestation who are deemed not to require resuscitation at birth, the NLS Task Force took into consideration the following points:

I. There is **high-certainty evidence** from **20 trials** including 3260 infants showing **reduced mortality** after deferred cord clamping compared to immediate cord clamping (OR 0.68, 95% CI 0.51 to 0.91) with the number needed to treat for benefit (NNTB) 40, 95% CI 143 to 26.
   The reduction in mortality appears to be robust across several participant-level and trial-level subgroups (including gestational age at birth, mode of birth, multiple birth, sex, trial year, and perinatal mortality rate).
II. The evidence is derived from individual patient data (IPD) rather than trial level data which increases the quality of the meta-analysis. It allows for comprehensive checking of data integrity and provides more robust evidence overall and for secondary analyses.
III. The meta-analysis results were consistent across all prespecified sensitivity analyses, including combining individual participant data with aggregate data (from trials not providing individual participant data), different outcome definitions, excluding trials with high risk of bias, and different analysis methods (e.g, two-stage model).
IV. The evidence is supported by the IPD network meta-analysis.
V. There is **moderate-certainty evidence** of **fewer blood transfusions** (OR 0.59, 95% CI 0.47 to 0.73) from **13 trials** including 1929 infants <32 weeks' gestation and of **higher hemoglobin concentrations** within the first 24 hours after birth (mean difference (MD)= 1.26 g/dL, 95% CI 0.72 to 1.80) and from **8 trials** including 523 infants after deferred cord clamping compared to immediate cord clamping. The higher hemoglobin concentration was also replicated in preterm infants ≥32 weeks' gestation.
VI. In choosing 60 seconds or more as the recommended interval for deferred cord clamping, we took into consideration that the recommendation is for infants who are deemed not to require resuscitation at birth and that most included infants (80%) in the deferred clamping arm received cord clamping after 60 seconds or more. The OR for reducing mortality after DCC≥ 60 seconds vs. immediate cord clamping = 0.63 (95% CI 0.44-0.88, p = 0.01)- *Note that this was a post-hoc analysis.*
VII.

Length of deferral	Trials(n)	Infants (n)	Infants (%)
short (15-59 seconds)	8	321	20%
medium (60-119 seconds)	9	1,066	65%
long (120+ seconds)	4	250	15%

VIII. Deferral of cord clamping for 120 seconds, or more (long DCC) was associated with the greatest reduction in mortality compared to immediate cord clamping in the IPD network meta-analysis (OR 0·31; 95% CrI 0·11-0·80). However, this evidence was based on 5 small trials including small numbers of extremely preterm infants (<121). Two of the trials excluded infants requiring resuscitation. {Rana 2018 655, Ranjit 2015 29}

The reported adherence to long DCC was the lowest at 67% (compared to about 80% for medium deferral and 95% for immediate clamping, milking and short deferral).

- While it is reasonable to consider this approach, the task force cannot recommend the long deferral for all infants based on this evidence. Instead, the long deferral could be considered only if there is no contraindication and if appropriate newborn stabilization can be provided on the intact cord (skilled team, proper training, appropriate equipment, enough space and ability to provide thermal management).
- More evidence is needed before recommending long DCC. Practicality, feasibility, cost-effectiveness, and equity issues need to be addressed.

IX. The Task Force acknowledges that there is **moderate-certainty** evidence, from **8 trials** including 1995 infants <32 weeks' gestation showing **more hypothermia** (body temperature <36·5°C) on admission after deferred cord clamping compared to immediate cord clamping (OR 1.28, 95% CI 1.06 to 1.56) with the number need to treat to harm (NNTH) 16, 95% CI 9 to 71. There were no important differences in rates of hypothermia in infants ≥32 weeks' gestation. Nevertheless, it is important that measures should be taken to maintain normal temperatures in all preterm infants when practising deferring cord clamping. Please refer to ILCOR statement: *Maintaining normal temperature immediately after birth in preterm infants: NLS 5101-2023. Available from* http://ilcor.org or summarised in {Berg 2023 e187}

X. Parents report that deferred cord clamping provides a positive experience with the mothers feeling closer and more attached to their infants. {Bradshaw 2019 225}

B- Justification: Despite the low-certainty evidence from 18 trials including 1565 infants, that umbilical cord milking may not reduce the critical outcome of death before discharge compared to immediate cord clamping (OR 0.73, 95% CI 0.44 to 1.20), there are hematologic effects that favour umbilical cord milking compared to immediate cord clamping:

