THE LANCET
Child & Adolescent Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Minotti C, Jost K, Aghlmandi S, et al. All-cause mortality and infection-related outcomes of hospital-initiated kangaroo care versus conventional neonatal care for low-birthweight infants: a systematic review and meta-analysis. *Lancet Child Adolesc Health* 2025; published online May 26. https://doi.org/10.1016/S2352-4642(25)00130-0.

Appendix

1. Search strategy: Full search terms for each database

Last search ran on 26th February 2025 (since 1st January 2013)

Medline (407 entries)

1 (exp "infant, newborn"/ or (newborn or new-born or preterm or premature or "low birth weight" or underweight or LBW or VLBW or infan* or neonat*).tw,kf.) and (exp "Kangaroo-Mother Care Method"/ or "kangaroo care".tw,kf. or "kangaroo mother care".tw,kf. or "kangaroo mother method".tw,kf. or "skin to skin".tw,kf.) and (randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ti,ab. OR placebo.ti,ab. OR randomly.ti,ab. OR trial.ti. NOT (exp animals / NOT exp humans /))

2 limit 1 to yr="2013 -Current"

Embase (504 entries)

1 (exp newborn/ or exp low birth weight/ or (newborn or neonate or preterm or premature or "low birth weight" or LBW or VLBW or infan* or neonat*).tw,kf.) and (exp "Kangaroo Care"/ or "kangaroo care".tw,kf. or "kangaroo mother care".tw,kf. or "skin to skin".tw,kf. or "skin to skin contact".tw,kf.) and (randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ti,ab. OR placebo.ti,ab. OR randomly.ti,ab. OR trial.ti. NOT (exp animals / NOT exp humans /))

2 limit 1 to yr="2013 -Current"

CENTRAL (896 entries)

[mh "infant, newborn"] OR [mh newborn] OR newborn:ti,ab,kw OR neonate:ti,ab,kw OR preterm:ti,ab,kw OR premature:ti,ab,kw OR "low birth weight":ti,ab,kw OR LBW:ti,ab,kw OR VLBW:ti,ab,kw OR infan*:ti,ab,kw OR neonat*:ti,ab,kw) AND ([mh "Kangaroo-Mother Care Method"] OR "kangaroo care":ti,ab,kw OR "kangaroo mother care":ti,ab,kw OR "skin to skin":ti,ab,kw OR "skin to skin contact":ti,ab,kw

Publication years 2013-2025

Web of Science (468 entries)

(ALL="infant, newborn" OR TS=(newborn OR new-born OR preterm OR premature OR "low birth weight"OR underweight OR LBW OR VLBW OR infan*OR neonat*)) AND (ALL="Kangaroo-Mother Care Method" OR TS="kangaroo care" OR TS="kangaroo mother care" OR TS="kangaroo mother method" OR TS="skin to skin") AND (ALL="randomized controlled trial" OR ALL="controlled clinical trial" OR (TI=randomized OR AB=randomized) OR (TI=placebo OR AB=placebo) OR (TI=randomly OR AB=randomly) OR TI=trial NOT (ALL=animals NOT ALL=humans))

Publication years 2013-2025

Search narrative

RCT Filter for Embase: We opted for the less sensitive SIGN filter instead of the Glanville et al. 2019 YHEC RCT Filter that is currently used to populate the CENTRAL database. Note: CENTRAL was searched in parallel with a translated search string.

2. Risk of bias assessment

The risk of bias assessment was performed according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB2), for each included study (see Table S2). The template for completion is provided at the end of this document.

3. GRADE approach for quality of the evidence

Two authors independently assessed the quality of the evidence for primary and secondary outcomes. We considered evidence from randomized controlled trials as high quality, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), inconsistency across studies, indirectness of the evidence, imprecision of estimates and presence of publication bias.

According to the GRADE approach we considered the quality of the evidence to be:

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

4. PRISMA Checklist

The PRISMA 2020 checklist is provided at the end of this document.

5. Supplementary Figures and Tables

Figure S1. Heatmap of World Bank Group country classifications by number of records/income level at the time of study publication

