NLS 5051 Consensus on Science 1

COMPARISON 1: DEFERRED CORD CLAMPING (DCC) COMPARED TO IMMEDIATE CORD CLAMPING (ICC)

The pairwise IPD MA identified **21 eligible studies** including 3,292 infants. Median sample size was 65 (interquartile range [IQR] 40-101). Median (IQR) gestational age at birth was 29 (27-33) weeks. DCC ranged from 30 to ≥180 seconds (some trials encouraging deferrals up to 5 minutes where feasible). For ICC, most trials (n=14) specified clamping within 10 seconds. Of all infants, 61% were born by cesarean delivery, 25% were multiples, and 56% were male. Trials were conducted in high-income (9/21), upper-middle-income (5/21) and lower-middle-income (7/21) countries as defined by world bank country classification (https://blogs.worldbank.org/opendata/new-world-bank-group-country-classifications-income-level-fy24). {Backes 2016 35, Chu 2011 S201, Datta 2017 418, Duley 2018 F6, Finn 2019 121, García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Liu 2018 , Oh 2011 S68, Okulu 2022 838444, Rana 2018 655, Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Salae 2016 , Tarnow-Mordi 2017 2445, Yunis 2021 157}

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) 0.51-0.91) {Backes, 2016, 35;Chu, 2011, S502;Datta, 2017, 418-424;Duley, 2018, F6-14;Finn, 2019, 121-126.e2;García, 2023 #44;Gharehbaghi, 2020, 11095-11101;Gregoraci, 2023, 203-207;Kamal, 2019, 66-87;Liu, 2018 #407;Oh, 2011, S68;Okulu, 2022, 838444;Rana, 2018, 655-661;Ranjit, 2015, 29-34;Ruangkit, 2019, 156-163;Sahoo, 2020, 881-889;Salae, 2016, S159-65;Tarnow-Mordi, 2017, 2445-2455;Yunis, 2021, 157-166}; number needed to treat for benefit (NNTB) 40, 95% CI 143 to 26; I^2 = 0%; 25 fewer infants per 1000 died before discharge [95% CI, 38 to 7 fewer per 1000]), **high certainty evidence** from 20 trials including 3,263 infants. {Backes 2016 35, Chu 2011 S201, 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 , Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Salae 2016 , Tarnow-Mordi 2017 2445, Yunis 2021 157}

Relevant outcomes for the subgroup of preterm infants <32 weeks' gestation

For the important outcome of ***any intraventricular hemorrhage****,* **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.98, 95% CI 0.79 to 1.22; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 13 trials involving 2124 infants. {Backes 2016 35, Chu 2011 S502, Duley 2018 F6, Finn 2019 121, Gharehbaghi 2020 11095, Gregoraci 2023 203, Oh 2011 S68, Rana 2018 655, Ranjit 2015 29, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the critical outcome of ***severe intraventricular hemorrhage*** *(grade III, IV),* **clinical benefit or harm cannot be determined** for DCC compared to ICC, **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 11 trials involving 2096 infants (OR 0·83, 95% CI 0·54 to 1·26; I^2 = 0%). {Backes 2016 35, Chu 2011 S502, Duley 2018 F6, Finn 2019 121, Gharehbaghi 2020 11095, Gregoraci 2023 203, Oh 2011 S68, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the critical outcome of ***bronchopulmonary dysplasia*** *(supplemental oxygen at 36 weeks' postmenstrual age)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.06, 95% CI 0·87 to 1.30; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of

bias and imprecision) from 10 trials including 1929 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 121, Gregoraci 2023 203, Kugelman 2007 307, Oh 2011 S68, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the critical outcome of **necrotizing enterocolitis** (Bell staging greater than or equal to stage 2 or per author's definition)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.82, 95% CI 0·59 to 1·13; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 11 trials including 2052 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 121, García 2023 , Gregoraci 2023 203, Kugelman 2007 307, Oh 2011 S68, Ruangkit 2019 156, Sahoo 2020 881, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the critical outcome of **patent ductus arteriosus receiving medical treatment***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.91, 95% CI 0.73-1.19; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 1928 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 121, Gregoraci 2023 203, Kugelman 2007 307, Oh 2011 S68, Ruangkit 2019 156, Tarnow-Mordi 2017 2445}