I. There is **low certainty evidence** from 12 trials including 944 infants showing **higher hemoglobin concentrations (g/dL) within the first 24 hours after birth** after umbilical cord milking compared to immediate cord clamping (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL) in infants <32 weeks' gestation. The finding is replicated in infants ≥32 weeks' gestation.
II. There is **moderate certainty evidence** from 15 trials including 1163 infants showing **fewer transfusions of packed red blood cells** after UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I2 = 20%; NNTB 10, 95% CI 5 to 55) in infants <32 weeks' gestation. The finding is replicated in infants ≥32 weeks' gestation.
III. There is no evidence of increased rates of adverse effects in preterm infants <37 weeks' gestation or their mothers after umbilical cord milking compared to immediate cord clamping.
IV. There are no important differences in the critical or important outcomes after umbilical cord milking compared to deferred cord clamping in the preterm infants born at 28-36^{+6} weeks' gestation.
V. The IPD meta-analyses did not distinguish between the two methods of cord milking (intact-cord and cut-cord). The intact-cord was milked (2-4 times) in 15 trials (1536 infants), whilst three trials (343 infants) milked the cut-cord once, therefore no specific recommendations are made for each method.

C- Justification: In making the suggestion against intact umbilical cord milking in infants <28 weeks' gestation, the Task force took into consideration that there is **low certainty evidence** from 7 trials including 860 infants <32 weeks' gestation that the critical outcome of **severe intraventricular haemorrhage is increased** after intact umbilical cord milking compared to deferred cord clamping (OR 2.20, 95% CI 1.13 to 4.31), however:

I. The evidence from the IPD pairwise meta-analysis is driven by an RCT that was stopped prematurely because of increased rates of severe intraventricular hemorrhage in the prespecified subgroup of preterm infants <28 weeks' gestation. {Katheria 2019 1877}
II. The following report from the same RCT that compared the outcomes of umbilical cord milking and deferred cord clamping in the other subgroup of preterm infants born at 28-32 weeks' gestation, did not find any evidence of increased severe intraventricular hemorrhage, mortality, or other clinical outcomes after umbilical cord milking compared to deferred cord clamping. {Katheria 2023 217.e1} The later study was not included in the analysis as it was published after the iCOMP meta-analysis was completed and the CoSTR development process was started.

D- Justification: We could not make a recommendation regarding cord management of preterm infants who are deemed to require resuscitation at birth.

I. The pairwise IPD review reported that adherence to deferred cord clamping was low (<75% in those trials reporting adherence), mostly because of the preference of health care providers to practice immediate cord clamping or cord milking when the infant was judged to require resuscitation at birth. In other studies, the adherence was not reported. These 2 factors limit the generalizability of the meta-analysis findings and limit extension of our recommendation to non-vigorous infants and those who are deemed to require resuscitation at birth.

II. Nevertheless, there is growing evidence from animal studies and feasibility studies in human infants that supports stabilization of the infant while deferring cord clamping (resuscitation with intact cord/physiologic cord clamping/baby-directed cord clamping). This approach is also supported by sound physiological principles. {Bhatt 2013 2113, Crossley 2009 4695, Duley 2018 F6, Hooper 2015 608}

III. We are awaiting the results of studies currently underway that evaluate the resuscitation/stabilization of infants with the cord intact. These studies are expected to help us define the best way to manage these infants. Questions related to the practicality, feasibility, cost-effectiveness, and equity will need to be addressed.

E- Justification: There is uncertainty regarding the optimal cord management strategy in deliveries complicated by monochorionic multiple pregnancies, infants who have major congenital abnormalities, fetal anemia, or other conditions that may impact maternal or fetal well-being at the time of birth as these conditions were largely excluded from most clinical trials. We were also unable to draw conclusions regarding optimal cord management in the setting of placental problems including abruption, incision through an anterior placenta, placenta previa, or abnormalities of placental vasculature or insertion. Until more data are available for specific situations such as these, decisions about cord management in the presence of maternal, placental, or fetal complications need to be individualized, based on severity of presentation and clinical assessment of risk to the mother or baby.