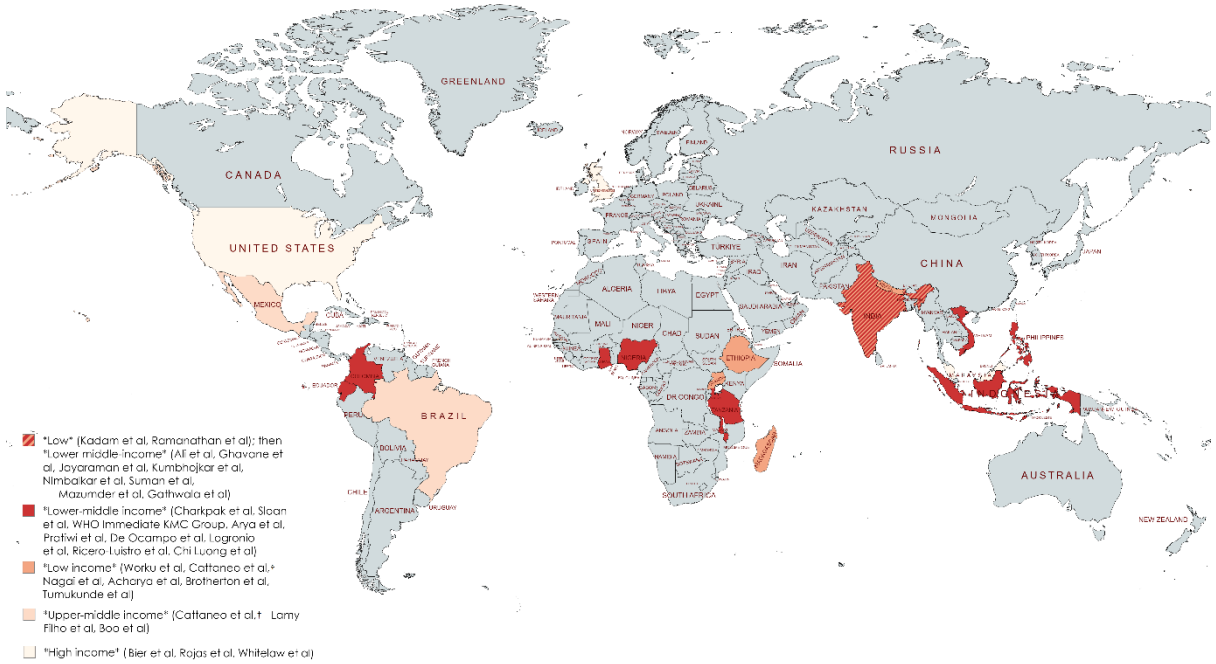


Table S1. Age at enrolment, further characteristics of KC and length of hospital stay

First author and Publication Year	Mean age at enrolment (h)		Median time to K(M)C initiation (h)		Mean/median† K(M)C duration h/day		Mean length of stay (days)		Median length of stay (days)	
	Intervention	Control (if KC provided)	Intervention	Control (if KC provided)	Intervention	Control (if KC provided)	Intervention	Control (if KC provided)	Intervention	Control (if KC provided)
Acharya, 2014[31]	..	..	..	..	..	..	**16.13***	**13.14***	..	..
Ali, 2009[32]	112.8	..	..	..	6.3	..	**13.7***	**15***	..	..
Arya, 2023[10]	..	..	1.3	53.6	20.2†	19†	14.9	15.2	..	..
WHO Immediate KMC Study Group, 2021[58]	..	..	1.3	53.6	20.2†	19†	14.9	15.2	..	..
Bier, 1996[33]	..	..	696	..	0.02	..	69	73	..	..
Boo, 2007[34]	..	..	624	..	1	..	..	..	**13.5***	**22.5***
Brotherton, 2021[35]	..	..	12	101.1	6.7†	2.1†	16.6	16.3	..	..
Cattaneo, 1998[36]	..	..	240	..	20	..	11	13	..	..
Charpak, 1997[37]	..	..	96	..	..	..	..	..	..	..
Chi Luong, 2016[38]	..	..	..	..	..	..	..	..	7	8
de Ocampo, 2021[39]	376.8	345.6	..	..	..	0	33.31	33.25	..	..
Gathwala, 2008[40]	41.3	..	..	..	10.21	..	**3.56***	**6.8***	..	..
Ghavane, 2012[41]	338.4	..	..	..	..	..	25.5	26	..	..
Jayaraman, 2017[42]	..	..	36	204	5.4	4.5	..	..	21.5	22
Kadam, 2005[43]	..	..	..	..	9.8	..	8.5	9.3	..	..
Kumbhojkar, 2016[44]	..	..	72	..	11.5	0	**12***	**17***	..	..
Lamy Filho, 2015[45]	..	..	..	..	1	0	..	..	..	..
Logronio, 2021[46]	..	..	..	..	..	..	3.48	4.83	3	4
Mazumder, 2019[47]	..	..	31	..	11.5 / 12†	0.2 / 0†	..	..	..	..
Nagai, 2010[48]	19.76	33	19	28.5	..	..	6.68	7.58	..	..
Nimbalkar, 2014[49]	0.72	..	..	..	16.98	..	..	..	..	..
Pratiwi, 2009[50]	..	..	..	..	10.06	..	..	..	..	..
Ramanathan, 2001[51]	..	..	283.2	..	..	..	**27.2***	**34.6***	..	..

Ricero-Luistro, 2021[52]	..	..	24	..	4	..	24.63	28.14	..	..
Rojas, 2003[53]	..	..	24	..	1.32	..	61	61	..	..
Sloan, 1994[54]	..	..	..	..	..	..	..	..	..	..
Suman, 2008[55]	..	..	..	..	13.5	..	12.78	12.86	..	..
Tumukunde, 2024[56]	..	..	..	..	10.1†	0†	7.3	6.1	..	..
Whitelaw, 1988[57]	384	..	..	..	0.6†	..	..	..	30	37
Worku, 2005[59]	10	..	..	..	..	..	4.6	5.4	..	..

