**NLS 5051 Evidence to decision table for cord management at birth for preteRm infants**

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

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

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

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| Question #1

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| **Should deferred cord clamping (DCC) vs. immediate cord clamping (ICC) be used for preterm infants?** |
| **Population:** | Preterm infants <37 weeks' gestation |
| **Intervention:** | Deferred cord clamping (DCC) |
| **Comparison:** | Immediate cord clamping (ICC) |
| **Main outcomes:** | Infant outcomes:- Mortality before discharge - Severe intraventricular hemorrhage (IVH) for infants <32 weeks' gestation: ultrasound diagnosis grades III and/or IV- Chronic lung disease (CLD) for infants <32 weeks' gestation: oxygen at 36 weeks' postmenstrual age (PMA)- Late onset sepsis for infants <32 weeks' gestation - Necrotizing enterocolitis (≥ Bell's Stage II) for infants <32 weeks' gestation - Patent ductus arteriosus requiring medical/surgical treatment for infants <32 weeks' gestation - Hyperbilirubinemia (treated by phototherapy)- Receipt of blood transfusion- Hypothermia on admission (body temperature <36.5*°*C)- Hemoglobin/Hematocrit within the first 24 h after birthMaternal outcomes:- Mortality- Postpartum hemorrhage - Use of therapeutic uterotonic agents- Post partum blood transfusion- Manual removal of the placenta - Postpartum infection  |
| **Setting:** | Locations where infants are born |
| **Perspective:** | Infants and their familiesHealth Care Providers for newborn infants and their mothers |
| **Background:** | Umbilical cord management affects every one of the 130 million infants born in the world each year. Cord management at birth impacts not only the volume of placental transfusion to the baby, but also the cardiovascular transition around the onset of breathing and/or ventilation. {Bhatt 2013 2113, Yao 1969 871} Placental transfusion at birth, through delayed cord clamping and cord milking, improves cardio-respiratory post-natal adaptation of preterm infants, hemoglobin concentration, and cerebral oxygenation. {Bhatt 2013 2113, Hooper 2015 147, Kluckow 2015 225, Niermeyer 2013 385} There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. Long-term neurodevelopmental outcomes in preterm infants are being investigated. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Meta-analyses to date have suggested that placental transfusion at birth significantly reduces mortality in preterm infants as well as improving cardiovascular and hematological parameters. A recent systematic review found that delayed cord clamping at birth for >30s reduced mortality in preterm infants <28 weeks’ gestation with number needed to treat for benefit (NNTB) of 20 infants, with a high GRADE level of evidence. {Fogarty 2018 1} In addition to examining timing of cord there has also been exploration of whether some or all of the benefits of delayed cord clamping, especially those attributable to placental transfusion may be achieved by milking the intact cord or a segment of cut cord. The optimal cord management at birth for preterm infants remains unclear. Cord management and resuscitation interventions may be simultaneous or sequential in time, and each may impact the performance and outcomes of the other.History, values, and preferences significantly impact interpretation of cord management studies. So-called “natural” cord management is based on the supposition that historically, immediate cord clamping has been an unusual practice and there have been natural delays between delivery and cord separation. As a result, early clamping and milking may be considered “medical interventions” that were increasingly practiced since the middle of the 20th century. This systematic review, however, chose early clamping as the control based on the (recent) commonest practice, and also because early cord clamping was the control condition in a large number of randomized trials of other methods.  |
| **Conflict of interests:** | Walid El-Naggar is a member of the iCOMP collaborative group, received NICHD grant as a co-investigator of the Umbilical Cord Milking in Non-Vigorous Infants (MiNVI Trial), received a grant from IWK Research as the principal investigator of the MoCC trial, received a grant from Nova Scotia Health Research Foundation (NSHRF) as a principal investigator of the study: The effect of umbilical cord milking on hemodynamic status of preterm infants: a randomized controlled trial, received a grant from National Health and Medical Research Council (NHMRC) as a co-investigator of the Australian Placental Transfusion study (APTS). Peter Davis is a member of the iCOMP collaborative group and received NHMRC funding for BabyDUCC trial, Justin Josephsen is a member of the iCOMP collaborative group, published an UCM trial that could be included in this analysis, and received NICHD funding as co-investigator of the VentFirst trial. Lene Seidler is the lead of iCOMP collaborative group, received a grant from the National Health and Medical Research Council (NHMRC) to support iCOMP. Daniela Costa-Nobre, Tetsuya Isayama, Roger Soll and Keith Couper have no relevant COI. Measures to manage conflicts of interest are described in the accompanying CoSTR statement.  |

Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Management of the umbilical cord at birth needs to be considered in the context of other resuscitation interventions. It may also alter responses to resuscitation and outcomes.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate● Large○ Varies○ Don't know | 1) The pairwise IPD metanalysis identified 21 trials including 3292 preterm infants.*For the critical outcome of* ***death before discharge,*** there was **clinical benefit** for DCC compared to ICC (odds ratio (OR) 0.68, 95% confidence interval (CI) 0.51 to 0.91; number needed to treat for benefit (NNTB) 40, 95% CI 143 to 26; I2 = 0%; 25 fewer infants per 1000 died before discharge [95% CI, 38 to 7 fewer per 1000]), **high certainty evidence** from 20 trials including 3,263 infants. {Backes 2016 35, Chu 2011 S502, Datta 2017 418, Duley 2018 F6, Finn 2019 121, García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 307, Liu 2018 , Oh 2011 S68, Okulu 2022 838444, Rana 2019 36, Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Salae 2016 S159, Tarnow-Mordi 2017 2445, Yunis 2021 157}**For infants < 32 weeks’ gestation****:**f*or the important outcome of* ***receiving transfusion of red blood cells***, there is **probable** **clinical benefit** (OR 0.59, 95% CI 0.47 to 0.73; I2 = 0%; NNTB=7, 95% CI 5 to 12; 131 fewer infants per 1000 received blood transfusion after DCC than after ICC, [95% CI, 186 fewer to 78 fewer]), **Moderate certainty evidence** (downgraded for serious risk of bias) from 13 trials including 1929 infants. {Chu 2011 S502, Duley 2018 F6, Finn 2019 121, García 2023 , Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 307, Oh 2011 S68, Rana 2018 655, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}For the important outcomes of ***hemoglobin concentrations (g/dL) and hematocrit values (%)*** *within the first 24 hours after birth*, hemoglobin concentrations and hematocrit values are **probably higher** after DCC compared to ICC (mean difference (MD)= 0.88 g/dL, 95% CI 0.52 to 1.24 (corresponds to MD of 8.8 mg/L, 95% CI 5.2 to 12.4), I2= 0% and MD= 2.69%, 95% CI 1.43 to 3.95%; I2 = 0% respectively), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 523 infants reporting ***hemoglobin concentrations*** {Chu 2011 S502, Finn 2019 121, García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}and 8 trials including 260 infants reporting ***hematocrit values*** {Backes 2016 35, García 2023 , Gharehbaghi 2020 11095, Kugelman 2007 307, Oh 2011 S68, Ranjit 2015 29, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.* **For infants ≥32 weeks’ gestation*****Hemoglobin concentrations*** within the first 24 hours after birth *(important outcome),* are **probably higher** after DCC compared to ICC (MD 1.26 g/dL, 95% CI 0.72 to 1.80 (corresponds to MD of 12.6 mg/L, 95% CI 7.2 to 18.2), I2= 0%, **low certainty evidence** (downgraded for risk of bias and inconsistency) from 7 trials including 302 infants. {García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Liu 2018 , Okulu 2022 838444, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.* ***Hematocrit values*** within the first 24 hours after birth are **probably higher** after DCC compared to ICC (MD 3.69%, 95% CI 2.43 to 4.95%; I2 = 0%), **moderate certainty evidence** (downgraded for risk of inconsistency) from 8 trials including 420 infants {García 2023 , Gharehbaghi 2020 11095, Kugelman 2007 307, Liu 2018 , Okulu 2022 838444, Ranjit 2015 29, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*  |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | ***For the important outcome of hypothermia on admission*** (body temperature <36·5°C), there is **probable clinical harm** as more infants developed hypothermia after DCC compared to ICC (OR 1.28, 95% CI 1.06 to 1.56; I2 = 0%; NNTH 16, 95% CI 9 to 71; 62 more infants per 1000 were hypothermic on admission, [95% CI, 14 more to 111 more]), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 1995 infants. {Duley 2018 F6, Finn 2019 121, García 2023 , Kugelman 2007 307, Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}***For the important outcome of body temperature on admission,*** the **temperature is possibly lower** after DCC compared to ICC clamping (MD -0.13, 95% CI -0.20 to -0.06; I2 =58.4), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 8 trials including 1995 infants.