Subgroup considerations

- Deferred cord clamping should still be considered in the different iCOMP study pre-specified subgroups as there is no clear evidence that gestational age at birth, multiple births (apart from mono-chorionic twins), mode of delivery, infant's sex, study year, setting/resources level (as indicated by country's perinatal mortality rate) influence the effect of deferred cord clamping, compared to immediate cord clamping, on the primary outcome of death before discharge. However, the certainty of evidence was low or very low due to insufficient sample size.

- No specific recommendation is made for the pre-specified subgroup analyses of whether initial resuscitation was provided at bedside with cord intact, and for the planned position of the infant relative to the placenta as the analysis could not be performed.

Implementation considerations

- The 3 investigated interventions; deferred cord clamping, umbilical cord milking and immediate cord clamping appear to be feasible in the context of the included trials.

- It should be noted that in many studies, infants randomized to deferred clamping may have received early clamping if they were thought to require resuscitation. For example, in the largest study{Tarnow-Mordi 2017 2445} 19.5% (146 of 748) infants in the later cord clamping group had non-adherence to their allocated study arm because of clinical concern about infant well-being. This is less likely to be the case with intact-cord milking, where the baby is more likely to have received a placental transfusion before the need for resuscitation was determined. We await the results of studies that are underway or planned that examine resuscitation with the cord intact, which may help determine the optimal umbilical cord management for infants at highest risk for mortality and neonatal morbidity.

Monitoring and evaluation

The details of cord management including the timing of clamping and initiation of breathing should be routinely recorded in clinical practice and research studies.

Research priorities

We identified the following knowledge gaps:

KNOWLEDGE GAPS:

- There are insufficient data on long-term neurodevelopment outcomes, or other post-discharge outcomes following different cord management strategies. We expect long-term data to become available from some trials currently underway.
- There are insufficient data on optimising cord management as a public health strategy to improve child health and development.
- There are insufficient data for cord management of preterm infants who are judged to require immediate resuscitation.
- There are insufficient data for cord management of preterm infants born under specific conditions, including fetal congenital anomalies, placental abnormalities, monochorionic multiple gestation, alloimmunization and/or fetal anemia, fetal compromise, maternal general anesthesia, and maternal illness.
- Further evaluation of measures to prevent hypothermia during deferred cord clamping is required.
- The optimal duration of deferred cord clamping remains uncertain. It is unclear whether it should vary with different maternal or fetal conditions.
- There are few studies of cut-cord milking as a management strategy.
- The impact of cord management on vertical transmission of infectious diseases is uncertain.
- There is a need for widely agreed nomenclature and definition of different interventions including “delayed”, “deferred”, “later”, “optimal”, and “physiologic” cord clamping, as well as “milking”, “stripping”, “intact-cord”, and “cut-cord”.

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QUESTION

Should rapid rewarming vs. slower rewarming be used for hypothermia immediately after birth in newborn infants?	
POPULATION:	Newborn infants with hypothermia immediately after birth

INTERVENTION:	Rapid rewarming
COMPARISON:	Slower rewarming
MAIN OUTCOMES:	Mortality; need for respiratory support during the first week of life; hypoglycemia (<47 mg/dl, 2.6 mmol/L); hypoglycemia (<30 mg/dl, 1.6 mmol/L); convulsions/ seizures during hospital stay; length of hospital stay; neurodevelopmental impairment; intraventricular hemorrhage (IVH); periventricular leukomalacia; necrotizing enterocolitis (NEC)
SETTING:	Locations where infants are born
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	The rate of rewarming of newborn infants after unintentional hypothermia infants was last reviewed by ILCOR in 2015 and the level of evidence was considered so low that no recommendation could be made. {Perlman 2015 S204} A subsequent ILCOR evidence update in 2020 indicated that there was some new evidence. {Wyckoff 2020 S185} Slow rate of rewarming was defined as less than 0.5˚C per hour and rapid rate of rewarming was considered as 0.5˚C per hour or greater.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Newborn infants are at high risk of becoming hypothermic during resuscitation and in the immediate newborn period, leading to lower than desired body temperatures at admission to neonatal intensive care. Unintentional hypothermia should be corrected because of evidence of poor outcomes {Laptook 2018 53, Wilson 2016 61} A small case series of infants with severe hypothermia suggested that faster rewarming might result in fewer complications than slow rewarming.{Kaplan 1984 470}. In 2020, the NLS Task Force undertook an Evidence Update (NLS 858: EvUp). {Wyckoff 2020 S185} The update found that there was additional literature which might result (after systematic review) in a treatment recommendation, instead of the 2015 ILCOR conclusion that: “The confidence in effect estimates is so low that a recommendation for	