Legend: h, hours; K(M)C, Kangaroo (Mother) Care; h, hour; ***(bold)**, statistically significant difference ($p<0.05$); † refers to median**.**

Table S2. Risk of bias summary: authors' judgements about each risk of bias item for each included study

	Domain 1: Risk of bias arising from the randomization process	Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Domain 3: Missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Overall risk of bias
Acharya et al.[31]	✓	✓	?	?	?	✓	?
Ali et al.[32]	✓	✓	?	✓	?	✓	✓
Arya et al.[10]	✓	?	✓	✓	✓	✓	✓
Bier et al.[33]	✓	?	?	✓	✓	?	?
Boo et al.[34]	✓	✓	?	✓	✓	?	?
Brotherton et al.[35]	✓	?	✓	✓	✓	✓	✓
Cattaneo et al.[36]	✓	?	?	✓	✓	?	?

Charpak et al.[37]	✓	✓	?	✓	✓	✓	✓
Chi Luong et al.[38]	✓	✓	✓	✓	?	✓	?
De Ocampo et al.[39]	✓	?	?	✓	✓	✓	?
Gathwala et al.[40]	✓	?	✓	✓	?	?	?
Ghavane et al.[41]	✓	?	✓	✓	?	?	?
Jayaraman et al.[42]	✓	?	✓	✓	?	✓	✓
Kadam et al.[43]	✓	?	✗	✓	?	✓	?
Kumbhojkar et al.[44]	✓	?	✓	✓	?	✓	✓
Lamy Filho et al.[45]	✓	✓	✓	✓	✓	✓	✓
Logronio et al.[46]	✓	?	✓	✓	?	?	?
Mazumder et al.[47]	✓	?	?	✓	✓	?	?
Nagai et al.[48]	✓	?	✓	✓	✓	?	?
Nimbalkar et al.[49]	✓	?	✓	✓	✓	?	?
Pratiwi et al.[50]	✓	?	✓	✓	✓	?	?
Ramanathan et al.[51]	?	?	✓	?	?	?	✗
Ricero-Luistro et al.[52]	✓	?	✓	✓	✓	✓	✓
Rojas et al.[53]	✓	?	?	✓	✓	?	?
Sloan et al.[54]	✓	✗	?	?	✓	?	✗
Suman et al.[55]	?	✓	✓	✗	?	?	✗
Tumukunde et al.[56]	✓	✓	✓	✓	✓	✓	✓
Whitelaw et al.[57]	✓	?	?	✓	?	✓	✓
WHO Immediate KMC Study Group[58]	✓	?	✓	✓	✓	✓	✓
Worku et al.[59]	✓	?	✗	?	?	✓	✗

Legend: The following table presents the authors' judgements about each risk of bias item, according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB2), for each included study. The template for completion is provided at the end of the Supplementary Materials.

✓	Low
?	Some concerns
✗	High

Table S3. Evidence table of the included studies

Condition in LBW infants: All-cause mortality Sepsis Invasive infection	**Author, year**	**N**	**Statistically significant?**	**Quality of study †**	**Magnitude of Benefit**	**Absolute Risk Reduction**	**Number Needed to Treat**
All-cause mortality	Acharya et al, 2014[31]	126	no	3	NA	NA	NA
Sepsis	Ali et al, 2009[32]	114	yes	3	Medium	0.16	7
Invasive infection			no		NA	0.04	25
Sepsis	Arya et al, 2023[10]*	3211	yes	3	Large	0.05	20
All-cause mortality	WHO Immediate KMC Study Group, 2021[59]*	3211	yes	3	Large	0.04	25
Sepsis	Bier et al, 1996[33]	50	no	2	NA	NA	NA
Invasive infection			no		NA	NA	NA
All-cause mortality	Boo et al, 2007[34]	126	no	3	NA	0.001	1000
Sepsis			no		NA	-0.01	-100
Invasive infection			no		NA	NA	NA
All-cause mortality	Brotherton et al, 2021[35]	279	no	3	NA	0.04	25
Sepsis			no		NA	- 0.04	-25
All-cause mortality	Cattaneo et al, 1998[36]	285	no	3	NA	0.002	500
Invasive infection			no		NA	0.09	12
All-cause mortality	Charpak et al, 1997[37]	746	no	3	NA	0.01	100
Sepsis			no		NA	0.05	20
Invasive infection			no		NA	0.04	25
All-cause mortality	Chi Luong et al, 2016[38]	100	no	2	NA	NA	NA
Sepsis			no		NA	0.34	3