{Duley F6, Finn 121, García , Kugelman 307, Rana 655, Ruangkit 156, Tarnow-Mordi 2445, Yunis 157}. Note that the GRADE certainty of evidence was assessed post-hoc.- This finding was not replicated in infants **>**32 weeks' gestation. - No evidence of harm was identified in any other clinical outcomes for the infants or mothers related to deferred cord clamping compared to immediate cord clamping. |  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low● Moderate○ High○ No included studies | - The certainty of evidence is high for the critical outcome of infant’s mortality before discharge and moderate for the important outcomes of receiving blood transfusion, hemoglobin and hematocrit levels within 24 hours of age and hypothermia on admission for infants <32 weeks’ gestation.- The certainty of evidence was low for most of the other outcomes. |  |
| ValuesIs 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 by health care providers and parents– they are critical outcomes. {Strand 2020 F328, Webbe 2020 425} |  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention● Favors the intervention○ Varies○ Don't know | - Deferred cord clamping for 30- ≥180 compared to immediate cord clamping reduces infants’ mortality before discharge (high quality evidence), reduces the receipt of blood transfusion (moderate quality evidence) and improves the hematologic status (Hemoglobin/hematocrit levels in the first 24 hours of age- moderate quality evidence).- The only undesired effect found for deferred cord clamping compared to immediate cord clamping is increased hypothermia (body temperature <36·5°C) on admission in infants <32 weeks' gestation (moderate certainty evidence).  |  |
| Resources requiredHow large are the resource requirements (costs)?" |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | No study evaluated required resources; however direct costs are expected to be similar regardless of method of umbilical cord management . | - For preterm infants requiring resuscitation at birth, additional equipment and additional training may be needed.  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | No direct data available. | Although there are no published cost data, it is unlikely that deferred cord clamping compared to immediate cord clamping will add costs for infants not requiring resuscitation. However, for infants requiring resuscitation additional equipment and additional training may be needed.  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention● Favors the intervention○ Varies○ No included studies | - No studies evaluated cost-effectiveness. - Although there are no published cost-effectiveness studies, it is likely that deferring cord clamping for 30-180 seconds compared to immediate clamping favors the intervention because of the following reasons:A- There is high quality evidence that it reduces mortality before discharge in preterm infants <37 weeks' gestation.B- There is moderate quality evidence that it reduces the receipt of blood transfusion in infants <32 weeks’ gestation.C- There is moderate quality evidence that it improves the hematologic status of preterm infants <37 weeks' gestation within the first 24 hours of age. |  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced○ Probably reduced○ Probably no impact● Probably increased○ Increased○ Varies○ Don't know | The improvement in the main outcomes using an intervention that doesn't need additional resources, probably improves equity.  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Deferred cord clamping for most preterm infants has been recommended by different governing bodies including WHO and has been practiced for many years in both high and low resources settings. | For preterm infants requiring resuscitation at birth, additional equipment and additional training may be needed.  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Deferred cord clamping for most preterm infants has been recommended by different governing bodies including WHO and has been practiced for many years now in both high and low resources settings.  | For preterm infants requiring resuscitation at birth, additional equipment and additional training may be needed.  |

