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| Question |
| **Should Lower initial oxygen concentration (FiO2 ≤0.5) vs. Higher initial oxygen concentration (FiO2 >0.5) be used for Newborn infants <35 weeks’ estimated gestational age who receive respiratory support at delivery?** |
| **Population:** | Newborn infants <35 weeks’ estimated gestational age who receive respiratory support at delivery |
| **Intervention:** | Lower initial oxygen concentration (FiO2 ≤0.5) |
| **Comparison:** | Higher initial oxygen concentration (FiO2 >0.5) |
| **Main outcomes:** | All-cause mortality in-hospital or 28 days (critical); All-cause mortality before 1-3 years (critical); Neurodevelopmental impairment at 1 to 3 years of age (critical); Major IVH (grade III or IV) (critical); Retinopathy of prematurity (critical); Necrotizing enterocolitis stage II or III (critical); Bronchopulmonary dysplasia (Chronic Neonatal Lung Disease) (important); Number with HR > 100 at 5 mins; Time from birth to SpO2 ≥80% (important); Advanced resuscitation (chest compressions with or without epinephrine (adrenaline)) (important); |
| **Setting:** | Delivery room or other locations where preterm infants are born |
| **Perspective:** | Population |
| **Background:** | A previous ILCOR systematic review {Welsford 2019 1} reported; “Ten *randomized controlled studies and 4 cohort studies included 5697 patients. There are no statistically significant benefits of or harms from starting with lower compared with higher FiO2* *in short-term mortality (n = 968; risk ratio = 0.83 [95% confidence interval 0.50 to 1.37]), long-term mortality, neurodevelopmental impairment, or other key preterm morbidities. A sensitivity analysis in which 1 study with a high RoB was excluded failed to reveal a reduction in mortality with initial low FiO2* *(n = 681; risk ratio = 0.63 [95% confidence interval 0.38 to 1.03])”.* As a result of these findings, the Task Force recommended that; “*We suggest* *starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks’ gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence)”* {Soar 2019 e826}A recent network meta-analysis and individual patient data meta-analysis (IPD NWMA - NetMotion) {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848} included 8 {Armanian 2012 25, Boronat 2016 e 20161405, Kapadia 2013 e1488, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}of the 12 RCTs included in {Welsford 2019 1} and 4 additional trials {Dekker 2019 10.3389/fped.2019.00504, Finer 2018 , Kaban 2022 104, Liyakat 2023 794} NetMotion obtained patient data for 1055 infants concluded that; *“High initial FiO2 (0.90) may be associated with reduced mortality in preterm infants born at less than 32 weeks’ gestation compared to low initial FiO2 (low certainty). High initial FiO2 is possibly associated with reduced mortality compared to intermediate initial FiO2 (very low certainty) but more evidence is required”.* Three of the 4 additional trials included in NetMotion were not published at the time of the previous ILCOR systematic review. {Dekker 2019 10.3389/fped.2019.00504, Kaban 2022 104, Liyakat 2023 794} For an additional study, the NetMotion investigators obtained unpublished results (not eligible for inclusion in the ILCOR systematic review) from study authors. {Finer 2018 } One additional trial that enrolled 42 infants was not included in the previous ILCOR systematic review, {Escrig 2008 875} because it was a pilot/feasibility study and most data were reported in subsequent larger trial that was included in the review. {Vento 2009 e439}The previous ILCOR systematic review {Welsford 2019 1} also included 4 observational studies {Dawson 2009 F87, Kapadia 2017 35, Rabi 2015 252, Soraisham 2017 1141} that were ineligible for NetMotion. {Sotiropoulos 2023 372}Due to the discordance between the conclusions of these two systematic reviews (conducted at different times and using different methods) the Task Force concluded that an updated ILCOR systematic review was required, to consider three types of evidence:1. Evidence from eligible randomized controlled trials included in {Welsford 2019 1} and any published since the last search date for that review (10th August 2018)2. Evidence from any large (preferably population-based) observational studies that is adjudicated using GRADE methods to provide similar or higher certainty of evidence to the RCTs3. Results of the IPD NWMA NetMotion {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}, by adolopment, considering the evidence therein but using it to develop the Task Force’s own conclusions about the Consensus on Science and Treatment recommendations, in combination with the evidence from study level metanalysis of RCTs and observational studies. The combined results of these are considered in this Evidence to Decision Table to determine whether the previous treatment recommendations are still applicable or need to be superseded. The updated systematic literature search identified for inclusion in the study-level meta-analysis the 3 RCTs that had been included in NetMotion {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}) that had been published too recently for inclusion in the previous ILCOR systematic review. {Welsford 2019 1} The search found one additional RCT {Law 2021 942}) which had not been included in NetMotion because it was cluster-randomized. The study-level meta-analysis therefore included 1289 infants (compared to the 1007 included in the previous ILCOR meta-analysis. Welsford 2019 1} Of the included studies, three reported aspects of a single two-country trial {Aguar 2013 , Boronat 2016 e 20161405, Rook 2014 1322}, one included most data from a previous pilot study {Escrig 2008 875, Vento 2009 e439}, and one reported neurodevelopmental follow-up data and late mortality {Thamrin 2018 55} from another trial. {Oei 2017 26} |
| **Conflict of interests:** | Co-author Schmölzer is a co-author on the NetMotion study {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}and was excluded from decisions about adolopment and bias assessment of this study. Co-author Schmölzer is a co-author on one study eligible for inclusion {Law 2021 942} and was excluded from decisions about inclusion and risk of bias assessment for this study.  |