Sepsis	de Ocampo et al, 2021[39]	52	no	3	NA	0.15	7
All-cause mortality	Gathwala et al, 2008[40]	100	no	3	NA	NA	NA
All-cause mortality	Ghavane et al, 2012[41]	140	no	3	NA	NA	NA
Sepsis			no		NA	8.2	1
All-cause mortality	Jayaraman, 2017[42]	160	no	3	NA	0.03	34
All-cause mortality	Kadam, 2005[43]	89	no	2	NA	-0.001	-1000
Sepsis			no		NA	0.04	25
Invasive infection			no		NA	0.04	25
All-cause mortality	Kumbhojkar, 2016[44]	120	no	3	NA	NA	NA
Sepsis			yes		Medium	0.2	5
All-cause mortality	Lamy Filho, 2015[45]	102	no	3	NA	NA	NA
All-cause mortality	Logronio et al, 2021[46]	46	no	3	NA	NA	NA
Sepsis			no		NA	0.04	25
All-cause mortality	Mazumder et al, 2019[47]	8384	yes	3	Large	0.01	100
All-cause mortality	Nagai et al, 2010[48]	73	no	3	NA	-0.03	-34
Invasive infection			no		NA	0.11	10
All-cause mortality	Nimbalkar et al, 2014[49]	45	no	3	NA	NA	NA
All-cause mortality	Pratiwi et al, 2009[50]	93	no	2	NA	NA	NA
Sepsis			no		NA	0.05	20
All-cause mortality	Ramanathan et al, 2001[51]	28	no	2	NA	NA	NA
All-cause mortality	Ricero-Luistro et al, 2021[52]	70	no	3	NA	0.03	34
Sepsis			yes		Small	0.11	10
Invasive infection			yes		Small	0.11	10
All-cause mortality	Rojas et al, 2003[53]	60	no	3	NA	-0.02	-50
Sepsis			no		NA	0.15	7
Invasive infection			no		NA	0.04	25
All-cause mortality	Sloan et al, 1994[54]	275	no	3	NA	0.002	500
Invasive infection			no		NA	0.12	9
All-cause mortality	Suman et al, 2008[55]	206	yes	3	Medium	0.04	25
Sepsis			yes		Medium	0.11	9
All-cause mortality	Tumukunde et al, 2024[56]	2221	no	3	NA	0.02	50
Sepsis			no		NA	NA	NA
Invasive infection			no		NA	-0.003	-334

All-cause mortality	Whitelaw et al, 1988[57]	71	no	3	NA	-0.002	-500
All-cause mortality	Worku et al, 2005[58]	123	yes	2	Medium	0.2	5

Legend: LBW, low-birthweight; all trials were individually randomised; N, total number of subjects included in the study; NA,

* publication refers to the same trial (iKMC trial)

† Quality of study: numerical score between 0 and 5 assigned according to the scale developed by Jadad et al. (Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996;17[1]:1-12), with 3 being the highest possible score in our scenario, given that for the type of intervention none of the included studies used masking or blinding.

Table S4. Summary of primary outcomes

First author and Publication Year	Primary Outcome 1		Primary Outcome 2		Primary Outcome 3	
	I - Death- all cause, n	C - Death- all cause, n	I - Sepsis, n	C - Sepsis, n	I - Invasive infection, n	C - Invasive infection, n
Acharya, 2014[31]	0/63	0/63	..	..	..	..
Ali, 2009[32]	..	..	**4/58 §**	**13/56 §**	**2/58 §**	**4/56 §**
Arya, 2023[10] †	..	..	**361/1575 §**	**434/1561 §**	..	..
WHO Immediate KMC Study Group, 2021[58] †	**191/1596 §**	**249/1587 §**	..	..	..	..
Bier, 1996[33] *	..	..	0/25	0/25	0/25	0/25
Boo, 2007[34]	1/64	1/62	2/64	1/62	0/64	0/62
Brotherton, 2021[35] †	29/138	34/139	28/138	21/141	..	..
Cattaneo, 1998[36]	3/149	3/136	..	..	14/149	25/136
Charpak, 1997[37]	6/364	10/345	39/364	39/345	14/364	27/345
Chi Luong, 2016[38] † ‡	0/50	0/50	9/50	26/50	..	..
de Ocampo, 2021[39]	..	..	3/26	7/26	..	..
Gathwala, 2008[40]	0/50	0/50	..	..	..	..
Ghavane, 2012[41]	0/71	0/69	2/71	2/69	..	..
Jayaraman, 2017[42]	1/80	3/80	..	..	..	..
Kadam, 2005[43]	1/44	1/45	6/44	8/45	0/44	1/45
Kumbhojkar, 2016[44]	0/60	0/60	**2/60 §**	**14/60 §**	..	..
Lamy Filho, 2015[45]	0/53	0/49	..	..	..	..
Logronio, 2021[46]	0/23	0/23	0/23	1/23	..	..
Mazumder, 2019[47]	**73/4470 §**	**90/3914 §**	..	..	..	..
Nagai, 2010[48]	2/37	1/36	..	..	3/37	7/36
Nimbalkar, 2014[49] †	0/22	0/23	..	..	..	..
Pratiwi, 2009[50]	0/48	0/45	1/48	3/45	..	..
Ramanathan, 2001[51]	0/14	0/14	..	..	..	..
Ricero-Luistro, 2021[52]†	2/35	3/35	**3/35 §**	**7/35 §**	**4/35 §**	**8/35 §**
Rojas, 2003[53]*	2/33	1/27	5/33	8/27	1/33	2/27
Sloan, 1994[54]	11/131	13/152	..	..	7/131	27/152

