Appendix A3 NLS-1 EtD Table
CORD MANAGEMENT AT BIRTH FOR PRETERM INFANTS (NLS # 787)

This evidence to decision (EtD) table will include evidence for three questions or comparisons: #1) later (delayed) cord clamping compared to early cord clamping (<30s), #2) intact-cord milking compared to early cord clamping (<30s), and #4) later (delayed) cord clamping (≥30s) compared to intact-cord milking. Evidence for the other questions included in the CoSTR will not be presented as there was insufficient evidence. Only one study was identified for comparison #3 – cut-cord milking compared to early cord clamping (<30s). No studies met inclusion criteria for comparisons #5 (later (delayed) cord clamping (≥30s) compared to cut-cord milking), #6 (intact-cord milking compared to cut-cord milking), #7 (later (delayed) cord clamping ≥60s versus later (delayed) cord clamping ≥30 and <60s), and #8 (later (delayed) cord clamping (≥30s) versus physiological approach).

QUESTION #1

Should later (delayed) cord clamping compared to early cord clamping (<30s) be used for preterm infants (ILCOR)?	
POPULATION:	Preterm infants born at <34 weeks gestational age
INTERVENTION:	Later (delayed) cord clamping
COMPARISON:	Early cord clamping (based on timing of delaying clamping <30s)
MAIN OUTCOMES:	Survival to discharge from hospital Mortality (post hoc analysis) Severe intraventricular hemorrhage (IVH): ultrasound diagnosis grades III and/or IV Chronic lung disease (CLD): oxygen at 36 weeks' postmenstrual age (PMA) Necrotising enterocolitis (≥ Bell's Stage II) Hyperbilirubinemia (treated by phototherapy) Respiratory support (mechanical ventilation or continuous positive pressure ventilation) Inotropic support for hypotension during the first 24 hours of life (after birth) Lowest mean arterial blood pressure in the first 12 hours of life Blood transfusion (infant) Number of blood transfusions per infant Hemoglobin concentrations within the first 24 h after birth Hematocrit within the first 24 h after birth Hemoglobin concentrations within 7 days after birth Hematocrit within 7 days after birth Postpartum hemorrhage (clinically estimated blood loss of ≥ 500 mL) Severe postpartum hemorrhage (blood loss ≥ 1000 mL) Use of therapeutic uterotonic agents Blood transfusion (maternal) Manual removal of the placenta Postpartum infection
SETTING:	DELIVERY ROOM

PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
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, neonatal morbidities, and long-term neurodevelopment in preterm infants. {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} Cord management at birth is not just a question of timing of cord clamping. Placental transfusion may be augmented 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 nature does not practice immediate cord clamping and cutting but has natural delays between delivery and cord separation. As a result, technically, early clamping and milking are "medical interventions" superimposed on a natural phenomenon. This systematic review, however, chose early clamping as the control based on the historical precedent of commonest practice and therefore commonest comparison.
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	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, neonatal morbidities, and long-term neurodevelopment in preterm infants. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 CD003248}	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate	The systematic review identified 23 trials (3513 infants). {Aladangady 2006 93, Armanian 2017 4909, Backes 2016 35, Baenziger 2007 455, Das 2017 157, Dipak 2017 112, Dong 2016 635, Duley 2018 F6, Finn 2019 121, Gokmen 2011 323, Hofmeyr 1988 104, Hofmeyr 1993	Using the same data for a post hoc mortality analysis, a 2% survival benefit approximately equates to a 20% reduction in mortality: one inference is that mortality is less frequent than

○ Large ○ Varies ○ Don't know	110, Kazemi 2017 , Kinmond 1993 172, Kugelman 2007 307, McDonnell 1997 308, Mercer 2003 466, Mercer 2006 1235, Oh 2011 S68, Rabe 2000 775, Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445} Although primary analysis of delaying cord clamping (≥30s) in infants who do not require immediate resuscitation **may have a survival benefit or may make no difference** over early clamping (16 trials; 2988 infants; risk ratio (RR) 1.02, 95% confidence interval (CI) 1.00 to 1.04; risk difference (RD) 0.02, 95% CI -0.00 to 0.04; number needed to treat for benefit (NNTB) 50, 95% CI 25 to >1,000; I^2 = 0%; 18/1000 more infants survived when later cord clamping was intended than when early cord clamping was intended, 95% CI 0/1000 more to 36/1000 more), a post hoc analysis of mortality **could not exclude either benefit or harm** (16 trials; 2988 infants; RR 0.80, 95% CI 0.63 to 1.02; RD -0.02, 95% CI -0.04 to 0.00; NNTB 50, 95% CI 25 to >1,000 I^2 = 0%). If CI were described to 4 decimal points one would see the lower confidence interval for survival cross 1.000 and reach 0.993. Delaying cord clamping results in fewer infants receiving inotropic support (6 trials, 351 infants; RR 0.36, 95% CI 0.17 to 0.75; RD -0.09, 95% CI -0.15 to -0.03; NNTB 11, 95% CI 7 to 33; I^2 = 0%; 91/1000 fewer infants received inotropic support for hypotension within the first 24 hours after birth when later cord clamping was intended than when early cord clamping was intended, 95% CI 30/1000 fewer to 143/1000 fewer), higher hemoglobin within 24h (4 trials, 196 infants; MD 1.24g/dL, 95% CI 0.01 to 2.47g/dL; I^2 = 79%), and higher hematocrit within 24h (14 trials, 1022 infants; MD 2.63%, 95% CI 1.85 to 3.42%; I^2 = 5%) and 7 days (1 trial, 1550 infants; MD 2.70%, 95% CI 1.88 to 3.52%) with fewer infants receiving transfusions (12 trials, 780 infants; RR 0.83, 95% CI 0.77 to 0.90; RD -0.07, 95% CI -0.11 to -0.04; NNTB 14, 95% CI 9 to 25; I^2 = 36%; 71/1000 fewer infants received any blood transfusions when later cord clamping was intended than when early cord clamping was intended, 95% CI 40/1000 fewer to 111/1000 fewer).	survival so there appears to be greater imprecision in the point estimate. Evidence on longer term neurodevelopmental outcomes was insufficient.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	There is no significant effect on need for respiratory support after birth or need for phototherapy, nor on severe IVH, chronic lung disease of prematurity, or necrotizing enterocolitis. There is no impact on a limited number of critical maternal outcomes.	Evidence on longer term neurodevelopmental outcomes was insufficient.

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 varies by outcome. Evidence was moderate for the critical outcome of survival and ranged from low to high for the critical outcomes of severe IVH, necrotizing enterocolitis, and chronic lung disease. For the critical maternal outcome of postpartum hemorrhage (≥500 mL) evidence was very low. For all the important outcomes evidence ranged from moderate to high.	

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 – they are critical outcomes. {Strand 2020 328, 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	Delaying cord clamping for 30s or more in infants who do not require immediate resuscitation may have a survival benefit or may make no difference over early clamping (see above summary of desirable and undesirable effects). Delaying cord clamping results in less inotropic support, and higher hemoglobin and hematocrit within the first 24h and 7 days after birth with fewer infants receiving transfusions.	

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 delaying cord clamping (≥30s) compared to early clamping does not add cost. For infants requiring resuscitation during cord management additional equipment and additional training may be needed.	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.

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 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	No data available.	Although there are no published cost data, it is unlikely that delayed cord clamping compared to early cord clamping will add costs for infants not requiring resuscitation. However, for infants requiring resuscitation additional equipment and additional training may be needed.

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 reduction in secondary, important outcomes, including need for inotropes and transfusions, may result in improved equity in low-resourced settings where these interventions may not be readily 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	The 2015 CoSTR suggested delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence). Although umbilical cord clamping practices may vary across sites and providers, there has been an increase in the practice of DCC over recent years. {El-Naggar 2020 58, Ibrahim 2017 216, Ortiz-Esquinas 2020 1738}	The intervention may cause some anxiety in providers who have always clamped early. Need for resuscitation might change the acceptability of the intervention.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Delayed (later) cord clamping is feasible. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072}. It should be noted that in many studies, infants randomized to later (delayed) 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.	It is 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	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
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