# 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 | Preterm infants are at risk for the toxic effects of oxygen that can have adverse effects on the lungs (leading to increased risk of bronchopulmonary dysplasia or neonatal chronic lung disease, eyes (leading to retinopathy of prematurity), brain and other organs. Although neonatal intensive care after birth may expose infants to much of their ongoing risk, studies demonstrating high levels of oxygen free radicals after resuscitation in high inspired oxygen concentrations suggests that exposure soon after birth may also impose clinically important risk. {Vento 2009 e439} Conversely, delivery room hypoxia adversely affects outcomes, and morbidity and mortality are increased in preterm infants with a gestational age less than 32 weeks who fail to achieve a peripheral oxygen saturation higher than 80% at 5 min of life, especially if combined with bradycardia. {Torrejón-Rodríguez 2023 244} Adverse outcomes of hypoxia and hyperoxia may be reduced if resuscitators rapidly and effectively titrate the inspired oxygen concentration during resuscitation. However, their responses may be limited by latencies in measurement and slow reactions to high or low oxygen saturation levels. In addition, in settings with very limited resources, the only choice may be air (FiO2 0.21) or in other resource-limited settings, air or pure oxygen (FiO2 1.00). Before any aeration of the newborn's lungs, the oxygen concentration provided may briefly make little difference. However, as soon as aeration commences and pulmonary blood flow starts to increase, a higher inspired oxygen concentration could provide benefits including enhanced respiratory drive and pulmonary arteriolar vasodilation. Potential benefits could include an enhanced response to resuscitation, reduced need for resuscitation interventions and improved survival without short- and long-term morbidity. Therefore, the problem is a priority because of potential to influence survival and important adverse consequences of prematurity, and also because of implications for resources to blend and titrate oxygen.  |  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know | **From the individual patient network meta-analysis:**NetMotion evaluated IPD for 1055 participants from 12 of 13 eligible studies. Eligibility included gestation <32 weeks at birth. {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848} See description in background for overlap with the previous and updated study level meta-analysis. For the **critical primary outcome of all-cause mortality** (in hospital or by 28 days) the NetMotion IPD NWMA) compared low (≤0.3), intermediate (0.5-0.65) and high (≥0.9) initial FiO2. * **High initial FiO2 (≥ 0.90) reduced all-cause mortality (in hospital or within 28 days) compared to low initial FiO2 (0.21-0.30)** (adjusted odds ratio (aOR) 0.45, 95% credible interval (CrI) 0.23-0.86, number needed to benefit (NNTB) 16 (95% CrI 10-66) ARD 67 more infants per 1000 survived with high initial FiO2 (95% CrI 15 more to 100 more), **low certainty** evidence from direct comparison of 833 patients included in 8 studies. {Dekker 2019 10.3389/fped.2019.00504, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}
* For **intermediate initial FiO2 (0.50-0.65) compared to low FiO2 (0.21-0.30)** clinical benefit or harm could not be excluded (aOR 1.33, 95% CrI 0.54-3.15), **very low certainty** evidence from direct comparison of 352 participants in 4 studies. {Aguar 2013 , Finer 2018 , Kaban 2022 104, Rook 2014 1322}
* For **high (≥0.90) compared to intermediate initial FiO2 (0.50-0.65) there was possible clinical benefit** (aOR 0.34; 95% CrI 0.11-0.99; number needed to treat, 11; 95% CrI, 4-1514) **very** **low certainty** evidence from an indirect comparison. (No studies compared high vs intermediate FiO2). {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}

