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| Question | |
| **Should respiratory function monitoring vs. no respiratory function monitoring be used for resuscitation of infants at birth?** | |
| **Population:** | resuscitation of infants at birth |
| **Intervention:** | respiratory function monitoring |
| **Comparison:** | no respiratory function monitoring |
| **Main outcomes:** | intubation in delivery room (DR); Intubation in DR or < 24 hours; Achieving targeted tidal volumes (TV) of 4-8mL/kg; CPAP in DR; bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD); severe (Grade 3 or 4) intraventricular hemorrhage (IVH); Intubation < 24 hours - not in DR; Death prior to hospital discharge; Pneumothorax; Intraventricular hemorrhage all grades (IVH) |
| **Setting:** | delivery room |
| **Perspective:** |  |
| **Background:** | At birth, successful transition requires the newborn to rapidly complete multiple physiologic changes, including lung aeration, airway liquid clearance, and the initiation of pulmonary gas exchange. Although most term and late preterm newborns require no assistance, approximately 5% of term newborns require positive-pressure ventilation (PPV) immediately after birth to support successful transition. Effective ventilation of the newborn’s lung is the single most important component of neonatal resuscitation. Previous studies and anecdotal evidence suggest that the delivery of excessive TV at birth is associated with lung and brain injury, therefore monitoring TV at birth via a respiratory function monitor may limit that injury. Technology has been incorporated into the delivery room to provide the resuscitation team with various patient parameters (e.g. heart rate, oxygen saturation, etc). This systematic review was pursued to investigate the clinical impact or harm of respiratory function monitors on the newborn patient in the delivery room. |
| **Conflict of interests:** | One author (MT) participated in the van Zanten RCT’s design and protocol development, but was not involved in the execution, data analysis, data interpretation or manuscript preparation. She was excluded from bias assessment of this study. One author (YR) holds patents for pulse oximeter technology to guide oxygen titration in the delivery room. Georg Schmölzer and Peter Davis are the authors of one study {Schmölzer 2012 37}. Both acknowledged their potential intellectual conflicts of interest and participated in the Task Force discussion of the consensus on science and treatment recommendations. |