COMPARISON 2: Should intact-cord milking compared to early cord clamping (<30s) be used for preterm infants?	
POPULATION:	Preterm infants born at <34 weeks gestational age
INTERVENTION:	Intact-cord milking
COMPARISON:	Early cord clamping (based on timing of delaying clamping <30s)
MAIN OUTCOMES:	INFANT: Survival to discharge from hospital Mortality (post hoc analysis) Moderate to severe neurodevelopmental impairment in early childhood Cerebral palsy Severe IVH: ultrasound diagnosis grades III and/or IV Chronic lung disease (CLD): oxygen at 36 weeks' PMA Necrotizing enterocolitis (≥ Bell's Stage II) Hyperbilirubinemia (treated by phototherapy) Respiratory support (mechanical ventilation or CPAP) Inotropic support for hypotension during the first 24 hours of life (after birth) Lowest mean arterial blood pressure in the first 12 hours of life Blood transfusion (infant) Total number of blood transfusions per infant Hemoglobin concentrations within the first 24 h after birth Hematocrit within the first 24 h after birth Hemoglobin concentrations within 7 days after birth Hematocrit within 7 days after birth MATERNAL: Severe postpartum hemorrhage (blood loss ≥ 1000 mL) Blood transfusion (maternal)
SETTING:	DELIVERY ROOM
PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
BACKGROUND:	As for comparison #1
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	As for comparison #1	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The systematic review identified 13 trials (1170 infants). {Mercer 2016 50, Finn 2019 121, Alan 2014 e493, El-Naggar 2019 F145, Elimian 2013 S22, Hosono 2008 F14, Katheria 2014 e94085, Kilicdag 2016 615, Lago Leal 2018 , Li 2020 184, March 2013 763, Silahli 2018 1560, Song 2017 527} For the critical outcomes of both survival to discharge (RR 1.02, 95% CI 0.98 to 1.06; I^2=24%) and mortality (post hoc RR 0.77, 95% CI 0.49 to 1.23) 10 trials involving 945 infants (moderate certainty, downgraded for imprecision) **could not exclude benefit or harm** from intact-cord milking compared to early cord clamping. Only one study (26 infants) looked at moderate to severe neurodevelopmental impairment in early childhood and was non-contributory. No other critical outcomes were significant. It is noteworthy that for the critical outcome of severe IVH, evidence of low certainty (downgraded for very serious imprecision) from 10 trials involving 889 infants **could not exclude benefit or harm** with intact-cord milking compared to early cord clamping (RR 0.72, 95% CI 0.44 to 1.19; I^2 = 0%). {Mercer 2016 50, Finn 2019 121, Alan 2014 e493, El-Naggar 2019 F145, Elimian 2013 S22, Hosono 2008 F14, Katheria 2014 e94085, Li 2020 184, March 2013 763, Song 2017 527} With respect to important outcomes, intact-cord milking resulted in fewer infants receiving inotropic support for hypotension in the first 24 hours after birth (5 trials, 431 infants; RR 0.61, 95% CI 0.44 to 0.84; RD -0.12, 95% CI -0.19 to -0.05; NNTB 8, 95% CI 5 to 20; I^2 = 0%; 125/1000 fewer infants received inotropic support for hypotension within the first 24 hours after birth when intact-cord milking was intended than when early cord clamping was intended, 95% CI 50/1000 fewer to 200/1000 fewer), higher hemoglobin concentrations within 24h after birth (10 trials, 914 infants; MD 1.18g/dL, 95% CI 0.65 to 1.71g/dL; I^2 = 71%; random effects), higher hematocrit within 24h after birth (7 trial, 774 infants; MD 3.04%, 95% CI 1.28 to 4.80%; I^2 = 69%; random effects), and fewer infants receiving blood transfusions (7 trial, 545 infants; RR 0.73, 95% CI 0.56 to 0.94; RD -0.17, 95% CI -0.30 to -0.04; NNTB 6, 95% CI 3 to 25; I^2 = 54%; random effects; 167/1000 fewer infants received any blood transfusions when intact-cord milking was intended than when early cord clamping was intended, 95% CI 40/1000 fewer to 333/1000 fewer).	The important cardiovascular and hematologic outcomes may be confounded by unreported variation in clinical practices such as fluid administration and transfusion thresholds, raising concerns about indirectness; thus clinical variation may be a reason for the inconsistency (I^2 values range from 21% to 77%).

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No significant undesirable effects were noted in the analyses.	For this comparison of intact-cord milking with early cord clamping no subgroup analysis by gestation was done. It is not known whether the signal of harm identified in comparison #4 (later (delayed) cord clamping vs intact-cord milking) is mirrored in this comparison. No critical or important outcomes showed undesirable effects, in particular, there were no significant differences in the important outcomes of respiratory support after birth and hyperbilirubinemia requiring phototherapy. Only 2 studies reported maternal complications, and none were significant.

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	Critical outcomes (all neutral to the question) ranged from very low to moderate certainty. Evaluation of the critical outcome of survival was based on a moderate level of certainty (downgraded for imprecision). The certainty of evidence for important outcomes varied from very low to moderate.	

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 – they are critical outcomes. {Strand 2020 328, Webbe 2020 425} For this comparison of intact cord milking with early cord clamping no subgroup analysis by gestation was done. It is not known whether the signal of harm identified in comparison #4 (later (delayed) cord clamping vs intact-cord milking) is mirrored in this comparison.	

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	No critical outcomes differ significantly between intact-cord milking and early cord clamping. However, intact-cord clamping has benefits over early cord clamping with respect to hematological status, and the number of infants receiving inotropes or transfusion.	One needs to consider intact-cord milking vs early cord clamping in the context of a third cord management strategy, delayed (or later) cord clamping.

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.

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.	As fewer infants receive inotropic support or transfusion with intact-cord milking, the cost-effectiveness leans in favour of the intervention.

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 reduction in secondary, important outcomes, including need for inotropes and transfusions, may result in improved equity in low-resourced settings where these interventions may not be readily 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	A recent retrospective multicenter study implies that this is an accepted practice among healthcare practitioners. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072}	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 doi: 10.1016/j.jpeds.2020.12.072}	

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	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies

	JUDGEMENT						
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 #4

COMPARISON 4: Should later (delayed) cord clamping (≥30s) compared to intact-cord milking be used for preterm infants?	
POPULATION:	Preterm infants born at <34 weeks gestational age
INTERVENTION:	Later (delayed) cord clamping (≥30s)
COMPARISON:	Intact-cord milking
MAIN OUTCOMES:	INFANT: Survival to discharge from hospital Mortality (post hoc analysis) Survival without moderate to severe neurodevelopmental impairment in early childhood Cerebral palsy Severe IVH: ultrasound diagnosis grades III and/or IV Chronic lung disease (CLD): oxygen at 36 weeks' PMA

	Necrotizing enterocolitis (≥ Bell's Stage II) Hyperbilirubinemia (treated by phototherapy) Respiratory support (mechanical ventilation or CPAP) Inotropic support for hypotension during the first 24 hours of life (after birth) Lowest mean arterial blood pressure in the first 12 hours of life Blood transfusion (infant) Total number of blood transfusions per infant Hemoglobin concentrations within the first 24 h after birth Hematocrit within the first 24 h after birth MATERNAL: Maternal death
SETTING:	DELIVERY ROOM
PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
BACKGROUND:	As for Comparison #1
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	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, neonatal morbidities, and long-term neurodevelopment in preterm infants. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 CD003248}	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The systematic review identified **7 trials** (1073 infants). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Krueger 2015 394.e1, Pratesi 2018 364, Rabe 2011 205, Shirk 2019 482.e1} For the critical outcome of both survival to discharge (RR 0.99, 95% CI 0.95 to 1.02; I^2=14%) and mortality (post hoc RR 1.21, 95% CI 0.76 to 1.94; I^2=14%), the evidence of moderate certainty (downgraded for imprecision) from 5 trials involving 1000 infants, **could not exclude benefit or harm** with delayed cord clamping compared to intact-cord milking.	In summary, no differences were noted between delayed cord clamping and intact-cord milking.

	There were no differences between delayed cord clamping compared to intact-cord milking for any of the outcomes: cerebral palsy (2 trials, 193 infants, RR 0.36, 95% CI 0.01 to 8.65); severe intraventricular hemorrhage (4 trials, 761 infants, RR 0.60, 95% CI 0.32 to 1.12; I^2 = 23%); chronic lung disease (4 trials, 734 infants, RR 0.91, 95% CI 0.67 to 1.25; I^2 = 0%); necrotizing enterocolitis (5 trials, 922 infants, RR 1.57, 95% CI 0.83 to 2.97; I^2 = 0%); hyperbilirubinemia receiving phototherapy (2 trials, 236 infants, RR 1.05, 95% CI 0.90 to 1.24; I^2 = 43%); hemoglobin at 24h after birth (6 trials, 914 infants, MD -0.002g/dL, 95% CI -0.56 to 0.53g/dL; I^2 = 52%); and hematocrit at 24h after birth (5 trials, 841 infants, MD -0.18%, 95% CI -1.90 to 1.54%; I^2 = 51%).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Overall, there were no undesirable effects of delayed cord clamping compared to intact-cord milking. For the critical outcome of severe intraventricular hemorrhage, evidence of moderate certainty (downgraded for imprecision) from 4 trials involving 761 infants **could not exclude benefit or harm** with later (delayed) cord clamping compared to intact-cord milking (RR 0.60, 95% CI 0.32 to 1.12; I^2 = 23%). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205} One large clinical trial comparing intact-cord milking with later (delayed) cord clamping closed recruitment before completion because of an increased rate of severe IVH in infants born at <28 weeks gestational age who received intact-cord milking. {Katheria 2019 1877}	A recent randomized controlled trial comparing delayed cord clamping with intact-cord milking was stopped early due to a higher incidence of severe IVH in the milking group in the subgroup of very preterm infants (<28 weeks' gestation). {Katheria 2019 1877}

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 was moderate for the critical outcome of survival and for the critical outcomes of severe IVH, necrotizing enterocolitis, and chronic lung disease. It was also moderate for the important outcomes of hyperbilirubinemia receiving phototherapy, hemoglobin concentration and hematocrit within 24h after birth.	For some important outcomes, the GRADE analysis was post hoc.

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 – they are critical outcomes. {Strand 2020 328, 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, there were no undesirable effects of delayed cord clamping compared to intact-cord milking. For the critical outcome of severe IVH, evidence of moderate certainty (downgraded for imprecision) from 4 trials involving 761 infants **could not exclude benefit or harm** with later (delayed) cord clamping compared to intact-cord milking (RR 0.60, 95% CI 0.32 to 1.12; I^2 = 23%). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205} One large clinical trial comparing intact-cord milking with later (delayed) cord clamping closed recruitment before completion because of an increased rate of severe IVH in infants born at <28 weeks gestational age who received intact-cord milking. {Katheria 2019 1877}	A recent randomized controlled trial comparing delayed cord clamping with intact-cord milking was stopped early due to a higher incidence of severe IVH in the milking group in the subgroup of very preterm infants (<28 weeks' gestation). {Katheria 2019 1877}

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 delaying cord clamping (30s) compared to intact-cord milking does not add cost. For infants requiring resuscitation additional equipment and additional training may be needed.	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.

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 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	No data available	Although there are no published cost data, it is unlikely that delayed cord clamping compared to intact-cord milking will add costs for infants not requiring resuscitation. However, for infants requiring resuscitation additional equipment and additional training may be needed.