Summary of judgements

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

Type of recommendation

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

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| Question #2

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

**Assessment**

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| **Problem**Is the problem a priority? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Management of the umbilical cord at birth needs to be considered in the context of other resuscitation interventions. It may also alter responses to resuscitation and outcomes. |  |
| **Desirable Effects**How substantial are the desirable anticipated effects? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Trivial● Small○ Moderate○ Large○ Varies○ Don't know | - The pairwise IPD MA identified **18 trials** (1565 infants). The cord was milked intact (2–4 times) in 12 trials (n=866 infants), whereas in four trials (n=340 infants) the cut-cord was milked once and in two trials (n=359) there was a delay before intact-cord milking. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}*For the critical outcome of* ***death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.73, 95% CI 0.44 to 1.20; I2 = 7.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 18 trials including 1565 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}*For the important outcome of* ***receiving red blood cell transfusions,*** there is **probable clinical benefit** for UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I2 = 20%; NNTB 10, 95% CI 5 to 55; 92/1000 fewer infants received red cell transfusion after UCM compared to ICC, 95% CI 167 fewer to 18 fewer), **moderate certainty evidence** (downgraded for serious risk of bias) from 15 trials including 1163 infants. {Alan 2014 e493, Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}***Hemoglobin concentrations (g/dL)*** within the first 24 hours after birth (*important outcome)* **were possibly higher** after UCM compared to ICC (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL; I2 = 66.6%), **low** **certainty evidence** (downgraded for serious risk of bias and inconsistency) from 12 trials including 944 infants. {Alan 2014 e493, El-Naggar 2019 F145, Hosono 2008 F14, Hosono 2015 abstr 2765.7, Josephsen 2022 436, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat } *Note that the GRADE certainty of evidence was assessed post-hoc.****Hematocrit values (%)*** within the first 24 hours after birth**were possibly higher** after UCM compared to ICC (MD 1.71%, 95% CI 0.78 to 2.64%; I2 = 36.9%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 12 trials including 900 infants. {Alan 2014 e493, Chellappan 2022 A178, Gharehbaghi 2020 11095, Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Yadav 2015 720} *Note that the GRADE certainty of evidence was assessed post-hoc.* |  |
| **Undesirable Effects**How substantial are the undesirable anticipated effects? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ● Trivial○ Small○ Moderate○ Large○ Varies○ Don't know | * No important undesirable effects were noted in the analyses except for a small decrease of body temperature of infants ≥32 weeks’ gestation, on admission to NICU.
* For the important outcome of **temperature on admission for infants ≥32 weeks’ gestation**, there is **possible clinical harm** from UCM compared to ICC (MD -0.20, 95% CI -0.35 to -0.05; I2 = 81.4%; evidence of **low** certainty (downgraded for serious risk of bias and inconsistency) from 2 trials including 190 infants. {Ram Mohan 2018 88, Xie 2022 31}
* However, the small decrease in temperature on admission was not associated with any increase in the rates of hypothermia on admission in either gestational age group, and is judged unlikely to be clinically important.
* Compared to ICC, there is no clinical benefit or harm from UCM for any IVH or severe IVH in infants <32 weeks’ gestation.
* Maternal outcomes OR were not estimable or showed no difference with wide confidence intervals, due to few trials collecting maternal outcomes and low event rates.
 |  |
| **Certainty of evidence**What is the overall certainty of the evidence of effects? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Very low● Low○ Moderate○ High○ No included studies | Evidence of critical outcomes of death at discharge was of low certainty, it was of moderate certainty for any IVH and receipt of blood transfusion and for all the other outcomes it ranged from low to very low.  |  |
| **Values**Is there important uncertainty about or variability in how much people value the main outcomes? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | The main outcomes are highly valued as they are critical outcomes. {Strand 2020 F328, Webbe 2020 425} |  |
| **Balance of effects**Does the balance between desirable and undesirable effects favor the intervention or the comparison? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison● Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | * There are no important differences in the rates of critical outcomes between UCM and ICC.
* *For the important outcome of* ***hemoglobin concentrations (g/dL)*** within the first 24 hours after birth, **there is possibly higher** hemoglobin concentrations after UCM compared to ICC (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL; I2 = 66.6%), **low** **certainty evidence** (downgraded for serious risk of bias and inconsistency) from 12 trials including 944 infants.
* *For the important outcome of* ***receiving red blood cell transfusions,*** there is **probable clinical benefit** for UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I2 = 20%; NNTB 10, 95% CI 5 to 55; 92/1000 fewer infants received red cell transfusion after UCM compared to ICC, 95% CI 167 fewer to 18 fewer), **moderate** **certainty evidence** (downgraded for serious risk of bias) from 15 trials including 1163 infants.
* The only undesirable effect found was lower temperature on admission, which was statistically significant. However, the effect was small and was considered unlikely to be clinically important.
 |  |
| **Resources required**How large are the resource requirements (costs)?" |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | There are no published cost data.  | - Cord clamping strategies in infants who do not require resuscitation need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. - Training is required.- Although there are no published cost data, the intervention is of no cost and possibly improves hematological status and probably reduces blood transfusion and therefore may reduce cost indirectly.  |
| **Certainty of evidence of required resources**What is the certainty of the evidence of resource requirements (costs)? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Very low○ Low○ Moderate○ High● No included studies | There are no data available.  | We perceive the additional resource requirements and costs to be low for both this intervention and its comparison.  |
| **Cost effectiveness**Does the cost-effectiveness of the intervention favor the intervention or the comparison? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | There are no data available.  | Umbilical cord milking probably reduces blood transfusions and possibly improves hematologic status which may lead to potential savings. |
| **Equity**What would be the impact on health equity? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Reduced○ Probably reduced○ Probably no impact● Probably increased○ Increased○ Varies○ Don't know | Improvement of hematologic status and reduced receipt of red cell transfusions may result in improved equity in low-resource settings where resources may not be readily available.  |  |
| **Acceptability**Is the intervention acceptable to key stakeholders? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | A retrospective multicenter study implies that this is an accepted practice among healthcare practitioners. {Kumbhat 2021 S0022} | There are no clear disadvantages to the caregiver or client with respect to the intervention.  |
| **Feasibility**Is the intervention feasible to implement? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | The intervention is feasible. {Kumbhat 2021 S0022} |  |

**Summary of judgements**

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

**Type of recommendation**

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

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Question #3

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

**Assessment**

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| **Problem**Is the problem a priority? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Umbilical cord management affects every one of the 130 million infants born in the world each year. There is a growing body of evidence that suggests that cord management at birth influences survival and neonatal morbidities. {Al-Wassia 2015 18, Fogarty 2018 1, Mercer 2016 50, Rabe 2012 Cd003248} Management of the umbilical cord at birth needs to be considered in the context of other resuscitation interventions. It may also alter responses to resuscitation and outcomes. |  |
| **Desirable Effects**How substantial are the desirable anticipated effects? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ● Trivial○ Small○ Moderate○ Large○ Varies○ Don't know | - The pairwise IPD MA identified 15 trials (1655 infants). One trial with six infants milked the cut cord once, whereas 14 studies with 1649 infants milked the intact cord (2-4 times). Deferral times in the DCC group ranged from 30 to 120 seconds.*For the critical outcome of* ***death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.95, 95% CI 0.59 to 1.53; I2 = 0.0%), **low certainty evidence** (downgraded for very serious imprecision) from **12 trials** including 1303 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}- For the outcomes of ***chronic lung disease, necrotizing enterocolitis, Patent ductus arteriosus receiving medical or surgical treatment, late-onset sepsis, retinopathy of prematurity, hemoglobin concentrations (g/dL) for infants, receiving transfusion of packed red blood cells, hypothermia*** on admission for infants <32 weeks´ gestation, **clinical benefit or harm cannot be determined** for UCM compared to DCC.- For the outcomes of ***hemoglobin concentrations (g/dL), hematocrit (%), receiving transfusion of red blood cells, hypothermia on admission*** for infants ≥32 weeks’ gestation, **clinical benefit or harm cannot be determined** for UCM compared to DCC. |  |
| **Undesirable Effects**How substantial are the undesirable anticipated effects? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | *For the critical outcome of* ***severe intraventricular hemorrhage,*** there is**possible clinical harm** after UCM compared to DCC (OR 2.20, 95% CI 1.13 to 4.31; I2 = 0.0%) NNTH 24 (95% CI 9 to 200 infants more have severe IVH after UCM compared to DCC), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 860 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}*For the critical maternal outcome of* ***post-partum receipt of blood transfusion****, there is* ***possible clinical harm*** *after UCM compared to DCC (OR 2.72, 95% CI 1.11 to 6.65; I2 = 0.0%; NNTH 26 (95% CI 8 to 333) 39 more/1000 (95% CI from 3 more to 118 more),* ***low certainty evidence*** *from 4 trials including 653 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2015 61}* | A new RCT published after the NMA was completed, showed no significant difference in the rates of severe intraventricular hemorrhage between preterm infants born at 28-32 weeks’ gestation who received umbilical cord milking compared to those who received deferred cord clamping. {Katheria 2023 217.e1} |
| **Certainty of evidence**What is the overall certainty of the evidence of effects? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Very low● Low○ Moderate○ High○ No included studies | In general, the evidence was low for the critical and important infant and maternal outcomes.  |  |
| **Values**Is there important uncertainty about or variability in how much people value the main outcomes? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability○ Probably no important uncertainty or variability● No important uncertainty or variability | The main outcomes are highly valued as they are critical outcomes. {Strand 2020 F328, Webbe 2020 425} |  |
| **Balance of effects**Does the balance between desirable and undesirable effects favor the intervention or the comparison? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Favors the comparison● Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | - Overall, clinical benefit or harm cannot be determined for UCM compared to DCC except for 2 outcomes:*For the critical outcome of* ***severe intraventricular hemorrhage,*** there is**possible clinical harm** after UCM compared to DCC (OR 2.20, 95% CI 1.13 to 4.31; I2 = 0.0%) NNTH 24 (95% CI 9 to 200 infants more have severe IVH after UCM compared to DCC), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 860 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}*For the critical maternal outcome of* ***post-partum receipt of blood transfusion****, there is* ***possible clinical harm*** *after UCM compared to DCC (OR 2.72, 95% CI 1.11 to 6.65; I2 = 0.0%; NNTH 26 (95% CI 8 to 333) 39 more/1000 (95% CI from 3 more to 118 more),* ***low certainty evidence*** *from 4 trials including 653 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2015 61}* |  |
| **Resources required**How large are the resource requirements (costs)?" |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | - There are no published cost data. However, for infants who do not require resuscitation, it is likely that umbilical cord milking and deferred cord clamping do not add cost. - For infants requiring resuscitation, additional equipment and additional training may be needed. | - Cord clamping strategies in infants need additional communication between caregivers to identify exclusion criteria and to ensure appropriate immediate neonatal management. - Training is required.  |
| **Certainty of evidence of required resources**What is the certainty of the evidence of resource requirements (costs)? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Very low○ Low○ Moderate○ High● No included studies | No data available.  | We perceive the additional cost and resource requirements to be low for both this intervention and its comparison. |
| **Cost effectiveness**Does the cost-effectiveness of the intervention favor the intervention or the comparison? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | No data available  | Although there are no published cost data, it is unlikely that umbilical cord milking compared to deferred cord clamping will add costs for infants not requiring resuscitation.  |
| **Equity**What would be the impact on health equity? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ Reduced○ Probably reduced● Probably no impact○ Probably increased○ Increased○ Varies○ Don't know | No data available. | Both the intervention and the comparison are widely available in all settings.  |
| **Acceptability**Is the intervention acceptable to key stakeholders? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | - In preterm infants <32 weeks’ gestation, who don’t require resuscitation at birth, umbilical cord milking may not be accepted for practice over deferred cord clamping because of the evidence of increased severe IVH.- In preterm infants ≥32 weeks’ gestation, umbilical cord milking may be acceptable for practice. | In preterm infants requiring resuscitation at birth, the evidence is insufficient to judge whether umbilical cord milking should/could be practiced. |
| **Feasibility**Is the intervention feasible to implement? |
| **Judgement** | **Research evidence** | **Additional considerations** |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | The intervention is feasible. {Kumbhat 2021 S0022} Umbilical cord milking appeared to be feasible in the context of the included trials.  | Current standard of care in some centers.  |

**Summary of judgements**

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

**Type of recommendation**

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

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# OVERALL Conclusions

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| Recommendation |
| **A- In preterm infants born at less than 37 weeks’ gestational age who are deemed not to require immediate resuscitation at birth, we recommend deferring clamping of the umbilical cord for at least 60 seconds. (Strong recommendation, high-certainty evidence).****B- In preterm infants born at 28+0 to 36+6 weeks’ gestational age who do not receive deferred cord clamping, we suggest umbilical cord milking as a reasonable alternative to immediate cord clamping to improve infant haematologic outcomes. Individual maternal and infant circumstances should be taken into account. (Conditional recommendation, low certainty evidence).** **C- We suggest against intact cord milking for infants born at less than 28 weeks’ gestation. (Weak recommendation; low certainty of evidence). There is insufficient evidence to make a recommendation regarding cut-cord milking in this gestational age group.****D- In preterm infants born at less than 37 weeks’ gestational age who are deemed to require immediate resuscitation at birth, there is insufficient evidence to make a recommendation with respect to cord management. (Weak recommendation; low certainty of evidence).****E- There is insufficient evidence to make recommendations on cord management for maternal, fetal, or placental conditions that were considered exclusion criteria in many studies (monochorionic multiple fetuses, congenital anomalies, placental abnormalities, alloimmunization and/or fetal anemia, fetal compromise, and maternal illness). In these situations, we suggest individualized decisions based on severity of the condition and assessment of maternal and neonatal risk. (Weak recommendation; very low certainty of evidence).****F- Whenever circumstances allow, the plan for umbilical cord management should be discussed between maternity and neonatal providers and parents before delivery, and should take into account individual maternal and infant circumstances. (Good practice point).**  |
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| Justification |
| **A-** Justification: In making a strong recommendation for deferring cord clamping for at least 60 seconds in preterm infants <37 weeks’ gestation who are deemed not to require resuscitation at birth, the NLS Task Force took into consideration the following points:1. There is **high-certainty evidence** from **20 trials** including 3260 infants showing **reduced mortality** after deferred cord clamping compared to immediate cord clamping (OR 0.68, 95% CI 0.51 to 0.91) with the number needed to treat for benefit (NNTB) 40, 95% CI 143 to 26.