For the critical outcome of **severe intraventricular hemorrhage clinical benefit or harm could not be excluded** (OR 0.56, 95% CrI 0.10-1.82), **very low certainty evidence** from 809 infants included in 8 studies. {Dekker 2019 10.3389/fped.2019.00504, Escrig 2008 875, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}**From the study-level meta-analysis:*****Randomized controlled trials*****For the comparison between lower (FiO2 ≤0.5) vs higher initial oxygen concentration (FiO2 >0.5)*** For the **critical primary outcome of all-cause mortality (in hospital or by 28 days) clinical benefit or harm could not be excluded** (Relative risk (RR); 1.12, 95% confidence intervals (95% CI); 0.84 to 1.49), **very low certainty evidence** from 1289 infants included in 14 RCTs {Aguar 2013 , Armanian 2012 25, Dekker 2019 10.3389/fped.2019.00504, Harling 2005 F401, Kaban 2022 104, Kapadia 2013 e1488, Law 2021 942, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Rook 2014 1322, Vento 2009 e439, Wang 2008 1083} The certainty of evidence was downgraded for risk of bias and imprecision.
* For the critical secondary outcome of **long term all-cause mortality (1-3 years)** **clinical benefit or harm could not be excluded** (RR 1.04, 95% CI 0.42-2.58) **very low certainty evidence** from 515 infants included in 2 RCTs. {Boronat 2016 e 20161405, Thamrin 2018 55} The certainty of evidence was downgraded for serious risk of bias and very serious imprecision. (These results are essentially the same as those reported in the previous ILCOR systematic review, but are replicated with updated assessment using Cochrane RoB2 and GRADE CoE, and using the denominator of infants included in each study, rather than the denominator of only those for whom follow-up was achieved).
* For the critical secondary outcome of **neurodevelopmental impairment** (1-3 years) **clinical benefit or harm could not be excluded** (RR;1.14, 95% 95% CI; 0.78 to 1.67), **very low certainty evidence** from 389 infants who were able to be followed up from 2 RCTs. {Boronat 2016 e 20161405, Thamrin 2018 55} The certainty of evidence was downgraded for risk of bias and imprecision. (These results are essentially the same as those reported in the previous ILCOR systematic review, but are replicated with updated assessment using Cochrane RoB2 and GRADE CoE).
* For the critical secondary outcome of **major IVH (grade III or IV)** **clinical benefit or harm could not be excluded** (RR; 1.10, 95%; 0.81 to 1.49), **very low certainty evidence** from 1129 infants included in 11 RCTs. {Boronat 2016 e 20161405, Dekker 2019 10.3389/fped.2019.00504, Harling 2005 F401, Kaban 2022 104, Kapadia 2013 e1488, Law 2021 942, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Vento 2009 e439, Wang 2008 1083} The certainty of evidence was downgraded for very serious risk of bias and for imprecision.
* For the important secondary outcome of **advanced resuscitation** (chest compressions with or without epinephrine (adrenaline)) **clinical benefit or harm could not be excluded** (RR; 0.84, 95% CI; 0.24 to 2.90), **very low certainty evidence** from 772 infants included in 7 RCTs {Escrig 2008 875, Kaban 2022 104, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Wang 2008 1083} The certainty of evidence was downgraded for serious risk of bias, and extremely serious imprecision.
* For other important outcomes of the review, they were not reported or there was insufficient evidence for meaningful analysis (e.g. outcome reported in only one small study with high risk of bias for the outcome).

| **Outcomes** | **№ of participants(studies)Follow-up** | **Certainty of the evidence(GRADE)** | **Relative effect(95% CI)** | **Anticipated absolute effects\* (95% CI)** |
| --- | --- | --- | --- | --- |
| **Risk with Higher initial oxygen concentration (FiO2 >0.5)** | **Risk difference with Lower initial oxygen concentration (FiO2 ≤0.5)** |
| All-cause mortality in-hospital or 28 days (critical) | 1289(14 RCTs)1,10,11,12,13,14,2,3,4,5,6,7,8,9 | ⨁◯◯◯Very lowa,b,c | **RR 1.12**(0.84 to 1.49) | Study population |
| 103 per 1,000 | **12 more per 1,000**(16 fewer to 50 more) |
| All cause mortality before 1-3 years (critical) | 515(2 RCTs)15,16 | ⨁◯◯◯Very lowb,d,e | **RR 1.04**(0.42 to 2.58) | Study population |
| 104 per 1,000 | **4 more per 1,000**(60 fewer to 164 more) |
| Neurodevelopmental impairment at 1 to 3 years of age (critical) | 389(2 RCTs)15,16 | ⨁◯◯◯Very lowb,d,f | **RR 1.14**(0.78 to 1.67) | Study population |
| 192 per 1,000 | **27 more per 1,000**(42 fewer to 129 more) |
| Major IVH (grade III or IV) (critical) | 1130(11 RCTs)1,12,13,16,2,4,5,6,7,8,9 | ⨁◯◯◯Very lowb,g,h | **RR 1.10**(0.81 to 1.49) | Study population |
| 113 per 1,000 | **11 more per 1,000**(21 fewer to 55 more) |
| Advanced resuscitation (chest compressions with or without epinephrine (adrenaline)) (important) | 772(7 RCTs)1,13,17,3,5,6,7 | ⨁◯◯◯Very lowb,i,j | **RR 0.84**(0.24 to 2.90) | Study population |
| 17 per 1,000 | **3 fewer per 1,000**(13 fewer to 32 more) |