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	The 2015 CoSTR suggest delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence); and suggest against the routine use of cord milking for infants born at 28 weeks of gestation or less, because there is insufficient published human evidence of benefit. {Perlman 2015 S204–S241} Although umbilical cord clamping practices may vary across sites and providers, there has been an increase in the practice of DCC over the last years. Cord milking is a less common practice of cord management. {El-Naggar 2020 58, Ortiz-Esquinas 2020 1738}	Both the intervention and the comparison are practiced.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	The intervention is feasible. {Kumbhat 2021 doi: 10.1016/j.jpeds.2020.12.072} Later cord clamping and cut cord milking appeared to be feasible in the context of the included trials. It should be noted that in many studies, infants randomized to later (delayed) clamping may have received	Current standard of care in some centers.

○ Varies ○ Don't know	early clamping if they were thought to require resuscitation. For example, in the Tarnow-Mordi 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.	

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	Large	Moderate	Small	Trivial		**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
○	○	●	○	○

TYPE OF RECOMMENDATION (OVERALL)

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for later (delayed) cord clamping > intact-cord milking > early clamping	Strong recommendation for the intervention
○	○	○	●	○

OVERALL CONCLUSIONS

Recommendation

In infants born at less than 34 weeks' gestational age who do not require immediate resuscitation after birth, we suggest deferring clamping the cord for at least 30 seconds (weak recommendation, low certainty of evidence).

In infants born at 28+0 to 33+6 weeks' gestational age who do not require immediate resuscitation after birth, we suggest intact-cord milking as a reasonable alternative to deferring cord-clamping (weak recommendation, moderate certainty of evidence).

We suggest against intact cord milking for infants born at less than 28 weeks' gestational age (weak recommendation; very low certainty of evidence).

In infants born at less than 34 weeks' gestational age who require immediate resuscitation, there is insufficient evidence to make a recommendation with respect to cord management.

There is also insufficient evidence to make recommendations on cord management for maternal, fetal, or placental conditions that were considered exclusion criteria in many studies (in particular 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).

Justification

The Task Force debated the certainty of evidence for the overall recommendation of later (delayed) cord clamping. Even though evidence for survival was 'moderate certainty' we felt that the doubt raised by the post hoc analysis of mortality justified downgrading our primary recommendation to 'low certainty of evidence'.

Exclusion criteria from clinical trials were a significant concern for the Task Force. Many pregnancies were excluded from studies for the following reasons:

- Multiple fetuses
- Congenital anomalies and hydrops
- Placental abnormalities, including placenta previa, vasa previa, and abruption
- Alloimmunization and/or fetal anemia
- Fetal compromise including fetal growth restriction
- Maternal conditions or obstetrical concern

We were unable to draw conclusions from subgroup analyses with respect to these exclusion criteria. We therefore suggest caution when making cord management decisions in the presence of any of these conditions. In the absence of evidence from these subgroups, decisions regarding cord management should be individualized and based on the severity of the presenting condition(s) and an assessment of risk to the mother or baby during and after delivery.

Our suggestions/recommendations were justified based on several inferences that included the following:

1. The critical outcome of survival with later (delayed) clamping versus early clamping suggests benefit or neutrality from delaying clamping.

2. There are no significant differences in other critical outcomes for all comparisons.
3. There is improvement in important cardiovascular (blood pressure), therapeutic (inotropic support and/or transfusions), and hematological outcomes with delayed (later) clamping and/or intact-cord milking versus early clamping.
4. There are no significant differences between later (delayed) clamping and intact-cord milking (except for the presence of a "signal for harm" from intact-cord milking in infants born at <28 weeks' gestational age in a single large study).
5. Only one small study was available for cut-cord milking.
6. Post hoc and subgroup analyses and GRADE evaluations did not conflict with our suggestions or recommendations.
7. There is a paucity of evidence available to make recommendations for cord management in the preterm infant needing immediate resuscitation.

1: Survival with delayed (later) clamping versus early clamping

This analysis was based on the preference of ILCOR to use survival to discharge as the primary outcome rather than mortality. It showed that later (delayed) cord clamping for 30 seconds or more in infants who do not require immediate resuscitation may have a survival benefit or make no difference when compared to early clamping (moderate certainty evidence, RR 1.02 and lower confidence interval just reaching 1.00). However, for mortality, the confidence intervals were wider and crossed 1.00.

When calculating confidence intervals around a relative risk, events that occur frequently (such as survival) will result in a narrower confidence interval than events that occur infrequently (in this case, mortality). In the included studies, survival was much more common than mortality. As a result, we anticipated that the confidence interval around survival and mortality would appear to have different precision. For transparency, we included the estimate for both outcomes. As a consequence of the wider confidence intervals, a post hoc analysis of mortality was unable to exclude benefit or harm (RR 0.80, 95% CI 0.63 to 1.02).

Our inference is that delayed cord clamping is safe and may be beneficial when compared to early clamping in infants born at <34 weeks who do not require immediate resuscitation. With a 2% increase in survival, the number needed to benefit is 50 (confidence interval 25 to >1000).

Overall, we interpret the data to suggest that later (delayed) cord clamping is likely to be safe and may have a benefit whether the outcome is described as survival or mortality.

2: No significant differences in other critical outcomes with any other comparison

With the exception of survival to discharge when later (delayed) clamping and early cord clamping were compared, no comparisons showed significant benefit or harm for any critical neonatal (or maternal) outcomes including severe intraventricular hemorrhage, chronic lung disease, necrotizing enterocolitis, neurodevelopment and maternal postpartum hemorrhage and infection.

3: Possible benefits in important outcomes with later (delayed) clamping or intact-cord milking versus early clamping.

Although there were no significant effects for all but one critical neonatal outcome, there were significant effects on some important outcomes. Later (delayed) cord clamping and intact-cord milking resulted in fewer infants receiving inotropic support, higher hemoglobin and hematocrit by 24 hours and 7 days, and fewer infants receiving blood transfusions. There were no significant effects on use of respiratory support after birth or use of phototherapy. However, although cut-cord milking improves neonatal hemoglobin and hematocrit, it is unknown if the intervention facilitates the post-natal cardiovascular transition in the same way as later cord clamping.

These beneficial effects have a clinically important impact on inpatient care. Together with the potential benefit for the critical outcome of survival to discharge, they influenced us to suggest either later (delayed) cord clamping or intact-cord milking (in the case of infants born at 28+0 to33+0 weeks' gestational age) over early clamping, despite the lack of evidence for benefit for other critical outcomes.

4: Lack of significant differences between later (delayed) clamping and intact-cord milking

The analysis, with moderate certainty, showed no significant differences in outcomes between later (delayed) clamping and intact-cord milking.

We noted that one large clinical trial comparing intact-cord milking with later (delayed) cord clamping closed recruitment before completion because of an increased rate of severe intraventricular hemorrhage in infants born at <28 weeks gestational age who received intact-cord milking. {Katheria 2019 1877} However, meta-analysis of **4 trials** involving 761 infants **could not exclude benefit or harm** from later (delayed) cord clamping compared to intact-cord milking (RR 0.60, 95% CI 0.32 to 1.12; I^2 = 23%). {Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205}

These findings influenced us to suggest intact-cord milking as a reasonable alternative to delayed cord clamping, except for infants born at <28 weeks' gestational age.

5: Cut-cord milking

Only one study was included in this comparison (60 infants). Given the small numbers and nonsignificant findings, this comparison was not considered in our suggestions or recommendations. {Ram Mohan 2018 88}

6: Post hoc and subgroup analyses and GRADE evaluations

Subgroup analyses are exploratory and must be interpreted with caution.

The p-values for interaction did not suggest important influences of gestational age (p = 0.26 for interaction) or duration of deferral of cord clamping on survival to discharge (p = 0.27 for interaction).

There was some evidence that the effect of later cord clamping on survival to discharge may be influenced by setting, with treatment effect being apparent only in studies performed in high-income countries (p= 0.01 for interaction; studies in high-income countries: RR 1.06, 95% CI 1.02 to 1.11; I^2 = 0%; studies in low-and-middle income countries: RR 0.97, 95% CI 0.92 to 1.01; I^2 = 39%). We caution that the difference in effect direction, size and significance between low-and-middle- and high- income countries could be a result of variation in resources available to individual participating hospitals within each country.

We do not have sufficient confidence in these findings to make separate recommendations for cord management by country income, by gestational age, or interval from birth to cord clamping (beyond 30s). We consider that the beneficial effect of delayed clamping in high-income countries is likely to be widely generalizable and should therefore be offered in all settings.

7: Cord management when immediate resuscitation is required

There is insufficient evidence to make any recommendation for cord management in preterm infants who require immediate resuscitation.

Overall justification:

In 2015, the ILCOR Neonatal Task Force stated: *"We suggest delayed umbilical cord clamping for preterm infants not requiring immediate resuscitation after birth (weak recommendation, very-low-quality evidence). There is insufficient evidence to recommend an approach to cord clamping for preterm infants who do receive resuscitation immediately after birth, because many infants who were at high risk of requiring resuscitation were excluded from or withdrawn from the studies."* {Perlman 2015 S204–S241} An updated review of the evidence does not substantially change this recommendation.

As all critical outcomes but one (survival to discharge with later (delayed) cord clamping versus early clamping) did not show either benefit or harm, we drew our conclusions from that one outcome and the important neonatal outcomes of fewer infants receiving inotropic support, higher hemoglobin and hematocrit concentrations, fewer blood transfusions, and otherwise no evidence of harm for the mother or neonate. Limited subgroup analyses were non-contributory but did not contradict the results of critical or important comparisons.

Two previous systematic reviews suggest benefits from later (delayed) clamping over early clamping in preterm infants for survival and other outcomes. {Fogarty 2018 1, Rabe 2008 138} The systematic review that informed this statement of Consensus on Science with Treatment Recommendations {Seidler 2021 } included an additional 11 studies, while removing studies with substantial late preterm populations. All three reviews are in general accord in suggesting that benefits outweigh harms of later (delayed) cord clamping in preterm infants resembling those enrolled in the included trials. A large systematic review derived from individual patient data is underway and may improve the certainty of evidence for some critical and important outcomes. {Seidler 2020 e034595}

It should be noted that in many studies, infants randomized to later (delayed) 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.