The reduction in mortality appears to be robust across several participant-level and trial-level subgroups (including gestational age at birth, mode of birth, multiple birth, sex, trial year, and perinatal mortality rate).1. The evidence is derived from individual patient data (IPD) rather than trial level data which increases the quality of the meta-analysis. It allows for comprehensive checking of data integrity and provides more robust evidence overall and for secondary analyses.
2. The meta-analysis results were consistent across all prespecified sensitivity analyses, including combining individual participant data with aggregate data (from trials not providing individual participant data), different outcome definitions, excluding trials with high risk of bias, and different analysis methods (e.g, two-stage model).
3. The evidence is supported by the IPD network meta-analysis.
4. There is **moderate-certainty evidence** of **fewer blood transfusions** (OR 0.59, 95% CI 0.47 to 0.73) from **13 trials** including 1929 infants <32 weeks’ gestation and of **higher hemoglobin concentrations** within the first 24 hours after birth (mean difference (MD)= 1.26 g/dL, 95% CI 0.72 to 1.80) and from **8 trials** including 523 infants after deferred cord clamping compared to immediate cord clamping. The higher hemoglobin concentration was also replicated in preterm infants ≥32 weeks’ gestation.
5. In choosing 60 seconds or more as the recommended interval for deferred cord clamping, we took into consideration that the recommendation is for infants who are deemed not to require resuscitation at birth and that most included infants (80%) in the deferred clamping arm received cord clamping after 60 seconds or more. The OR for reducing mortality after DCC≥ 60 seconds vs. immediate cord clamping = 0.63 (95% CI 0.44-0.88, p = 0.01)- *Note that this was a post-hoc analysis.*

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

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

The reported adherence to long DCC was the lowest at 67% (compared to about 80% for medium deferral and 95% for immediate clamping, milking and short deferral).* While it is reasonable to consider this approach, the task force cannot recommend the long deferral for all infants based on this evidence. Instead, the long deferral could be considered only if there is no contraindication and if appropriate newborn stabilization can be provided on the intact cord (skilled team, proper training, appropriate equipment, enough space and ability to provide thermal management).
* More evidence is needed before recommending long DCC. Practicality, feasibility, cost-effectiveness, and equity issues need to be addressed.
1. The Task Force acknowledges that there is **moderate-certainty** evidence, from **8 trials** including 1995 infants <32 weeks' gestation showing **more hypothermia** (body temperature <36·5°C) on admission after deferred cord clamping compared to immediate cord clamping (OR 1.28, 95% CI 1.06 to 1.56) with the number need to treat to harm (NNTH) 16, 95% CI 9 to 71. There were no important differences in rates of hypothermia in infants ≥32 weeks’ gestation. Nevertheless, it is important that measures should be taken to maintain normal temperatures in all preterm infants when practising deferring cord clamping. Please refer to ILCOR statement: *Maintaining normal temperature immediately after birth in preterm infants: NLS 5101-2023. Available from* [*http://ilcor.org*](http://ilcor.org) or summarised in {Berg 2023 e187}
2. Parents report that deferred cord clamping provides a positive experience with the mothers feeling closer and more attached to their infants. {Bradshaw 2019 225}

**B-** Justification: Despite the low-certainty evidence from 18 trials including 1565 infants, that umbilical cord milking may not reduce the critical outcome of death before discharge compared to immediate cord clamping (OR 0.73, 95% CI 0.44 to 1.20), there are hematologic effects that favour umbilical cord milking compared to immediate cord clamping:1. There is **low certainty evidence** from 12 trials including 944 infants showing **higher hemoglobin concentrations (g/dL) within the first 24 hours after birth** after umbilical cord milking compared to immediate cord clamping (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL) in infants <32 weeks’ gestation. The finding is replicated in infants ≥32 weeks’ gestation.
2. There is **moderate certainty evidence** from 15 trials including 1163 infants showing **fewer transfusions of packed red blood cells** after UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I2 = 20%; NNTB 10, 95% CI 5 to 55) in infants <32 weeks’ gestation. The finding is replicated in infants ≥32 weeks’ gestation.
3. There is no evidence of increased rates of adverse effects in preterm infants <37 weeks’ gestation or their mothers after umbilical cord milking compared to immediate cord clamping.
4. There are no important differences in the critical or important outcomes after umbilical cord milking compared to deferred cord clamping in the preterm infants born at 28-36+6 weeks’ gestation.
5. The IPD meta-analyses did not distinguish between the two methods of cord milking (intact-cord and cut-cord). The intact-cord was milked (2-4 times) in 15 trials (1536 infants), whilst three trials (343 infants) milked the cut-cord once, therefore no specific recommendations are made for each method.