*For the critical outcome of **patent ductus arteriosus receiving surgical treatment***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.93, 95% CI 0.73-1.15; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 1678 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 121, Gregoraci 2023 203, Kugelman 2007 307, Oh 2011 S68, Tarnow-Mordi 2017 2445}

*For the critical outcome of **late onset sepsis** (sepsis that occurred at least 72 hours after birth or as per author's definition)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.93, 95% CI 0·74 to 1·17; I^2 = 0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 9 trials including 2052 infants. {Chu 2011 S201, Duley 2018 F6, Finn 2019 121, Gregoraci 2023 203, Oh 2011 S68, Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

For the important outcomes of ***hemoglobin concentrations (g/dL) and hematocrit values (%)** within the first 24 hours after birth*, hemoglobin concentrations and hematocrit values are **probably higher** after DCC compared to ICC (mean difference (MD)= 0.88 g/dL, 95% CI 0.52 to 1.24 (corresponds to MD of 8.8 mg/L, 95% CI 5.2 to 12.4), I^2= 0% and MD= 2.69%, 95% CI 1.43 to 3.95%; I^2 = 0% respectively), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 523 infants reporting ***hemoglobin concentrations*** {Chu 2011 S201, 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 the important outcome of **receiving transfusion of red blood cells***, there is **probable clinical benefit** (OR 0.59, 95% CI 0.47 to 0.73; I^2 = 0%; NNTB=7, 95% CI 5 to 12; 131 fewer infants per 1000 received blood transfusion after DCC than after ICC, [95% CI, 186 fewer to 78 fewer]), **Moderate certainty evidence** (downgraded for serious risk of bias) from 13 trials including 1929 infants. {Chu 2011 S201, 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 outcome of **hypothermia on admission** (body temperature <36·5°C)*, there is **probable clinical harm** as more infants developed hypothermia after DCC compared to ICC (OR 1.28, 95% CI 1.06 to 1.56; I^2 = 0%; NNTH 16, 95% CI 9 to 71; 62 more infants per 1000 were hypothermic on admission, [95% CI, 14 more to 111 more]), **moderate certainty evidence** (downgraded for serious risk of bias) from 8 trials including 1995 infants. {Duley 2018 F6, Finn 2019 121, García 2023 , Kugelman 2007 307, Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the important outcome of **body temperature on admission**,* the temperature is **possibly lower** after DCC compared to ICC clamping (MD -0.13, 95% CI -0.20 to -0.06; I^2 =58.4), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 8 trials including 1995 infants.{Duley F6, Finn 121, García , Kugelman 307, Rana 655, Ruangkit 156, Tarnow-Mordi 2445, Yunis 157}. *Note that the GRADE certainty of evidence was assessed post-hoc.*

*For the important outcome of **respiratory support after birth**,* **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 2.01, 95% CI 0.58 to 7.03), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) from 11 trials including 1845 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 **receiving inotropic support for hypotension** within the first 24 hours after birth*, **clinical benefit or harm cannot be determined** from DCC compared to ICC (OR 0.85, 95% CI 0.33 to 2.21), **very low certainty evidence** (downgraded for serious risk of bias and very serious of imprecision) from 5 trials including 172 infants. {Finn 2019 121, Gregoraci 2023 203, Oh 2011 S68, Ruangkit 2019 156, Yunis 2021 157}

Relevant outcomes for the subgroup of preterm infants ≥32 weeks' gestation

Hemoglobin concentrations within the first 24 hours after birth *(important outcome),* are **probably higher** after DCC compared to ICC (MD 1.26 g/dL, 95% CI 0.72 to 1.80 (corresponds to MD of 12.6 mg/L, 95% CI 7.2 to 18.2), I^2= 0%, **low certainty evidence** (downgraded for risk of bias and inconsistency) from 7 trials including 302 infants. {García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Liu 2018 , Okulu 2022 838444, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*

Hematocrit values within the first 24 hours after birth are **probably higher** after DCC compared to ICC (MD 3.69%, 95% CI 2.43 to 4.95%; I^2 = 0%), **moderate certainty evidence** (downgraded for risk of inconsistency) from 8 trials including 420 infants {García 2023 , Gharehbaghi 2020 11095, Kugelman 2007 307, Liu 2018 , Okulu 2022 838444, Ranjit 2015 29, Ruangkit 2019 156, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*