There is currently insufficient evidence to make a recommendation with respect to cord management for preterm infants who require immediate resuscitation. There is also uncertainty regarding the optimal cord management strategy in deliveries complicated by 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. There is also uncertainty 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.

The uncertainty of the updated evidence (including its generalisability to infants at highest risk for adverse outcomes) influences the decision to continue to make a 'weak' recommendation.

Subgroup considerations

As described in the "Justification" (preceding section)

Implementation considerations

Early cord clamping, and the 3 cord management approaches evaluated as interventions appear to be feasible in the context of the included trials.

It should be noted that in many studies, infants randomized to later (delayed) 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

Many of the included studies did not record the exact time of cord clamping. The details of cord management including the timing of clamping should be routinely recorded in clinical practice and research studies.

Research priorities

We identified the following knowledge gaps:

- There are insufficient data on long-term neurodevelopment outcomes, or any other post-discharge outcomes.
- There are insufficient data on cord management as a public health strategy to impact child health and development
- There are insufficient data for cord management among preterm infants who require immediate resuscitation.
- There are insufficient data for cord management among preterm infants with specific conditions, such as congenital heart or lung disease.
- The long-term neurodevelopmental outcomes of intact-cord milking in extremely preterm infants is uncertain.
- The optimal timing of cord clamping is not known, nor is how it should be determined with different maternal or fetal conditions.
- There are limited numbers of 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 “physiological” cord clamping, as well as “milking”, “stripping”, “intact-cord”, and “cut-cord”.

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Appendix A3 NLS-2 EtD Table
CORD MANAGEMENT AT BIRTH FOR TERM AND LATE PRETERM INFANTS (NLS # 1551)

This evidence to decision (EtD) table will include evidence for three questions or comparisons examined in the review, as follows.

Comparison 1: Later (delayed) cord clamping at ≥ 30 seconds compared to early cord clamping at < 30 seconds after birth	**33 studies, 5263 mothers and their infants**	**EtD table included**
Comparison 2: Intact cord milking versus early cord clamping	1 study, 24 infants	No
Comparison 3: Cut-cord milking vs early cord clamping	1 study, 200 infants	No
Comparison 4: Later (delayed) cord clamping vs intact-cord milking	1 study – serious methodological problems	No
Comparison 5: Later (delayed cord clamping at ≥30 seconds versus cut-cord milking	**3 studies, 740 infants**	**EtD table included**
Comparison 6: Intact-cord milking vs cut-cord milking	No studies	No
Comparison 7: Later (delayed) cord clamping ≥60 seconds versus later (delayed) cord clamping at< 60 seconds	**7 studies, 2745 mothers and their infants**	**EtD table included**
Comparison 8: Later (delayed) cord clamping at ≥ 30 seconds versus physiological approach to cord clamping (waiting until cessation of pulsation of the cord or based on vital signs monitoring or initiation of breathing)	3 studies, 1113 mothers and their infants	No

Evidence to Decision tables were not prepared for the other comparisons, because of insufficient data, or in the case of comparison #8, findings of very little difference between the intervention and control.

QUESTION #1

Should later (delayed) cord clamping vs. early cord clamping be used for term and late preterm infants?	
POPULATION:	Term and late preterm infants.
INTERVENTION:	Later (delayed) cord clamping at ≥ 30 seconds
COMPARISON:	Early cord clamping at <30 seconds after birth
MAIN OUTCOMES:	Survival without moderate to severe neurodevelopmental impairment in early childhood; anemia four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL or as defined by the trial authors); neonatal mortality; moderate to severe hypoxic ischemic encephalopathy; resuscitation (positive pressure ventilation ± intubation ± chest compression); respiratory distress of any type or duration as described by the authors; admission to neonatal intensive care unit or special care nursery; hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth; hematocrit (%) within the first 24 hours and within 7days after birth after birth; hyperbilirubinemia treated with phototherapy; polycythemia (hematocrit greater than 65%); partial exchange transfusion; exchange transfusion; moderate to severe neurodevelopmental impairment in early childhood; ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L). Maternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors); severe postpartum hemorrhage (clinically estimated blood loss of at least 1000 mL); manual removal of the placenta; post-partum infection.

SETTING:	Delivery Room
PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
BACKGROUND:	Umbilical cord management affects every one of the 140 million babies born in the world each year. At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266}
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	Umbilical cord management affects every one of the 140 million babies born in the world each year.{https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266}	The widespread practice of early umbilical cord clamping is not evidence-based. Umbilical cord management varies greatly among professional groups and across different regions.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The prevalence of iron deficiency and iron deficiency anemia has been reported to be as high as 26% and 3-7%, respectively among young children in Europe {Bramhagen 1999 1333, Persson 1998 618, Thane 2000 433} The global prevalence of iron deficiency anemia has been reported to be 33%, with the highest burden in children less than five years of age.{Kassebaum 2014 615} Iron deficiency in young children has been associated with impaired motor development, behavioral problems and cognitive delay. {Grantham-McGregor 2001 649S, Gunnarsson 2007 391, Lozoff 2006 1108} A delay in cord clamping at	Cord management and placental transfusion at birth may play a significant role, at no cost, in reducing iron deficiency in both well-resourced and resource-limited countries. This could potentially have a global impact on neurodevelopment later in childhood.

	birth may improve iron status, reduce iron deficiency in infancy and may consequently improve long-term neurodevelopmental outcomes. {Andersson 2011 d7157, Andersson 2015 631} Our review of the evidence of benefits of later cord clamping identified higher hemoglobin and hematocrit concentration during the neonatal period and lower iron deficiency in infancy without significant maternal adverse effects. However, no evidence was found to support a significant benefit of later cord clamping for the other critical and important outcomes.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Our review of the evidence found later cord clamping increased polycythemia (hematocrit >65%) and possibly increased the use of phototherapy for treatment of hyperbilirubinemia compared to early cord clamping. However, there was no evidence of increased rates of exchange transfusion and there was no evidence of harm found in other important or critical outcomes.	It is not clear if there is any clinical impact of the increased rates of polycythemia (hematocrit >65%) with the later cord clamping. Rates of *symptomatic* polycythemia were not available and there was no evidence of an increase in the rates of partial exchange transfusion. The outcome of phototherapy for treatment of jaundice is not objectively and consistently defined. This area merits further research with measurement of bilirubin concentrations and thresholds for treatment. More research is required in middle- and low-income countries to refine our estimates of the risks of undesirable effects.

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 was very low for the critical outcomes of neonatal mortality and neurodevelopmental impairment in childhood and was low for the critical outcome of maternal postpartum hemorrhage. The certainty of evidence ranged from very low to low for the important outcomes as resuscitation at birth and hematological status in neonatal period and in infancy.	

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 of the systematic review were: anemia at four to six months after birth, survival without moderate to severe neurodevelopmental impairment in early childhood, and maternal postpartum hemorrhage. Given that the intervention is simple and at no cost, and considering the main outcomes are critical, there is no important uncertainty or variability in how much people value the main outcomes despite the very low certainty of evidence of the effects.	Collection of cord blood for banking may pose a competing interest.

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 improved hemoglobin and iron status associated with later cord clamping in the neonatal period and in early infancy, may help in the prevention of the complications of iron deficiency, such as anemia and developmental delay. Rates of iron deficiency are highest in resource-limited settings and therefore the potential benefits of later cord clamping may be greatest in these areas. However, as later cord clamping is associated with increased rates of polycythemia and a possible increase in use of phototherapy for hyperbilirubinemia, monitoring for hyperbilirubinemia should be conducted for all newborns, with access to treatment when indicated. This may necessitate strengthening of monitoring and referral systems in some settings.	

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 have reported resource implications	The intervention is simple and of no cost, however, there is limited data about the possible cost-saving associated with the potential benefits (reducing iron deficiency and the consequent neurodevelopmental impairments) and the possible costs of monitoring and managing the adverse effects of increased polycythemia and hyperbilirubinemia.

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		

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 have examined cost-effectiveness	The costs associated with iron deficiency and its consequences vs. the possible increase in monitoring and treatment of hyperbilirubinemia, are not known in any setting. In middle- and low-income countries, the benefit-risk assessment can be complicated and different from one setting to another depending on the available resources and the prevalence of iron deficiency. More research is needed to address this important area.

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	This is a simple, easy and inexpensive intervention that can be implemented by health care providers in any place in the world to improve the hematological status and prevent iron deficiency which is prevalent globally (in high- as well as middle- and low-income countries). Embracing such intervention would foster health equity. Research studies conducted thus far, reflect the high interest from low- and middle- income countries {Ceriani Cernadas 2006 e779, Chaparro 2006 1997, Chopra 2018 234, Emhamed 2004 218, Jahazi 2008 523, Salari 2014 287, Vural 2019 555, Yadav 2015 720} as well as high-income countries. {Al-Tawil 2012 319, Andersson 2011 d7157, Chen 2018 251, Philip 1973 334} However, there might be disparity in monitoring and management of the potential adverse effects (hyperbilirubinemia treated with phototherapy) related to the lack of resources in the lower 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	The intervention has been recommended by many governing bodies including WHO and has been practiced as the standard of care for most infants at birth over the past decade? The research studies related to the intervention (later cord clamping) were conducted in different settings with variable resources.	There is a high level of interest in later cord clamping among pregnant women, as reflected on social media sites and childbirth education courses.

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 simple and easy to implement at no cost. The intervention is feasible for any health care provider worldwide after minimal guidance/training and has been recommended by WHO since 2012. {World Health Organization 2012 } The research studies related to the intervention (later cord clamping) were conducted in different settings with variable resources which shows that the intervention is feasible.	The intervention has been the standard practice in many centers providing childbirth care worldwide.