1. {Wang 2008 1083}
2. {Vento 2009 e439}
3. {Rabi 2011 e374}
4. {Lundstrøm 1995 F81}
5. {Liyakat 2023 794}
6. {Kaban 2022 104}
7. {Kapadia 2013 e1488}
8. {Harling 2005 F401}
9. {Dekker 2019 10.3389/fped.2019.00504}
10. {Armanian 2012 25}
11. {Aguar 2013 }
12. {Law 2021 942}
13. {Oei 2017 26}
14. {Rook 2014 1322}
15. {Thamrin 2018 55}
16. {Boronat 2016 e 20161405}
17. {Escrig 2008 875}
18. For this outcome, 8 trials were at low overall risk of bias, 3 had some concerns in one domain, and 3 had high risk. Less than half the data came from studies rated as low risk.
19. I2 = 0%
20. OIS not met for control group event rate 0.104
21. For this outcome, one study had low overall risk of bias, one was high
22. OIS not met for control group event rate 0.059
23. OIS not met for control group event rate 0.19
24. For this outcome, 2 trials at low overall risk of bias, 3 had some concerns and 2 were high
25. OIS not met for control group event rate 0.11
26. For this outcome, 4 trials at high overall risk of bias, 2 with some concerns
27. OIS not met for control group event rate 0.01

***Observational studies:***There were no new observational studies found for inclusion in this updated review. The previous ILCOR systematic review included 4 observational studies and reported for **long-term mortality** that "two observational cohort studies involving 1225 preterm newborns receiving respiratory support at birth revealed **a statisticially significant benefit of starting with lower compared to higher FiO2** (RR 0.77, 95% CI 0.59 to 0.99; I 2 =6%)". {Kapadia 2017 35, Soraisham 2017 1141} These studies were deemed to be at **"unclear" overall risk of bias** using ROBINS-I assessment. {Welsford 2019 1} For **neurodevelopmental impairment**, two studies including 930 infants "revealed **no statistically significant difference in starting with lower compared with higher FiO2** (RR = 0.89 [95% CI 0.66 to 1.20]; I2 = 59%. {Kapadia 2017 35, Soraisham 2017 1141} These studies were deemed to be at **"unclear" overall risk of bias** using ROBINS-I assessment {Welsford 2019 1} |  |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small○ Moderate○ Large○ Varies● Don't know | **From the individual patient network meta-analysis:**For the following important outcomes, **the comparison between high (>0.90) and low (≤0.30) FiO2** **could not exclude benefit or harm:*** **chronic lung disease** (aOR 1.17, 95% CrI 0.55-2.52) from 783 infants included in 8 studies {Dekker 2019 10.3389/fped.2019.00504, Escrig 2008 875, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}
* **retinopathy of prematurity** (OR 1.17, 95% CrI 0.58-2.20), 767 infants included in 8 studies {Dekker 2019 10.3389/fped.2019.00504, Escrig 2008 875, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}

In each case, the evidence was of **very low certainty.** The comparisons between high (>0.90) and intermediate (0.50 to 0.65) FiO2 included 483, 519 and 480 infants respectively from 4 included studies and have even greater imprecision due to smaller numbers of included infants, so are not presented. {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}Other critical and important outcomes of the PICOST were not reported. **From the study-level meta-analysis:****For the comparison between lower (FiO2 ≤0.5) vs higher initial oxygen concentration (FiO2 >0.5)*** For the critical secondary outcome of **severe retinopathy of prematurity clinical benefit or harm could not be excluded** (RR; 1.06, 95% CI; 0.62 to 1.82), **very low certainty evidence** from 1046 infants included in 9 RCTs. {Boronat 2016 e 20161405, Harling 2005 F401, Kaban 2022 104, Kapadia 2013 e1488, Law 2021 942, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Vento 2009 e439}The certainty of evidence was downgraded for risk of bias and for imprecision.
* For the critical secondary outcome of **necrotizing enterocolitis (grade 2 or 3) clinical benefit or harm could not be excluded** (RR; 1.07, 95% CI; 0.58 to 2.00), **very low certainty evidence** from 1007 infants included in 9 RCTs. {Boronat 2016 e 20161405, Harling 2005 , Kaban 2022 104, Kapadia 2013 e1488, Law 2021 , Liyakat 2023 794, Lundstrøm 1995 , Oei 2017 26, Vento 2009 e439The certainty of evidence was downgraded for very serious risk of bias and serious imprecision.
* For the important secondary outcome of **bronchopulmonary dysplasia** **clinical benefit or harm could not be excluded** (RR; 1.04, 95% CI; 0.70 to 1.56), **very low certainty evidence** from 921 infants included in 8 RCTs. {Boronat, 2016 #60;Harling, 2005 #57;Kaban, 2022 #28;Kapadia, 2013 #47;Law, 2021 #31;Lundstrøm, 1995 #55;Oei, 2017 #50;Vento, 2009 #45} The certainty of evidence was downgraded for very serious risk of bias, and for inconsistency and imprecision.