	either rapid rewarming (0.5°C/h or greater) or slow rewarming (0.5°C/h or less) of unintentionally hypothermic newborn infants (temperature less than 36°C) at hospital admission would be speculative". {Perlman 2015 S204}	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Based on the available evidence rapid rewarming may not confer any significant advantage over slow rewarming other than achieving normothermia sooner. A higher rewarming rate was associated with a lower rate of respiratory distress syndrome in preterm infants. {Rech Morassutti 2015 557} However this was an observational study with low numbers (n=182 newborn infants) and a wide confidence interval (OR 0.39, 95% CI 0.17-0.87; p=0.02) for this outcome. For the outcome of hypoglycemia, one small randomized controlled trial (n=36 newborns), in whom 8 developed hypoglycemia (defined as glucose <30mg/dl), could not exclude clinical benefit or harm with rapid rewarming ((RR 0.3, 95% CI 0.09-1.05), ARD 292 fewer per 1000 (95% CI from 379 fewer to 21 more)), very low certainty evidence (downgraded for serious indirectness and very serious imprecision). {Motil 1974 546}. For the outcome of hypglycemia, an observational study (n=182 newborns, in whom 47 developed hypoglycemia (defined as glucose <47mg/dL), could not exclude clinical benefit or harm when comparing rapid with slow rewarming rates (OR 0.46, 95% CI 0.20-1.07), ARD 130 more per 1000 (95% CI from 211	Whether or not the lower rates of respiratory distress syndrome were associated with lower rates of need for respiratory support was not reported. {Rech Morassutti 2015 557}

	fewer to 14 more)), very low certainty evidence (downgraded for serious indirectness and very serious imprecision. {Rech Morassutti 2015 557}	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● **Don't know**	The available evidence does not demonstrate undesirable effects of rapid rewarming; however, sample sizes are small and may be insufficient to detect uncommon, but potentially serious adverse outcomes.	One additional retrospective observational study in which correlation between rate of rewarming and various outcomes was calculated was not included in the systematic review because a division into rapid rewarming and slower rewarming groups was not shown for all outcomes. {Rossi 2023 1113897} In this study, 43/344 (12.5%) infants developed hyperthermia (>37.5˚C). Rewarming rate was significantly correlated with hyperthermia (p=0.007). These findings may be clinically important because recent observational studies have confirmed an association between hyperthermia on NICU admission and adverse outcomes. {Brophy 2022 1706, Wilson 2016 61} Previous large studies have found an association between hypothermia in perterm and term infants and neonatal mortality and morbidity. {Boo 2013 447, Guinsburg 2016 1005, Laptook 2007 e643, Meyer 2001 395, Miller 2011 S49, Mullany 2010 650, S 2012 , Zayeri 2005 1367} It could be speculated that the more prolonged the hypothermia the greater the risk for mortality and morbidity. However, the included studies were too small to comprehensively assess the rate of rewarming on neonatal mortality and major morbidities.

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	Overall, the certainty of evidence was low due to small sample size, wide confidence intervals and heterogeneity in populations and in some cases, outcome definition (e.g. hypoglycemia). No benefit of rapid rewarming compared to slow rewarming was	

	found for the following outcomes, but the certainty of evidence was low or very low for each:
	• The critical outcome of mortality and intraventricular hemorrhage: (2 observational studies, n=280 neonates, **low certainty evidence** (downgraded for very serious imprecision) {Feldman 2016 295, Rech Morassutti 2015 557}
	• The important outcomes of
	  ○ length of stay (1 observational study, n=182, **low certainty evidence** (downgraded for very serious imprecision) {Rech Morassutti 2015 557}
	  ○ hypoglycemia (1 small RCT, n=36, very low certainty evidence downgraded for serious indirectness and imprecision) {Motil 1974 546} and 1 observational study, n=182, **very low certainty evidence** (downgraded for serious indirectness and very serious imprecision), {Rech Morassutti 2015 557}
	  ○ convulsions/seizure (1 observational study, n=182, **low certainty evidence** (downgraded for very serious imprecision) {Rech Morassutti 2015 557}	

	○ necrotizing enterocolitis (1 observational study, n=98, **low certainty evidence** (downgraded for very serious imprecision). {Feldman 2016 295} • No data were found for the critical outcomes of neurodevelopmental impairment and periventricular leukomalacia and the important outcome of need for respiratory support during the first 48 hours of life.	