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	Large	Moderate	Small	Trivial		**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**

	JUDGEMENT						
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 5

Should later (delayed) cord clamping vs. cut-cord milking be used for term and late preterm infants ?	
POPULATION:	Term and late preterm babies
INTERVENTION:	Later (delayed) cord clamping at ≥ 30 seconds
COMPARISON:	Cut-cord milking
MAIN OUTCOMES:	Survival without moderate to severe neurodevelopmental impairment in early childhood; anemia four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL or as defined by the trial authors); neonatal mortality; moderate to severe hypoxic ischemic encephalopathy; resuscitation (positive pressure ventilation ± intubation ± chest compression); respiratory distress of any type or duration as described by the authors; admission to neonatal intensive care unit or special care nursery; hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth; hematocrit (%) within the first 24 hours and within 7days after birth after birth; hyperbilirubinemia treated with phototherapy; polycythemia (hematocrit greater than 65%); partial exchange transfusion; exchange transfusion; moderate to severe neurodevelopmental impairment in early childhood; ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L). *Maternal; m*aternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors); severe postpartum hemorrhage (clinically estimated blood loss of at least 1000 mL); manual removal of the placenta; post-partum infection.
SETTING:	Delivery Room
PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
BACKGROUND:	Umbilical cord management affects every one of the 140 million babies born in the world each year. {https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266}. Cut-cord milking may be an alternative to later cord clamping as a means for added blood transfusion to the baby at birth {Jaiswal 2015 1159, Yadav 2015 720} especially when later cord clamping is not feasible or contraindicated.
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	Umbilical cord management affects every one of the 140 million babies born in the world each year. {https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015	

	631, Mercer 2018 266} Cut-cord milking may be an alternative to later cord clamping as a means for added blood transfusion to the baby at birth {Jaiswal 2015 1159, Yadav 2015 720} especially when later cord clamping is not feasible or contraindicated.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The prevalence of iron deficiency and iron deficiency anemia has been reported to be as high as 26% and 3-7%, respectively among young children in Europe.{Bramhagen 1999 1333, Persson 1998 618, Thane 2000 433} The global prevalence of iron deficiency anemia has been reported to be 33%, with the highest burden in children less than five years of age (Kassebaum 2014 615). Iron deficiency in young children has been associated with impaired motor development, behavioral problems and cognitive delay {Grantham-McGregor 2001 649S, Gunnarsson 2007 391, Lozoff 2006 1108} A delay in cord clamping at birth may improve iron status, reduce iron deficiency in infancy and may consequently improve long-term neurodevelopmental outcomes. {Andersson 2011 d7157, Andersson 2015 631} Cut-cord milking may be an alternative to later cord clamping as a means for added blood transfusion to the baby at birth {Jaiswal 2015 1159, Yadav 2015 720} especially when later cord clamping is not feasible or is contraindicated. Our review of the evidence of benefits of cut-cord milking identified higher hemoglobin and hematocrit concentration during the neonatal period. However, no evidence was found to support a significant benefit of later cord clamping on the other critical and important outcomes.	Assisted ventilation in combination with cut-cord milking, may provide a more physiological approach to facilitate placental transfusion when newborn infants are not breathing at birth.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	The few available studies comparing later cord clamping to cut-cord milking {Jaiswal 2015 1159, Vatansever 2018 877, Yadav 2015 720} did not report significant adverse effects. The available evidence did not exclude benefit or harm related to hyperbilirubinemia treated with phototherapy, when cut-cord milking was compared to later cord clamping. Since later cord clamping was found to increase polycythemia and hyperbilirubinemia treated with phototherapy when compared to early cord clamping, these may represent potential undesirable effects of cut-cord milking as well.	It is unclear whether cut-cord milking causes adverse effects if conducted before establishing breathing at birth.

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 was very low for the reported 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 of the systematic review were: anemia at four to six months after birth, survival without moderate to severe neurodevelopmental impairment in early childhood, and maternal postpartum hemorrhage. Given that the interventions are simple and of no cost, and considering the main outcomes are critical, there is no important uncertainty or variability in how much people value the main outcomes despite the very low certainty of evidence of the effects.	Collection of cord blood for banking may pose a competing interest.

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 number of the studies (3) and the studied population (740) included in the systematic review were low. - Apart from neonatal mortality, which was addressed only by one small study {Yadav 2015 720}, no other critical outcomes were reported. - Compared to later cord clamping, two small studies {Jaiswal 2015 890, Yadav 2015 720} showed an increase in neonatal hemoglobin and hematocrit in the cut-cord milking group, without a significant increase in phototherapy-treated hyperbilirubinemia. - The improved hemoglobin with cut-cord milking in the neonatal period, may help in the prevention of the complications of iron deficiency, such as anemia and developmental delay. However, there are no available studies to address the long-term effects of cut-cord milking on iron deficiency, anemia or neurodevelopment in infancy or childhood.	It is unclear if there are long-lasting benefits or harms from either intervention when compared to the other.

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 have reported resource implications	Both interventions can be conducted at no cost and with minimal training but there is limited data on the potential costs related to their outcomes as not all the important outcomes were studied/reported.

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		

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 have addressed cost effectiveness	Both interventions can be conducted at no cost and with minimal training but there is limited data on the potential costs related to their outcomes as not all the important outcomes were studied/reported.

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	There are no studies examining health equity	Both interventions are feasible and accessible at no cost for any health care provider regardless of resource availability. Not all the outcomes that might affect health equity have been studied.

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is simple, inexpensive and practical but may need minimal training. Cut-cord milking has the potential to be an alternative to later cord clamping in situations where later cord clamping is not feasible or contraindicated.	More research is needed as currently there are only a few small studies which inform this question.

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 simple, easy to implement at no cost. It may need minimal training. It is feasible for all health care providers worldwide.	

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	Large	Moderate	Small	Trivial		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**

	JUDGEMENT						
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 7

Should Delayed cord clamping ≥ 60 seconds vs. < 60 seconds be used for term and late preterm infants	
POPULATION:	Term and late preterm babies
INTERVENTION:	Later (delayed) cord clamping at ≥ 60 seconds
COMPARISON:	Later (delayed) cord clamping at < 60 seconds
MAIN OUTCOMES:	Survival without moderate to severe neurodevelopmental impairment in early childhood; anemia four to six months after birth (lowest hematocrit or hemoglobin or as reported by the study authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL or as defined by the trial authors); neonatal mortality; moderate to severe hypoxic ischemic encephalopathy; resuscitation (positive pressure ventilation ± intubation ± chest compression); respiratory distress of any type or duration as described by the authors; admission to neonatal intensive care unit or special care nursery; hemoglobin concentrations (g/dL) within the first 24 hours and within 7days after birth; hematocrit (%) within the first 24 hours and within 7days after birth after birth; hyperbilirubinemia treated with phototherapy; polycythemia (hematocrit greater than 65%); partial exchange transfusion; exchange transfusion; moderate to severe neurodevelopmental impairment in early childhood; ferritin concentrations and low ferritin concentration at 3 to 6 months after birth (µg/L). Maternal death or severe morbidity composite (major surgery, organ failure, intensive care unit (ICU) admission, or as defined by trial authors); postpartum hemorrhage (clinically estimated blood loss of at least 500 mL, or as defined by the trial authors); severe postpartum hemorrhage (clinically estimated blood loss of at least 1000 mL); manual removal of the placenta; post-partum infection.
SETTING:	Delivery Room
PERSPECTIVE:	Infants and their families Health care practitioners providing care for newborn infants
BACKGROUND:	Umbilical cord management affects every one of the 140 million babies born in the world each year. {https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100} At the time of birth a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} The optimal duration of later cord clamping was among knowledge gaps identified by ILCOR in the 2015 statement.
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	Umbilical cord management affects every one of the 140 million babies born in the world each year. At the time of birth, a considerable amount of the fetal-placental circulation is outside the fetus. {Yao 1969 871} 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} There is a growing body of evidence that suggests that later (delayed) cord clamping at birth influences iron status, brain myelination, and neurodevelopment of full-term infants. {Andersson 2011 d7157, Andersson 2015 631, Mercer 2018 266} The optimal timing of later cord clamping is unknown and was considered among knowledge gaps identified by ILCOR in the 2015 statement.	The optimal timing of cord clamping after birth has not been determined. Early studies of the time course of placental transfusion {Yao 1969 871} suggest that the rate of transfer is most rapid in the first minute, but transfer continues beyond this time.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The prevalence of iron deficiency and iron deficiency anemia has been reported to be as high as 26% and 3-7%, respectively among young children in Europe. {Bramhagen 1999 1333, Persson 1998 618, Thane 2000 433} The global prevalence of iron deficiency anemia has been reported to be 33%, with the highest burden in children less than five years of age. {Kassebaum 2014 615} Iron deficiency in young children has been associated with impaired motor development, behavioral problems and cognitive delay. {Grantham-McGregor 2001 649S, Gunnarsson 2007 391, Lozoff 2006 1108} A delay in cord clamping at birth may improve iron status, reduce iron deficiency in infancy and may consequently improve long-term neurodevelopmental outcomes. {Andersson 2011 d7157, Andersson 2015 631} Our review of the evidence of benefits of later cord clamping ≥ 60 seconds vs. < 60 seconds, identified higher hemoglobin and hematocrit concentration during the neonatal period and higher neuro-developmental scores in childhood, in the group that received later cord clamping for ≥ 60 seconds. However, no evidence was found to support a significant benefit of later cord clamping for ≥ 60 seconds on the other critical and important outcomes.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Our review of the evidence found later cord clamping for ≥ 60 seconds possibly increased the use of phototherapy for treatment of hyperbilirubinemia compared to later cord clamping for < 60 seconds.	The possible increase in the rates of phototherapy-treated hyperbilirubinemia may have less impact in high- income countries where resources are in place for detecting and managing affected infants. In middle- and low-income countries, the benefit-risk assessment can be complicated and different from one setting to another depending on available resources. More research is needed to address this important area.