# Assessment

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| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | The respiratory function monitoring topic was reviewed in 2015 (Use of a Device to Assess Respiratory Function, Perlman JM Circulation 2015) based on 1 pilot randomized control trial (RCT) (n=49) with low certainty evidence (downgraded for risk of bias and imprecision). This study is included in the current review {Schmölzer GM 2012 377}. No evidence was found regarding time to heart rate >100 bpm, neurologically intact survival, BPD or pneumothorax.  Treatment recommendation suggested against the routine use of flow and volume monitoring for babies receiving PPV at birth, until more evidence became available. |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know | The systematic review identified 3 RCTs {Schmölzer 2012 377; Zeballos Sarrato 2019 1368; van Zanten 2021 317}, involving 443 newborns. One newborn infant died in the delivery room in the van Zanten et.al study which accounted for the total of 443 newborns, there is one less newborn reported in many of the longer-term outcomes due to this death.  **In response to resuscitation:**  For the important outcome of ***rate of intubation in the delivery room,*** evidence of **very** **low certainty** (downgraded for risk of bias, inconsistency and imprecision) from **3 RCTs** {Schmölzer 2012 377; Zeballos Sarrato 2019 1368; van Zanten 2021 317} involving 443 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.90, 95% CI 0.55 – 1.48; p=0.69; I2 = 61%).  For the important outcome of ***achieving desired tidal volumes in the delivery room,*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {Schmölzer 2012 3773; van Zanten 2021 3176} involving 337 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.96, 95% confidence interval (CI) 0.69 – 1.34; p=0.8; I2 = 0%).  For the important outcome of ***pneumothorax,*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {Zeballos Sarrato 2019 13687; van Zanten 2021 3176} involving 393 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.54, 95% CI 0.26 – 1.13; p=0.10; I2 = 0%).  For the important outcome of ***time to heart rate >100bpm in the delivery room***, no data were reported in the included studies.  For the outcome of ***face-mask leak***, the 3 RCTs could not be meta-analyzed as the measurement of leak was reported differently in each study. One trial reported median (IQR) percentage of leak per infant, and found less leak when RFM was visible (p=0.01) {Schmölzer 2012 3773}. Another trial reported percentage of leak >75% over all inflations, and found less leak when RFM was visible (p=0.001) {Zeballos Sarrato 2019 13687}. The third and largest trial reported median (IQR) percentage of leak >60% per infant and found no significant difference in leak (p=0.126) between RFM visible and the RFM not visible {van Zanten 2021 3176}.  **Longer-term clinical outcomes:**  For the critical outcome of ***death before hospital discharge,*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **3 RCTs** {Schmölzer 2012 3773; Zeballos Sarrato 2019 13687; van Zanten 2021 3176} involving 442 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 1.00 95% CI 0.66 – 1.52; p=0.99; I2 = 0%).  For the critical outcome of ***severe intraventricular hemorrhage (grades 3 or 4),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **1 RCT** {van Zanten 2021 3176} involving 287 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.96 95% CI 0.38 – 2.42; p=0.93). Statistical heterogeneity could not be calculated because events occurred in only one trial {van Zanten 2021 3176}.  For the important outcome of ***intraventricular hemorrhage (all grades),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {Zeballos Sarrato 2019 13687; van Zanten 2021 3176} involving 393 patients with **possible clinical benefit** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.69 95% CI 0.49-0.96; p=0.03; I2 = 0%).  For the important outcome of ***bronchopulmonary dysplasia/chronic lung disease (any),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {Zeballos Sarrato 20197 1368, van Zanten 2021 3176} involving 393 patients **could not exclude clinical benefit or harm** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.85 95% CI 0.7 – 1.04; p=0.12; I2 = 0%).   | **Outcomes** | **№ of participants (studies) Follow-up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with no respiratory function monitoring** | **Risk difference with respiratory function monitoring** | | Intubation in delivery room | 443 (3 RCTs)1,2,3 | ⨁◯◯◯ Very lowa,b,c | **RR 0.90** (0.55 to 1.48) | Study population | | | 353 per 1,000 | **35 fewer per 1,000** (159 fewer to 169 more) | | Achieving targeted tidal volumes (4-8mL/kg) | 337 (2 RCTs)1,3 | ⨁⨁◯◯ Lowa,d | **RR 0.96** (0.69 to 1.34) | Study population | | | 301 per 1,000 | **12 fewer per 1,000** (93 fewer to 102 more) | | Bronchopulmonary dysplasia | 393 (2 RCTs)2,3 | ⨁⨁◯◯ Lowa,e | **RR 0.85** (0.70 to 1.04) | Study population | | | 527 per 1,000 | **79 fewer per 1,000** (158 fewer to 21 more) | | Intraventricular hemorrhage (Grade 3 or 4) | 287 (1 RCT)3 | ⨁⨁◯◯ Lowa,e | **RR 0.96** (0.38 to 2.42) | Study population | | | 60 per 1,000 | **2 fewer per 1,000** (37 fewer to 86 more) | | Death prior to hospital discharge | 442 (3 RCTs)1,2,3 | ⨁⨁◯◯ Lowa,c | **RR 1.00** (0.66 to 1.52) | Study population | | | 165 per 1,000 | **0 fewer per 1,000** (56 fewer to 86 more) | | Pneumothorax | 393 (2 RCTs)2,3 | ⨁⨁◯◯ Lowa,d | **RR 0.54** (0.26 to 1.13) | Study population | | | 95 per 1,000 | **43 fewer per 1,000** (70 fewer to 12 more) | | Intraventricular hemorrhage (all grades) | 393 (2 RCTs)2,3 | ⨁⨁◯◯ Lowa,c | **RR 0.69** (0.49 to 0.96) | Study population | | | 318 per 1,000 | **99 fewer per 1,000** (162 fewer to 13 fewer) |  1. {Schmölzer 2012 3773} 2. {Zeballos Sarrato 2019 1368} 3. {van Zanten 2021 3176} 4. Lack of blinding for intervention; 2 studies with some concerns for selective reporting; 3 studies had high or serious concerns for overall risk of bias 5. Moderate - I2 = 61% 6. Wide confidence interval 7. Wide confidence interval / Small sample size 8. Wide confidence interval, small sample size, single study, remote outcome | **Face-mask leak**:  The direction in two studies towards benefit in reducing mask leak is consistent with training simulation studies, whereby using RFM reduced the percent of leak {O'Currain 2019 F582} (p<0.0001).  **Delivered TV above 8 mL/kg**  Two studies reported % of infants with TV >8mL/kg, showing a smaller proportion of infants with "excessive TV" when RFM was displayed compared to when it was not displayed, in a post-hoc analysis (14.8 vs 36.5%, p<0.001) in one study {Zeballos Sarrato 2019 1368}, 31 vs 36%, RR(95%CI) of 0.81(0.67-0.98) in the other study {Schmölzer 2012 3773}. However, the largest RCT reported % TV >8mL/kg per infant and duration of TV >8mL/kg in seconds per infant, showing no benefit or harm (p=0.932 and p=0.141, respectively) {van Zanten 2021 3176}.  **Duration of PPV:** 2 RCTs reported on this outcome using medians (IQR). Neither found a significant difference. Zeballos Sarrato et al. reported a median (IQR) PPV duration of 100 seconds (63-131) when RFM was visible and 80 seconds (45-146) when it was masked, p=0.444 {Zeballos Sarrato 2019 1368}. van Zanten reported PPV duration of 184 seconds (101-331) when RFM was visible and 170 seconds (82-292) when it was masked, p=0.242 . {van Zanten 2021 317}.  **Attention:** When RFM is used, providers look at the monitor screen and pay particular attention to TV being displayed {Katz T 2019 F259}. |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | Review of the 3 RCTs did not find any undesirable clinical effects from using respiratory function monitoring.  Potential undesirable effects:  1. TV below 4-8 mL/kg range  One study reported % TV <4 mL/kg per infant, showing no benefit or harm (p=0.094) {van Zanten 2021 3176}.  One study reported % of infants with delivered VT<4 mL/kg, this proportion was larger when RFM was displayed than when it was not displayed (43% versus 36%, statistical analysis not reported) {Schmölzer 2012 3773}.  2. TV above 8 mL/kg  Two studies reported % of infants with TV >8mL/kg, showing a smaller proportion of infants with "excessive TV" when RFM was displayed compared to when it was not displayed, in a post-hoc analysis (31 vs 36%, p<0.001) in one study {Zeballos Sarrato 2019 1368}, 14.8 vs 36.5%, RR(95%CI) of 0.81(0.67-0.98 in the other study {Schmölzer 2012 3773}. However, the largest RCT reported % TV >8mL/kg per infant and duration of TV >8mL/kg in seconds per infant, showing no benefit or harm (p=0.932 and p=0.141, respectively) {van Zanten 2021 3176}. | One potential undesirable effect that was not reported in these studies is distraction: Attention to the device may distract from paying attention to the newborn infant during resuscitation interventions (sample size n=12) {Herrick HM 2020 666}. Visual attendance to the RFM was 29% when it was visible versus 1% when it was masked (p=0.02); there was a non-significant reduction of gaze duration on the infant (29% vs 46%, p=0.05). The potential risk reduction in gaze attention to the newborn infant is unknown but might have a detrimental effect. |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | Certainty of the evidence was low, primarily due to risk of bias, imprecision and inconsistency. |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability | Authors and clinicians place value on achieving an appropriate tidal volume and reducing face mask leak during resuscitation, with several recent publications on this topic, the majority of which are simulation studies. |  |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know | The included studies did not provide evidence of benefit or harm. No undesirable effects were reported, so the balance of desirable/undesirable effects does not favor the intervention or the comparison, except for IVH (all grades).  For the important outcome of ***intraventricular hemorrhage (all grades),*** evidence of **low certainty** (downgraded for risk of bias and imprecision) from **2 RCTs** {Zeballos Sarrato 2019 13687; van Zanten 2021 3176} involving 393 patients with **possible clinical benefit** from displaying a respiratory function monitor compared to not displaying a respiratory function monitor (RR 0.69 95% CI 0.49-0.96; p=0.03; I2 = 0%). |  |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | There is an increased cost associated with the introduction of RFM into the delivery room (equipment, maintenance, supplies, training of personnel). |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies | No specific device cost or training cost were reported in these trials. However, there is moderate cost of purchasing and implementing new devices. |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | There are no data to comment on the cost-effectiveness of this intervention. |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know | The cost of equipment and training resources may be significantly more limited in low-resource settings, so health equity may be potentially reduced and the gap between well-resourced and resource-limited environments may therefore become larger. However, none of the included studies specifically addressed equity. |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know | There were no staff surveys looking into acceptability in these studies. |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | The use of an RFM in the delivery room is feasible based upon the include studies, however these studies were performed in highly resourced settings under study conditions. Further research is needed to assess feasibility in other resuscitation settings. |  |