*For the important outcome of **hypothermia on admission** (body temperature <36·5°C)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.95, 95% CI 0.51 to 1.79; I^2 = 0%), **very low certainty evidence** (downgraded for serious risk of imprecision and inconsistency) from 8 trials including 396 infants. {Duley 2018 F6, García 2023 , Kugelman 2007 307, Liu 2018 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the important outcome of **body temperature on admission,*** **clinical benefit or harm cannot be determined** for DCC compared to ICC (MD -0.03, 95% CI -0.04 to 0.10; I^2= 0%), **moderate certainty evidence** (downgraded for risk of bias) from 8 trials including 396 infants. {Duley 2018

F6, García 2023 , Kugelman 2007 307, Liu 2018 , Rana 2018 655, Ruangkit 2019 156, Tarnow-Mordi 2017 2445, Yunis 2021 157} *Note that the GRADE certainty of evidence was assessed post-hoc.*

Relevant maternal outcomes:

*For the critical outcome **maternal mortality**,* an OR was **not estimable** (no reported death after deferred cord clamping or immediate cord clamping).

*For the critical maternal outcome of **postpartum hemorrhage** (blood loss >500 ml, or as estimated by the investigator)*, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.95, 95% CI 0.49 to 1.83; I^2 = 13%) **very low certainty evidence** (downgraded for serious risk bias and very serious risk of imprecision) from 9 trials including 853 mothers. {Duley 2018 F6, Finn 2019 121, Gregoraci 2023 203, Kamal 2019 66, Liu 2018 , Ranjit 2015 29, Ruangkit 2019 156, Salae 2016 , Yunis 2021 157}

*For the critical maternal outcome of **post-partum blood transfusion,** **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.74, 95% CI 0.41 to 1.85; I^2 = 9.7%), **very low certainty evidence** from 8 trials including 2017 mothers. {Duley 2018 F6, Finn 2019 121, Gregoraci 2023 203, Liu 2018 , Sahoo 2020 881, Salae 2016 , Tarnow-Mordi 2017 2445, Yunis 2021 157}

*For the critical maternal outcome of **manual removal of the placenta***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 0.99, 95% CI 0.55 to 1.80; I^2 = 0%), **very low certainty evidence** (downgraded for serious risk bias and very serious risk of imprecision) from 5 trials including 657 mothers. {Duley F6, Finn 121, Kamal 66, Liu 2018 , Salae }

*For the critical maternal outcome of **postpartum infection***, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.00, 95% CI 0.59 to 1.70), **very low** certainty evidence (downgraded for serious risk of bias and very serious risk of imprecision) from **4 trials** including 448 mothers. {Duley 2018 F6, Finn 2019 121, Liu 2018 , Salae 2016 } *Note that the GRADE certainty of evidence was assessed post-hoc.*

*For the important maternal outcome of **administration of uterotonic agents***, the effect was **not estimable**.

Post hoc analysis:

*For the important outcome of **hyperbilirubinemia treated with phototherapy*** for infants <32 weeks' gestation, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.7, 95% CI 1.00 to 2.90, I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk of bias, indirectness and imprecision) from 12 trials including 585 infants. {Backes 2016 35, Duley 2018 F6, Finn 2019 121, García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 307, Rana 2018 655, Ranjit 2015 29, Sahoo 2020 881, Yunis 2021 157}

*For the important outcome of **hyperbilirubinemia treated with phototherapy*** for infants ≥32 weeks' gestation, **clinical benefit or harm cannot be determined** for DCC compared to ICC (OR 1.12, 95% CI 0.79 to 1.58, I^2 = 30.8%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 11 trials including 801 infants. {García 2023 , Gharehbaghi 2020 11095, Gregoraci 2023 203, Kamal 2019 66, Kugelman 2007 307, Liu 2018 , Okulu 2022 838444, Ranjit 2015 29, Ruangkit 2019 156, Salae 2016 , Yunis 2021 157}

COMPARISON 2: UMBILICAL CORD MILKING (UCM) COMPARED TO IMMEDIATE CORD CLAMPING (ICC).