Suman, 2008[55]	**1/103 §**	**5/103 §**	**4/103 §**	**15/103 §**	..	..
Tumukunde, 2024[56] * †	119/1051	134/1049	34/1110	35/1111	10/1110	7/1111
Whitelaw, 1988[57]	2/35	2/36	..	..	..	..
Worku, 2005[59] * †	**14/62 §**	**24/63 §**	..	..	..	..

Legend: I, intervention; C, control, K(M)C, Kangaroo Mother Care; * including ELBW, extremely low birthweight (<1000g); † including unstable/not stabilised infants; ‡ including infants on mechanical ventilation; **§ (bold)**, statistically significant difference ($p<0.05$)

Table S5. Summary of secondary outcomes and adverse events

First author and Publication Year	Secondary Outcome 1				Secondary Outcome 2		Secondary Outcome 3 (adverse event)		Secondary Outcome 4 (adverse event)	
	I - Death by sepsis/invasive infection, n	C- Death by sepsis/invasive infection	I -Death by antibiotic resistant sepsis/invasive infection, n	C -Death by antibiotic resistant sepsis/invasive infection, n	I – Colonisation, n	C- Colonisation, n	I – Hypothermia, n	C- Hypothermia, n	I – Apnoea , n	C- Apnoea, n
Acharya, 2014[31]	..	..	..	..	..	..	**2/63 §**	**8/63 §**	0/63	3/63
Ali, 2009[32]	..	..	..	..	..	..	**1/58 §**	**10/56 §**	**1/58 §**	**8/56 §**
Arya, 2023 [10]†	**70/1575 §**	**109/1561 §**	..	..	..	..	..	..	..	..
WHO Immediate KMC Study Group, 2021[56] †	..	..	..	..	..	..	..	..	..	..
Bier, 1996[33] *	..	..	..	..	..	..	..	..	..	..
Boo, 2007[34]	..	..	..	..	..	..	..	..	..	..
Brotherton, 2021[35] †	3/138	4/139	3/138	3/139	..	..	51/134	55/135	..	..
Cattaneo, 1998[36]	2/149	3/136	..	..	..	..	..	..	..	..
Charpak, 1997[37]	..	..	..	..	..	..	..	..	..	..
Chi Luong, 2016[38] † ‡	0/50	0/50	0/50	0/50	..	..	**1/50 §**	**35/50 §**	..	..
de Ocampo, 2021[39]	..	..	..	..	..	..	**6/64 §**	**17/62 §**	6/64	4/62
Gathwala, 2008[40]	..	..	..	..	..	..	2/50	3/50	..	..
Ghavane, 2012[41]	0/71	0/69	0/71	0/69	..	..	1/71	0/69	0/71	2/69
Jayaraman, 2017[42]	..	..	..	..	..	..	0/80	0/80	**19/80§**	**32/80§**
Kadam, 2005[43]	1/44	1/45	..	..	..	..	**10/44 §**	**21/45 §**	6/44	8/45
Kumbhojkar, 2016[44]	0/60	0/60	..	..	..	..	**3/60 §**	**20/60 §**	**3/60 §**	**18/60§**
Lamy Filho, 2015[45]	..	..	..	..	**25/53 §**	**38/49 §**	..	..	..	..
Logronio, 2021[46]	0/23	0/23	0/23	0/23	..	..	2/23	4/23	..	..
Mazumder, 2019[47]	..	..	..	..	..	..	..	..	..	..
Nagai, 2010[48]	1/37	1/36	..	..	..	..	3/37	5/36	0/37	1/36

Nimbalkar, 2014[49] †	..	..	..	..	..	..	**1/22 §**	**10/23 §**	..	..
Pratiwi, 2009[50]	..	..	..	..	..	..	..	..	..	..
Ramanathan, 2001[51]	..	..	..	..	..	..	..	..	..	..
Ricero-Luistro, 2021[52] †	..	..	..	..	..	..	2/35	10/35	..	..
Rojas, 2003[53] *	0/33	1/27	..	..	..	..	1/33	5/27	4/33	1/27
Sloan, 1994[54]	..	..	..	..	..	..	..	..	..	..
Suman, 2008[55]	..	..	..	..	..	..	**6/103 §**	**38/103 §**	**1/103 §**	**8/103§**
Tumukunde, 2024[56] *†	..	..	..	..	..	..	**448/1096§**	**585/1101§**	29/1110	37/1111
Whitelaw, 1988[57]	..	..	..	..	..	..	..	..	..	..
Worku, 2005[59] * †	..	..	..	..	..	..	..	..	..	..