| **Outcomes** | **№ of participants(studies)Follow-up** | **Certainty of the evidence(GRADE)** | **Relative effect(95% CI)** | **Anticipated absolute effects\* (95% CI)** |
| --- | --- | --- | --- | --- |
| **Risk with Higher initial oxygen concentration (FiO2 >0.5)** | **Risk difference with Lower initial oxygen concentration (FiO2 ≤0.5)** |
| Retinopathy of prematurity (critical) | 1046(9 RCTs)1,2,3,4,5,6,7,8,9 | ⨁◯◯◯Very lowa,b,c | **RR 1.06**(0.62 to 1.82) | Study population |
| 49 per 1,000 | **3 more per 1,000**(19 fewer to 40 more) |
| Necrotizing enterocolitis stage II or III (critical) | 1007(9 RCTs)1,10,2,4,5,6,7,8,9 | ⨁◯◯◯Very lowc,d,e | **RR 1.07**(0.58 to 2.00) | Study population |
| 47 per 1,000 | **3 more per 1,000**(20 fewer to 47 more) |
| Bronchopulmonary dysplasia (Chronic Neonatal Lung Disease) (important) | 921(8 RCTs)1,2,3,4,6,7,8,9 | ⨁◯◯◯Very lowf,g,h | **RR 1.04**(0.70 to 1.56) | Study population |
| 239 per 1,000 | **10 more per 1,000**(72 fewer to 134 more) |