The pairwise IPD MA identified 18 trials including 1565 infants. Median sample size was 60 [IQR] 45-122. Median (IQR) gestational age at birth was 29 (27-31) weeks. 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. Of all infants, 64% were born by cesarean section, 13% were multiples, and 56% were male. Trials were conducted in high-income (n=10/18), upper-middle-income (n=4/18) and lower-middle-income (4/18) countries. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Okulu 2022 838444, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

For the critical outcome of ***death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.73, 95% CI 0.44 to 1.20; I^2 = 7.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 18 trials including 1565 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Gharehbaghi 2020 11095, Hosono 2008 1359, Hosono 2015 , 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 ***any intraventricular hemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.02, 95% CI 0.76 to 1.38; I^2 = 8.6%), **moderate certainty evidence** (downgraded for serious imprecision) from 15 trials including 1069 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Gharehbaghi 2020 11095, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Ram Mohan 2018 88, Tanthawat }

For the critical outcome of ***severe intraventricular hemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.78, 95% CI 0.45 to 1.35; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 14 trials including 939 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Gharehbaghi 2020 11095, Hosono 2008 1359, Hosono 2015 , Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat }

For the critical outcome of ***bronchopulmonary dysplasia,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.96, 95% CI 0.63 to 1.47; I^2 = 0.0%), **low certainty evidence** (downgraded for very serious imprecision) from 12 trials including 836 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Josephsen 2022 436, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

For the critical outcome of ***necrotizing enterocolitis,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.90, 95% CI 0.52 to 1.56; I^2 = 3.7%), **low certainty evidence** (downgraded for very serious imprecision) from 13 trials including 1047 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat , Xie 2022 31}