**C-** Justification: In making the suggestion against intact umbilical cord milking in infants <28 weeks’ gestation, the Task force took into consideration that there is **low certainty evidence** from 7 trials including 860 infants <32 weeks’ gestation that the critical outcome of **severe intraventricular haemorrhage is increased** after intact umbilical cord milking compared to deferred cord clamping (OR 2.20, 95% CI 1.13 to 4.31), however:1. The evidence from the IPD pairwise meta-analysis is driven by an RCT that was stopped prematurely because of increased rates of severe intraventricular hemorrhage in the prespecified subgroup of preterm infants <28 weeks’ gestation. {Katheria 2019 1877}
2. The following report from the same RCT that compared the outcomes of umbilical cord milking and deferred cord clamping in the other subgroup of preterm infants born at 28-32 weeks’ gestation, did not find any evidence of increased severe intraventricular hemorrhage, mortality, or other clinical outcomes after umbilical cord milking compared to deferred cord clamping. {Katheria 2023 217.e1} The later study was not included in the analysis as it was published after the iCOMP meta-analysis was completed and the CoSTR development process was started.

**D-** Justification: We could not make a recommendation regarding cord management of preterm infants who are deemed to require resuscitation at birth. 1. The pairwise IPD review reported that adherence to deferred cord clamping was low (<75% in those trials reporting adherence), mostly because of the preference of health care providers to practice immediate cord clamping or cord milking when the infant was judged to require resuscitation at birth. In other studies, the adherence was not reported. These 2 factors limit the generalizability of the meta-analysis findings and limit extension of our recommendation to non-vigorous infants and those who are deemed to require resuscitation at birth.
2. Nevertheless, there is growing evidence from animal studies and feasibility studies in human infants that supports stabilization of the infant while deferring cord clamping (resuscitation with intact cord/physiologic cord clamping/baby-directed cord clamping). This approach is also supported by sound physiological principles. {Bhatt 2013 2113, Crossley 2009 4695, Duley 2018 F6, Hooper 2015 608}
3. We are awaiting the results of studies currently underway that evaluate the resuscitation/stabilization of infants with the cord intact. These studies are expected to help us define the best way to manage these infants. Questions related to the practicality, feasibility, cost-effectiveness, and equity will need to be addressed.

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

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| Subgroup considerations |  |
| * Deferred cord clamping should still be considered in the different iCOMP study pre-specified subgroups as there is no clear evidence that gestational age at birth, multiple births (apart from mono-chorionic twins), mode of delivery, infant’s sex, study year, setting/resources level (as indicated by country’s perinatal mortality rate) influence the effect of deferred cord clamping, compared to immediate cord clamping, on the primary outcome of death before discharge. However, the certainty of evidence was low or very low due to insufficient sample size.
* No specific recommendation is made for the pre-specified subgroup analyses of whether initial resuscitation was provided at bedside with cord intact, and for the planned position of the infant relative to the placenta as the analysis could not be performed.
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| Implementation considerations |  |
| * The 3 investigated interventions; deferred cord clamping, umbilical cord milking and immediate cord clamping appear to be feasible in the context of the included trials.
* It should be noted that in many studies, infants randomized to deferred clamping may have received early clamping if they were thought to require resuscitation. For example, in the largest study{Tarnow-Mordi 2017 2445} 19.5% (146 of 748) infants in the later cord clamping group had non-adherence to their allocated study arm because of clinical concern about infant well-being. This is less likely to be the case with intact-cord milking, where the baby is more likely to have received a placental transfusion before the need for resuscitation was determined. We await the results of studies that are underway or planned that examine resuscitation with the cord intact, which may help determine the optimal umbilical cord management for infants at highest risk for mortality and neonatal morbidity.
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| Monitoring and evaluation |
| The details of cord management including the timing of clamping and initiation of breathing should be routinely recorded in clinical practice and research studies. |
| Research priorities |
| We identified the following knowledge gaps: **KNOWLEDGE GAPS:** * There are insufficient data on long-term neurodevelopment outcomes, or other post-discharge outcomes following different cord management strategies. We expect long-term data to become available from some trials currently underway.
* There are insufficient data on optimising cord management as a public health strategy to improve child health and development.
* There are insufficient data for cord management of preterm infants who are judged to require immediate resuscitation.
* There are insufficient data for cord management of preterm infants born under specific conditions, including fetal congenital anomalies, placental abnormalities, monochorionic multiple gestation, alloimmunization and/or fetal anemia, fetal compromise, maternal general anesthesia, and maternal illness.
* Further evaluation of measures to prevent hypothermia during deferred cord clamping is required.
* The optimal duration of deferred cord clamping remains uncertain. It is unclear whether it should vary with different maternal or fetal conditions.
* There are few studies of cut-cord milking as a management strategy.
* The impact of cord management on vertical transmission of infectious diseases is uncertain.
* There is a need for widely agreed nomenclature and definition of different interventions including “delayed”, “deferred”, “later”, “optimal”, and “physiologic” cord clamping, as well as “milking”, “stripping”, “intact-cord”, and “cut-cord”.
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