# Summary of judgements

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

# Type of recommendation

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

# Conclusions

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| Recommendation |
| There is insufficient evidence to make a recommendation for or against the use of a respiratory function monitor in newborn infants receiving respiratory support at birth (low certainty evidence). |
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| Justification |
| In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:  For newborn infants who receive respiratory support at birth, the Task Force did not make a recommendation for or against the use of a respiratory function monitor in part because of the low confidence in effect estimates for either benefit or harm (low certainty evidence).  One study reported the proportion of infants with tidal volume >8mL/kg {Zeballos Sarrato, 2019 1368} showing less excessive tidal volume when using RFM in infants <30 weeks' gestation (p<0.001 in n=21 infants 28-29 weeks' gestation, p<0.001 in n=51 infants <28 weeks' gestation). However, this was a post hoc analysis with relatively few patients and, therefore, did not influence our treatment recommendation.  IVH (all grades), but not severe IVH, was statistically significantly decreased in the RFM visible group (low certainty). However, there is a lack of certainty whether the difference in IVH between groups in 2 RCTs (n=393 patients) was attributable to the RFM or a chance finding as IVH (all grades) was one of many secondary outcomes. The composite outcome of IVH (all grades) and periventricular leukomalacia (PVL) was not considered for this recommendation as it was a post-hoc secondary outcome.  No specific device cost or training cost were reported in these trials. However, the cost of purchasing and implementing new devices is significant. In addition, there are several human factor issues that should be addressed if RFM use were to become more widespread.  The lack of clinical benefit, except the possible benefit in reducing IVH (all grades), and the lack of cost-effectiveness data, contributed to the recommendation statement. |

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| Subgroup considerations |
| No subgroup analyses were pre-planned or performed. |

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| Implementation considerations |
| We anticipate implementing RFM into routine clinical practice would require significant training and cost. In addition, there are human factor issues that need to be addressed should RFM be more widespread (see Research priorities section below). |

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| Monitoring and evaluation |
| If respiratory function monitoring is implemented, clinical outcome monitoring should continue, for both short term (e.g. face-mask leak, time to HR >100 bpm, TV within desired range and outside the range) and long term clinical outcomes (e.g. BPD, neurodevelopment impairment). |

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| Research priorities |
| Research priorities should include human factor assessment, methods exploring opportunities to reduce inequity, and cost-benefit analysis. Standardized operational definitions for outcomes in future studies would permit meta-analysis of results such as mask leak.  Potential research questions are listed below:  Does the use of a RFM vs no RFM during neonatal resuscitation in the delivery room result in a difference in the percentage of time spent delivering a target tidal volume? What is the definition of clinically significant mask leak (in terms of % leak and % of time spent with that degree of leak)?  Does the use of a RFM vs no RFM during neonatal resuscitation in the delivery room result in a faster time to a heart rate >60 bpm (and >100 bpm)?  What is the optimal manner in which RFM data and alarms should be displayed to achieve the most accurate and timely acquisition, interpretation and translation to actionable information?  What are the training requirements to achieve and maintain competency in the acquisition and accurate interpretation of data derived from RFM during neonatal resuscitation?  What is the cost effectiveness for the use of RFM (vs no RFM) during neonatal resuscitation? |

# References Summary

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