For the important outcome of ***Patent ductus arteriosus receiving medical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.25, 95% CI 0.88 to 1.76; I^2 = 0.0%)**, very low certainty evidence** (downgraded for serious risk of bias and very serious imprecision) from 12 trials including 893 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Tanthawat }
For the critical outcome of ***Patent ductus arteriosus receiving surgical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.84, 95% CI 0.46 to 1.52; I^2 = 0.0%), **low** certainty evidence (downgraded for serious risk of bias and imprecision) from **11 trials** including 888 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912}
For the critical outcome of ***late-onset sepsis*****, clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.07, 95% CI 0.76 to 1.51; I^2 = 39.2%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 12 trials including 977 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Hosono 2015 , Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Ram Mohan 2018 88, Xie 2022 31}
For the important outcome of severe ***retinopathy of prematurity*****, clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.05, 95% CI 0.73 to 1.51; I^2 = %), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) from 7 trials including 762 infants. {Alan , El-Naggar F145, Hosono 1359, Hosono 2015 , Josephsen 436, Ram Mohan 88, Shen 912}
Hemoglobin concentrations (g/dL) within the first 24 hours after birth (*important outcome)* **were possibly higher** after UCM compared to ICC (MD 0.45 g/dL, 95% CI 0.17 to 0.73 g/dL; I^2 = 66.6%), **low certainty evidence** (downgraded for serious risk of bias and inconsistency) from 12 trials including 944 infants. {Alan 2014 , El-Naggar 2019 F145, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Shen 2022 912, Tanthawat } *Note that the GRADE certainty of evidence was assessed post-hoc.*
Hematocrit values (%) within the first 24 hours after birth **were possibly higher** after UCM compared to ICC (MD 1.71%, 95% CI 0.78 to 2.64%; I^2 = 36.9%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 12 trials including 900 infants. {Alan 2014 , 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 } *Note that the GRADE certainty of evidence was assessed post-hoc.*
For the important outcome of ***receiving red blood cell transfusions,*** there is **probable clinical benefit** for UCM compared to ICC (OR 0.69, 95% CI 0.51 to 0.93; I^2 = 20%; NNTB 10, 95% CI 5 to 55; 92/1000 fewer infants received red cell transfusion after UCM compared to ICC, 95% CI 167 fewer to 18 fewer), **moderate certainty evidence** (downgraded for serious risk of bias) from 15 trials including 1163 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, George 2022 291, Hosono 2008 1359, Hosono 2015 , 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 ***hypothermia on admission,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.95, 95% CI 0.69 to 1.31; I^2 = 52.4%), **very low certainty evidence** (downgraded for serious inconsistency and very serious imprecision) from 8 trials including 688 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Hosono 2015 , Josephsen 2022 436, Katheria 2014 e94085, Lago Leal 2019 57, Mercer 2016 50, Ram Mohan 2018 88, Tanthawat }
For the important outcome of ***body temperature on admission,*** **clinical benefit or harm cannot be determined** for UCM compared to ICC (MD -0.03, 95% CI -0.12 to 0.06; I^2 = 41.3), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 688 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Katheria 2014 e94085, Mercer 2016 50, Ram Mohan 2018 88, Xie 2022 31} *Note that the GRADE certainty of evidence was assessed post-hoc.*
For the important outcome of ***receiving inotropic support for hypotension*** *within the first 24 hours after birth*, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 0.89, 95% CI 0.57 to 1.38), **very low certainty evidence** (downgraded for serious risk of bias and very serious of imprecision) from 10 trials including 827 infants. {Alan 2014 , Chellappan 2022 A178, El-Naggar 2019 F145, Finn 2019 121, Hosono 2008 1359, Hosono 2015 , 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.*
Relevant outcomes for the subgroup of preterm infants ≥32 weeks' gestation:
Hemoglobin concentrations (g/dL) within the first 24 hours after birth (*important outcome)* were **possibly higher after** UCM compared to ICC (MD 1.69 g/dL, 95% CI 0.90 to 2.48 g/dL); I^2 = 67.5%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 5 trials including 143 infants. {George 2022 291, Gharehbaghi 2020 11095, Lago Leal 2019 57, Okulu 2022 838444, 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 4.47%, 95% CI 2.85 to 6.09%); I^2 = 55.9%), **low certainty evidence** (downgraded for serious risk of bias and indirectness) from 7 trials including 332 infants. {George 2022 291, Gharehbaghi 2020 11095, Lago Leal 2019 57, Okulu 2022 838444, Ram Mohan 2018 88, Tanthawat , Xie 2022 31} *Note that the GRADE certainty of evidence was assessed post-hoc.*
For the important outcome of ***receiving transfusion of red blood cells*****,** there is **possible clinical benefit** for UCM compared to ICC (OR 0.31, 95% CI 0.09 to 0.99); I^2 = 0.0%; NNTB 22, 95% CI 16 to 1000; 44/1000 fewer infants received blood transfusion with UCM compared to ICC, 95% CI 59 fewer to 1 fewer), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 6 trials including 330 infants. {George 2022 291, Lago Leal 2019 57, Okulu 2022 838444, Ram Mohan 2018 88, Tanthawat , Xie 2022 31}
For the important outcome of ***hypothermia on admission***, **clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.57 (0.84 to 2.93) I2 = 28.3%), **very low certainty evidence** (downgraded for very serious risk of bias and extremely serious imprecision) from 2 trials including 190 infants. {Ram Mohan 2018 88, Xie 2022 31}
Temperature on admission *(important outcome) was* **possibly lower** after UCM compared to ICC (MD -0.20, 95% CI -0.35 to -0.05; I^2 = 81.4%, **low certainty evidence** (downgraded for

serious risk of bias and inconsistency) from 2 trials including 190 infants. {Ram Mohan 2018 88, Xie 2022 31} *Note that the GRADE certainty of evidence was assessed post-hoc.*

Relevant Maternal Outcomes

*For the critical outcome **maternal mortality**,* an OR was not estimable (only one death after ICC).

*For the critical outcome of **post-partum hemorrhage**, **post-partum infection**, **post-partum blood transfusion**,* and ***manual removal of the placenta***, the effect size was not estimable.

Post hoc analysis:

*For the important outcome of **hyperbilirubinemia treated with phototherapy** for infants <32 weeks' gestation*, **clinical benefit or harm cannot be determined** for UCM clamping compared to ICC (OR 1.09, 95% CI 0.73 to 1.63, I^2 = 3.2%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 12 trials including 1097 infants. {Alan 2014 , El-Naggar 2019 F145, Finn 2019 121, Gharehbaghi 2020 11095, Hosono 2015 , Katheria 2014 e94085, Lago Leal 2019 57, March 2013 763, Mercer 2016 50, Shen 2022 912, Tanthawat , Xie 2022 31}