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 was very low for the critical outcomes of neonatal mortality and neurodevelopmental impairment in early childhood as well as for the important outcomes of resuscitation at birth, hemoglobin concentration in the first 24 hours after birth and hyperbilirubinemia treated with phototherapy.	

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 of the systematic review were: anemia at four to six months after birth, survival without moderate to severe neurodevelopmental impairment in early childhood, and maternal postpartum hemorrhage. Given that the intervention is simple and at no cost, and considering the main	Collection of cord blood for banking may pose a competing interest.

○ No important uncertainty or variability	outcomes are critical, there is no important uncertainty or variability in how much people value the main outcomes despite the very low certainty of evidence of the effects.	

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 improved hemoglobin associated with later cord clamping ≥ 60 seconds in the neonatal period may help in the prevention iron deficiency and its complications, such as anemia and developmental delay. Rates of iron deficiency are highest in resource-limited settings and therefore the potential benefits of later cord clamping ≥ 60 seconds may be greatest in these areas. There is some evidence that later cord clamping for ≥ 60 seconds may improve neurodevelopment in early childhood as evidence by higher ASQ 3 scores at 12 months of age. However, as later cord clamping for ≥ 60 seconds is associated with possible increase in use of phototherapy for hyperbilirubinemia, the potential for harm may be more pronounced in settings where resources for monitoring and treatment of hyperbilirubinemia are limited. It is crucial to weigh the benefits vs. the risks of later cord clamping for ≥ 60 seconds in different resource settings	Collection of cord blood for banking may pose a competing interest.

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 have reported resource implications	Both interventions are simple and of no cost, however, there is limited data about the possible cost-saving associated with the potential benefits of higher hemoglobin (reduced iron deficiency and the consequent neurodevelopmental impairments) and the possible costs of monitoring and managing the adverse effects of the possibly increased hyperbilirubinemia.

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		

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 have examined cost-effectiveness	The intervention itself is low-cost, but studies to examine cost-benefit await additional data on neurodevelopment and the objective need for treatment of hyperbilirubinemia.

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	This is a simple, easy and inexpensive intervention that can be implemented by health care providers in any place in the world to improve the hematological status and prevent iron deficiency which is prevalent globally (in high- as well as middle- and low-income countries). Embracing such intervention would foster health equity. Research studies conducted to date reflect the high interest from low- and middle- income countries {Kc 2017 264, Nouraie 2019 45, Rana 2019 36} as well as high-income countries. {Katheria 2017 e0187730} However, there might be disparity in monitoring and management of the possible adverse effects (hyperbilirubinemia treated with phototherapy) related to the lack of resources in the lower income countries.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	The intervention (later cord clamping ≥ 60 seconds) has been recommended by many governing bodies including WHO {World Health Organization 2012 } and in many countries, has been practiced as the standard of care for many infants at birth for years.	There is a high level of interest in delayed cord clamping among pregnant women, as reflected on social media sites and childbirth education courses.

○ Varies ○ Don't know	Research studies related to the intervention (later cord clamping ≥ 60 seconds) were conducted in different settings with variable resources.	

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 simple, easy to implement at no cost. - The intervention is feasible for any health care provider worldwide after minimal guidance/training and has been recommended by WHO since 2012. {World Health Organization 2012 } - Research studies related to the intervention were conducted in different settings with variable resources which shows that the intervention is feasible.	The intervention has been the standard practice in many centers providing childbirth care.

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	Large	Moderate	Small	Trivial		**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
○	○	●	○	○

OVERALL CONCLUSIONS

Recommendation

For term and late preterm infants born at ≥34 weeks' gestation who are vigorous or deemed not require immediate resuscitation at birth; we suggest later (delayed) clamping the cord at ≥ 60 seconds (weak recommendation, very low certainty evidence).

Justification

In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:

- Most studies comparing later (delayed) cord clamping to early cord clamping in late preterm and/or full-term infants delayed clamping of the cord for ≥ 60 seconds.
- Later (delayed) cord clamping facilitates postnatal cardiovascular transition, {Bhatt 2013 2113} increases hemoglobin and hematocrit in the neonatal period and improves iron status in early infancy. Although there were no studies that showed that later (delayed) cord clamping prevented the complications of iron deficiency anemia or associated developmental delay, we value the benefits of increased hemoglobin and the potential for improved iron status to benefit neurodevelopment during the critical periods of early infancy. These potential benefits may be greatest in settings where resources for evaluation of nutritional status are limited and iron deficiency and anemia are prevalent.
- Later (delayed) cord clamping is associated with increased rates of polycythemia and possible increase in use of phototherapy for hyperbilirubinemia. Although there was no reported increase in the rates of exchange transfusions, these considerations are important in settings where resources for evaluation and treatment of hyperbilirubinemia are limited.
- Only a few studies examined a physiological approach to cord clamping (delaying clamping until cessation of pulsation of the cord or based on vital signs monitoring/initiation of breathing). Compared to early, or time-based later cord clamping, this intervention improved neonatal hemoglobin and hematocrit. However, the effect on iron status, anemia in infancy, or neurodevelopment is uncertain.
- Although cut-cord milking improves neonatal hemoglobin and hematocrit, it is unknown if the intervention facilitates the postnatal cardiovascular transition in the same way as later (delayed) cord clamping. The number and size of studies is small and no long-term outcomes were addressed, limiting assessment of safety. Although cut-cord milking may be useful when later cord clamping is contraindicated or not feasible, no included studies report its use in these situations.
- There is insufficient evidence to recommend milking of the intact cord for term and late preterm infants.

- Across all comparisons, there was no evidence that any of the studied cord management strategies improved the primary infant outcome of survival without neurodevelopmental impairment. Likewise, there was no evidence that cord management strategies altered important maternal outcomes including post-partum hemorrhage. The small sample size of most trials and the associated risks of bias and imprecision limited the certainty of evidence for all outcomes of interest. Analysis of many outcomes could not exclude benefits or harms.

Subgroup considerations

The number of pre-specified subgroup analyses was large, was multiplied by the number of comparisons, and their p-values were not adjusted for multiple comparisons. As a consequence, GRADE evaluations were not done for all subgroup analyses: instead, post hoc GRADE evaluations were requested for outcomes that were significant or that contributed positively or negatively to our justification, values and preferences statements.

We assessed the influence of key factors on the intervention effect using a test of interaction, including gestational age (full-term vs. late preterm), resource setting (low- or middle income vs. high-income countries), Timing of uterotonic administration (before vs. after cord clamping) and size for gestational age (small vs. appropriate for gestational age). We planned to test for subgroup interactions within and between studies where appropriate. We noted whether randomization was stratified by the characteristic of interest. If subgroup data were not available, we performed subgroup analysis according to study characteristics, where applicable. These subgroup analyses are exploratory and must be interpreted with caution, especially for interaction tests between studies and by strata that were not used in randomization.

A- Subgroups according to gestational age: More term infants in the later cord clamping group received phototherapy for hyperbilirubinemia compared to early cord clamping group (low certainty evidence). Among late preterm infants (34 – 36+6 weeks' gestation), there was no benefit or harm from later cord clamping compared to early cord clamping (low certainty evidence). However, the test of interaction between the two subgroups was non-significant.

B- Subgroups according to different resource settings, based upon World Bank country classifications: Later cord clamping resulted in higher hematocrit values in the compared to early cord clamping in both low- or middle-income countries and high-income countries. The effect was greater in studies performed in high-income countries than in low- or middle-income countries. However, we do not have sufficient confidence in these findings to make separate recommendations for cord management by country income. We consider that the beneficial effect of delayed clamping is likely to be widely generalizable and should therefore be offered in all settings.

C- Subgroup analyses according to the timing of uterotonic administration and according to size for gestational age did not reveal significant differences between subgroups.

Implementation considerations

Later (delayed) cord clamping for at least 60 seconds for term and late preterm infants who are vigorous or do not require immediate resuscitation at birth is a simple, easy to implement and feasible intervention that requires no added equipment or special skills.

The intervention has been in practice for many years as it was recommended by WHO in 2012. {World Health Organization 2012 }

The implementation in lower-resources settings should be considered after carefully weighing the benefit/risk ratio for each setting.

Monitoring and evaluation

Continuous monitoring and evaluation of both desired and undesired effects of the intervention are needed. This includes:

- Monitoring the possible impact of the increased phototherapy-treated hyperbilirubinemia especially in low- and middle-income countries.
- Monitoring the long-term effects of the intervention in reducing iron deficiency complications such as anemia and neurodevelopmental impairment in childhood.
- Evaluating the associated costs and the potential economic impact of implementing later cord clamping >60 seconds or intact or cut-cord miking on the short- and long-term outcomes in different settings.
- Investigating the effects of the intervention, if implemented, in the less studied populations including non-vigorous babies (including resuscitation with cord intact), multiple births, small for gestational age babies.

Many of the included studies did not record the exact time of cord clamping. The details of cord management including the timing of clamping should be routinely recorded in clinical practice and research studies.

Research priorities

High quality studies are needed,

- to determine if the demonstrated reduction in early iron deficiency seen after later cord clamping improves long-term neurodevelopment and to determine the impact of cord management practices on these outcomes. These studies need to be performed in low-resourced and high-resourced settings.
- to address the effects of cord management practices on polycythemia and hyperbilirubinemia using standardized protocols for diagnosis and management.
- to define the optimal duration of later cord clamping and address important outcomes in the neonatal period, infancy, childhood and for mothers.
- to identify optimal cord management practices (i) for infants who are not vigorous or are deemed to require immediate resuscitation at birth and (ii) when there are contraindications to later cord clamping (e.g. interrupted placental circulation). These studies should report important short and long-term child outcomes including hyperbilirubinemia, polycythemia, anemia and neurodevelopmental outcomes as well as maternal outcomes.
- to address optimal cord management practice in cesarean deliveries (under spinal or general anesthesia), intrauterine growth restriction, multiple gestations, fetal anemia, fetal anomalies.
- to address the impact of cord management on vertical transmission of infectious diseases.
- to address the economic impact of different cord management practices.
- to widely agree on nomenclature and definition of different interventions including “delayed”, “deferred”, “later”, “optimal”, and “physiological” cord clamping, as well as “milking”, “stripping”, “intact-cord”, and “cut-cord”.
- to ascertain parents’ views regarding cord management practices at birth.