1. {Law 2021 942}
2. {Oei 2017 26}
3. {Vento 2009 e439}
4. {Lundstrøm 1995 F81}
5. {Liyakat 2023 794}
6. {Kaban 2022 104}
7. {Kapadia 2013 e1488}
8. {Boronat 2016 e 20161405}
9. {Harling 2005 F401}
10. {Wang 2008 1083}
11. For this outcome, 3 trials had overall low risk of bias, 3 had some concerns and 3 were high
12. I2 = 0%
13. OIS not met for control group event rate 0.05
14. For this outcome, 2 trials at low overall risk of bias, 3 had some concerns and 2 were high
15. I2 = 3%
16. For this outcome, 2 trials were at high overall risk of bias, 3 had some concerns and 3 were low
17. I2 = 56%, likely due to variations between studies in criteria for outcome
18. OIS not met for control group event rate 0.24
 |  |
| 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 | **From the individual patient network meta-analysis:**The results for "high vs. low" and "intermediate vs. low" were based on direct comparisons, whereas "intermediate vs. high" was an indirect comparison as no included study compared "intermediate vs. high". {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848} Using the AMSTAR2 checklist {Shea 2017 j4008}, we concluded that the NETMOTION IPD NWMA was of **overall high quality**. The only shortcomings included a lack of information about the included studies as the paper did not report individual study outcomes, funding etc. The authors did not justify including only RCTs and only papers written in English and did not provide a list of excluded studies. (The study level meta-analysis also excluded papers not written in English and no additional non-RCTs were found). NetMotion used IPD which allowed adjustment for various important modifiers such as gestation at birth and birthweight, so should have greater precision of estimates than the study level meta-analysis. {Sotiropoulos 2023 372} There is such extensive overlap of included data that it is unlikely that differences in the results of NetMotion and the updated study level meta-analysis are accounted for by study exclusions.There is some indirectness of NetMotion compared to our PICOST, because it included only infants <32 weeks' gestation, and therefore does not inform a decision about infants 32 to 34+6 weeks' gestation. However, for infants <32 weeks' gestation, the results were considered by the Task Force to be more precise than those of the study level meta-analysis even though the overall certainty of evidence was similar. Nevertheless, NetMotion is subject to the same concerns as the study-level meta-analysis about overall sample size being well below the optimal information size for all critical and important outcomes. The certainty of evidence in the NetMotion study was upgraded for large effect size, but this is a consideration usually applied in GRADE to observational, not intervention studies. Current guidance from GRADE for systematic review authors is to consider a fully contextualized approach, in which “thresholds for decision-making are determined with considerations across all important and critical outcomes before rating the final certainty in the evidence. This includes considering the range of possible effects on all critical outcomes, bearing in mind the decision(s) that need to be made, and, as for the partially contextualized approach, the importance (value) of these outcomes. For each outcome, certainty ratings represent our confidence that the direction of the net effect (positive or negative) and decision will not differ from one end of the certainty range to the other”. {Schünemann 2022 225}On this basis, the Task Force judged that the certainty, considered across all critical and important outcomes in the IPD NMA was **very low**. We concluded that the certainty of evidence relating to mortality is, at best **low** for the comparison between low and high FiO2 for short-term mortality, **very low** for the comparison between intermediate and high categories, **very low** for all for morbidity outcomes and receipt of chest compressions and **low** for the overall ranking of FiO2 categories. NetMotion did not examine long-term outcomes (mortality or neurodevelopmental impairment).The prediction intervals (i.e., range between which results of a future study would be expected to fall) crossed the line of no effect for both the high vs. low comparison (prediction interval 0.44, 95% CrI 0.15-1.34) and high vs. intermediate comparison (prediction interval 0.33, 95% CrI 0.08-1.40), which may be considered to further reduce the certainty of evidence. {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}**From the study-level meta-analysis:**For comparisons between any lower and any higher FiO2, the certainty of evidence was **very low** for all mortality and morbidity outcomes and receipt of chest compressions. There was insufficient evidence for meaningful meta-analysis of other resuscitation outcomes. The most frequent reasons for downgrading of certainty were risk of bias and very serious imprecision. Contributions to the risk of bias included that it was inevitable in nearly all the trials that the study group allocation could not be masked, which we considered most likely to affect determination of resuscitation outcomes. Many did not report whether outcome assessors for major morbidity were blinded to treatment group allocation, and earlier trials were less likely to have pre-registered protocols to allow determination of whether there was selective outcome reporting, or to report the method of random sequence generation. Very serious imprecision was determined because the combined sample size did not meet the Optimal Information Size for any outcome. Of note, two included studies used a method of cluster randomization, which was considered to have the potential to increase risk of bias in domains 1 and 2 of the RoB 2 tool. However one of these {Liyakat 2023 794} randomized oxygen and air cylinders and the days on which they were used and may have resulted in better concealment of randomization and blinding of the intervention than patient level randomization. It is not stated in the paper whether there were any actual clusters (which would only have occurred if two eligible infants were born on the same day). The other study randomly allocated different 2-month time periods and there were unquestionably clusters. {Law 2021 942} Because it was a small pilot study that contributes very little weight to the analysis, no adjustment for clustering has been applied. (This study was excluded from NetMotion).For **long term mortality,** as in the previous ILCOR systematic review, {Welsford 2019 1} there were only two papers included {Boronat 2016 e 20161405, Thamrin 2018 55}, which reported the 1-3 year outcomes of {Aguar 2013 } plus {Rook 2014 1322}, and {Oei 2017 26} respectively. The missing proportions from the follow-up in these trials were 7.5% and 17.6% respectively. Missing mortality data or mis-attribution for as few as 2-3 infants who died could have changed the statistical significance of the effect estimate. Of note, there were inconsistencies in the CONSORT diagrams in the follow-up paper by {Thamrin 2018 55}, and the original Torpido study paper {Oei 2017 26} that were not fully resolved by enquiry of study authors. In the follow-up study, {Thamrin 2018 55}, a higher total number of babies is shown as included in the study, the number of babies attributed to the high oxygen group was higher than the number originally allocated to that group, and the number in the low oxygen group was lower.  |  |
| 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 | Consistent with previous ILCOR systematic reviews, the importance of outcomes has been assigned in accord with consensus of the Neonatal Life Support Task Force {Strand 2020 } and other expert and parent consensus. {Webbe 2020 } |  |
| 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 | **From the individual patient data network meta-analysis:**From direct comparisons, NetMotion found benefit to high vs. low oxygen for commencing resuscitation for the critical primary outcome for the review, **short-term mortality** (low certainty evidence), with no evidence of benefit for other critical or important outcomes. The study also suggested benefit for **high vs intermediate oxygen** for short term mortality but with very low certainty evidence. {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}**From the study-level meta-analysis:****RCTs**For all critical and important outcomes that were reported in the included studies, there was low or very low certainty evidence that could not exclude benefit or harm from the use of a low compared to a high level of oxygen for initiating resuscitation in preterm infants <35 weeks' gestation.Most studies included detailed provisions for titrating or changing FiO2 depending on response to oxygen saturation (SpO2) measured using pulse oximetry and utilising early and frequent observations and adjustments. The remaining studies had provisions for crossover or adjustments in certain circumstances, or after a specified time interval. It seems likely that the better the adherence to these strategies, the greater the likelihood that any differential in study outcomes between high and low initial oxygen concentrations would be reduced. However, the effect on short-term mortality of low oxygen vs high oxygen in those studies that used no or late titration (RR 1.10, 95% CI 0.81 to 1.60) {Harling 2005 F401, Law 2021 942, Liyakat 2023 794, Rabi 2011 e374, Wang 2008 1083} was very similar to that in studies that used early titration (RR 1.25, 95% CI 0.65-2.40). {Armanian 2012 25, Boronat 2016 e 20161405, Dekker 2019 10.3389/fped.2019.00504, Kaban 2022 104, Kapadia 2013 e1488, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439} The test for subgroup differences was not significant: Chi2 = 0.14 df = 1, p = 0.71 I2 = 0%. (Note that in this comparison, one study is included twice and the low FiO2 group is represented twice because it was a 3-arm study, one high FiO2 group with titration (managed by the study investigator) and one with no titration. {Rabi 2011 e374}). One trial compared FiO2 0.30 to 0.50, both of which are within our definition of "low", and the difference between these oxygen concentrations may have been small enough to mask an overall difference between low and high. {Kaban 2022 104} However, removing this trial from the analysis resulted in confidence intervals that still crossed the line of no effect. There was also no apparent influence of the level of oxygen used in the low oxygen group; with effect sizes being:* RR 1.12, 95% CI 0.76 to1.64 for studies that used FiO2 0.21 as the low oxygen group. {Kapadia 2013 e1488, Liyakat 2023 794, Lundstrøm 1995 F81, Oei 2017 26, Rabi 2011 e374, Wang 2008 1083}
* RR 1.46 95% CI 0.73 to 2.88 for studies that used FiO2 0.30 as the low oxygen group {Aguar 2013 , Armanian 2012 25, Dekker 2019 10.3389/fped.2019.00504, Kaban 2022 104, Law 2021 942, Rook 2014 1322, Vento 2009 e439}
* RR 0.80 95% CI 0.24 to 2.65 for the one study that used FiO2 0.50 as the low oxygen group. {Harling 2005 F401}