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	The value attributed to the main outcomes was based on consensus of the ILCOR NLS Task Force and a larger group of neonatal resuscitation experts. {Strand 2020 F328}	

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 three included studies did not show clinical benefit or harm in either rewarming rate. However the overall certainty of evidence was low with wide confidence intervals and small numbers of participants. Based on low certainty evidence, rapid rates of rewarming may be associated with lower rate of RDS in preterm infants, but whether this resulted in a difference in the need for respiratory support was not reported. {Rech Morassutti 2015 557}.	

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 included studies assessed the resources required	Two of the three included studies used servo-controlled devices for rewarming. {Motil 1974 546, Rech Morassutti 2015 557} If future studies demonstrate superiority of servo-controlled devices, this could have important implications in resource limited settings.

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 assessed the certainty of resources required	

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	No included studies investigated cost-effectiveness.	

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	No included studies addressed equity. However, unintended hypothermia after birth is a common problem in low-, middle- and high-income countries	

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 included in the review specifically addressed acceptability. However, the task force considered that rapid rewarming was likely to be an acceptable intervention.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	While feasibility was not specifically addressed within the studies, the task force considered that rapid rewarming was a feasible intervention.	

Acceptability

Is the intervention acceptable to key stakeholders?

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
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**

	JUDGEMENT						
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

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

Recommendation

In newborn infants who are unintentionally hypothermic after birth, rewarming should be commenced, but there is insufficient evidence to recommend either rapid (≥0.5 ˚C per hour) or slow (<0.5 ˚C per hour) rates of rewarming. (Low certainty evidence)

Irrespective of the rewarming rate chosen, a protocol for rewarming should be used. Frequent or continuous monitoring of temperature should be undertaken while rewarming, particularly if using a supraphysiological set temperature point to accelerate the rewarming rate, due to potential risk of hyperthermia. In any hypothermic infant, monitoring of blood glucose should occur due to risk of hypoglycemia. (Good practice point)

Justification

The available evidence does not confirm clinical benefit or harm in either rewarming rate; however, the overall certainty of evidence was low with wide confidence intervals and small numbers.

We are aware of the increased risk of mortality associated with hypothermia, however the present studies are too small to find an impact of rewarming rate on mortality. One small randomized controlled trial showed an association of slow rewarming with occurrence of asymptomatic hypoglycemia. {Motil 1974 546} However, a somewhat larger observational study did not show an effect on hypoglycemia. {Rech Morassutti 2015 557} Finally, one study showed an association with a reduced rate of respiratory distress syndrome (RDS) in preterm infants. However, numbers were small with wide confidence intervals. {Rech Morassutti 2015 557} Furthermore, the authors did not report whether there was a clinical difference in need for respiratory management related to RDS.

Both intervention and control are considered to be acceptable and feasible, however two out of the three studies used servo control to monitor rate of rewarming. If servo control is in an important factor in regulating rewarming, then this could be an important consideration in resource limited settings.

The rate of rewarming varied widely in the rapid rewarming groups in the included studies. Furthermore, none of the studies included hyperthermia as an outcome. However, one observational study which did not meet the inclusion criteria found that 43 out of 344 (12.5%) infants developed hyperthermia (>37.5˚C). {Rossi 2023 1113897} In this study, rapid, compared to slow rewarming rate was significantly associated with hyperthermia (p=0.007). It is unclear whether this related to specific settings of the devices (radiant warmers and inclubators in manual mode) used for rewarming in this particular study. Future studies should consider this important outcome.

Subgroup considerations

The three included studies did not provide sufficient evidence for any subgroup analysis.

Two of the three included studies considered only preterm and very low birthweight infants. {Feldman 2016 295, Rech Morassutti 2015 557} Further studies are needed to analyse according to varying gestational age and birthweight, and to address methods and outcomes in high- and low-resource settings.