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Appendix A3 NLS-3 EtD Table
PPV Devices

QUESTION

Should T-piece resuscitator vs. Self-inflating bag be used for administering PPV at birth?	
POPULATION:	Neonates needing positive pressure ventilation (PPV) at birth
INTERVENTION:	T-piece resuscitator
COMPARISON:	Self-inflating bag
MAIN OUTCOMES:	In-hospital mortality; Intraventricular hemorrhage (all grades); Intraventricular hemorrhage (grade III-IV); Air leak; Bronchopulmonary dysplasia; Duration of positive pressure ventilation (PPV) in the delivery room (DR); Intubation in DR; cardiopulmonary resuscitation (CPR) or medications in DR; Admission to a neonatal intensive care unit (NICU); Length of hospitalisation
SETTING:	Delivery room
PERSPECTIVE:	
BACKGROUND:	It is established that PPV is the most important intervention during neonatal resuscitation and the equipment for providing PPV has been extensively assessed in bench and animal studies. Three device types are commonly used for providing respiratory support, namely the flow-inflating anaesthetic bag, the self-inflating bag (SIB) and T-piece resuscitator (TPR) system. While appropriate treatment with suitable devices can be life-saving, inappropriate use or inadequate equipment can have detrimental effects. Identification of the most effective device for administering PPV in newborns needing resuscitation at birth is a priority for healthcare providers involved in the care of neonates.
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	About 3 to 5% of all newborns (~ 6 million worldwide) receive positive pressure ventilation (PPV) at birth. {Wyckoff 2020 S185} Identifying the most appropriate device for administering PPV is a priority because aerating the newborn's lungs is the single most important and effective step in neonatal resuscitation. It is important to determine which device most effectively aerates the newborn's lungs while avoiding lung injury with potential short-term (e.g.,pneumothorax, intraventricular hemorrhage(IVH)) and long-term (e.g., bronchopulmonary dysplasia(BPD)) consequences.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large	Although the intervention did not impact in-hospital mortality and effects on IVH are uncertain, our findings suggest benefit of the TPR over the SIB for decreasing the duration of PPV in the delivery room (19.8 seconds shorter) and reducing the proportion with BPD (32 fewer infants with BPD per 1000	A large observational study {Guinsburg 2018 F49} showed that critical outcomes, including in-hospital mortality (NNT 8), IVH -all grades (NNT 8), and IVH grade III-IV (NNT 24) were significantly

○ Varies ○ Don't know	infants). Interventions performed in the delivery room may contribute to the development of BPD. Reducing BPD is one of the most important goals in the care of preterm infants.	reduced in the group receiving PPV with a TPR compared to the group receiving PPV with an SIB.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	For the critical outcome of severe IVH (grade III-IV), unpublished data provided by the author of one small RCT {Thakur 2015 21} and by the author of a cluster randomised clinical trial {Szyld 2014 165} suggested possible harm with the use of a TPR compared with SIB. However, the lack of adjustment for treatment center and the risk of ascertainment bias result in extremely low certainty in these results. Therefore, the data were not included. It is important to note that the direction of effect for severe IVH from these two randomised trials differs from the large observational study.{Guinsburg 2018 F49} The observational study demonstrated that receiving PPV with a TPR was associated with a decreased risk of IVH (all grades, NNT 8) and severe IVH (grade III-IV, NNT 24).	Although there are findings from 2 randomised trials, the evidence available from them is of extremely low certainty. Thus, the potential role of the device used for ventilation on the critical outcome of severe IVH (grade III-IV) requires further research.

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 for most outcomes is very low because of serious risk of bias, inconsistency, indirectness, and imprecision. The certainty of evidence from 4 randomised trials (1247 infants) supporting the benefit of the TPR for the critical outcome BPD is very low because of serious risk of bias, inconsistency, and indirectness. {Dawson 2011 912; Kookna 2019 66; Szyld 2014 165; Thakur 2015 21} The certainty of evidence from 3 randomised trials (1098 infants) {Kookna 2019 66; Szyld 2014 165; Thakur 2015 21} supporting the benefit of the TPR for the important outcome duration of PPV in the delivery room is moderate because of serious risk of bias. For most critical and important outcomes assessed in the meta analyses of RCTs, the 95% confidence intervals of relative risks (RR) were wide enough to include both potential harm and potential benefit.	The results supporting use of TPR are consistent with animal studies showing beneficial short-term effects of the TPR over the SIB when administering PPV at birth.

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 valuation of the main outcomes is consistent with the values assigned by the ILCOR NLS task force and a larger group of neonatal resuscitation experts. {Strand 2020 328} In addition, parents emphasize the importance of these outcomes. {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	We have considered the balance between the evidence supporting a reduction in risk of BPD (NNT=32) and the lack of evidence of benefit for other outcomes. Moreover, we have considered the reduction in mortality, IVH, severe IVH, and BPD in preterm infants demonstrated in a large observational study. Overall, we suggest that the balance between desirable and undesirable effects for preterm and very preterm newborns probably favors the use of a TPR. The balance of effects is less clear for late preterm and term infants where the desired effect is limited to decreased duration of PPV, and there is no evidence suggesting undesirable effects.	

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	Although there are no published cost data, pressurized gases, gas blenders, and single-use ventilatory circuits are necessary for a TPR. In contrast, SIBs can function without pressurized gas and some devices can be cleaned for multiple patient use. In addition, whenever a TPR is used, a SIB must be available as a back-up device. It is likely that the costs and resources used may be higher when using the TPR compared to the SIB.	It is possible that a reduction in the risk of BPD among preterm infants may balance the costs associated with TPR use in selected settings. The costs may vary depending on the healthcare resources of the setting. For example, in a setting with high healthcare resources, it is expected that both devices would be used with pressurized gases. In a very low resource setting, a self-inflating bag can be used as a stand alone device. The availability of single-use devices and the costs of use of these vs cleaning and reuse of multiple-use devices may also be a factor. Although they can be operated without a pressurized gas source, SIBs can also be subject to device failure and so whichever device is used, the device should be checked before use and a back-up device 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 data available. No studies were found that compared the costs or required resources for routine use of TPR vs SIB.	

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. No studies were found that compared the cost-effectiveness of routine use of TPR vs SIB.	Although there are no published cost-effectiveness data, it is likely that TPR use increases the cost of delivery room supplies. These costs may be balanced by decreased resource use in the NICU and increased quality-adjusted life years for preterm and very preterm infants if the risk of BPD is decreased.

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. Although there are no data available, a recommendation to use a TPR may reduce health equity. The TPR may differentially benefit preterm infants. The resource requirements for use of a TPR likely mean that providers in low resource settings would not have access to the device, and preterm newborns in low resource settings would not have the same opportunity to benefit from the TPR.	The large observational study included in the review was performed in a World Bank upper middle-income country {Guinsburg 2018 F49}. The TPR was available in the 20 participating public hospitals. The authors commented that the equipment rapidly became available after national guidelines recommended TPR use.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The TPR is widely used internationally. It is likely to be accepted by stakeholders in settings where the resources are available. In settings with limited resources or where the birth and stabilization of preterm infants is rare, acceptability may be lower. {El-Naggar 2012 491; O'Donnell 2004 208; Murthy 2012 F154; Roehr 2010 493}	

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 to be implemented. Both devices are widely used internationally, and for both, resources for purchase of equipment and training of staff are 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	Large	Moderate	Small	Trivial		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

Where resources permit, we suggest the use of a T-Piece resuscitator over the use of a self-inflating bag in infants receiving positive pressure ventilation at birth. (Weak recommendation, very low certainty of evidence). A self-inflating bag should be available as a back-up device for the T-piece resuscitator (technical remark).

Justification

Although the clinical evidence supporting the use of a T-piece resuscitator is of very low certainty, we have also taken into account the direction of evidence from animal studies showing that PEEP facilitates lung aeration. Animal studies suggest a benefit to using devices providing controlled levels of PEEP and peak inspiratory pressure (PIP) to assist establishment of a functional residual capacity (FRC) during transition of a fluid-filled lung to an air-filled lung capable of supporting air-breathing and to reduce lung damage secondary to barotrauma {Bjorklund 1997 348; Haddad 2017 1405; Hillman 2007 575}. Benchtop and manikins demonstrate more consistent pressures and tidal volumes when using a T-piece resuscitator than a self-inflating bag {Hawkes 2012 797; Hussey 2004 F490}.
However, the certainty of clinical evidence is not sufficient to recommend against using a self-inflating bag during neonatal resuscitation, particularly in regions where pressurized gases are not readily available.

Subgroup considerations

Although subgroup analyses by gestation were not feasible, in contemporary neonatal practice, BPD is mainly an outcome that affects very preterm infants. Therefore, the reduction in the incidence of BPD suggests that use of a T-piece resuscitator may be of greatest benefit for preterm infants.
For use of self-inflating bag with PEEP valve vs use of self-inflating bag without PEEP valve, the data are too uncertain, so no recommendation can be made.

Implementation considerations

Implementation will require resources to obtain equipment and train personnel if T-piece devices are not already in use but may be offset by decreased NICU resource utilization after stabilization in the delivery room.

Monitoring and evaluation

As the recommendation for use of a T-piece resuscitator remains weak and is based on very low certainty evidence, continued monitoring and evaluation is highly recommended.