The test for subgroup differences was not significant: Chi2 = 11.76, df = 11, p = 0.47, I2 = 0%. Thus for short term mortality, the results did not show differences by or pre-specified subgroup analyses, (or by gestation - see Subgroup Considerations below). In a study level post-hoc analysis by NetMotion subgroups:* RR 1.73, 95%CI 0.53-5.58 for studies that compared intermediate vs low initial FiO2 (0.5-0.65 vs ≤0.3) {Aguar 2013 , Harling 2005 F401, Kaban 2022 104, Law 2021 942, Rook 2014 1322}
* RR 1.29 95% CI 0.89 to 1.87 for studies that used high vs low initial FiO2 (≥0.9 vs ≤0.3) {Armanian 2012 25, Dekker 2019 10.3389/fped.2019.00504, Kapadia 2013 e1488, Liyakat 2023 794, Oei 2017 26, Rabi 2011 e374, Vento 2009 e439, Wang 2008 1083}

The test for subgroup differences was not significant; Chi2 = 0.21, df = 1, p = 0.65 I2 = 0%**Non-RCTs**These studies (included in the previous meta-analysis) could not exclude benefit or harm for short term mortality, and are at high risk of bias. For long term mortality they suggested benefit for long term mortality but not neurodevelopmental impairment, but the risk of bias due to incomplete outcome data was sufficiently high that we do not think they should influence the estimate of balance of effects.  | In clinical care outside clinical trials, there may be latencies in obtaining accurate measurements of saturation and heart rate and in the responses of resuscitation personnel.  |
| Resources required |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs○ Moderate costs● Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | No studies specifically addressed the required resources.  | The Task Force concluded that there was unlikely to be a difference in resources, beyond those needed for training in any new strategy.  |
| 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 studies specifically addressed the required resources.  |  |
| 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 included studies addressed cost-effectiveness. |  |
| 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 | No direct evidence from included studies. There were included studies from both high- and middle-income countries.  |  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | The rate of deviations from study protocols was low in studies that reported it.  |  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know |  |  |

# 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 |
| ○  | ○  | **●**  | ○  | ○  |

# Conclusions

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| Recommendation |
| Among newborn infants <32 weeks’ gestation, it is reasonable to begin resuscitation with more than 30% oxygen. (Weak recommendation, low COE). For infants born at 32 to 34+6 weeks' gestation, there is insufficient evidence to make a recommendation. Subsequent titration of oxygen concentration using pulse oximetry is advised. (Weak recommendation, very low certainty evidence).The uncertainty over the optimal initial oxygen concentration means that it is reasonable to study a full range of oxygen concentrations (21-100%) within a research protocol. |