Legend: I, intervention; C, control, K(M)C, Kangaroo Mother Care; *including ELBW, extremely low birthweight (<1000g); † including unstable/not stabilised infants; ‡ including infants on mechanical ventilation; **§ (bold)**, statistically significant difference ($p<0.05$)

Table S6. GRADE

Study design	Confidence in estimates / Certainty of evidence	Lower if	Higher if
Randomised trials	High	Risk of bias -1 serious -2 very serious Inconsistency -1 serious -2 very serious Indirectness -1 serious -2 very serious Imprecision -1 serious -2 very serious Publication bias -1 likely -2 very likely	Dose-response gradient +1 evidence of a gradient Large magnitude of effect +1 large +2 very large Confounding +1 would reduce a demonstrated effect +1 would suggest a spurious effect when results show no effect
	Moderate		
	Low		
	Very low		

6. Funnel plots details

Figure S2. Funnel plot – all-cause mortality

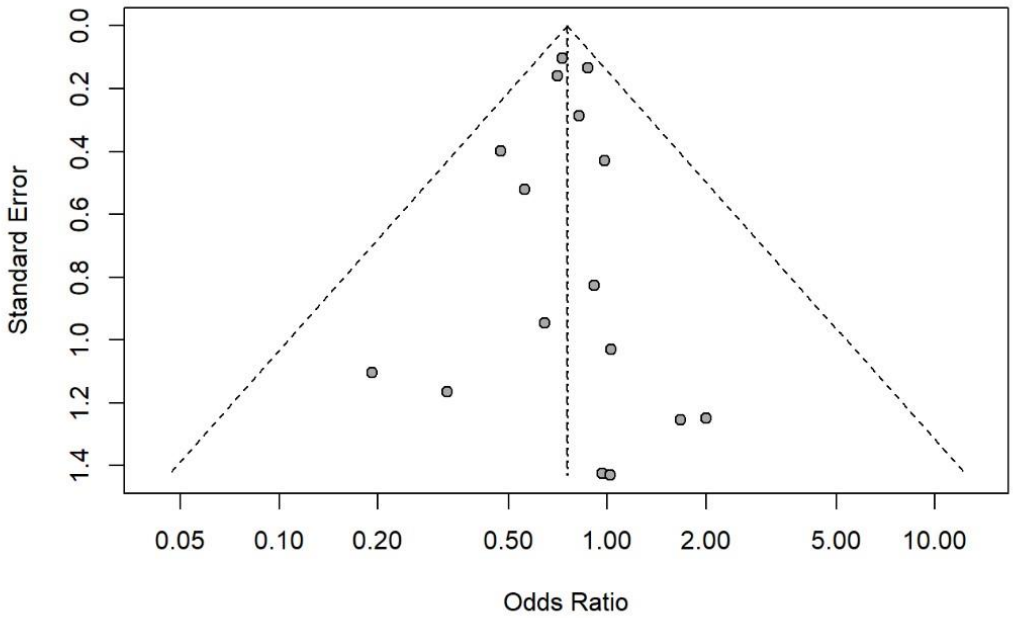


Figure S3. Funnel plot – sepsis

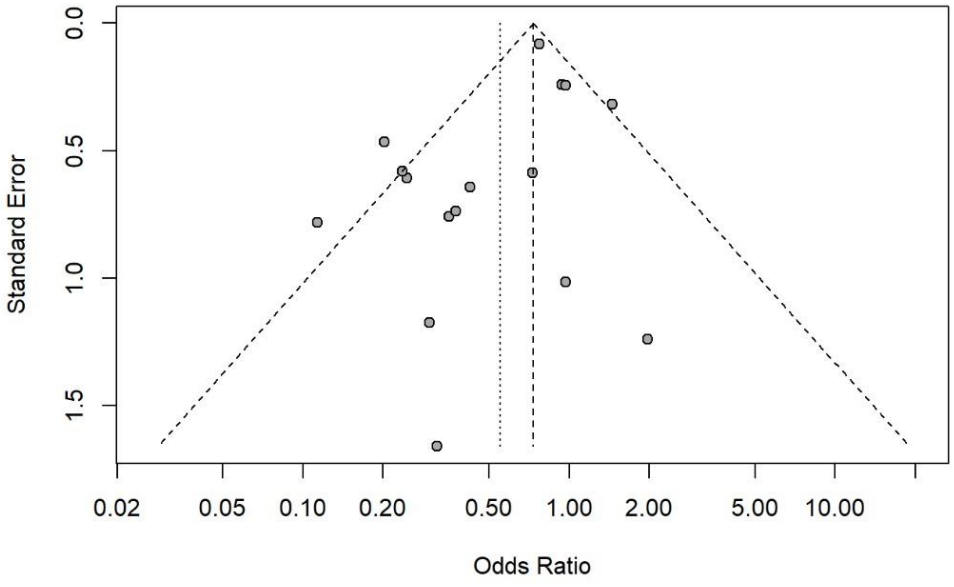


Figure S4. Funnel plot – invasive infection

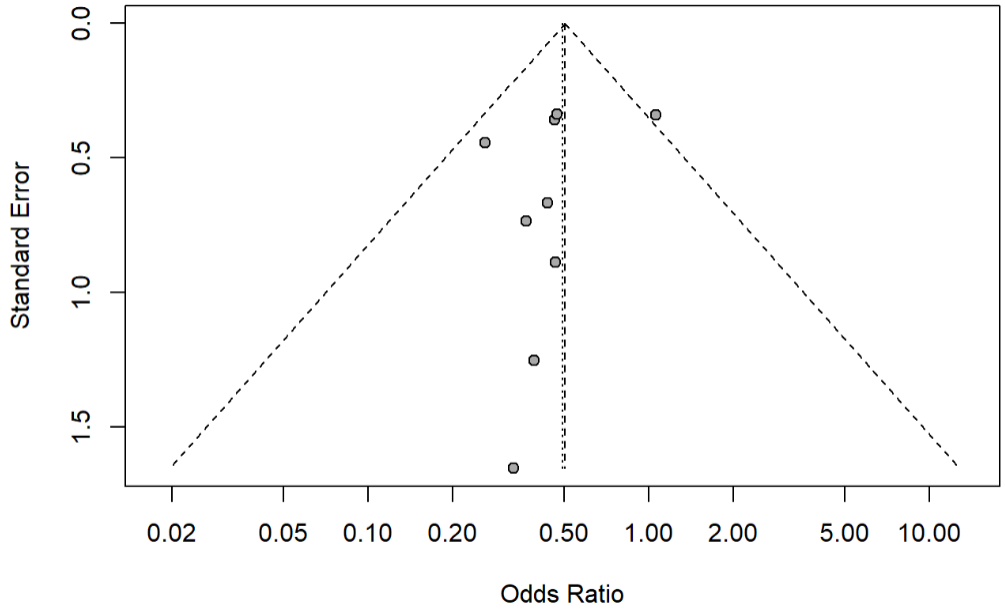


Figure S5. Funnel plot – sepsis/invasive infection-related mortality