Research priorities

There are insufficient studies allowing comparison of benefits and risks of T-piece resuscitators to self-inflating bags by gestation subgroups. Such studies should include outcomes relevant to each gestation subgroup (e.g. severe IVH, BPD, neurodevelopmental impairment for very and extremely preterm infants, admission to neonatal intensive or special care unit, receiving subsequent respiratory support, length of hospital stay, air leaks for term and near-term infants).
There are no studies comparing the cost-effectiveness of routine use of T-piece resuscitators compared to self-inflating bags.
There are no studies specifically comparing how both T-piece resuscitators and self-inflating bags are used in practice (e.g. pressures delivered, set-up time, ease of use, adjustments to pressures made during use, perceived feedback from the device to the user).
There are no studies comparing the flow-inflating bag to either the T-piece resuscitator or the self-inflating bag (with or without PEEP) for neonatal resuscitation.
There are no clinical trials comparing one T-piece device to another and one self-inflating bag to another, although benchtop experiments demonstrate variations in performance that are of potential clinical importance. The specific devices used in comparative studies should be reported {Hinder 2019 F122; Tracy 2019 F403}.

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Appendix A3 NLS-4 EtD Table
Family Presence During Neonatal Resusciation

QUESTION

POPULATION:	In neonates requiring resuscitation in any setting
INTERVENTION:	Does family presence during resuscitation
COMPARISON:	Compared to no family presence during resuscitation
MAIN OUTCOMES:	Result in improved patient outcomes (short and long term), family-centered outcomes (short and long term, perception of the resuscitation), and health care provider-centered outcomes (perception of the resuscitation, psychological stress
SETTING:	In-hospital (any setting) or out-of-hospital
PERSPECTIVE:	Population
BACKGROUND:	Whilst family presence during neonatal resuscitation is practiced in some settings, it has never undergone systematic review and practice varies internationally. During the COVID-19 pandemic some services have moved neonatal resuscitation sites to locations separated from parents making this question a priority for the Neonatal Life Support Task Force. Therefore the NLS Task force chose to be nodal to this pediatric task force high priority question.
CONFLICT OF INTERESTS:	None

ASSESSEMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Whilst common practice in some settings and some countries is for neonates requiring resuscitation to receive it in the birthing room, this is not universal. The effect of parental presence during resuscitation at birth or at other locations during the neonatal period has never been subjected to systematic review.	International practice varies due to culture, facilities and practice traditions. COVID-19 has meant that parents and their babies may be separated at birth in the presence of maternal COVID-19 positivity.

Desirable Effects

How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Parents report being more aware of events and are not on the whole uncomfortable being present as long was well supported and informed. Partners do not have to leave mother and can be present with both. Parents and health care providers report a requirement for training to support parental presence during resuscitation. Communication is a key feature related by both groups. Some fathers were worried, distressed, petrified, panic-stricken or scared. However, none regretted being present {Harvey 2012 F439}. Even observational data from surveys lacks comparison groups. One study suggested that perceived health care professional workload was reduced if a family member was present during resuscitation/stabilization {Zehnder 2020 F1}	The judgement of trivial here does not mean that the experiences or potential effects upon parents are trivial. It refers to the quality of evidence available for any of the relevant outcomes. Almost all studies were selection biased in terms of who was approached and who actually reported. There was much discussion in the group as to whether this should be "Trivial" or "Don't know, however, one well designed study did find advantages in terms of parental presence reducing retrospectively perceived professional workload { Zehnder 2020 F1}. Need to be aware that few parents report remembering events specifically but are aware of "feelings" and "emotions". {Harvey 2012 F439}. Communication and training is key but presence allows family involvement, confidence in care and awareness of "what was going on"{Sawyer 2015 e008495}. One large study of 60 parents found none who were uncomfortable with stabilization or resuscitation procedures {Katheria 2018 100}, However, this was part of a prepared interventional study and therefore support would have been high. All evidence is from only 8 papers from high resource services in three countries UK, USA and Canada.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Both health care providers and parents voice some concerns that parental presence may affect the performance of resuscitation teams {Yoxall 2015 e008494, Sawyer 2015 e008495, Harvey 2013 27} although there is no direct evidence for this. Furthermore, this was not borne out by the only study which was directed at workload of health care providers {Zehnder 2020 F1} Some fathers were worried, distressed, petrified, panic-stricken or scared. However, none regretted being present {Harvey 2012 F439}.	Health care providers felt that effect on staff less likely with increased experience {Harvey 2013 27, Yoxall 2015 e008494} All evidence is from only 8 papers, all from high resource services in three countries UK, USA and Canada.

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 very low due to the risk of bias in the available studies and because none of the PICOST questions originally posed was addressed by the included studies. Different techniques and approaches were used with selected groups. Apart from one paper {Zehnder 2020 F1} in which the methodology was well described, methodologies were neither sufficiently described nor validated. Therefore comparisons and relevance is impossible to judge. All evidence is from only 8 papers from high resource services in three countries UK, USA and Canada.	There is no evidence available comparing different settings, level of resources, or cultural and training aspects.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT		ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	Parents and health care providers are likely to value the outcomes included in this systematic review {Strand 2019 F328}	

● 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	There is insufficient evidence to indicate an interventional effect on patient or family outcome. Being present during the resuscitation of their baby seems to be a positive experience for some parents but concerns about an effect upon performance exist in health care providers and family members. We suggest it is reasonable for mothers/fathers/partners to be present during the resuscitation of neonates where circumstances, facilities and parental inclination allow. This is a weak recommendation based on very low certainty of evidence.	In the review of pediatric FPDR, the findings reflected that, being present during the resuscitation of their child, was a very helpful experience for parents. In all studies, parents who were present discussed their belief that their presence brought their child comfort and that it helped them to adjust to the loss of their child when that occurred {Ebrahim 2013 40, Maxton 2008 3168, McGahey-Oakland 2007 217, Stewart 2019 58, Tinsley 2008 e799}. This is especially true for one which compared parents who had been present vs those who had not {Tinsley 2008 e799} In a neonatal setting the only available evidence suggested that the perceived health care providers workload might be reduced by parental presence {Zehnder 2020 F1}

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 were identified specifically comparing resources including costs required for either parental presence or absence at resuscitation. The mother is always present at birth. However, parents and health care providers highlighted the need for training and personnel to support parental presence. There are no data to assess the resources needed to provide this.	Cost may be greater if changes in architecture or furnishings are required (e.g. to provide a separate area for resuscitation) or for healthcare practitioner education and training if a change of practice was required. The need for parental support and staff training was identified in included studies

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 studies were identified comparing resources including costs between the two interventions.	Resource requirement may be greater if a separate area is required for resuscitation.

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 were identified comparing cost-effectiveness between the two interventions. However, parents and health care providers highlighted the need for training to support parental presence.	

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 studies were identified addressing health equity. All included studies were performed in UK, USA or Canada (high resource settings). There were no data available from medium or low resource settings or varied cultural settings.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Whilst family presence during neonatal resuscitation is practiced in some settings, practice varies internationally. All included studies were performed in UK, USA or Canada (high resource, culturally similar settings).	Parents and healthcare providers highlight the need for training in order to support parental presence.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No studies were identified addressing feasibility in neonatal resuscitation. Whilst family presence during neonatal resuscitation is practiced in some settings, practice varies internationally. Implementation would depend upon resources, facilities, and different socioeconomic, cultural and organizational settings.	

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	Large	Moderate	Small	Trivial		Varies	**Don't know**

	JUDGEMENT						
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
○	●	○	■	○

CONCLUSIONS

Recommendation

We suggest it is reasonable for mothers and fathers (or their partners) to be present during the resuscitation of neonates where circumstances, facilities and parental inclination allow. This is a weak recommendation based on very low certainty of evidence.

There is insufficient evidence to indicate an interventional effect on patient or family outcome. Being present during the resuscitation of their baby seems to be a positive experience for some parents but concerns about an adverse effect upon performance exist among both healthcare providers and family members.

Justification

In making these recommendations, the Neonatal Life Support Task Force considered the following:

- Whilst family presence during neonatal resuscitation is practiced in some settings, it has never undergone systematic review and practice varies internationally. During the COVID-19 pandemic some services have moved neonatal resuscitation sites to locations separated from parents making this question a priority for the Neonatal Life Support Task Force.
- All the included papers originate in the UK, USA or Canada.
- All the included papers related to resuscitation at birth.
- Mothers are always present at birth and it seems that most healthcare providers surveyed in included publications feel partner/support person presence should be offered but with the caveat that facilitation and support of the families requires sufficient numbers and training of healthcare personnel.

- Of note, we did not identify any eligible randomized controlled trials or large cohort studies comparing family presence to no family presence during neonatal resuscitation. We acknowledge the lack of clinical trial data for this topic in our knowledge gaps.
- It is notable that the evidence came from the opinions of only 144 parents and 350 healthcare providers in total, all sampled in tertiary centres in the UK, USA or Canada.

Subgroup considerations

There is insufficient data to address different gestations and subgroups of neonates requiring resuscitation. There is insufficient data to address different locations, such as within the NICU, emergency department or different socioeconomic and cultural settings.

Implementation considerations

Although still a relatively uncommon occurrence, some respiratory intervention is needed in up to 5% of infants at birth. Mothers are, of course, always present at birth, but the presence of other family members and indeed the presence of any family members during neonatal resuscitation varies around the world. There is insufficient evidence available to advise any change of current practice.

Monitoring and evaluation

Adverse events should be monitored and reported.

Research priorities

KNOWLEDGE GAPS

There were no studies identified that provided adequate comparative data to address this PICO question in the setting of a neonate receiving resuscitation at birth or within the first month of life. The majority of published work used retrospective survey or qualitative methods and included births where resuscitation was not required. There would be serious ethical constraints on performing a randomized controlled trial to address this question, among which would be the extreme difficulty of obtaining informed consent. Therefore, larger scale observational studies with appropriate quantitative and qualitative outcome and experience measures are recommended. In addition to addressing parent- and health care provider-centered outcomes, studies are needed to address whether or not family presence affects the outcome of a resuscitation and whether family presence impacts decisions to continue or discontinue resuscitation.

The included studies all came from delivery rooms studied in high resource settings. Subsequent studies are needed that recruit from different socioeconomic, cultural and organizational settings.

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