*For the important outcome of **hyperbilirubinemia treated with phototherapy** for infants* ≥32 *weeks' gestation***, clinical benefit or harm cannot be determined** for UCM compared to ICC (OR 1.19, 95% CI 0.71 to 1.98, I^2 = 0.0), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 5 trials including 350 infants. {George 2022 291, Gharehbaghi 2020 11095, Lago Leal 2019 57, Okulu 2022 838444, Xie 2022 31}

COMPARISON 3: UMBILICAL CORD MILKING (UCM) COMPARED TO DEFERRED CORD CLAMPING (DCC)

The pairwise IPD MA identified 15 trials (1655 infants). Median sample size was 44 (IQR 36-171). Median (IQR) gestational age at birth was 30 (28-33) weeks. 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. Off all infants, 64% were born by cesarean delivery, 15% were multiples, and 54% were male. Trials were conducted in high-income (8/15), upper-middle-income (3/15) and lower-middle-income (4/15) countries. {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 critical outcome of **death before discharge***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.95, 95% CI 0.59 to 1.53; I^2 = 0.0%), **low certainty evidence** (downgraded for very serious imprecision) from **12 trials** including 1303 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}

Relevant outcomes for the subgroup of preterm infants <32 weeks' gestation:

*For the important outcome of **any intraventricular hemorrhage,** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.04, 95% CI 0.75 to 1.44; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 9 trials including 1022 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, Sura 2020 S612, Trongkamonthum 2018 22}

For the critical outcome of ***severe intraventricular hemorrhage,*** there is **possible clinical harm** after UCM compared to DCC (OR 2.20, 95% CI 1.13 to 4.31; I^2 = 0.0%) NNTH 24 (95% CI 9 to 200 infants more have severe IVH after UCM compared to DCC), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 860 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Pratesi 2018 364, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}

For the critical outcome of ***bronchopulmonary dysplasia,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.02, 95% CI 0.56 to 1.87; I^2 = 0.0%,), **very low certainty evidence** (downgraded for very serious risk of bias and serious imprecision) from 4 trials including 293 infants. {Finn 2019 121, Katheria 2015 61, Rabe 2011 205, Trongkamonthum 2018 22}

For the critical outcome of ***necrotizing enterocolitis,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.95, 95% CI 0.55 to 1.66; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 976 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205, Trongkamonthum 2018 22}

For the important outcome of ***patent ductus arteriosus receiving medical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.88, 95% CI 0.56 to 1.37; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 5 trials including 631 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2015 61, Trongkamonthum 2018 22}

For the critical outcome of ***patent ductus arteriosus receiving surgical treatment,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.43, 95% CI 0.63 to 3.25; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 5 trials including 631 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2019 1877, Trongkamonthum 2018 22}

For the critical outcome of ***late-onset sepsis,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.91, 95% CI 0.57 to 1.48; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 6 trials including 787 infants. {Al-Wassia 2015 18, Finn 2019 121, Katheria 2019 1877, Sura 2020 S612, Trongkamonthum 2018 22}

For the important outcome of ***retinopathy of prematurity***, **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.73, 95% CI 0.43 to 1.24; I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) from 6 trials including 753 infants. {Al-Wassia 2015 18, Atia 2022 714, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205}

For the important outcome of ***hemoglobin concentrations (g/dL)*** within 24 hours after birth**, clinical benefit or harm cannot be determined** for UCM compared to DCC (MD 0.28g/dL mg/dL, 95% CI -0.04 to 0.60 g/dL); I^2 = 3.3%), **low certainty evidence** (downgraded for serious

risk of bias and imprecision) from 9 trials including 867 infants. {Atia 2022 714, Finn 2019 121, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Rabe 2011 205, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **hematocrit (%)** within 24 hours after birth**,** **clinical benefit or harm cannot be determined*** for UCM compared to DCC (MD 0.67%, 95% CI -0.39 to 1.73%; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 637 infants. {Atia 2022 714, Gharehbaghi 2020 11095, Katheria 2019 1877, Ling 2021 332, Rabe 2011 205, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **receiving transfusions of red cells,** **clinical benefit or harm cannot be determined*** for UCM compared to DCC (OR 1.07, 95% CI 0.77 to 1.50; I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 985 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Ling 2021 332, Rabe 2011 205, Trongkamonthum 2018 22}