Implementation considerations

Rapid or slower rates of rewarming may be accomplished with similar cost, personnel, or equipment resources. Both approaches require close monitoring of temperature. In two of the three included studies, monitoring and rewarming were accomplished using servo-controlled devices. If demonstrated to be preferable, the use of servo control may have implications in resource limited settings.

Monitoring and evaluation

Continued monitoring of rewarming practices and short- and long-term clinical outcomes are suggested. The monitoring should include monitoring for and attempting to avoid hyperthermia.

Research priorities

Research priorities include identification of the optimal method of rewarming.
Research gaps include:

- impact of rate of rewarming on:
  - critical short and long term neonatal outcomes
  - risk of hyperthermia
  - metabolic markers such as metabolic and lactic acidosis, blood glucose level
  - cost-effectiveness considerations, including equipment, need for NICU admission, length of stay
  - parental separation
  - breastfeeding rates
- subgroup analysis according to:
  - gestational age and birthweight
  - degree of hypothermia at initiation of rewarming
  - location of birth (e.g., in or out of hospital/birthing centre) and resource setting
- superiority/inferiority of servo versus manual control of rewarming
- safety and effectiveness of skin-to-skin care for rewarming

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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

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% CI 113 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% CI 146 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; I^2 = 54%; ARD 64 fewer infants per 1000 [95% CI, 112 fewer to 5 more]), **moderate certainty evidence** from	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.

	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}	

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	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	While death was not found to be different amongst the intervention and control groups, the rates of other outcomes such as neurodevelopmental

○ No important uncertainty or variability	in rates of disability would be favorable in both high and low resource settings.	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						
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			

	JUDGEMENT						
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

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

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)

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.

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): $\chi^2 = 22.43$, 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): $\chi^2 = 14.80$, 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): $\chi^2 = 7.39$, 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; I^2 = 74.40%), and the outcomes of **death at hospital discharge** (RR, 1.17; 95% CI, 0.89 to 1.54; P = 0.26; I^2 = 41.40%), **death at any follow-up** (RR, 1.12; 95% CI, 0.90 to 1.07; P = 0.31; I^2 = 35.30%), **death at 18-24 months** (RR, 1.13; 95% CI, 0.91 to 1.07; P = 1.42; I^2 = 47.8%), **blindness** (RR, 0.51; 95% CI, 0.18 to 1.4656; P = 0.2112; I^2 = n/a), **deafness** (RR, 0.51; 95% CI, 0.13 to 2.01; P = 0.34; I^2 = n/a), and **PPHN** (RR, 1.53; 95% CI, 0.84 to 2.79; P = 0.17; I^2 = 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; I^2 = 0.0%) , **neurodevelopmental impairment at 18-24 months** (RR, 0.51; 95% CI, 0.36 to 0.72; P = 0.0002; I^2 = 0.0%), **death or neurodevelopmental impairment at any follow-up** (RR, 0.68; 95% CI, 0.48 to 0.98; P = 0.04; I^2 = 73.00%), and **cerebral palsy** (RR, 0.46; 95% CI, 0.29 to 0.71; P = 0.0004; I^2 = 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; I^2 = n/a) **,** and the outcomes of **death at hospital discharge** (RR, 0.66; 95% CI, 0.50 to 0.88; P = 0.004; I^2 = 14.9%), **death at any follow-up** (RR, 0.34; 95% CI, 0.19 to 0.61; P = 0.0002; I^2 = 0.0%), **neurodevelopmental impairment at any follow-up** (RR, 0.39; 95% CI, 0.28 to 0.54; P = <0.0001; I^2 = 0.0%), **neurodevelopmental impairment at 18-24 months** (RR, 0.52; 95% CI, 0.36 to 0.77; P = 0.0009; I^2 = 0.0%), **death or neurodevelopmental impairment at any follow-up** (RR, 0.30; 95% CI, 0.21 to 0.44; P = <0.0001; I^2 = 0.0%), and **deafness** (RR, 0.33; 95% CI, 0.11 to 0.97; P = 0.04; I^2 = 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; I^2 = n/a), **cerebral palsy** (RR, 0.33; 95% CI, 0.04 to 2.99; P = 0.33; I^2 = n/a), **blindness** (RR, 0.38; 95% CI, 0.11 to 1.33; P = 0.13; I^2 = 0.0%), and **PPHN** (RR, 0.60; 95% CI, 0.15 to 2.40; P = 0.47; I^2 = n/a).

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.

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.

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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