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| Justification |
| **Overall justification**The previous ILCOR treatment recommendation (2020 ) was: *We* ***suggest*** *starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks’ gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence).* {Soar 2019 e826}This was based on (1) evidence from RCTs appraised at the time that for all critical and important outcomes of the review, there was no benefit or harm of using either lower or higher oxygen concentrations for commencing resuscitation, (2) evidence from observational studies suggesting benefit of lower oxygen concentrations for long term mortality and (3) the evidence from "*decades of research (that) demonstrate that oxygen exposure is a determinant of critical neonatal outcomes in preterm infants. Concern remains that oxygen concentrations to which preterm infants are exposed if they need resuscitation immediately after birth may be a critical contributor to outcomes regardless of subsequent oxygen exposure*". {Soar 2019 e826}The updated study level meta-analysis found that benefit or harm could not be excluded for lower vs. higher concentrations of oxygen for commencing resuscitation, with low certainty of evidence for all outcomes. The NetMotion individual patient network meta-analysis suggested benefit of higher concentrations and that 90-100% may result in the lowest mortality {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848}, but the Task Force concluded that the overall certainty of evidence is still very low. Concerns persist regarding unmeasured adverse effects of hyperoxia and hypoxia, and most very preterm infants whose resuscitation has started in 21% or 100% will need prompt adjustments of inspired oxygen concentration, and as a result, two pending multicenter trials are utilizing 30% vs 60% oxygen for their treatment arms. Among the included trials, 6 (all of which allowed early/frequent titration of oxygen concentration) included measurements of various different markers of oxidative stress, inflammation and cerebral blood flow after resuscitation. Three of these six found differences in markers. {Kapadia 2013 e1488, Lundstrøm 1995 F81, Vento 2009 e439} This may be because of differences in study protocols or differences in the sensitivity of the different biomarkers. However, taken together, the studies do not establish conclusively the extent to which oxygen concentration for commencing resuscitation, (provided there are subsequent adjustments in response to oxygen saturation monitoring and other clinical events) affects biomarkers for injury caused by hypoxia or hyperoxia. Whichever initial oxygen concentration was used, oxygen saturation monitoring and individualized adjustments of inspired oxygen concentration were used in most of the clinical trials and are likely to be needed to optimize outcomes. **Detailed justification***Certainty of evidence*In determining the relative importance of evidence from the study level meta-analysis vs the IPD NWMA the Task Force noted the following: Both the study-level meta-analysis (according to usual ILCOR default) (and NetMotion) used Random Effects for calculation of confidence intervals, but even using the less conservative Fixed Effects for the study level meta-analysis, all confidence intervals in the study level meta-analysis crossed the line of no effect. The combined sample size did not meet the 'optimal information size' for any outcome (and was well below this level for several of them) the IPD NWMA. For this reason, the "prediction intervals" (the estimate of where results might lie in future studies) for the IPD NMA all cross the line of no effect. {Sotiropoulos 2024 10.1001/jamapediatrics.2024.1848} The use of individual patient data for network meta-analysis allows adjustment for important baseline characteristics of participants as well as differences in protocol-driven differences such as titration strategy, but there remains the possibility of unmeasured effect modifiers within and between studies. The Task Force noted that at the study level, there was no apparent dose-effect (subgroup interaction) for analysis by either the protocol-prespecified definitions of categories for low oxygen, or by the NetMotion categories of low, intermediate and high.  |

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| Subgroup considerations |
| *Oxygen level used for low oxygen group and titration strategy:*See section on Balance of Effects. *Gestation groups:*The effect size for short term mortality was similar for studies reporting infants (or subgroups) < 28 weeks' (or mostly <28 weeks') gestation or 28 to 34+6 weeks' gestation. * <28 weeks' gestation RR 1.67 95% CI 0.88 to 3.15 {Escrig 2008 875, Law 2021 942, Oei 2017 26, Vento 2009 e439}
* 28 - 34+6 weeks gestation RR 1.19 95% CI 0.77 to 1.83 {Armanian 2012 25, Liyakat 2023 794, Oei 2017 26}

The test for subgroup differences was not significant; Chi2 = 0.75, df = 1, p = 0.339, I2 = 0%. Note - one study is listed twice because a breakdown was provided by gestation subgroups. {Oei 2017 26} For the higher gestation group, the analysis attached heavy weighting to a study done in a low-resource setting where no titration of oxygen was possible and overall mortality was high. {Liyakat 2023 794}*Method of umbilical cord management:*There were insufficient data distinguishing infants by method of umbilical cord management to conduct this preplanned subgroup analysis.  |

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| Implementation considerations |
| Whichever initial oxygen concentration is chosen, protocols and training to ensure subsequent titration may be very important to achieving good outcomes, although the optimal titration targets and strategy have not yet been determined. Following the titration strategies derived from one or more of the included clinical trials may suffice until there is an evidence basis for the choice.  |

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| Monitoring and evaluation |
| Monitoring of the mortality, morbidity and resuscitation outcomes that were the pre-specified outcomes of this review is recommended.  |

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| Research priorities |
| * Human factors aspects of resuscitation performance depending on initial oxygen concentration for commencing resuscitation.
* Comparison of targets and strategies for oxygen saturation levels in the first 10-20 min after birth in preterm infants.
* Optimal oxygen concentration for commencing resuscitation in preterm newborn infants (noting that two trials comparing FiO2's of 0.30 to 0.60 are expected).
* Effect of initial oxygen concentrations and titration strategies on biomarkers of both hypoxic and hyperoxic injury to organs including the brain, lungs and retina.
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