*For the important outcome of **hypothermia on admission,** **clinical benefit or harm cannot be determined*** for UCM compared to DCC (OR 0.90, 95% CI 0.64 to 1.26; I^2 = 34.1%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 7 trials including 875 infants. {Atia 2022 714, Finn 2019 121, Katheria 2019 1877, Katheria 2015 61, Pratesi 2018 364, Rabe 2011 205, Trongkamonthum 2018 22}

Relevant outcomes for the subgroup of preterm infants ≥32 weeks' gestation:

*For the important outcome of **hemoglobin concentrations (g/dL)*** within 24 hours after birth, **clinical benefit or harm cannot be determined** for UCM compared to DCC (MD -0.12g/dL mg/dL, 95% CI -0.50 to 0.26 g/dL); I^2 = 0.0%), **low certainty evidence** (downgraded for serious risk of bias and imprecision) from 8 trials including 456 infants. {Atia 2022 714, Gharehbaghi 2020 11095, Ling 2021 332, Okulu 2022 838444, Rabe 2011 205, Schober 2018 NCT03748914, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **hematocrit values (%)*** within 24 hours**, clinical benefit or harm cannot be determined** for UCM compared to DCC (MD -0.53%, 95% CI -1.66 to 0.60%); I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk of bias and imprecision) from 9 trials including 469 infants. {Atia 2022 714, Gharehbaghi 2020 11095, Ling 2021 332, Mangla 2020 1119, Okulu 2022 838444, Rabe 2011 205, Schober 2018 NCT03748914, Sura 2020 S612, Trongkamonthum 2018 22}

*For the important outcome of **receiving red cell transfusion**,* **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.67, 95% CI 0.60 to 4.60); I^2 = 0.0%), **very low certainty evidence** (downgraded for very serious risk of bias and imprecision) from 8 trials including 251 infants. {Al-Wassia 2015 18, Atia 2022 714, Ling 2021 332, Okulu 2022 838444, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}

*For the important outcome of **hypothermia on admission,** **clinical benefit or harm cannot be determined*** for UCM compared to DCC (OR 1.40 (0.54 to 3.69) I2 = 0.0%), **very low certainty evidence** (downgraded for very serious risk of bias and imprecision) from 5 trials including 209 infants. {Atia 2022 714, Katheria 2015 61, Rabe 2011 205, Schober 2018 NCT03748914, Trongkamonthum 2018 22}

Maternal outcomes:

*For the critical outcome **maternal mortality**,* an OR could not be estimable (only one death after UCM and after DCC).

*For the critical outcome of **post-partum hemorrhage,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 1.29, 95% CI 0.48 to 3.67), **very low certainty evidence** (downgraded for serious risk of bias and very serious risk of imprecision) imprecision from 5 trials including 632 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Sura 2020 S612, Trongkamonthum 2018 22}

*For the critical maternal outcome of **post-partum receipt of blood transfusion***, there is **possible clinical harm** after UCM compared to DCC (OR 2.72, 95% CI 1.11 to 6.65; I^2 = 0.0%; NNTH 26 (95% CI 8 to 333) 39 more/1000 (95% CI from 3 more to 118 more), **low certainty evidence** from 4 trials including 653 mothers. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Katheria 2015 61}

*For the critical maternal outcome of **manual removal of the placenta,*** **clinical benefit or harm cannot be determined** from UCM compared to DCC (OR 0.21, 95% CI 0.04 to 0.99; I^2 = 0.0%), **very low certainty evidence** (downgraded for serious risk bias and very serious risk of imprecision) from **3 trials** including 341 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121}

*For the important maternal outcome of **administration of uterotonic agents***, the effect was not estimable.

Post hoc analysis:

*For the important outcome of **hyperbilirubinemia treated with phototherapy** for infants <32 weeks' gestation***, clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 0.73, 95% CI 0.48 to 1.11, I^2 = 16.5%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from 8 trials including 1080 infants. {Al-Wassia 2015 18, Atia 2022 714, Finn 2019 121, Gharehbaghi 2020 11095, Katheria 2019 1877, Katheria 2015 61, Rabe 2011 205, Sura 2020 S612}

*For the important outcome of **hyperbilirubinemia treated with phototherapy*** for *infants ≥32 weeks' gestation**,*** **clinical benefit or harm cannot be determined** for UCM compared to DCC (OR 101, 95% CI 0.62 to 1.66, I^2 = 36.1%), **very low certainty evidence** (downgraded for serious risk of bias and indirectness and very serious risk of imprecision) from **8 trials** including 448 infants. {Al-Wassia 2015 18, Atia 2022 714, Garg 2020 CTRI/2020/02/023364, Gharehbaghi 2020 11095, Okulu 2022 838444, Pratesi 2018 364, Schober 2018 NCT03748914, Sura 2020 S612}

SUBGROUP ANALYSES

Several participant-level and hospital/trial-level subgroups were pre-specified using a test of interaction to assess differential treatment effects ***for the primary outcome of death*** before discharge. There was no evidence of differential treatment effects for any of the pre-specified subgroups, but **certainty was low or very low** due to insufficient sample size. Pre-specified participant-level subgroups included:

- ***Gestational age at birth**:* Gestational age at birth did not influence the effect of DCC on mortality before discharge when:
    - DCC was received compared to ICC (interaction OR (iOR) 0.93 95% CI 0.78 to 1.11), **high certainty evidence** from 13 trials.
    - UCM was received compared to ICC (iOR 1.01 95% CI 0·97 to1·05), **low certainty evidence** from 11 trials.

    - UCM was received compared to DCC (iOR 1.08 95% CI 0.80 to1.47), **low certainty evidence** from 7 trials.
- ***Multiple birth (singleton/multiple pregnancy)****:* Multiple births did not influence the effect of DCC on mortality before discharge when:
    - DCC was received compared to ICC (OR 1.11 95% CI 0.49 to 2.50), **low certainty evidence** from 4 trials.
    - UCM was received vs ICC (iOR 1.52 95% CI 0.37 to 6.32), **very low certainty evidence** from 7 trials.
    - UCM was received vs DCC (iOR 1.26 95% CI 0.34 to 4.67), **very low certainty evidence** from 4 trials.
- ***Mode of birth (cesarean/ vaginal):*** Mode of delivery did not influence the effect of DCC on mortality before discharge when:
    - DCC was received compared to ICC (iOR 0.69 95% CI 0.39-1.22), **low certainty evidence** from 4 trials
    - UCM was received compared to ICC (iOR 0.59 95% CI 0.20 to 1.75), **very low certainty evidence** from 13 trials
    - UCM was received compared to DCC (iOR 0.83 95% CI 0.33 to 2.12), **low certainty evidence** from 8 trials.
- ***Study start (year):*** Study year did not influence the effect of DCC on mortality before discharge when**:**
    - DCC was received compared to ICC (iOR 1.00 95% CI 0.92 to 1.08), **very low certainty evidence** from 13 trials.
    - UCM was received vs ICC (iOR 1.02 95% CI 0.99 to 1.04). Evidence of **low** certainty from 8 trials.
    - UCM was received vs DCC (iOR 0.89 95% CI 0.74 to 1.08).
- ***Country's perinatal mortality rate (per 1,000***): Country's perinatal mortality rate did not influence the effect of DCC on mortality before discharge when:
    - DCC was received compared to ICC (iOR 1.00 95% CI 0.97 to 1.02), **low certainty evidence** from 13 trials.
    - UCM was received vs ICC (iOR 0.98 95%CI 0.85 to 1.12), **very low certainty evidence** from 13 trials.
    - UCM was received vs DCC (iOR 0.98 95% CI 0.88 to 1.09), **low** certainty evidence from 8 trials.
- ***Sex (male/female)***: (note that this subgroup analysis was conducted post-hoc). Infant's sex did not influence the effect of DCC on mortality before discharge when:
    - DCC was received compared to ICC (iOR 1.00 95% CI 0.64 to 1.86), evidence from 11 trials,
    - UCM was received vs ICC (iOR 1.22 95% CI 0.44 to 3.37), evidence from 11 trials,
    - UCM was received vs DCC (iOR 0.54 95% CI 0.20 to 1.48), evidence from 7 trials.

Pre-specified subgroup analyses of **whether initial resuscitation was provided at bedside with cord intact, planned position of the infant relative to the placenta, and non-linear interactions of gestational age** could not be performed due to insufficient data or convergence issues.