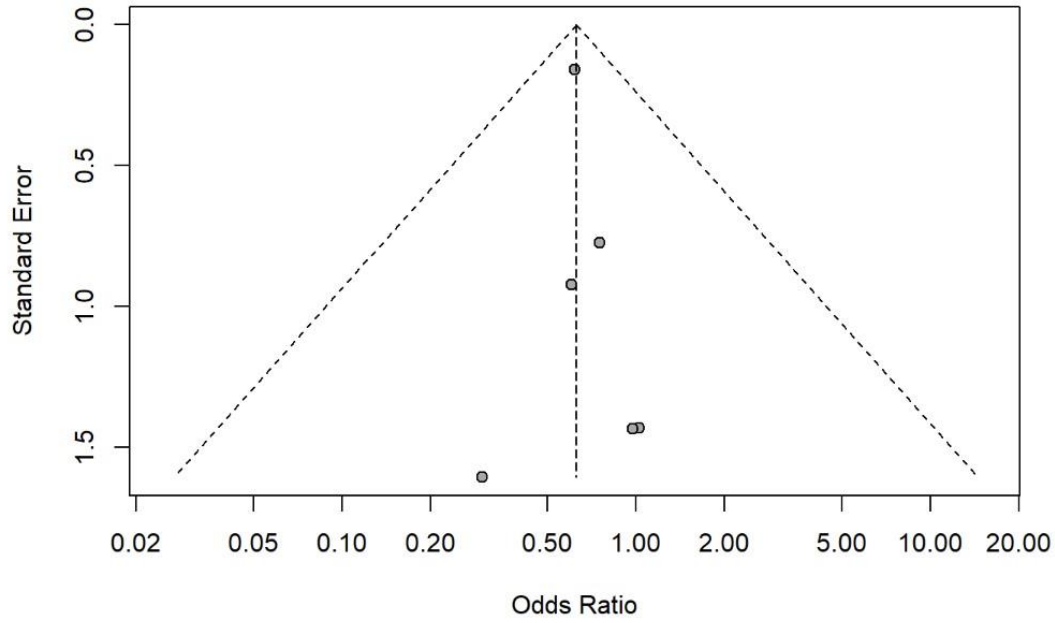


Figure S6. Funnel plot – hypothermia

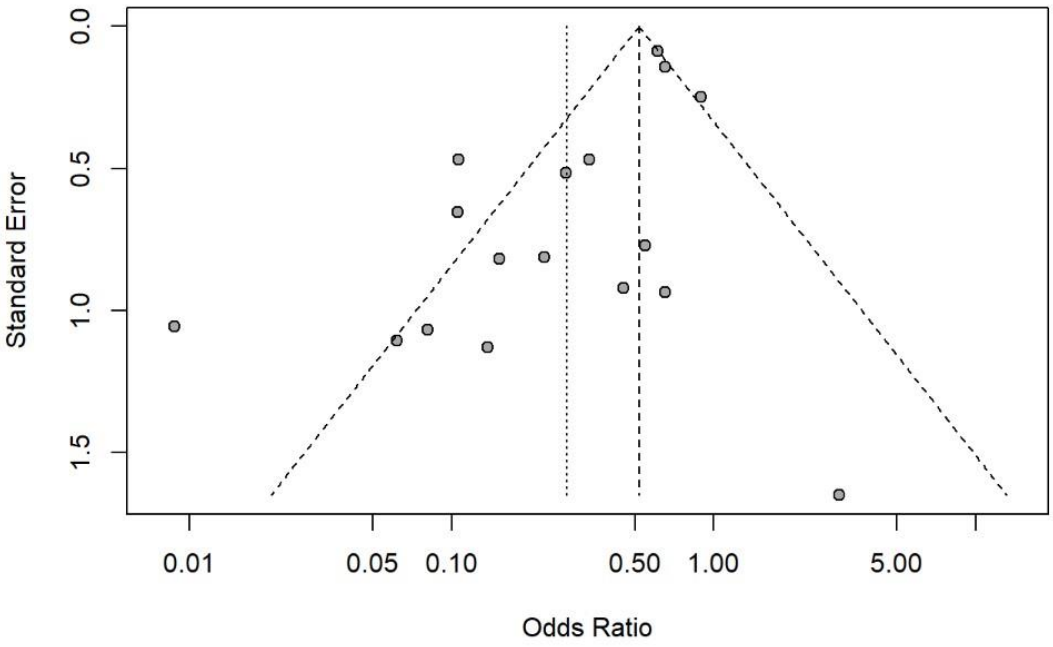
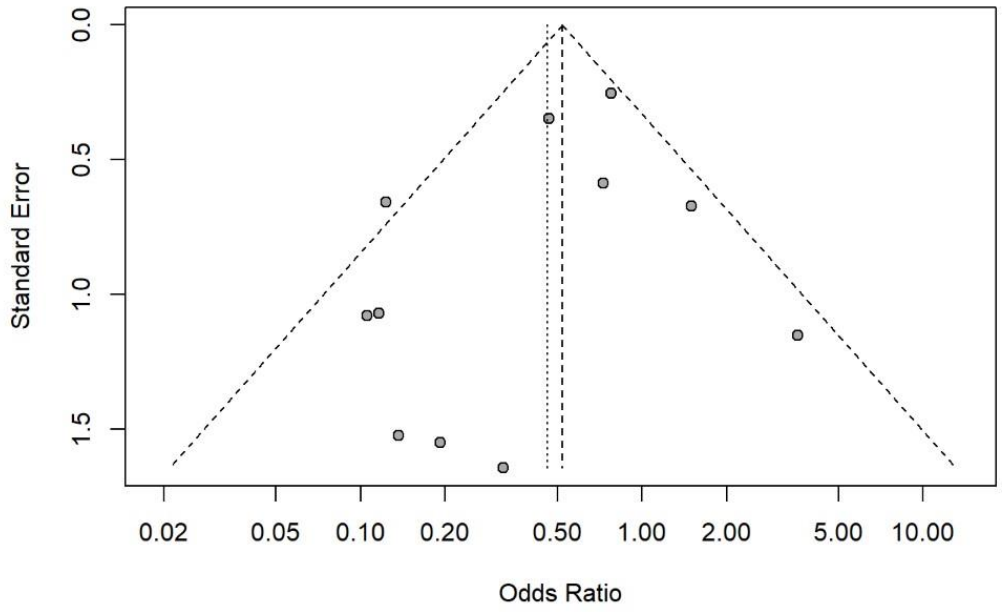


Figure S7. Funnel plot – apnoea



PRISMA 2020 Checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	RiC panel & Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	RiC panel & Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods 2.2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods 2.1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods 2.1& Supplementary
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods 2.4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods 2.5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods 2.3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods 2.3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods 2.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods 2.7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods 2.7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods 2.7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods 2.7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods 2.7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods 2.7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods 2.7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods 2.6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods 2.6

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results
Study characteristics	17	Cite each included study and present its characteristics.	Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results, Supplementary Materials
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results, Supplementary Materials
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Methods

Competing interests	26	Declare any competing interests of review authors.	Declaration of interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data sharing

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Comparator:

Specify which outcome is being assessed for risk of bias	
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial
Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	(look at adjusted results)	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	(confidence intervals and width)	Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable