QUESTION

Should passive ventilation vs. standard CPR be used for patients in cardiac arrest?	
POPULATION:	Adults and children in cardiac arrest
INTERVENTION:	Any passive ventilation technique (eg positioning the body, opening the airway, passive oxygen administration, Boussignac tube, constant flow insufflation of oxygen) in addition to chest compression
COMPARISON:	Standard CPR
MAIN OUTCOMES:	ROSC, survival to hospital admission, survival to ICU discharge, neurologically intact survival to hospital discharge
SETTING:	in-hospital and out-of-hospital setting
PERSPECTIVE:	Patient
BACKGROUND:	Administration of adequate ventilation is essential to successful resuscitation after cardiac arrest. Positive-pressure ventilation, through bag-valve-mask or an advanced airway, has been the fundamental approach during CPR. Passive ventilation during CPR may provide a viable out-of-hospital cardiac arrest treatment alternative. During chest compression-only CPR in the out of hospital setting, some EMS systems have chosen to provide passive ventilation in the form of an airway maneuver and/or device combined with an oxygen-delivery mask.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

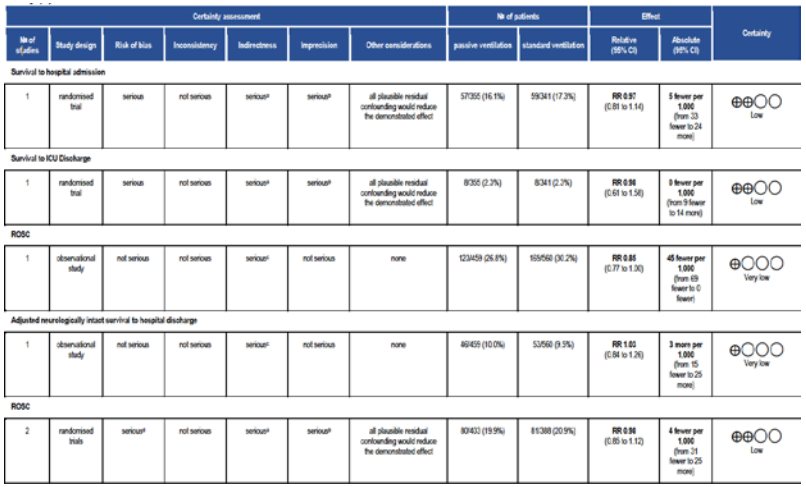
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Mortality after cardiac arrest remains high, and there is broad consensus that new treatments and strategies are needed.	Passive ventilation may represent a new alternative positive-pressure ventilation. In addition, this approach may: - Shorten interruptions in chest compression for advance airway management - Overcome the potential detrimental effects of positive-pressure ventilation: rising in intrathoracic pressure; reduced venous return to the heart; reduced coronary perfusion pressure; increased pulmonary vascular resistance.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	 Two RCTs compared intermittent positive-pressure ventilation via an endotracheal tube with continuous insufflation of oxygen through a modified endotracheal tube. The third study compared placement of an oropharyngeal airway and administration of oxygen by nonrebreather mask or by bag-mask ventilation during a bundle of care involving 200 continuous chest compressions and delayed intubation. Additional data from a pilot RCT reported no statistical difference in ROSC when chest compression-induced ventilation with continuous positive airway pressure in 9 patients was compared to standard volume-controlled ventilation in 11 patients (22% vs. 9%).	The overall quality of evidence was rated as very low primarily due to a critical risk of bias. The individual studies were all at a critical risk of bias due to confounding and indirectness. Because of a high degree of heterogeneity, the meta-analyses included only 2 RCTs, in which passive ventilation through constant flow insufflation of oxygen with the aid of a modified endotracheal tube was compared to mechanical ventilation. Additional data from the largest RCT included in the meta-analysis (Bertand 2006) showed that the percentage of patients with measurable SpO2 and with values above 70% were both significantly greater in the constant flow insufflation of oxygen group compared to standard CPR. The Boussignac tube used in these studies is known to generate a constant endotracheal pressure of approx. 10 cmH2O. In addition, the active compression decompression device, when available, was used to perform CPR. The above adjuncts may have played a role in the generation and in the magnitude of passive ventilation by chest compression. The observational study presents critical problems related to indirectness. Indeed, different CPR protocols were compared, characterized not only by different ventilation strategies but also by different rhythm check timings, compression/ventilation ratios, and compression intervals between shocks. No studies were found describing this approach in the lay rescuer setting.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	There is a lack of evidence for or against undesirable effects of passive ventilation.	No studies investigated this approach in the lay rescuer setting.

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	The overall certainty of evidence is VERY LOW. All the included studies had a very high risk of bias. The 2 RCTs included in the meta-analyses, employed CPR protocols including the use of the Boussignac tube, known to generate a constant endotracheal pressure of approx. 10 cmH2O, and the active compression decompression device, when available. The observational study compared different CPR protocols, characterized not only by different ventilation strategies but also by different rhythm check timings, compression/ventilation ratios, and compression intervals between shocks. No studies were found describing this approach in the lay rescuer setting.	

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	With reference to the guidance provided by the COSCA initiative ("Core Outcome Set for Cardiac Arrest" - a partnership between patients, their partners, clinicians, research scientists, and the International Liaison Committee on Resuscitation, sought to develop a consensus core outcome set for cardiac arrest for effectiveness trials), there is no important uncertainty about how much people would value favourable survival or survival as an outcome.	Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD; COSCA Collaborators. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2018 Jun;127:147-163. doi: 10.1016/j.resuscitation.2018.03.022.

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	No differences in both critical and important outcomes have been observed. Similarly, no undesirable effects have been reported. Nevertheless, due to the above reported critical risk of bias, both desirable and undesirable effects of the intervention remain very uncertain.	

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	The cost or need for resources to implement the intervention is uncertain. Introducing the passive ventilation approach in a resuscitation system will require resources for training and education. If passive ventilation would be delivered through the Boussignac tube and/or with the use of an active compression-decompression device, the costs then could be higher compared to current standard.	

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 evidence identified.	

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	We have not identified any evidence evaluating the cost-effectiveness of passive ventilation during CPR. There is a high degree of uncertainty regarding cost effectiveness as both effectiveness and cost of intervention is uncertain.	

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	As the cost of this intervention is uncertain, there is little to inform potential impact on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Acceptability to stakeholders is uncertain since there is no benefit evidence in support of passive ventilation in comparison to standard CPR. The intervention might be well accepted in experimental settings and in EMS systems that have already adopted a bundle of care that includes minimally interrupted cardiac resuscitation with passive ventilation.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Passive ventilation is feasible, however its implementation would require training and education.	

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	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

	JUDGEMENT						
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

Recommendation

We suggest against the routine use of passive ventilation techniques during conventional CPR (weak recommendation, very low-quality evidence)

Justification

This topic was prioritized by the BLS Task Force as the topic had not been reviewed since the 2015 Consensus on Science and Treatment recommendations.

Passive ventilation may represent an alternative to intermittent positive-pressure ventilation. In addition, this approach may shorten interruptions in chest compression for advance airway management and may overcome the potential detrimental effects of positive-pressure ventilation: rising in intrathoracic pressure; reduced venous return to the heart; reduced coronary perfusion pressure; increased pulmonary vascular resistance.

In making this recommendation, we place priority on consistency with our previous recommendations in the absence of compelling evidence for improvement in any of our critical outcomes.

The overall quality of evidence was rated as very low primarily due to a critical risk of bias due to confounding and indirectness.

The RCTs compared intermittent positive-pressure ventilation via an endotracheal tube with continuous insufflation of oxygen through a modified endotracheal tube, ie Boussignac tube. The Boussignac tube used in these studies is known to generate a constant endotracheal pressure of approximately 10 cmH2O. In addition, the active compression decompression device, when available, was used to perform CPR. The above adjuncts may have played a role in the generation and in the magnitude of passive ventilation.

The observational study presented critical problems related to indirectness. Indeed, different CPR protocols were compared, characterized not only by different ventilation strategies but also by different rhythm check timings, compression/ventilation ratios, and compression intervals between shocks.

Finally, No studies were found describing this approach in the lay rescuer setting.

We acknowledge that where EMS systems have adopted a bundle of care that includes minimally interrupted cardiac resuscitation with passive ventilation, it is reasonable to continue in the absence of compelling evidence to the contrary.

Subgroup considerations

No studies investigated passive ventilation in the lay rescuer setting.

Implementation considerations

None

Monitoring and evaluation

None

Research priorities

Which elements of the bundled care (compressions, ventilations, delayed defibrillation) are most important? What is the optimal method for ensuring a patent airway? Is there a critical volume of air movement required to maintain effectiveness? How effective is passive insufflation in children?

QUESTION

Should minimization of pauses in chest compressions (higher CPR fraction and shorter peri-shock pause compared to control) vs. standard CPR (lower CPR fraction and longer peri-shock pause compared to intervention) be used for adult patients in cardiac arrest?	
POPULATION:	adult patients in cardiac arrest
INTERVENTION:	minimization of pauses in chest compressions (higher CPR fraction and shorter peri-shock pause compared to control)
COMPARISON:	standard CPR (lower CPR fraction and longer peri-shock pause compared to intervention)
MAIN OUTCOMES:	Survival in randomized controlled trials designed to evaluate interventions affecting quality of CPR; Survival in observational studies comparing outcomes before and after interventions designed to improve quality of care ; Survival in observational studies exploring associations between pauses in chest compressions and outcomes ; Survival in observational studies where outcomes where compared between groups in different chest compression pause categories; Survival in observational studies where pauses in compressions were compared between survivors and non-survivors;
SETTING:	in-hospital and out-of-hospital setting
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Mortality after cardiac arrest remains high, and there is broad consensus that new treatments and strategies are needed.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know		The data is very uncertain with no studies directly evaluating the question. The effect estimates also vary both in magnitude and direction.

Outcomes	Impact
Survival in randomized controlled trials designed to evaluate interventions affecting quality of CPR	**The first trial** included 845 patients and evaluated an experimental AED algorithm that observed higher CPR fractions (61% vs. 48%, p<0.001) and shorter pre-shock (9 vs. 19 sec, p<0.001) and post-shock pauses (11 vs. 33, p<0.001) when comparing intervention vs. control. However, there were no significant difference in survival to hospital admission (43.2% vs. 42.7%, p=0.87) or discharge (13.3% vs. 10.6%, p=0.19).(Jost 2010) **The second trial** included 23,711 patients and evaluated a continuous chest compression strategy that observed higher CPR fractions (83% vs. 77%, p<0.001) when comparing intervention vs. control (30:2 CPR). While there was higher survival to hospital admission (24.6% vs. 25.9%, p=0.03), there was no significant difference in survival to discharge (9.0% vs. 9.7%, p=0.07).(Nichol 2015) **The third trial** included 456 patients and evaluated an experimental AED algorithm that observed higher CPR fractions (58% vs. 42%, p<0.001) and shorter pre-shock (6 vs. 20 sec, p<0.001) and post-shock pauses (7 vs. 27, p<0.001) when comparing intervention vs. control. However, there were no significant differences in survival to hospital admission (62% vs. 65%, p=0.51) or discharge (42% vs. 38%, p=0.46).(Beseems 2016)
Survival in observational studies comparing outcomes before and after interventions designed to improve quality of care	For the critical outcome ***survival with favourable outcome***, we identified very low certainty evidence (downgraded for critical risk of bias) from 2 observational studies (Grunau 2018, Olasveengen 2009) enrolling 16,122 adult out-of-hospital cardiac arrests. The first study evaluated incremental changes in various CPR quality metrics and outcomes over time, and found that both CPR fraction and proportion of survivors with favourable survival increased from 2006 to 2016 (along with several other quality metrics).(Grunau 2019) The second study compared outcomes for patients treated by a physician-manned ambulance with patients treated with paramedic-manned ambulance, and observed higher CPR fraction (90% vs. 83%, p<0.001) and shorter pre-shock pauses (4 vs. 16 sec, 0<0.001) in patients treated by the physician-manned ambulance, but there were no significant differences in survival with favourable outcome (13% vs. 10%, p=0.38). For the critical outcome ***survival to hospital discharge or 30 days***, we identified very low certainty evidence (downgraded for critical risk of bias) from 3 observational studies (Bleijenberg 2017, Grunau 2018, Olasveengen 2009) enrolling 16,246 adult out-of-hospital cardiac arrests. A study comparing outcomes before and after implementation of training and feedback interventions, found improved CPR fraction after intervention (86% vs. 79%, p<0.001), but did not observe any statistically significant difference in survival (20% vs. 15%, p=0.43).(Bleijenberg 2017)

		A study evaluating incremental changes with time, found CPR fraction increased from 81% to 87% and adjusted risk of discharge rate increased from 8.6% to 16% (p < 0.01 for trend) from the beginning to the end of the observation period (2006-2016).(Grunau 2019) The study comparing cardiac arrests treated by physician- vs. paramedic-manned ambulances observed similar survival to discharge between groups (11% vs. 13%, p=0.28).(Olasveengen 2009) For the important outcome ***survival to hospital admission***, we identified very low certainty evidence (downgraded for critical risk of bias) from 3 observational studies (Bleijenberg 2017, Lakomek 2020, Olasveengen 2009) enrolling 1,393 adult out-of-hospital cardiac arrests. A study comparing outcomes before and after implementation of training and feedback interventions, found improved CPR fraction after intervention (86% vs. 79%, p<0.001), but did not observe any statistically significant difference in admission (42% vs. 46%, p=0.59).(Bleijenberg 2017) A study evaluating the effect of CPR monitoring and feedback found an increase in CPR fraction (80% vs. 88%, p<0.001), but no significant difference in admission (32% vs. 36%, p=0.52).(Lakomek 2020) A study comparing outcomes before and after implementation of system level feedback and targeted training, and observed higher CPR fraction (79% vs. 73%, p=0.007), but no significant differences in survival to hospital admission (12% vs. 12%, p=0.9).(Lyon 2012) The study comparing cardiac arrests treated by physician- vs. paramedic-manned ambulances observed similar admission to hospital between groups (25% vs. 28%, p=0.50).(Olasveengen 2009) For the important outcome ***ROSC***, we identified very low certainty evidence (downgraded for critical risk of bias) from 5 observational studies (Grunau 2018, Lakomel 2020, Lyon 2012, Olasveengen 2009) enrolling 16,525 adult out-of-hospital cardiac arrests. A study evaluating incremental changes with time, found CPR fraction increased from 81% to 87% and adjusted risk of ROSC rate increased from 40.7% to 51.4% (p < 0.01 for trend) from the beginning to the end of the observation period (2006-2016).(Grunau 2019) A study evaluating the effect of CPR monitoring and feedback found an increase in CPR fraction (80% vs. 88%, p<0.001), but no significant difference in ROSC (45% vs. 50%, p=46).(Lakomek 2020) A study comparing outcomes before and after implementation of system level feedback and targeted training observed higher CPR fraction (79% vs. 73%, p=0.007), but no significant differences in survival to hospital admission (32% vs. 40%, p=0.56).(Lyon 2012) The study comparing cardiac arrests treated by physician- vs. paramedic-manned ambulances observed similar ROSC between groups (33% vs. 34%, p=0.74).(Olasveengen 2009)	
	Survival in observational studies exploring associations between pauses in	*CPR fraction* For the critical outcome survival to discharge or 30 days, we identified 4 observational studies (Bouwer 2015, Cheskes 2017, Christenson 2009, Wik 2016) enrolling 18,390 adult out-of-hospital cardiac arrests. Two of these studies found increasing CPR fractions to be	

chest compressions and outcomes	associated with improved survival (adjusted OR 6.34; 95% CI 1.02-39.5 and OR 1.11; 95% CI 1.01-1.21),(Christenson 2009, Wik 2016) whereas the remaining two did not. (Bouwer 2015, Cheskes 2017) For the important outcome ROSC, we identified one observational study enrolling 2,103 adult out-of-hospital cardiac arrests which did not find increasing CPR fraction to be associated with improved survival (adjusted OR 1.05; 95% CI 0.99-1.12).(Vaillancourt 2011) *Peri-shock pauses* For the critical outcome survival to discharge or 30 days, we identified 2 observational studies (Bouwer 2015, Cheskes 2017) enrolling 15,887 adult out-of-hospital cardiac arrests. One of these studies found increasing peri-shock pause to be associated with lower survival (adjusted OR for survival 0.85 per 5 min increase; 95% CI 0.77-0.93),(Bouwer 2015) while the other found no significant association between pre-shock pause and survival (adjusted OR for survival 1.07 per 5 sec increase; 95% CI 0.99-1.16).(Cheskes 2017)	
Survival in observational studies where outcomes where compared between groups in different chest compression pause categories	*CPR fraction*For the critical outcome survival with favourable outcome, we identified 1 observational study (Rea 2014) enrolling 446 adult out-of-hospital cardiac arrests which showed higher survival in arrests with CPR fraction >80.4% compared to <80.4% (20% vs. 7%, P=0.015) in the sub-group with 20 minute CPR duration. There were no significant differences in sub-groups with 5 or 10 min CPR durations. For the critical outcome survival to discharge or 30 days, we identified 5 observational studies (Cheskes 2015, Cheskes 2017, Christenson 2009, Rea 2014, Vaillancourt 2020) enrolling 31,459 adult out-of-hospital cardiac arrests. One study observed higher survival in arrests with CPR fraction >80.4% compared to <80.4% (20% vs. 8%, P=0.032) in the sub-group with 20 minute CPR duration,(Rea 2014) whereas two other studies observed higher adjusted odds ratio for survival in arrests with lower CPR fractions (2.00; 95% CI 1.16-3.32 when <40% was compared to >80%)(Vaillancourt 2020) and lower adjusted odds ratio for survival in higher CPR fractions (0.30; 95% CI 0.20-0.44 and 0.49; 95% CI 0.36-0.68 when <60% was compared to <80% and 60-79%).(Cheskes 2015) There were no significant differences in outcomes in the remaining two studies. (Cheskes 2017, Christenson 2009) For the important outcome ROSC, we identified 4 observational studies (Rea 2014, Talikowska 2017, Vaillancourt 2011, Vaillancourt 2020) enrolling 15,679 adult out-of-hospital cardiac arrests. One study observed higher ROSC rates in arrests with CPR fraction >80.4% compared to <80.4% in the sub-group with 10 minute (59% vs. 40%, P=0.004) and 20 minute (40% vs. 18%, P=0.004) CPR duration,(Rea 2014) and another study observed lower adjusted odds ratio for ROSC in arrests with CPR fraction 40-60% (0.83; 95% CI 0.72-0.95) and 60-80% (0.85; 95% CI 0.77-0.94) compared to CPR fraction >80%.(Vaillancourt 2020) A third study observed lower adjusted odds ratio for ROSC with CPR fraction >80 compared to <80% (0.49, 95%CI: 0.28–0.87).(Talikowska 2017) There	

	were no significant differences in outcomes in the remaining study.(Vaillancourt 2011) *Peri-shock pauses*For the critical outcome survival to discharge or 30 days, we identified 4 observational studies (Cheskes 2011, Cheskes 2014, Cheskes 2015, Cheskes 2017) enrolling 20,400 adult out-of-hospital cardiac arrests. Three of these studies observed higher survival in patients with shorter pre-shock pauses (< 10 sec) compared to longer pre-shock pauses (>10-20 sec), (Cheskes 2011, Cheskes 2014, Cheskes 2015) and two observed higher survival in patients with shorter peri-shock pauses (< 20 sec) compared to longer peri-shock pauses (>20-40 sec). (Cheskes 2011, Cheskes 2015) The largest (15,568 patients), most recent study did not find improved survival with pre-shock pause < 10 sec compared to > 10 seconds in adjusted analysis (adjusted OR 0.86; 95% CI 0.69-1.05).(Cheskes 2017)	
Survival in observational studies where pauses in compressions were compared between survivors and non-survivors	*CPR fraction* For the important outcome chest compression fraction, we identified very low certainty evidence (downgraded for critical risk of bias) from 8 observational studies (Abella 2005, Brouwer 2015, Cheskes 2011, Cheskes 2014, Talikowska 2017, Uppiretla 2020, Valenzuela 2005, Wik 2005) enrolling 3722 adult out-of-hospital cardiac arrests with diverging results. While two studies observed significantly higher CPR fractions in non-survivors compared to survivors in certain subgroups (74% vs. 71%, p=0.04 and 83% vs. 73%, p=0.02),(Brouwer 2015, Talikowska 2017) another study observed significantly higher CPR fractions in survivors compared to non-survivors (81% vs. 61%, p=0.001).(Uppiretla 2020) The remaining five studies did not observe any differences.(Abella 2005, Cheskes 2011, Cheskes 2014, Valenzuela 2005, Wik 2005)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	There is a lack of evidence for or against undesirable effects of lack of pauses during CPR. Pauses in chest compressions during cardiac arrest will lead to cessation of circulation, and the lack of resuscitation eventually leads to certain death. Experimental animal data have to a limited degree explored possible positive effects of post-conditioning (limited pauses in CPR). There is no human data to inform post-conditioning during cardiac arrest. Weighing a theoretically possibility of positive effects from limited pauses in chest compressions against a certain detrimental effect of lack of chest compressions, it is reasonable to assume low risk of harm from lack of chest compression pauses.	

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	The overall certainty of evidence is VERY LOW. All the included studies had a very high risk of bias (high risk of confounding that most studies did not attempt to make any adjustments for). There were also problems with indirectness. There is serious doubt whether the evidence directly answers the health care question asked as the studies identified were either designed to evaluate a related intervention or observational studies exploring possible associations between CPR fraction/peri-shock pauses and survival. Lastly, there was concern of inconsistency with very heterogenous results, varying in both magnitude and direction.	

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	With reference to the guidance provided by the COSCA initiative ("Core Outcome Set for Cardiac Arrest" - a partnership between patients, their partners, clinicians, research scientists, and the International Liaison Committee on Resuscitation, sought to develop a consensus core outcome set for cardiac arrest for effectiveness trials), there is no important uncertainty about how much people would value favourable survival or survival as an outcome.	Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD; COSCA Collaborators. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2018 Jun;127:147-163. doi: 10.1016/j.resuscitation.2018.03.022.

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	As both desirable and undesirable effects are very uncertain. Still, undesirable effects are considers unlikely - and the possibility for desirable effects from intervention would therefore outweigh the possible undesirable effects.	

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	The cost or need for resources to implement the intervention is uncertain. Increasing CPR fraction or shorten peri-shock pauses in a resuscitation system will require resources for training and education. However, it is unclear whether the requirements surpass the resources systems already have in place for continued education and training. If increasing CPR fraction or shorten peri-shock pauses nessecitates advanced and costly equipment to monitor CPR metrics, there could be substatial cost.	

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 evidence identified.	

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	We have not identified any evidence evaluating the cost-effetiveness of interventions to increase CPR fraction or shorten peri-shock pauses. There is a high degree of uncertainty regarding cost effectiveness as both effectiveness and cost of intervention is uncertain.	

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	As the cost of this intervention is uncertain, there is little to inform potential impact on health equity. Increasing CPR fraction or shorten peri-shock pauses in a resuscitation system will require resources for training and education. However, it is unclear whether the requirements surpass the resources systems already have in place for continued education and training. If increasing CPR fraction or shorten peri-shock pauses nessecitated advanced and costly equipment to monitor CPR metrics, there could potentially be a negative impact on health 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 is general consensus within the resuscitation community is that high quality CPR is important for patient outcomes, and that high quality CPR includes high CPR fraction and short peri-shock pauses. Although the exact targets of these CPR metrics are uncertain, interventions to improve CPR quality (including increasing CPR fraction and shortening peri-shock pauses) are acceptable to key stakeholders.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Current guidelines highlight the importance of high quality CPR, and commonly used education and training materials already emphazise minimizing pauses in chest compressions. CPR monitoring is common practice in many systems. Implementation if interventions to monitor and increase CPR fraction and shorten peri-shock pauses is feasible.	

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	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

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

Recommendation

We suggest CPR fraction and peri-shock pauses in clinical practice be monitored as part of a comprehensive quality improvement program for cardiac arrest designed to ensure high-quality CPR delivery and resuscitation care across resuscitation systems (weak recommendation, very-low-certainty evidence).

We suggest preshock and postshock pauses in chest compressions be as short as possible (weak recommendation, very-low-certainty evidence).

We suggest the CPR fraction during cardiac arrest (CPR time devoted to compressions) should be as high as possible and at least 60% (weak recommendation, very-low-certainty evidence).

Justification

This topic was prioritized by the BLS Task Force as the topic had not been reviewed since the 2015 Consensus on Science and Treatment recommendations.

There is general consensus within the resuscitation community is that high quality CPR is important for patient outcomes, and that high quality CPR includes high CPR fraction and short peri-shock pauses. Although the exact targets of these CPR metrics are uncertain, the strong belief in minimizing pauses in compressions (along with physiological rationale in the detrimental effect of no compressions) make prospective clinical trials of long vs. short compression pauses unlikely. The evidence identified in this review was either indirect (in that the interventional studies were developed for related purposes) or observational. Observational studies are challenged by the association between pauses in compressions and good outcome as short resuscitations in patients with shockable rhythms tend to have better outcomes that long resuscitation efforts in non-shockable cardiac arrest patients. The number and proportion of pauses will be dependent on both cardiac rhythm and resuscitation length, and an optimal target will therefore depend on the cardiac arrest characteristics. These factors make interpreting observational data and providing guidance for CPR metrics particularly challenging.

Experimental animal data have to a limited degree explored possible positive effects of post-conditioning (limited pauses in CPR).(Matsuura 2017 8, Segal 2012 1397) There is no human data to inform post-conditioning during cardiac arrest. Weighing a theoretically possibility of positive effects from limited pauses in chest compressions against a certain detrimental effect of lack of chest compressions, it is reasonable to assume low risk of harm from lack of chest compression pauses and that the possibility for desirable effects from fewer pauses outweigh the possible undesirable effects.

The cost or need for resources to implement the intervention is uncertain. Increasing CPR fraction or shorten peri-shock pauses in a resuscitation system will require resources for measuring CPR quality, training and education. However, it is unclear whether the requirements surpass the resources systems already have in place for continued education and training. The task force assessed the resources needed would likely be covered by standard operating costs of high performing systems.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

QUESTION

Impact of ambulance transport on quality of cardiopulmonary resuscitation: Transport with ongoing CPR vs. Completing CPR on scene	
POPULATION:	Adults and children receiving manual CPR following out-of-hospital cardiac arrest
INTERVENTION:	Transport with ongoing manual CPR
COMPARISON:	Completing manual CPR on scene
MAIN OUTCOMES:	Quality of CPR metrics Survival
SETTING:	out-of-hospital
PERSPECTIVE:	
BACKGROUND:	Poor quality CPR may adversely impact survival outcomes in cardiac arrest. Provision of high-quality CPR is challenging, especially in a moving ambulance. If CPR quality is lower during ambulance transport it may be appropriate to advocate that EMS remain on scene and focus upon delivery of high-quality CPR.
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no **X** Probably yes ○ Yes ○ Varies ○ Don't know	The cornerstone of high-quality CPR comprises delivery of chest compressions at a rate of 100-120 compression per minute, to a depth of 50-60mm, while allowing full recoil of the chest between compressions. Interruptions should be minimized and should not exceed 10 seconds. Defibrillation should occur as soon as a defibrillator is available and then at 2-minute intervals thereafter if still appropriate. If EMS crews will initiate resuscitation at the scene of cardiac arrest. If they fail to achieve ROSC they must either terminate resuscitation on scene or transport the patient to hospital with ongoing CPR Transport with ongoing CPR may be problematic for the following reasons: 1) Extrication from the scene of the cardiac arrest, to the ambulance, results in interruptions to CPR and reduces quality of CPR. This may adversely impact the likelihood of achieving ROSC 2) There is limited evidence to suggest quality of manual CPR may be reduced during ambulance transport which may adversely impact the likelihood of achieving ROSC. 3) EMS providers are at increased risk of injury during transport in the event of a collision if standing unrestrained while performing CPR.	When EMS cannot provide interventions that may be beneficial to the victim of cardiac arrest, e.g. ECMO or resuscitative hysterotomy, then the potential benefits of those interventions may outweigh the risks associated with transport.

	4) In many modern EMS systems, the interventions provided on scene by EMS crews are now the same as are routinely provided in the emergency department. As such there may be no additional benefit to transporting the patient to hospital. 5) Most patients transported to hospital will have received resuscitation on scene for a number of minutes. The likelihood of survival from cardiac arrest reduces with increasing resuscitation duration. Most patients transported to hospital following unsuccessful scene resuscitation will have lower than average likelihood of survival.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small **X** Moderate ○ Large ○ Varies ○ Don't know	There is limited evidence to suggest that survival is improved by continuing resuscitation at scene rather than transporting to hospital. Grunau et al (2020) reported that survival to hospital discharge was 3.8% for patients who underwent intra-arrest transport and 12.6% for those who received on-scene resuscitation. In a propensity-matched cohort, survival to hospital discharge occurred in 4.0% of patients who underwent intra-arrest transport vs 8.5% who received on-scene resuscitation (risk difference, 4.6% [95% CI, 4.0%- 5.1%]). Favorable neurological outcome occurred in 2.9% of patients who underwent intra-arrest transport vs 7.1% who received on-scene resuscitation (risk difference, 4.2% [95% CI, 3.5%-4.9%]). Quality of CPR will be higher if resuscitation is carried out at scene as it avoids the need to extricate from scene to ambulance, leading to fewer interruptions to CPR. Evidence suggests quality of manual CPR is higher on scene than during transport. Higher quality resuscitation at scene may improve the likelihood of achieving ROSC. The risk of injury to EMS providers (and other road users) as a result of vehicle collision is avoided. In some systems, termination of resuscitation on scene when ROSC is not achieved, may help minimize the financial liability associated with futile care. Fewer patients being transported to hospital will help reduce the burden on limited health care resources	The data are uncertain with no randomized controlled trials studies directly evaluating the question.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate **X** Small ○ Trivial ○ Varies ○ Don't know	Some victims of cardiac arrest may benefit from interventions that cannot be provided by EMS crews, but that are available at hospital. For example ECMO, resuscitative hysterotomy Relatives of victims of cardiac arrest may feel their loved one was disadvantaged by not being taken to hospital for further care. There may be costs associated with termination of resuscitation on scene (e.g. EMS crews delayed on scene waiting for police or doctor)	Resuscitation guidelines could address which patient groups are likely to benefit from transport where the risk/benefit balance favours transport

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X Very low o Low o Moderate o High o No included studies	The overall certainty of evidence is VERY LOW. The majority of included studies had a high risk of bias. There are also problems with indirectness and generalizability as much of the evidence arises from manikin studies or from high performance EMS systems.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability **X** Possibly important uncertainty or variability o Probably no important uncertainty or variability o No important uncertainty or variability	With reference to the guidance provided by the COSCA initiative ("Core Outcome Set for Cardiac Arrest" - a partnership between patients, their partners, clinicians, research scientists, and the International Liaison Committee on Resuscitation, sought to develop a consensus core outcome set for cardiac arrest for effectiveness trials), there is no important uncertainty about how much people would value favourable survival or survival as an outcome. However, it is not certain that potential survivors would not be missed by advocating to continue resuscitation on scene rather that to initiate transport with CPR	Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD; COSCA Collaborators. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2018 Jun;127:147-163. doi: 10.1016/j.resuscitation.2018.03.022. There may be cultural barriers to EMS stopping resuscitation. There may be legal barriers to non-medical personnel stopping resuscitation.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison	As both desirable and undesirable effects are very uncertain.	

o Probably favors the intervention o Favors the intervention o Varies **X** Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings **X** Moderate savings o Large savings o Varies o Don't know	The overall cost or need for resources to implement the intervention is likely to be reduced. Resources needed at scene are likely to remain the same. There may be costs associated with education and training for EMS crews with respect to termination of resuscitation decisions and pastoral support of bereaved relatives. If fewer patients are transport there will be lower use of limited emergency department resource.	If legal barriers to stopping resuscitation exist there may be considerable political challenge to implement

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High **X** No included studies	There is no evidence of increased need for physical resources. There may be an increase in educational costs to prepare EMS crews to widen their scope for termination of resuscitation.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison **X** Probably favors the intervention o Favors the intervention o Varies o No included studies	There is no evidence to indicate resuscitation at scene is more cost effective that transporting to hospital. There is indirect evidence to suggest that very few patients who are transported with CPR in progress survive. Drennan IR, Lin S, Sidalak DE, Morrison LJ. Survival rates in out-of-hospital cardiac arrest patients transported without prehospital return of spontaneous circulation: an observational cohort study. Resuscitation. 2014 Nov 1;85(11):1488-93. Of 3374 patients transported to hospital who did not meet termination of resuscitation criteria only 122 (3.6%) survived. Continuing resuscitation at scene and terminating those who did not respond to further resuscitation may significantly reduce the number of cases transported and ease the burden on scarce ED resources.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies **X** Don't know	The wider costs of delivering CPR on scene are uncertain, there is little to inform potential impact on health equity. Extending the delivery of resuscitation on scene will require resources for training and education. It is unlikely the requirements surpass the resources systems already have in place for continued education and training. If increasing on scene resuscitation reduces the number of patients transported for ECMO or other similar advanced interventions, there could potentially be a negative impact on health equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no **X** Probably yes o Yes o Varies o Don't know	There is limited evidence to suggest that patient outcomes are improved by providing resuscitation at scene rather than transporting. There is general consensus within the resuscitation community is that high quality CPR is important for patient outcomes. There is limited evidence to suggest that quality of CPR is lower during ambulance transport. There is limited evidence to suggest that survival is lower for patients transported rather than resuscitated at scene. There is limited evidence to suggest that survival is low for patients transported with CPR.	There may be cultural barriers to stopping resuscitation in some regions of the world

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes	Current guidelines highlight the importance of high-quality CPR.	

X 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	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

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
○	○	○	x	○

CONCLUSIONS

Recommendation

We suggest providers deliver resuscitation at scene rather than undertake ambulance transport with ongoing resuscitation, unless there is an appropriate indication to justify transport (e.g. ECMO) (weak recommendation, very low certainty evidence)

Quality of manual CPR may be reduced during transport. We recommend that whenever transport is indicated EMS providers should focus upon the delivery of high-quality CPR throughout transport (strong recommendation, very low certainty evidence).

Delivery of manual CPR during transport increases the risk of injury to providers. We recommend that EMS systems have a responsibility to assess this risk and, where practicable, to implement measures to mitigate the risk (Good Practice Statement).

Justification

In making these recommendations the BLS task force considered the complexity of the decision to transport or remain on scene including patient factors (age, comorbidities), clinical considerations (scope of practice of providers, aetiology, rhythm, response to treatment), logistic considerations (location of arrest, challenges of extrication, resources required, journey to hospital), patient and provider safety considerations, and hospital capability (ECMO or other advanced interventions).

The BLS task force interpretation of available evidence for CPR quality outcomes:

1) Correct hand positioning	Transport appears to have little impact on correct hand positioning
2) Chest compression rate	Appropriate chest compression rates can be achieved during transport, however there is greater variation in chest compression rate during transport compared with when at scene
3) Chest compression depth	Appropriate chest compression depth can be achieved during transport, however there is greater variation in chest compression depth during transport compared when when at scene
4) Pauses	Transport appears to have little impact on extending pauses
5) Leaning/ incomplete release	Transport appears to have little impact on reducing complete release

6) CPR fraction	There is significant variation in chest compression fraction. Transport appears to have a negative impact on chest compression fraction
7) Ventilation	Transport appears to have little impact on ventilation rates
8) Overall correct CPR	There is significant variation in overall correct CPR. Transport appears to have a negative impact on overall correct CPR

The BLS task force interpretation of available evidence for survival outcomes was that the single study identified reported lower survival among transported patients.42 The certainty of evidence was very low, with considerable risk of remaining confounding despite the use of propensity score matching. Overall, the task force's concerns about decreased CPR quality and provider safety delivering CPR during transport outweighed the benefits of bringing patients to hospital unless the hospital could offer specific treatments not available in the pre-hospital setting (e.g., ECMO, coronary angiography, echocardiography or other potential investigations or treatments).

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- There are only a few studies in humans
- There are no studies in children
- There are no studies addressing the impact on patient outcomes of CPR quality during transport

QUESTION

Should TTM vs. no TTM be used for cardiac arrest?

POPULATION:	**Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest**
INTERVENTION:	**TTM [TTM studies targeting hypothermia at 32-34 C included in the systematic review]**
COMPARISON:	**No TTM [TTM studies targeting normothermia or fever prevention included in the systematic review]**
MAIN OUTCOMES:	**Survival to hospital discharge ; Favourable neurological outcome at hospital discharge or 30 days; Survival to 90 or 180 days; Favourable neurological outcome at 90 or 180 days**
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review. Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM CHH, JCR, KGH, RWN, CWC declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	TTM has been an important part of post-resuscitation care since 2002, when 2 RCTs reported improved outcomes among comatose OHCA patients who were cooled to 32-34 C for 12-24 h. These initial studies enrolled only patients with cardiac arrests from shockable rhythms. Since then, RCTs have reported conflicting results for the comparison of mild hypothermia with normothermia. The "TTM1 trial" in 2013 did not show a benefit with a target of 33°C compared to a target of 36°C. Since publication of TTM trial many settings have moved to targeting normothermia or possibly no temperature management Last ILCOR update was in 2015 (Donnino 2015) 4 RCTs since 2015 with 2 looking at hypothermia v normothermia/fever prevention. The HYPERION trial reported improved functional outcomes among post-cardiac arrest patients with non-shockable rhythms who were treated at 33oC compared with normothermia. The TTM-2 study reported no difference in outcomes when all rhythm OHCA patients were treated with 33 C compared with normothermia. In TTM2 trial protocol: In the normothermia arm the aim was early treatment of fever (greater than or equal to 37.8°C) using pharmacological measures and physical cooling when needed. For participants who developed a temperature of 37.8°C (trigger), a device was used and set at 37.5°C. Normothermia was defined in TTM2 as 36.5-37.7°C. pharmacological measures (acetaminophen), uncovering the patient, and lowering ambient temperature was used to maintain a temperature of ≤ 37.5 C (99.5 F) in the 'normothermia group/fever prevention group'. If the temperature was > 37.7 C (99.9 F) a cooling device was used and set at a target temperature of ≤ 37.5 C (99.5 F). [HACA - fever controlled, technique used not specified] Since publication of TTM trial many settings have moved to targeting normothermia or possibly no temperature management. There are concerns that this has led to worsened outcomes. Interventions and effectiveness of fever prevention in control groups was variable	TTM includes hypothermia at 32-34C 'No TTM' included normothermia/fever prevention 36.5-37.7C The term TTM is not helpful and using hypothermia TTM, normothermia, fever control is more useful .

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Evidence shows no difference, benefit or harm from hypothermia at 32-34 C**	Concerns raised with available data: 1. Target temperature achieved too late. Time to TTM target similar in most recent trials and observational studies 2. Select patient group of primary cardiac arrest and may not be generalisable to all post ROSC cardiac arrest patients. 3. No or very few patients with IHCA or non primary cardiac arrest.

32-34 v normothermia/fever prevention

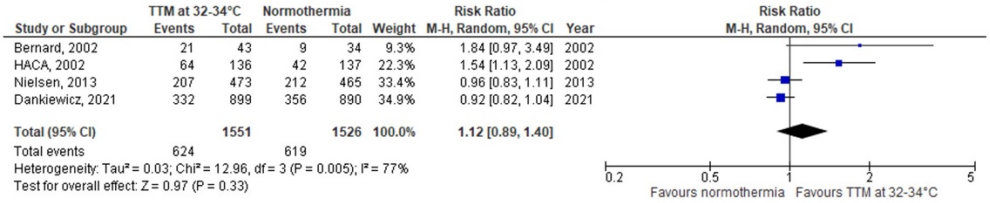
Outcomes	With no TTM	With TTM [32-34 C]	Difference	Relative effect (95% CI)
Survival to hospital discharge	460 per 1,000	**515 per 1,000** (423 to 621)	**55 more per 1,000** (37 fewer to 161 more)	**RR 1.12** (0.92 to 1.35)
Favourable neurological outcome at hospital discharge or 30 days	384 per 1,000	**499 per 1,000** (318 to 779)	**115 more per 1,000** (65 fewer to 395 more)	**RR 1.30** (0.83 to 2.03)
Survival to 90 or 180 days	435 per 1,000	**469 per 1,000** (387 to 565)	**35 more per 1,000** (48 fewer to 130 more)	**RR 1.08** (0.89 to 1.30)
Favourable neurological outcome at 90 or 180 days	363 per 1,000	**440 per 1,000** (331 to 585)	**76 more per 1,000** (33 fewer to 222 more)	**RR 1.21** (0.91 to 1.61)

When TTM1 trial added (33 v 36) and 36 C included in definition of normothermia/no TTM, there was no difference in outcome.

Sensitivity analysis – TTM trial of 33 v 36 C added to no normothermia/fever prevention studies: there is no difference in outcome

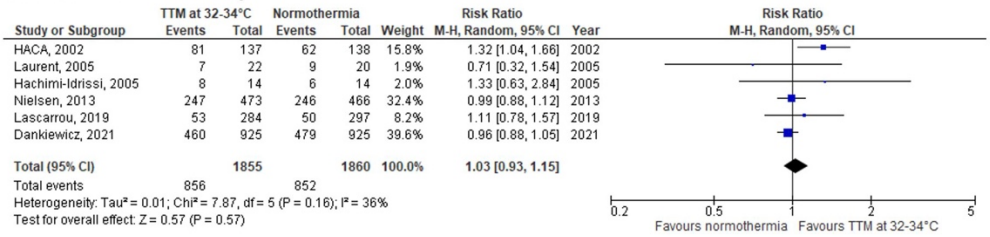
[TTM2 and HACA similar demographic?]

Favorable neurologic outcome at hospital discharge or 30 days



Debate as to whether TTM2 and RCT populations are different to real world practice.

Survival to 90 or 180 days



Paper on etiologies (Chen N, Callaway CW, Guyette FX, Rittenberger JC, Doshi AA, Dezfulian C, Elmer J; Pittsburgh Post-Cardiac Arrest Service. Arrest etiology among patients resuscitated from cardiac arrest. Resuscitation. 2018 Sep;130:33-40.] suggests significant proportion of patients have a non-cardiac arrest cause

Favorable neurologic outcome at 90 or 180 days

Active warming was used in the Hyperion control group - ? harmful

Prolonged sedation used in TTM2 control group up to 40 hours.

Concern that time to target temperature was too slow in the RCTs - seems reasonable compared to other RCTS/observational data where time for consent/randomisation did not have any impact

Trials assessing TTM at 32-34°C				
Trial	**Target**	**Time to randomization from ROSC**	**Time to target from randomization**	**Time from ROSC to target**
HACA, 2002[1]	32-34°C	105 min.*	NR	8 hours
Bernard, 2002[2]	33°C	NR	NR	2 hours**
Nielsen, 2013[3]	33°C	NR	≈ 3 hours to 34°C***	NR
Moler, 2015[4]*****	32-34°C	5.9 hours*	1.6 hours	≈ 7.5 hours
Lascarrou, 2019[5]	33°C	≈ 216 min.	317 min	≈ 8.9 hours
Lopez-de-Sa, 2018[6]	33°C	157 min.	≈ 1.5 hours***	≈ 4.1 hours
Dankiewicz, 2021[7]	33°C	≈ 111 min.	3 hours to 34°C	≈ 4.9
COACT*****	34°C	≈ 184 min.	= 1-2 hours***	≈ 4-5 hours

* Time to initiation of cooling from ROSC
** "In the hypothermia group, the core temperature decreased from 34.9°C 30 minutes after return of spontaneous circulation to 33.5°C 120 minutes after the return of spontaneous circulation"
*** NR. Estimated from figure.
**** Pediatric trial
***** Unpublished. Data from presentation.

Other newer post-cardiac arrest trials				
Trial	**Target**	**Time to randomization from ROSC**	**Time to target from randomization**	**Time from ROSC to target**
Deye, 2015[8]	32-34°C	≈ 3.8 hours*	NR	Internal: 5.5 hours External: 8.5 hours
Kirkegaard, 2017[9]	32-34°C	NA	NA	≈ 5 hours
Lemkes, 2019[10]	NR	NA	NA	≈ 5 hours
François, 2019[11]	32-34°C	NA	NA	≈ 5-6 hours**

* Described as "Delay to start hypothermia"
** From cardiac arrest

Multicenter observational studies				
Study	**Target**	**Time to initiation of TTM from ROSC**	**Time to target from initiation**	**Time from ROSC to target**
Nielsen, 2009[12]	32-34°C	≈ 70 min.	NR	≈ 4 hours
Perman, 2015[13]	33°C	≈ 110 min.	≈ 200 min.	≈ 5 hours
Khera, 2018[14]	Multiple, median 34°C	160 min*	NR*	NR*
Sonder, 2018[15]	32, 33, or 34°C	Transferred: 214 – 378 min.** Non-transferred: 78 – 102 min.**	NR	Transferred: 7.6 – 8.4 hours** Non-transferred: 3.4 – 5.4 hours**
Sawyer, 2019[16]	33°C	213 min.***	89 min.	≈ 4.8 hours ***
Okazaki, 2019[17]	32-34°C or 35-36°C	≈ 110 min.****	NR	NR
Hifumi, 2020[18]	34°C	NR	180 min.	NR

* Reported as "Time from ROSC to TTM". Also state that time to TTM from hospital arrival is 84 min and that "Time from ED to hypothermia" was 138 minutes. Not clear what exactly is being reported.
** From cardiac arrest. Range depending on device. Reports time to 34°C
*** From cardiac arrest
**** "Door-to-TTM initiation"

1. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346(8):549-556.
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3. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med.* 2013;369(23):2197-2206.
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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● **Moderate** ● **Small** ○ Trivial ○ Varies ○ Don't know	**Range of TF opinion <u>small to moderate</u>** Task force mixed as to whether the level of harm caused by 33 C v normothermia/fever prevention is significant or trivial given no difference in overall outcomes. Majority of TF gave this as one of the reasons against the use of hypothermia Adverse events increased TTM2 in 33 C group – arrhythmia resulting in haemodynamic compromise 24% v 16% See table s.14 in TTM2 paper that lists specific arrythmia or complication. No difference in other complications - pneumonia, sepsis, bleeding, skin problems	Use of TTM at 32-34 C may delay prognostication and prolong sedative effects of drugs. Benefit from earlier trials (HACA, Bernard) could have been due to delay in prognostication caused by intervention, lack of standardised/delayed prognostication Unblinded reporting of complications. 10/17 voting TF members considered side effects a reason against hypothermia (including need for sedation, shivering) [7/11 non voting members also did so] Pointed out that control groups (normothermia/fever preventions) could have been harmed by

Table S14. All events reported as potential unexpected serious adverse events.

	Group	uSAE Category	Description	Meets critera for uSAE
1	Normothermia	Limb complication	Leg ischemia, treated by PTCA	No
2	Normothermia	Limb complication	Leg ischemia, no intervention possible	No
3	Normothermia	Tamponade	Cardiac tamponade, pacing wire perforation. Managed in OR	No
4	Normothermia	Bleeding	Splenic bleeding. Managed in the OR	No
5	Normothermia	Bleeding	Bleeding from femoral artery (PCI) requiring transfusion	No
6	Normothermia	Bleeding	Severe liver bleeding after CPR, managed in OR	No
7	Normothermia	Sepsis	Ventilator associated pneumonia and sepsis	No
8	Normothermia	Bradycardia	Temporary pacemaker needed	No
9	Normothermia	Bleeding	Major bleeding. Thoracostomy performed	No
10	Normothermia	Stroke	Major stroke after intervention	No
11	Normothermia	Other	Intravenous catheter not working resulting in inadequate sedation	No
12	Normothermia	Venous Thromboembolism	Cardiac arrest after removal of intravascular cooling device. Suspected PE	Yes
13	Normothermia	Venous Thromboembolism	Minor pulmonary embolism in patient with intravascular cooling device	Yes
14	Hypothermia	Hemodynamics	Overcooling, below 31 with severe hemodynamic instability, bradycardia and subsequent death	Yes
15	Hypothermia	Arrhythmia	Bradycardia, requiring adrenalin	No
16	Hypothermia	Arrhythmia	PEA-arrest, due to LVOT-obstruction	No
17	Hypothermia	Pneumothorax	Tension pneumothorax resulting in death	No
18	Hypothermia	Bleeding	Bleeding from femoral artery (PCI), stenting required	No
19	Hypothermia	Arrhythmia	Ventricular arrhythmia, needed CPR	No
20	Hypothermia	Arrhythmia	Hemodynamic instability and VT	No
21	Hypothermia	Bowel ischemia	Bowel ischemia resuting in death	No
22	Hypothermia	Arrhythmia	VT during rewarming (faster than according to protocol), resolved spontaneously	No
23	Hypothermia	Bradycardia	Bradycardia requiring atropine	No
24	Hypothermia	Vascular	Carotid/Jugular fistula as a result of ECCO2-cannulation - stented	No
25	Hypothermia	Vascular	Compartment syndrome needing decompression after ECCO2	No
26	Hypothermia	Tracheal injury	Tracheal injury during intubation	No
27	Hypothermia	Arrhythmia	Re-arrest, WPW syndrome, CPR required	No
28	Hypothermia	Bleeding	Liver bleeding after CPR - rewarming and transfusion	No
29	Hypothermia	Bleeding	Bleeding treated with FFP	No
30	Hypothermia	Coagulopathy	On warfarin with worsening coagulopathy during cooling. No bleeding. Rewarmed.	No
31	Hypothermia	Hypercapnia	Hypercapnia, transported for ECMO	No
32	Hypothermia	Bleeding	Minior intracranial bleed	No
33	Hypothermia	Cervical injury	Cervical fracture with complete medullar injury, resulting in death	No
34	Hypothermia	Bleeding	Massive bleeding during PCI, resulting in death	No
35	Hypothermia	Bleeding	Intracranial bleed, hematoma evacuated in the OR	No
36	Hypothermia	Bleeding	Liver bleeding, coiled by IR. Subsequent liver abscess	No
37	Hypothermia	Bleeding	Hemothorax, drained. Lung suture needed	No
38	Hypothermia	Bleeding	Major bleeding and shock due to rib fractures, intervention discontinued	No
39	Hypothermia	Vascular	Aortic dissection during surgery resulting in death	No
40	Hypothermia	Hemodynamics	Hemodynamic instability and low heart rate, rewarmed	No
41	Hypothermia	Sepsis	Septic shock	No
42	Hypothermia	Bleeding	Liver bleeding after CPR - treated medically	No
43	Hypothermia	Arrhythmia	New VF arrest, CPR performed	No
44	Hypothermia	Bradycardia	Bradycardia with ventricular bigeminy	No
45	Hypothermia	Bradycardia	Bradycardia treated with isoprenaline, intervention discontinued	No
46	Hypothermia	Arrhythmia	New VT-arrest, CPR performed, ROSC 1 min	No
47	Hypothermia	Venous Thromboembolism	Clot seen in IVC. Intravascular device used	Yes

prolonged sedation in TTM2 to match sedation in 33 C group, or active warming to achieve normothermia in HYPERION studies

Certainty of evidence

What is the overall certainty of the evidence of effects?

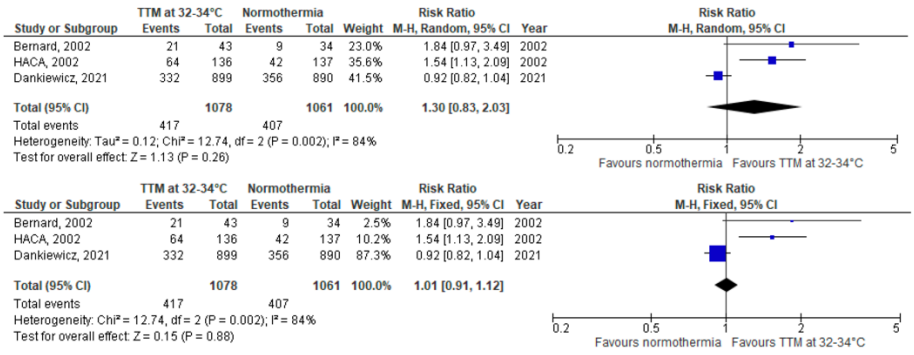
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Low certainty due to serious risk of bias and imprecision** Table below based on meta-analysis that used random effects model decided a priori	Concern that despite more data - we have lower certainty evidence than previous CoSTR In retrospect we have probably over stated the results of the HACA and Bernard studies as compared to the more recent TTM and Hyperion studies

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no TTM	Risk with TTM				
Survival to hospital discharge	Study population		**RR 1.12** (0.92 to 1.35)	2836 (5 RCTs)	⊕⊕◯◯ LOW[a,b,c]	
	460 per 1,000	**515 per 1,000** (423 to 621)				
Favourable neurological outcome at hospital discharge or 30 days	Study population		**RR 1.30** (0.83 to 2.03)	2139 (3 RCTs)	⊕⊕◯◯ LOW[a,c,d]	
	384 per 1,000	**499 per 1,000**				

		(318 to 779)				
Survival to 90 or 180 days	Study population		**RR 1.08** (0.89 to 1.30)	2776 (5 RCTs)	⨁⨁◯◯ LOW[a,c,d]	
	435 per 1,000	**469 per 1,000** (387 to 565)				
Favourable neurological outcome at 90 or 180 days	Study population		**RR 1.21** (0.91 to 1.61)	2753 (5 RCTs)	⨁⨁◯◯ LOW[a,b,c]	
	363 per 1,000	**440 per 1,000** (331 to 585)				

a. All included trials were assessed as having a intermediate risk of bias
b. Confidence interval includes both no difference and potential benefit
c. Although there were some inconsistency between the trials, we decided not to downgrade for this since the inconsistency was indirectly accounted for in the width of the confidence interval and the subsequent downgrading for imprecision
d. Confidence interval includes both benefit and harm

Task force discussion:
The point estimate of the random-effects meta-analysis favours hypothermia (a random effects meta-analysis was chosen a priori). However, the random effects model assigns a relatively higher weight per patient included to smaller studies; thus, the older, less methodologically robust studies published in 2002 had a greater influence on the point estimate than would be expected. When a fixed effect model is used the individual study weighting and point estimates and confidence intervals change e.g. for favourable outcome at 30 days (random effect top, fixed effects bottom:



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	All the outcomes assessed are judged critical by the ALS Task Force	

Outcomes	Importance	Certainty of the evidence (GRADE)
Survival to hospital discharge	CRITICAL	⨁⨁◯◯ LOW[a,b,c]
Favourable neurological outcome at hospital discharge or 30 days	CRITICAL	⨁⨁◯◯ LOW[a,c,d]

or variability ● No important uncertainty or variability	Survival to 90 or 180 days	CRITICAL	⊕⊕◯◯ LOW[a,c,d]	
	Favourable neurological outcome at 90 or 180 days	CRITICAL	⊕⊕◯◯ LOW[a,b,c]	

a. All included trials were assessed as having a intermediate risk of bias
b. Confidence interval includes both no difference and potential benefit
c. Although there were some inconsistency between the trials, we decided not to downgrade for this since the inconsistency was indirectly accounted for in the width of the confidence interval and the subsequent downgrading for imprecision
d. Confidence interval includes both benefit and harm

ALS TF has based these outcome priorities on:
Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Böttiger BW, Brooks A, Castrén M, Ong MEH, Hazinski MF, Koster RW, Lilja G, Long J, Monsieurs KG, Morley PT, Morrison L, Nichol G, Oriolo V, Saposnik G, Smyth M, Spearpoint K, Williams B, Perkins GD; COSCA Collaborators. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2018 Jun;127:147-163.

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	Research evidence limited - majority of TF support comparison given no difference with intervention and undesirable effects of intervention TF voting members (n=17): 'Normothermia' supported by 10/17 [No COI declared] Hypothermia or Normothermia 4/17 [3 with COI declared] Undecided/unclear 2/17 [1 COI declared] Did not respond 1/17 [1 COI declared] Non voting adhoc TF members 'Normothermia' 8/12 [1 COI] Hypothermia/Normothermia 2/12 [1 COI] Undecided 1/12 [no COI] Did not respond 2/12 [1 COI] Majority supported a recommendation against hypothermia but accepted that certain subpopulations of cardiac arrest patients (such as those with a non-cardiac cause of cardiac arrest or in-hospital cardiac arrest) may benefit from targeting hypothermia at 32-34 C, a more rapid induction of hypothermia, or a longer duration of temperature prevention and sedation remains unknown.	In 2015 we wrote an additional statement: Whether certain subpopulations of cardiac arrest patients may benefit from lower (32 C–34 C) or higher (36 C) temperatures remains unknown, and further research may help elucidate this.

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	In TTM 2: All patients in 'hypothermia group' require cooling intervention versus 46% in 'normothermia' group	Cost of cooling will vary between settings and particular device/technique used to provide cooling Cost has not been formally assessed in our SR and meta-analysis. Costs of a 32-34 v normothermia approach are likely to vary according to setting Ice/fan/Surface devices - relatively easy to start

		Intravascular requires skills for insertion and invasive. Additional resource for 32-34 - sedation, cost, training, feedback device, more patients Task force opinion mixed on this issue as many units already use 33 C, and patients will still require close monitoring and intervention of fever prevention/normothermia target used. Concern from TF members that hypothermia leads to longer ventilation/delayed prognostication/ and that fewer patients require active cooling when normothermia or fever control targeted.

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	We have not identified recent studies on this issue	Post resuscitation care and TTM at any temperature target does require significant critical care resources to optimise outcome and costs will vary across settings. Additional cost of TTM over other post resuscitation care intervention will vary. Fewer patients require active cooling when normothermia or fever control targeted.

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	We did not do a specific cost effectiveness analysis. We identified one modelling study. Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. Circ Cardiovasc Qual Outcomes. 2009;2(5):421-428.	No current cost effectiveness data.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No studies identified - probably varies	Both interventions require active temperature management and equity impact will vary. The cost and access to cooling devices and disposables will vary Post resuscitation care and TTM at any temperature target does require significant resources to optimise outcome

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No formal studies looked at regarding acceptability of hypothermia. Intervention is 32-34 and normothermia being used already Observational data suggests that some settings have moved from a target of 33 to normothermia/ or no temperature control.	Within ALS TF and different settings/regions there is considerable variation as to the acceptance of either intervention at 32-34 v normothermia Animal data of early/immediate post ROSC cooling show a consistent and strong protective effect across animal species and models. Reasons have been put forward as to why the largest and most recent RCTs have not managed

		to replicate animal data - cooling too late, too slow, wrong dose duration, wrong patient population. Some observational evidence or concerns that using 'normothermia' targets or switch from 32-34 to 36 C has been associated with worse outcomes. Most recent large observational study from UK does not suggest this and raises the issue that ICU risk models and risk adjustment cannot differentiate between therapeutic and pathological temperature changes when looking at observational data. Nolan JP, et al. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021 May;162:304-311.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Both intervention (hypothermia) and normothermia/fever prevention are feasible in most settings that care for post cardiac arrest patients and already use TTM.	TF considered that post resuscitation care is resource intensive, and temperature control is feasible in most settings that provide this care. Yes - in high resource settings. Hypothermia more challenging in low resource settings

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

	JUDGEMENT						
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

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

Recommendation

We suggest actively preventing fever by targeting a temperature ≤37.5 for those patients who remain comatose after ROSC from cardiac arrest (weak recommendation, low certainty evidence).

Whether subpopulations of cardiac arrest patients may benefit from targeting hypothermia at 32-34ºC remains uncertain.

Comatose patients with mild hypothermia after ROSC should not be actively warmed to achieve normothermia (good practice statement).

Justification

- *This topic was prioritized by the ALS Task Force based on new RCTs of TTM since our previous systematic review, CoSTR (Callaway 2015 s84, Soar 2015 e71) and advisory statement in (Donnino 2015 2448, Donnino 2015 97) in 2015.*
- *All members of the Task Force agreed that we should continue to recommend active temperature control in post-cardiac arrest patients, although the evidence for this is limited.*
- *Further details of Task Force discussions are provided in the evidence to decision tables (ETDs).*

Defining Post-Cardiac Arrest Temperature Management Strategies

- *The term TTM on its own is not helpful and it is preferable to use the terms active temperature control, hypothermia, normothermia, or fever prevention. To provide additional clarity for interpreting future clinical trials, systematic reviews and CoSTRs we propose the following terms are used:*
    - *Hypothermic TTM (H-TTM) = active temperature control with the target temperature below the normal range.*
    - *Normothermic TTM = active temperature control with the target temperature in the normal range.*
    - *Fever prevention TTM (FP-TTM) = monitoring temperature and actively preventing and treating temperature above the normal range*
    - *No TTM = no protocolised active temperature control strategy.*

Hypothermia v normothermia or prevention of fever

- *The majority of the Task Force favored fever prevention for comatose patients following ROSC as opposed to hypothermia, based on the systematic review and because this intervention requires fewer resources and had fewer side effects than hypothermia treatment.*
- *The Task Force noted that in the TTM2 trial (Dankiewicz 2021 2283), pharmacological measures (acetaminophen), uncovering the patient, and lowering ambient temperature were used to maintain a temperature of ≤ 37.5 C (99.5 F) in the normothermia/fever prevention group. If the temperature was > 37.7 C (99.9 F) a cooling device was used and set at a target temperature of ≤ 37.5 C (99.5 F). 95% of patients in the hypothermia group and 46% in the fever prevention group received temperature control with a device.*
- *We chose prevention of fever as opposed to normothermia in the treatment recommendation.*
- *The Task Force acknowledged that the systematic review found no difference in overall outcomes between patients treated with hypothermia and normothermia or fever prevention.*

- *Several members of the Task Force were keen to leave open the option to use hypothermia (33°C). The discussions included:*
    - *No trials have shown that normothermia is better than hypothermia.*
    - *Among non-shockable cardiac arrest patients, the Hyperion trial (Lascarrou 2019 2327) showed better survival with favorable functional outcome in the hypothermia group (although 90-day survival was not significantly different and the Fragility Index was only 1).*
    - *Although our systematic review did not find evidence favoring TTM with hypothermia in multiple subgroups, there remained a view that some populations of cardiac arrest patient could potentially benefit from hypothermia treatment at 32-34 C. Specifically, the largest TTM studies (TTM1 and TTM2) have mainly included cardiac arrests with a primary cardiac cause and this may not reflect the total population of post cardiac arrest patients treated (Chen 2018 33).*
    - *There was a suggestion that we should only advocate fever prevention for those with a primary cardiac arrest in the main treatment recommendation – our systematic review did not find any evidence supporting targeting hypothermia in patients with a cardiac arrest due to other causes.*
    - *Concerns were raised that the TTM2 trial cooling rates were too slow and that the time to target temperature was outside the therapeutic window. In animal studies rapid induction of hypothermia after ROSC is required for a beneficial effect (Arrich 2021 47). The time to target temperature in TTM-2 is consistent with virtually all other human observational studies and RCTs including those where there was no delay caused by the need for consent/randomization (see ETD). Of the RCTs included, only the Bernard study (Bernard 2002 557) had a rapid time (2 hours after ROSC) to achieve target temperature (33.5 C). It remains possible that there is a therapeutic window within which hypothermia is effective that has not been rigorously tested in randomized clinical trials.*

    - *There was a unanimous desire to leave open the opportunity for further research on post-cardiac arrest hypothermia, not least because animal models have shown consistent and convincing evidence of benefit.*
    - *Finally, there are concerns that poor implementation of temperature control may lead to patient harm - for example the publication of the TTM trial in 2013 (Nielsen 2013 2197) may have led to some clinicians abandoning temperature control after cardiac arrest which in turn was associated with worse outcomes (Bray 2017 39, Salter 2018 1722, Nolan 2021 304). Whether this was caused by abandoning the use of temperature control is uncertain.*
- *In our meta-analysis we decided to use a random effects model a priori (as opposed to fixed effects). The point estimates of the random-effects meta-analysis favors hypothermia. However, the random effects model assigns a relatively higher weight to smaller studies; thus, the smaller and older less methodologically robust studies published in 2002 (Bernard 2002 557, HACA 2002 549) had a greater influence on the point estimate than would be expected based on the trial sizes.*
- *We chose the term 'comatose' instead of 'unresponsive' to define the population of patients who do not wake up after ROSC. Another option considered was 'unconscious' – in the TTM2 trial this was defined as not being able to obey verbal commands and no verbal response to pain after sustained ROSC. The Task Force acknowledges that patients are unconscious and sedated after ROSC for a number of reasons in addition to a hypoxic ischemic brain injury including the need for airway protection with a tracheal tube, lung injury, and to facilitate interventions.*
- *We have made no comments on sedation use or its duration but noted that in the TTM2 trial, patients in the normothermia/fever prevention arm were sedated for 40 hours to ensure a similar duration of sedation to the hypothermia arm.*
- *Although there was no direct evidence in our systematic review, the Task Force made a good practice statement supporting the avoidance of active warming of patients who have passively become mildly hypothermia (e.g. 32-36) immediately after ROSC there was concern that this may be a harmful intervention. The Task Force noted that in the TTM2 trial, patients in the normothermia/fever prevention arm with an initial temperature above 33 C were not actively warmed. The Task Force noted that in the Hyperion trial (Lascarrou 2019 2327), patients allocated to normothermia whose temperature was below 36.5 C at randomization were warmed at 0.25 - 0.5 C/hour and then maintained at 36.5 - 37.5 C.*
- *There was discussion about the definitions of normothermia and fever. Among a diverse cohort of 35,488 hospital patients the 99% range for normal temperature was 35.3-37.7°C, and 95% range was 35.7 to 37.3 C (Obermeyer 2017 j5468). Whether these ranges can be generalized to the adult post cardiac arrest patient population is uncertain.*

Alternate temperature comparisons

- *In addition, in our systematic review and meta-analysis we looked at comparisons between 33 v 36 C (Nielsen 2013 2197), 32 v 34 C (Lopez-de-Sa 2018 1807, Lopez-de-Sa 2012 2826), 33 v 34 C (Lopez-de-Sa 2018 1807) and 33 v 32 C (Lopez-de-Sa 2018 1807). There was no difference between control and intervention groups for all these comparisons and the certainty of evidence was low for all comparisons.*
- *The comparison between 33 v 36 C (Nielsen 2013 2197) was included in a sensitivity analysis of 33 C v normothermia/fever prevention, as 36 C falls within the normothermia temperature range – this did not change the point estimates in favor of either group.*

Research priorities

- *There are no RCTs of no TTM versus fever prevention TTM.*
- *There are few RCTs of TTM after eCPR.*
- *There are no large RCTs of TTM after in-hospital cardiac arrest.*
- *Is there a therapeutic window within which hypothermic TTM (H-TTM) is effective in the clinical setting?*
- *If a therapeutic window exists, are there clinically feasible cooling strategies that can rapidly achieve therapeutic target temperatures within the therapeutic window?*
- *Is the clinical effectiveness of hypothermia dependent on providing the appropriate dose (target temperature and duration) based on the severity of brain injury?*
- *Are there unidentified subsets of post-cardiac arrest patient who would benefit from H-TTM as currently practiced?*
- *Is TTM using a cooling device with feedback more effective than TTM without a feedback controlled cooling device?*

QUESTION

Should prehospital cooling vs. no prehospital cooling be used for cardiac arrest?	
POPULATION:	**Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest**
INTERVENTION:	**TTM induction before a specific time point (e.g. prehospital or intra-cardiac arrest, i.e. before return of spontaneous circulation (ROSC))**
COMPARISON:	**TTM induction before a specific time point (e.g. prehospital or intra-cardiac arrest, i.e. before return of spontaneous circulation (ROSC))**
MAIN OUTCOMES:	**Survival to hospital discharge ; Favourable neurological outcome at hospital discharge or 30 days; Survival to 90 or 180 days; Favourable neurological outcome at 90 or 180 days**
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review. Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM CHH, JCR, KGH, RWN, CWC declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Animal data suggest that following hypoxic-ischaemic injury, neuroprotection from targeted temperature is more likely to be effective if started early after return of spontaneous circulation (ROSC) or even before ROSC. Following out-of-hospital cardiac arrest (OHCA) , early cooling implies the need to start TTM prehospital. Given the high mortality from OHCA any benefit from earlier initiation of TTM would result in a substantial increase in lives saved. Eleven trials have assessed timing of TTM initiation: • Ten trials have compared prehospital with no prehospital cooling for patients with out-of-hospital cardiac arrest. • Six trials tested post-cardiac arrest rapid intravenous cold fluid infusion • Two trials tested intra-cardiac arrest intravenous cold fluid infusion • Two tested intra-cardiac arrest intra-nasal cooling	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Meta-analysis of prehospital vs. no prehospital cooling showed that prehospital cooling did not result in improved survival to hospital discharge (risk ratio: 1.01 [95%CI: 0.92, 1.11]) or survival to hospital discharge with a favorable neurologic outcome (risk ratio: 1.00 [95%CI: 0.90, 1.11]).	*We are aware of 2 recent meta-analyses (Taccone 2021 196; Annoni 2021 365) that suggest in the subgroup of the intra-arrest-intranasal studies initial shockable OHCA intranasal intra-arrest cooling is associated with favorable neurological outcome at hospital discharge.*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prehospital cooling	Risk with prehospital cooling				
Survival to hospital discharge	Study population		**RR 1.01** (0.92 to 1.11)	4808 (10 RCTs)	⨁⨁⨁◯ MODERATE[a]	
	242 per 1,000	**244 per 1,000** (223 to 269)				
Favorable neurological outcome at hospital discharge	Study population		**RR 1.00** (0.90 to 1.11)	4666 (9 RCTs)	⨁⨁⨁◯ MODERATE[a]	
	218 per 1,000	**218 per 1,000** (196 to 242)				

a. All included trials were assessed as having a intermediate risk of bias

There was no indication of effect measure modification according to the cooling method (P = 0.61 and P = 0.40 for the two outcomes).

Trials of intra-arrest cooling did not result in a difference in ROSC/admission alive (risk ratio: 0.95 [95%CI: 0.84, 1.07].

A meta-analysis of two studies of intra-nasal cooling showed a risk ratio of favourable neurological outcome of 1.37 [95%CI: 0.97, 1.94]

Our review (random effect)s: OR 1.37 (0.97, 1.94), 54/163 vs. 40/167
Taccone ("as treated"): RR: 1.43 (1.01, 2.02), 54/158 vs. 40/167
Taccone ("ITT"): RR: 1.26 (1.00, 1.56), 56/165 vs. 40/167
Annoni: OR: 1.62 (1.00, 2.64), 56/154 vs. 41/156

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	One study of prehospital IV cold fluid post-ROSC compared with delaying TTM until admission to hospital showed that the intervention was not associated with improved neurological outcome (Kim 2014 45). But the intervention had a higher rate of re-arrest prehospital and a higher incidence of pulmonary oedema on the initial chest x-ray. One study of intra-arrest infusion of cold saline showed no improvement in survival to discharge (Bernard 2016 797). For patients with an initial shockable cardiac rhythm, there was a decrease in the rate of return of a spontaneous circulation in patients who received cold saline compared with standard care (41.2% compared with 50.6%, P=0.03).	*The rapid infusion of large amounts of cold fluid immediately after achieving ROSC and in the prehospital setting could theoretically be harmful, as indicated by increased rates of rearrest and pulmonary edema in the largest of the included studies (Kim 2014 45). Any potential harm from this therapy may relate specifically to the prehospital setting, where there may be less control over the environment, fewer personnel, and reduced monitoring capabilities.*

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		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prehospital cooling	Risk with prehospital cooling				
Survival to hospital discharge	Study population		**RR 1.01** (0.92 to 1.11)	4808 (10 RCTs)	⨁⨁⨁◯ MODERATE[a]	
	242 per 1,000	**244 per 1,000** (223 to 269)				
Favorable neurological outcome at hospital discharge	Study population		**RR 1.00** (0.90 to 1.11)	4666 (9 RCTs)	⨁⨁⨁◯ MODERATE[a]	
	218 per 1,000	**218 per 1,000** (196 to 242)				

a. All included trials were assessed as having a intermediate risk of bias

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	Patients value survival with favourable neurological outcome over long term severe disability	

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	Given the lack of benefit from prehospital cooling and harmful effects in some studies the balance probably favours no routine prehospital cooling of patients.	Time taken to get to hospital. Passive cooling due to ambient temperature vs. active cooling.

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	Prehospital cold fluids requires cold storage facilities on EMS vehicles. Intra-nasal cooling is associated with additional cost although we have not analysed the additional cost in detail.	

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	We did not identify cost studies	

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	We did not identify cost-effectiveness studies for prehospital cooling	

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	Depending on the cooling technique selected, prehospital cooling would not be available to all EMS systems	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Given the lack of beneficial effect and likely increased cost, the intervention is unlikely to be acceptable to stakeholders	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	It is feasible but the precise feasibility varies with the technique used.	

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	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

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

Recommendation

We recommend against the routine use of prehospital cooling with rapid infusion of large volumes of cold IV fluid immediately after ROSC (strong recommendation, moderate certainty evidence)

[unchanged from 2015-2020 TR]

Justification

· Our TR for prehospital cooling is unchanged from our 2015 recommendation.
· We found no evidence that any method of prehospital cooling improved outcomes.
· The rapid infusion of large amounts of cold fluid immediately after achieving ROSC and in the prehospital setting could theoretically be harmful, as indicated by increased rates of rearrest and pulmonary edema in the largest of the included studies (Kim 2014 45). Any potential harm from this therapy may relate specifically to the prehospital setting, where there may be less control over the environment, fewer personnel, and reduced monitoring capabilities.
· We have not made a treatment recommendation about intra-arrest cooling for OHCA. We are aware of 2 recent studies (Taccone 2021 196; Annoni 2021 365) that suggest in the subgroup of the intra-arrest-intranasal studies initial shockable OHCA intranasal intra-arrest cooling is associated with favorable neurological outcome at hospital discharge.

- *Our review (random effect)s:* *OR 1.37 (0.97, 1.94), 54/163 vs. 40/167*
- *Taccone ("as treated"):* *RR: 1.43 (1.01, 2.02), 54/158 vs. 40/167*
- *Taccone ("ITT"):* *RR: 1.26 (1.00, 1.56), 56/165 vs. 40/167*
- *Annoni:* *OR: 1.62 (1.00, 2.64), 56/154 vs. 41/156*

Research priorities

Is there a therapeutic window for hypothermia treatment after cardiac arrest?

QUESTION

Should endovascular cooling vs. surface cooling be used for cardiac arrest?

POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest
INTERVENTION:	endovascular cooling
COMPARISON:	surface cooling
MAIN OUTCOMES:	Survival to hospital discharge/28 days ; Favorable neurological outcome at hospital discharge/28 days;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review. Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM CHH, JCR, KGH, RWN, CWC declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Seven trials compared different methods of TTM but the majority were small feasibility or pilot trials. Three trials compared endovascular with surface cooling and were included in a meta-analysis (Pittl 2013; Deye 2015; Look 2018)	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Ultimately, the desirable effect is improved neurological outcome. The ideal cooling technique would be easily implementable, would acheive target temperature rapidly and enable tight tempertaure control without complications	The desirable effects assume that TTM is beneficial. In addition there is an assumption that a stable constant temperature during TTM is best and there is no evidence that this is the case.

Outcomes	With surface cooling	With endovascular cooling	Difference	Relative effect (95% CI)
Survival to hospital discharge/28 days	399 per 1,000	**455 per 1,000** (371 to 551)	**56 more per 1,000** (28 fewer to 152 more)	**RR 1.14** (0.93 to 1.38)
Favorable neurological outcome at hospital discharge/28 days	291 per 1,000	**355 per 1,000** (276 to 453)	**64 more per 1,000** (15 fewer to 163 more)	**RR 1.22** (0.95 to 1.56)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Complications associated with intravascular cooling include bleeding and venous thromboembolism	Thrombosis associated with intravascular cooling catheters (Andremont 2018 1; Maze 2014 1354)

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	The overall certainty in the evidence for endovascular vs. surface cooling was assessed as low for both survival to hospital discharge and survival to hospital discharge with a favourable neurologic outcome.	

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without endovascular cooling	With endovascular cooling	Difference		
Survival to hospital discharge/28 days № of participants: 523 (3 RCTs)	**RR 1.14** (0.93 to 1.38)	Study population 39.9%	**45.5%** (37.1 to 55.1)	**5.6% more** (2.8 fewer to 15.2 more)	⨁⨁◯◯ LOW[a,b]	
Favorable neurological outcome at hospital discharge/28 days № of participants: 523 (3 RCTs)	**RR 1.22** (0.95 to 1.56)	Study population 29.1%	**35.5%** (27.6 to 45.3)	**6.4% more** (1.5 fewer to 16.3 more)	⨁⨁◯◯ LOW[a,b]	

a. The 95%CI includes both no effect and clinically relevant benefit
b. All included trials were assessed as having an intermediate risk of bias

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	People generally value good functional outcome over survival. They are likely to favour a cooling technique that resulted in better functional outcome.	

uncertainty or variability ● No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There are no significant differences in the outcome between intravascular and other methods of cooling	

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	Intravascular cooling and external cooling with a feedback system are more expensive than simple surface cooling with wet towels and ice pack.	

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 included studies	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No cost-effectiveness studies in our SR	

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 more expensive cooling methods, such as intravascular cooling, are unlikely to be available in low-income countries	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is wide variation in the use of different cooling methods but they are generally accepted by stakeholders	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Most of these cooling methods have been widely implemented.	

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	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**			

	JUDGEMENT						
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

Recommendation

We suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low certainty of evidence).

When a cooling device is used, we suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).

Justification

Cooling devices

· Task Force members agreed that based on our SR either surface or endovascular cooling should be suggested.

· There is no consensus on whether a feedback surface cooling device should be routinely used so this was added as a good practice statement as there is no evidence this approach improves outcomes. There was consensus that temperature should be continually monitored by the cooling device in order to maintain a stable temperature.

There was a comment that endovascular cooling is superior – there are two recent SRs with conflicting conclusions: Bartlett ES (Resuscitation 2020 82) showed intravascular cooling is associated with improved neurological outcome, and Kim JG (Resuscitation 2020 14) found no associated with survival or neurological outcomes.

Research priorities

Is temperature control using a cooling device with feedback more effective?

QUESTION

Duration of TTM?

POPULATION:	**Adult patients with cardiac arrest**
INTERVENTION:	**TTM for a specific duration (e.g. 48 hours)**
COMPARISON:	**TTM at a different specific duration (e.g. 24 hours)**
MAIN OUTCOMES:	**Survival at 6 months ; Favorable neurological outcome at 6 months**
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Soar J, Nolan JP, Andersen LW, Granfeldt A Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review. Soar J, Nolan JP Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM CHH, JCR, KGH, RWN, CWC declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The optimal duration for TTM is unknown. It may depend on the likely severity of the hypoxic-ischaemic injury. There is just one RCT comparing 24 h versus 48 h TTM after OHCA [Kirkegaard 318 2017].	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		

Outcomes	With 24 hours of TTM	With 48 hours of TTM	Difference	Relative effect (95% CI)
Survival at 6 months	659 per 1,000	**725 per 1,000** (633 to 837)	**66 more per 1,000** (26 fewer to 178 more)	**RR 1.10** (0.96 to 1.27)
Favorable neurological outcome at 6 months	636 per 1,000	**687 per 1,000** (592 to 795)	**51 more per 1,000** (45 fewer to 159 more)	**RR 1.08** (0.93 to 1.25)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The proportion of patients with 1 or more adverse events was significantly higher in the 48-hour group (97%) than in the 24-hour group (91%) (difference, 5.6%; 95% CI, 0.6%-10.6%; relative risk, 1.06; 95%CI, 1.01-1.12; P = .04). Significantly more patients had hypotension in the 48-hour group than in the 24-hour group (62% vs 49%; P = .013). There were no significant differences in the rates of pneumonia or bleeding between the groups; however, severe bleeding was more common in the 24-hour than in the 48-hour group (4% vs 1%; P = .03).	

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		

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 24 hours of TTM	Risk with 48 hours of TTM				
Survival at 6 months	Study population		**RR 1.10** (0.96 to 1.27)	351 (1 RCT)	⨁⨁◯◯ LOW[a,b]	
	659 per 1,000	**725 per 1,000** (633 to 837)				
Favorable neurological outcome at 6 months	Study population		**RR 1.08** (0.93 to 1.25)	351 (1 RCT)	⨁⨁◯◯ LOW[a,b]	
	636 per 1,000	**687 per 1,000** (592 to 795)				

a. Risk of bias intermediate for the included trial
b. The 95% confidence interval includes no difference and potential benefit

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	People would value a good neurological outcome over death or severe disability.	

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 point estimate for the primary outcome CCPC 1–2 at 6 months) favours TTM48 but it is not significantly different.	

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	The median ICU length of stay was longer in the 48-hour than in the 24-hour group (151 hours [IQR, 127-178 hours] vs 117 hours [IQR, 99-138 hours]; P < .001), but there was no significant difference in hospital length of stay. There were no significant differences between groups in the use of mechanical assist devices, tracheostomy, echocardiography, gastroscopy, or other operative procedures. Four patients in the 48-hour group had coronary artery bypass grafting compared with none in the 24-hour group.	

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	The additional period of cooling did appear to lead to an additional day of ICU care and this would be associated with additional cost.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No studies included	

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	Any ICU providing 24 h of TTM should be able to provide 48 h of the therapy	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	If there was evidence of benefit, 48 h of TTM would be acceptable to most. Many are already providing 48–72 of TTM	May delay treatments decisions and increase cost

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Any ICU providing 24 h of TTM should be able to provide 48 h of the therapy	

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	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**			

	JUDGEMENT						
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

Recommendation

We suggest active prevention of fever for at least 72 hours in post-cardiac arrest patients who remain comatose [good practice statement].

Justification

- *Our TR is a good practice statement is based on trials controlling temperature for at least 72 h in those patients who remained sedated or comatose.*
- *One trial showed no difference between 24 and 48 hours of hypothermia (Kirkegaard 2017 3410)*
- *This could mean strategies such as 72 hours of active temperature control with avoidance of fever, or up to 24 hours of hypothermia followed by 48 hours of fever prevention if hypothermia treatment is used.*
- *We did not identify any RCTs of rewarming patients treated with hypothermia and note that a rate of 0.33 C/hour was used in TTM2 trial (Dankiewicz 2021 2283) , and 0.25 to 0.5 C/hour in the Hyperion study (Lascarrou 2019 2327).*

Research priorities

How long should temperature be actively controlled after cardiac arrest?

QUESTION

POPULATION:	Adults in any setting in cardiac arrest
INTERVENTION:	A particular finding on point-of-care ultrasound during CPR
COMPARISON:	An external confirmatory test or process including some component other than point-of-care ultrasound
MAIN OUTCOMES:	True positive, false positives, false negatives, true negatives
SETTING:	1) In hospital cardiac arrest (including operative setting) 2) Out of hospital cardiac arrest

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	One goal of cardiac arrest resuscitation is to identify reversible etiologies of circulatory collapse. Historical case details or physical exam findings may suggest certain etiologies and a limited number of bedside laboratory and radiographic tests are available for screening or to further inform the likelihood of a suspected etiology. Point-of-care ultrasound (POCUS) is a clinically-oriented sonographic assessment performed at the bedside by the treating clinician. POCUS is routinely used as a diagnostic screening tool in other acute care conditions such as trauma and undifferentiated shock and these paradigms have been adapted for use in cases of cardiac arrest with active cardiopulmonary resuscitation. There are at least seven proposed structured POCUS assessments during cardiac arrest (see below), which largely overlap and guide assessment for evidence of acute myocardial infarction, cardiac tamponade, massive pulmonary embolism, tension pneumothorax, aortic dissection, ruptured aortic aneurysm, and/or hypovolemia. The potential for misinterpretation during cardiac arrest may be under-recognized and the diagnostic test accuracy of POCUS used in this fashion is unknown. POCUS during cardiac arrest has become common in clinical practice without recognizing the potential pitfalls or potential for misinterpretation. Known frameworks to assess for etiologies of cardiac arrest: 1. CAUSE (Hernandez 2008 198) 2. FEEL (Breitkreutz 2010 1527) 3. FEER (Breitkreutz 2007 S150) 4. PEA (Testa 2010 77) 5. SESAME (Lichtenstein 2015 471) 6. SHoC (Atkinson 2017 459) 7. CASA (Gardner 2018 729)	This topic was prioritized by the ALS Task Force based on the frequent use of point-of-care ultrasound (POCUS) during cardiac arrest despite the potential pitfalls for misinterpretation as a diagnostic tool. A comprehensive and rigorous summary of its intra-arrest diagnostic capabilities provides valuable information to both the resuscitation science community and bedside clinicians.

Desirable Effects
How substantial are the desirable anticipated effects?

<table>
<tr><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr>
<td>○ Trivial
○ Small
○ Moderate
○ Large
● Varies
○ Don't know</td>
<td>
The primary desirable effect is to identify the underlying etiology of cardiac arrest with a high degree of sensitivity and/or specificity. In this manner, POCUS could serve as a screening tool (e.g. higher sensitivity) or as a confirmatory test for a suspected etiology (e.g. higher specificity). In either case, POCUS would ideally guide the use or withholding of specific therapies to target reversible etiologies of cardiac arrest.
<table>
<tr><th></th><th>Disease (+)
(e.g. massive pulmonary embolism)</th><th>Disease (-)
(e.g. No massive pulmonary embolism)</th></tr>
<tr><td>POCUS finding (+)
(e.g. right ventricular enlargement present)</td><td>True Positive</td><td>False Positive</td></tr>
<tr><td>POCUS finding (-)
(e.g. right ventricular enlargement absent)</td><td>False Negative</td><td>True Negative</td></tr>
</table>
In one observational study of 48 subjects with high risk of bias (van der Wouw 1997 780), no sonographic finding had sufficiently narrow confidence intervals around point estimates of sensitivity to ‘rule out’ the etiology of cardiac arrest, but the certainty of this evidence is very low.

In one observational study of 48 subjects with high risk of bias (van der Wouw 1997 780), sonographic findings tended to have higher point estimates of specificity or narrower confidence intervals around these point estimates to ‘rule in’ the etiology of cardiac arrest, but the certainty of this evidence is very low.
<table>
<tr><th rowspan="3">POCUS Findings</th><th colspan="6">Disease (Autopsy and/or Clinical Adjudication)</th></tr>
<tr><th colspan="2">Myocardial Infarction</th><th colspan="2">Cardiac Tamponade</th><th colspan="2">Pulmonary Embolism</th></tr>
<tr><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>Reduced contractility in a region of myocardium</td><td>0.86 (0.57 - 0.98)</td><td>0.94 (0.71-0.99)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pericardial effusion with collapse of at least one cardiac chamber</td><td></td><td></td><td>1.00 (0.29-1.00)</td><td>1.00 (0.88-1.00)</td><td></td><td></td></tr>
<tr><td>Dilated right ventricle and right atrium with poor filling of left atrium and left ventricle</td><td></td><td></td><td></td><td></td><td>1.00 (0.16-1.00)</td><td>0.97 (0.82-0.99)</td></tr>
</table>
Eleven observational studies with high risk of bias report the prevalence of a given POCUS finding and a description of subsequent imaging, procedural success, or post-procedural clinical outcomes that suggest confirmation of this POCUS finding. (Chua 2018 310; Hilberath 2014 926; Jung 2020 31; Lien 2018 125; Lin 2006 167; Memtsoudis 2006 1653; Shillcutt 2012 362; Tayal 2003 315; Varriale 1997 1717; Zengin 2012 68; Zengin 2016 105) These estimates of positive predictive value are restricted to small subgroups of subjects among the total number enrolled in each study.
</td>
<td>
Preceding medical history, medication lists, recent interactions with the healthcare system, and case features of the cardiac arrest all inform the likelihood of different etiologies of cardiac arrest.

Indirect observational evidence from the systematic review notes that POCUS “changed management” or “influenced care”, which suggests that POCUS yielded some diagnostic information. (Breitkreutz 2010 1527; Gaspari 2016 33; Gaspari 2017 103; Ketelaars 2018 406; Pyo 2021 62). However, it is not clear that these interventions improved clinical outcomes and the studies do not report data to estimate diagnostic test accuracy.

Indirect observational evidence from a conference abstract estimated
</td>
</tr>
</table>

Study (Author Year Population)	Total sample in study (n)	Reference Standard	POCUS finding	TP	FP	Positive Predictive Value (95% CI)
Myocardial Infarction						
Lien 2018 OHCA	177	Invasive coronary angiography	Anterior wall akinesis (LV)	1	0	100% (3-100%)
Lin 2006 OR	10	Elevated serum troponin T values and/or ST-segment changes on ECG and/or coronary angiography	Segmental wall motion abnormality (TEE)	5	0	100% (48-100%)
Memtsoudis 2006 OR	21	Surgical revascularization	Regional wall motion abnormality (TEE)	3	3	50% (12-88%)
Memtsoudis 2006 OR	21	IABP placement	Regional wall motion abnormality (TEE)	1	5	17% (1-64%)
Memtsoudis 2006 OR	21	Post-operative medical management of myocardial infarction	Regional wall motion abnormality (TEE)	2	4	33% (4-78%)
Shillcutt 2012 OR	4	Percutaneous coronary intervention	Severe LV systolic and diastolic dysfunction	1	0	100% (3-100%)
Cardiac Tamponade						
Hilberath 2014 OR	6	Aspirate from pericardiocentesis and/or performance of pericardial window and primary surgical repair	Tamponade (no specifics provided) (TEE)	4	0	100% (40-100%)
Jung 2020 OHCA	158	ROSC after pericardiocentesis	Tamponade (no specifics provided) (TEE)	3	1	75% (19-99%)
Lien 2018 OHCA	177	ROSC after pericardiocentesis	RV compression with pericardial effusion	2	6	25% (3-65%)
Lien 2018 OHCA	177	Aspirate from pericardiocentesis	RV compression with pericardial effusion	4	4	50% (16-84%)
Memtsoudis 2006 OR	21	Pericardiotomy	Tamponade (no specifics provided) (TEE)	2	0	100% (16-100%)
Zengin 2012 OHCA & ED	73	ROSC after pericardiocentesis	Tamponade (no specifics provided)	2	2	50% (7-93%)
Zengin 2016 ED	173	ROSC after pericardiocentesis	Tamponade (no specifics provided)	4	6	40% (12-74%)
Pericardial Effusion						
Tayal 2003 OHCA	20	Separate formal TTE	Anechoic fluid collection in pericardial sac	5	3	63% (24-91%)
Tayal 2003 OHCA	20	CT thorax	Anechoic fluid collection in pericardial sac	3	5	38% (9-76%)
Pulmonary Embolism						
Chua 2017 OHCA	104	Right femoral DVT + ROSC after systemic fibrinolysis	D sign (straightening of interventricular septum) with dilated RV	1	0	100% (3-100%)
Lin 2006 OR	10	Pulmonary embolectomy	Thrombus in RV or pulmonary artery (TEE)	2	0	100% (16-100%)
Memtsoudis 2006 OR	21	Pulmonary embolectomy	Central thrombus (pulmonary artery, RA, or SVC) (TEE)	4	1	80% (28-99%)
Varriale 1997 IHCA	20	VQ scan	Occluded right pulmonary artery	1	0	100% (3-100%)
Aortic Dissection						
Zengin 2016 ED	173	Intention to perform operative intervention	Aortic dissection (no specifics provided)	2	0	100% (16-100%)
Hypovolemia						
Lin 2006 OR	10	Absolute decrease in hemoglobin of	Empty LV with large hemothorax (TEE)	1	0	100% (3-100%)

diagnostic test accuracy of POCUS against autopsy in 163 expired, adult, nontraumatic out-of-hospital cardiac arrest subjects with attempted resuscitation. POCUS identified cardiac tamponade (sensitivity 70% [95% CI 55-77%]; specificity 99% [95% CI 67-99%]), abdominal or thoracic aortic aneurysm (sensitivity 75% [95% CI 38-75%]; specificity 100% [95% CI 99-100%]), and pulmonary embolism (sensitivity 14% [95% CI 3-14%]; specificity 100% [95% CI 99-100%]) with higher specificity than sensitivity. (Matsuoka 2013 S91)

Indirect evidence from other acute time-sensitivity conditions suggest that POCUS is more specific than sensitivity to identify the presence of pathology. A 2018 Cochrane review of the E-FAST (extended-focused assessment with

		9.5 g/dL despite transfusion of 15 units of whole blood and packed red cells				
Shillcutt 2012 OR	4	ROSC after transfusion and fluid resuscitation	Low end-diastolic volume	1	0	100% (3-100%)
Varriale 1997 IHCA	20	ROSC after intravenous volume replacement	Pseudo-PEA with hypercontractile LV	1	0	100% (3-100%)

TP true positive. FP false positive. CI confidence interval. IHCA in-hospital cardiac arrest. OHCA out-of-hospital cardiac arrest. OR operating room. TEE transesophageal echocardiogram. RV right ventricle. RA right atrium. LA left atrium. LV left ventricle. TTE transthoracic echocardiogram. ED Emergency Department. CT computed tomography. ROSC return of spontaneous circulation. DVT deep vein thrombus. VQ ventilation perfusion. PEA pulseless electrical activity.

sonography in trauma) exam estimated sensitivity 0.74 (95% CI 0.65-0.81) and specificity 0.96 (95% CI 0.94-0.98) to indicate thoracoabdominal injury after blunt trauma. A 2019 systematic review of POCUS estimated higher pooled specificity than sensitivity to indicate the type of shock (hypovolemic, cardiogenic, obstructive, distributive) among cases of undifferentiated shock. However, studies had high risks of bias and unclear descriptions of the index test and reference standard.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● **Varies** ○ Don't know	The primary undesirable effect is falsely interpreting sonographic findings or overestimating the diagnostic test accuracy of sonographic findings during resuscitation. This could either result in treating pathology that is not actually present (e.g. false positive) or not treating pathology that is actually present (e.g. false negative). Treating pathology that is not present may introduce additional morbidity or iatrogenic complications should subjects regain spontaneous circulation. However, post-cardiac arrest subjects are already highly complex patients that require a large burden of healthcare resources. The incremental amount of additional iatrogenic morbidity will vary based on the treatment administered. Not treating pathology that is present may inadvertently lead to declaration of futility or premature termination of resuscitation in patients that could have otherwise survived.	Most clinicians perceive little additional 'harm' that can be conferred on subjects in active cardiac arrest and the 'treatment threshold' for a suspected etiology based on bedside assessment is typically low given

	We found wide variability in the confidence intervals around point estimates to diagnose etiologies of cardiac arrest. The prognostic implications of sonographic findings during cardiac arrest are at high risk of over-interpretation or providing false reassurance. Another undesirable effect is additional interruptions in otherwise continuous chest compressions (Huis In't Veld 2017 95, Clattenburg 2018 65). Although there are several logistical strategies that may be used to mitigate this issue (Clattenburg 2018 69; Gaspari 2021 100094; Teran 2019 409).	the emergent and time-sensitive nature of the condition.

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	The certainty of evidence of the diagnostic test performance of POCUS during cardiac arrest was uniformly very low due to risk of bias, inconsistency, and imprecision.	The certainty of evidence of the prognostic ability of point-of-care echocardiography is also uniformly very low due to risk of bias, inconsistency, and imprecision. (Reynolds 2020 56)

US Findings	Disease (Autopsy and/or Clinical Adjudication)					
	Myocardial Infarction		Cardiac Tamponade		Pulmonary Embolism	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Reduced contractility in a region of myocardium	VERY LOW	VERY LOW				
Pericardial effusion with collapse of at least one cardiac chamber			VERY LOW	VERY LOW		
Dilated right ventricle and right atrium with poor filling of left atrium and left ventricle					VERY LOW	VERY LOW

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No	None of the identified studies specifically address this question.	Clinicians tend to value diagnostic tests with sufficiently high sensitivity and/or specificity to be clinically useful.

important uncertainty or variability		
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**	No POCUS finding had sufficiently high and/or certain sensitivity or specificity to support its use as a sole diagnostic test to 'rule out' or 'rule in' the cause of cardiac arrest during resuscitation. POCUS findings tended to have higher point estimates of specificity or narrower confidence intervals around these point estimates. This pattern is also present in indirect evidence from other acute care conditions such as thoracoabdominal trauma and undifferentiated shock. In this manner, POCUS may ultimately be better utilized as a confirmatory test to prompt treatment aimed at specific reversible causes of cardiac arrest, but the wide variability in confidence intervals around point estimates and the very low certainty of evidence render these data difficult to interpret. Conversely, POCUS cannot exclude the presence of the same pathology with a sufficient degree of certainty. Thus, paradoxically, the presence of certain POCUS findings might encourage treatment directed at specific reversible causes of cardiac arrest, but absence of the same does not rule them out. Given the current available evidence, if POCUS is used in a diagnostic capacity during cardiac arrest, it should be considered an adjunct to inform the likelihood of a given cause of cardiac arrest based on clinical suspicion and other available information while acknowledging its limitations and potential for misinterpretation. POCUS should not be the sole criterion used to 'rule out' or 'rule in' a given cause of cardiac arrest.	These same considerations apply to POCUS as a prognostic tool during cardiac arrest. No sonographic finding had sufficiently or consistently high sensitivity to support its use as a sole criterion to terminate resuscitation. Some sonographic findings tended to have higher ranges of specificity than others for clinical outcomes. In this manner, point-of-care echocardiography might be useful to identify sonographic findings that support continuation of resuscitation. However, the presence or absence of any particular finding had insufficient sensitivity to use a sole criterion for termination of resuscitation. Thus, paradoxically, the presence of certain

		sonographic findings might encourage the continuation of resuscitative efforts, but absence of the same is not sufficient justification (in isolation) to cease resuscitative efforts.

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	None of the identified studies directly addressed this question, however, they do describe the prior training of the sonographers that collected data in each study. These range from more general descriptions (e.g. 'structured training program – lectures with hands-on practice on simulated and real patients') to specific details (e.g. 150 ultrasound exams, 20-hour didactic course, 10 proctored ultrasound exams on live patients, etc.). Some studies note that all sonographers were cardiologists or anesthesiologists with formal echocardiogram training. Additionally, some studies specify the presence of a continuous quality assurance process on all ultrasound exams. If an institution has an existing POCUS program, the incremental resource requirements will be small. If an institution does not have an existing POCUS program, we expect the incremental resource requirements to start a new program and implement it in the setting of cardiac arrest will be at least moderate.	Point-of-care ultrasound is available in many Emergency Departments although there may be some global disparities. We expect additional fixed and/or recurring equipment and training costs to be low. Introducing point-of-care ultrasound to new inpatient or prehospital settings carries new fixed and recurring equipment and training costs.

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**	None of the identified studies specifically address this question.	Unknown

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**	None of the identified studies specifically address this question.	Considerations of cost are noted above under "Resources required". The effectiveness of diagnosing the etiology of cardiac arrest with point-of-care ultrasound during cardiac arrest is currently uncertain.

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**	None of the identified studies specifically address this question.	Due to fixed and recurring equipment costs, there may be global or regional discrepancies in the availability of point-of-care ultrasound during cardiac arrest.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● **Don't know**	None of the identified studies specifically address this question.	POCUS is commonly used in the Emergency Department in many regions to guide prognostic decisions during cardiac arrest. It is difficult to estimate the prevalence of use among cases of cardiac arrest treated in the Emergency Department, but the existence of multiple professional society statements and proposed sonographic protocols support its wide acceptance. Introducing POCUS to new inpatient or prehospital settings may generate new challenges to acceptability in those clinical settings.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes	None of the identified studies specifically address this question. A central component to the operational feasibility of diagnosing etiologies of cardiac arrest with POCUS is a sufficient reference standard. An acceptable reference standard likely varies by target condition.	POCUS is already commonly used in the Emergency Department in many regions to guide treatment

○ Varies ● **Don't know**	Another key issue is sufficient inter-rater reliability of POCUS. No study reported inter-rater reliability of the POCUS index test in the context of diagnosis.	decisions during cardiac arrest. It is difficult to estimate the prevalence of use among cases of cardiac arrest treated in the Emergency Department, but the existence of multiple professional society statements and proposed sonographic protocols support its wide acceptance. Introducing POCUS to new inpatient or prehospital settings may generate new challenges to feasibility in those clinical settings. Indirect evidence from two observational studies of POCUS as a prognostic tool during cardiac arrest estimate the inter-rater reliability to classify cardiac motion with Kappa 0.63 and 0.93. (Flato 2015 1; Gaspari 2016 33)

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**

	JUDGEMENT						
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

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

Recommendation

We suggest against routine use of point of care ultrasound during CPR to diagnose reversible causes of cardiac arrest (weak recommendation, very low-certainty evidence).

We suggest that if point of care ultrasound can be performed by experienced personnel without interrupting CPR, it may be considered as an additional diagnostic tool when clinical suspicion for a specific reversible cause is present (weak recommendation, very low-certainty evidence).

Any deployment of diagnostic point of care ultrasound during CPR should be carefully considered and weighed against the risks of interrupting chest compressions and misinterpreting the sonographic findings (good practice statement).

Justification

This topic was prioritized by the ALS Task Force based on the frequent utilization of point-of-care ultrasound during cardiac arrest without recognizing the potential pitfalls for misinterpretation as a diagnostic tool. A comprehensive and rigorous summary of its intra-arrest diagnostic capabilities provides valuable information to both the resuscitation science community and bedside clinicians.

In making these recommendations, the ALS Task Force considered the following:

- The inconsistent definitions and terminology used for sonographic evidence of specific causes of cardiac arrest was the primary source of clinical heterogeneity. We strongly encourage the establishment of uniform definitions and terminology to describe sonographic findings of reversible causes of cardiac arrest.

- The identified studies suffer from high risk of bias related to selection bias and ascertainment bias. Additionally, the logistics of cardiac arrest resuscitation introduce potential for spectrum bias (when diagnostic test accuracy is influenced by the case mix of subjects and/or prevalence of the target condition) and verification bias (when availability or use of the reference standard is influenced by 'test positive' or 'test negative' status). Verification bias was present in all but one of the included studies, largely restricting contingency tables to positive predictive value. The evidence supporting use of POCUS as a diagnostic tool is uniformly of very low certainty. Clinicians should cautiously interpret sonographic findings during cardiac arrest in light of these limitations. We strongly encourage subsequent investigations of POCUS during cardiac arrest to employ methodology that mitigates these risks of bias. This includes enrolling a consecutive, prospective sample; utilizing clear definitions of the index test, credentials of the sonographer, and testing interval; selecting an objective, uniform reference standard; and blinding appropriately.

- No included studies reported estimates of inter-rater reliability. The influence of acoustic window, sonographer training/experience, and particular pathology in question on inter-rater reliability is also unknown. As POCUS matures as a field, there are now validated image quality rating scales to promote standardization of assessment. (Gaspari 2021 100097).

- No POCUS finding had sufficient sensitivity to be used as sole criterion to 'rule out' the cause of cardiac arrest, but the certainty of this evidence is very low.

- POCUS findings had higher point estimates and/or narrower confidence intervals of specificity to 'rule in' certain causes of cardiac arrest, but this evidence is from a single study and of very low certainty.

- The diagnostic utility of POCUS is affected by the clinical context. For example, a post-operative cardiac surgery patient with acute cardiac arrest has given pre-test probabilities for specific causes such as cardiac tamponade, pulmonary embolism, or acute hemorrhage. Conversely, the diagnostic utility of POCUS may be more limited in the context of undifferentiated cardiac arrest in the out-of-hospital setting.

- Clinicians should be cautious about introducing additional interruptions in chest compressions with a transthoracic approach to point-of-care echocardiography during cardiac arrest. (Huis In't Veld 2017 95, Clattenburg 2018 65) Several logistical strategies mitigate these concerns, including use of transesophageal echocardiography. (Clattenburg 2018 69; Gaspari 2021 100094; Teran 2019 409).

- The task force noted several pitfalls and logistical questions around the feasibility of diagnosing a myocardial infarction in the context of pulseless electrical activity or similar low-flow states. In this context, wall motion abnormalities may result from the ischemia of a low-flow state or a pre-existing infarct, as opposed to a *de novo* myocardial infarction.

- Not treating a reversible cause of cardiac arrest risks failure of resuscitation or more severe post-cardiac arrest injury. Treating an incorrect diagnosis suggested by POCUS risks iatrogenic injury or delayed identification of the true underlying cause.

- POCUS is subject to the availability of equipment and skilled operators. Starting a new POCUS program requires material fixed and recurring costs and resources to obtain equipment and train clinicians. An existing POCUS program requires fewer incremental resources to be used in the context of cardiac arrest. In either case, the development and maintenance of the requisite skill sets both obtain and interpret images under the compromised conditions of cardiac arrest presents an additional burden for a POCUS program. The task force expects that most diagnostic applications of POCUS will occur in a hospital-based setting as opposed to the prehospital setting.

- Given the items listed, many task force members advocated for restriction of diagnostic applications of POCUS to circumstances in which the clinical suspicion for a readily treatable abnormality is high and justifies interruption of CPR. In such instances, the time allotted for imaging should be as brief as possible.

- The prognostic utility of POCUS to predict clinical outcomes is covered in a separate PICOST (https://costr.ilcor.org/document/prognostication-with-point-of-care-echocardiography-during-cardiac-arrest-task-force-systematic-review-costr).

Subgroup considerations

We planned *a priori* subgroup analysis of shockable and nonshockable initial cardiac rhythm. However, risk of bias and other confounding precluded the ability to pool data or conduct meaningful analyses of these subgroups.

Implementation considerations

The lack of uniform definitions and terminology to describe sonographic findings during cardiac arrest, the high risks of bias and confounding in the existing literature, the uncertainty of inter-rater reliability, and the material risks of interrupting CPR all represent implementation challenges for POCUS assessment for reversible causes during cardiac arrest.

We distinguish between clinical contexts of undifferentiated cardiac arrest when POCUS is employed to screen for reversible causes, and clinical contexts of cardiac arrest in which there is material pre-test suspicion for a specific reversible cause that could be confirmed by POCUS.

POCUS findings tended to have higher point estimates of specificity or narrower confidence intervals around these point estimates. This pattern is also present in indirect evidence from other acute care conditions such as thoracoabdominal trauma and undifferentiated shock. In this manner, POCUS may ultimately be better utilized as a confirmatory test to prompt treatment aimed at reversible causes of cardiac arrest, but the wide variability in confidence intervals around point estimates and the very low certainty of evidence render these data difficult to interpret.

Otherwise, POCUS is already commonly used in the Emergency Department to guide treatment decisions during cardiac arrest. It is difficult to estimate the prevalence of use among cases of cardiac arrest treated in the Emergency Department, but the existence of multiple professional society statements and proposed sonographic protocols support its wide acceptance.

Introducing POCUS to new inpatient or prehospital settings may generate new implementation challenges.

Monitoring and evaluation

We encourage the use of robust quality assurance programs with expert oversight to ensure valid and reliable interpretation of sonographic findings, and to measure the contributions of POCUS to interruptions in CPR.

Research priorities

There are no studies of the diagnostic accuracy of point-of-care ultrasound during cardiac arrest with methodology that sufficiently minimizes risk of bias, especially selection bias, ascertainment bias, and verification bias.

There are no uniform definitions and terminology to describe sonographic findings of reversible causes of cardiac arrest or the associated reference standards.

The inter-rater reliability of POCUS diagnostic findings during cardiac arrest is unknown.

No identified studies provided data on resource requirements, cost-effectiveness, equity, acceptability, or feasibility.

Some studies reported a 'change in management' driven by the diagnostic use of POCUS, but these assertions are not well characterized or quantified. Furthermore, it is unknown whether these 'changes in management' led to improved clinical outcomes.

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QUESTION

Should Vasopressin and Corticosteroids vs. usual care without vasopressin and corticosteroids be used for Adults in IHCA?	
POPULATION:	Adults in IHCA
INTERVENTION:	Vasopressin and Corticosteroids
COMPARISON:	usual care without vasopressin and corticosteroids
MAIN OUTCOMES:	Return of spontaneous circulation ; Survival to hospital discharge; Survival to Hospital Discharge with Good Neurological Outcome; Health Related Quality of Life; Health Related Quality of Life;
SETTING:	In-Hospital Cardiac Arrest
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Across the world, sudden cardiac arrest is an important cause of premature death and morbidity. Survival rates are low. Optimising outcomes from cardiac arrest is a key international priority.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The anticipated effects are very substantial if the intervention improves ROSC and even more so if it improves survival with good neurological outcome. The effect of the intervention on return of spontaneous circulation is substantial (relative effect- odds ratio 2.09, 95% CI 1.54 to 2.09; absolute effect 181 more per 1,000, 95% CI 108 more to 250 more). The evidence is categorised as low certainty. Even at the lower end of the 95% confidence interval, this would still represent a substantial benefit. This improvement in return of spontaneous circulation does not translate in to a benefit in survival or survival with good neurological outcome across the three eligible studies. As such, there is	

	uncertainty as to whether the intervention improves these longer-term outcomes that are considered important by patients.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	There was no evidence that the intervention might cause direct harm. However, an intervention that improves ROSC but not overall survival might be viewed as undesirable, depending on cultural norms. There are potential side-effects that may be associated with use of vasopressin and steroids (e.g. infection, hyperglycaemia, peripheral ischaemia). However, these effects are likely to be considered acceptable by patients and clinicians if the outcome improves patient outcomes, such as survival.	

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	Overall, evidence certainty was categorised as low or very low to reflect indirectness and imprecision.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The current evidence shows that the interventions improves rates of return of spontaneous circulation, but this does not translate in to improvements in survival. For some, any intervention that improves ROSC may be viewed as valuable. Obtaining ROSC is an essential step in the pathway to overall survival, but even in patients that do not survive, it might be viewed as providing an opportunity for organ donation or for the patient's relatives to spend time with them while they are alive.	

	The consequences of this include increased burden on the healthcare system (particularly ICU beds). This might be a particular challenge in systems where there is limited ICU capacity. It is also known that post-arrest/ ICU interventions may be painful or distressing for the patient, even if they appear to be adequately sedated. The balance of these values likely varies across cultures.	

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 balance between desirable and undesirable effects likely depends on a value judgement, based on the importance of obtaining ROSC where this does not translate in to an effect on overall survival.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There are no studies directly addressing this. Corticosteroids are relatively cheap and readily available across most systems. In some systems they may only be available in powder form , requiring reconstitution before use, which might have an effect on how rapidly they can be available for use. Vasopressin is relatively expensive. For integration in to resuscitation care, some systems may require that vasopressin be made available in pre-filled syringes which would further increase its costs. Vasopressin also ideally requires refrigeration until use, potentially creating additional costs and complexity in availability. Aside from drugs and refrigeration costs, there are likely to be no other significant costs.	

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	We identified no relevant studies.	

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	We did not identify any studies that addressed the cost effectiveness of the addition of vasopressin and corticosteroids to standard care during cardiac arrest. An increase in ROSC without associated increase in improved functional recovery would likely increase healthcare costs through increased demand on ICU beds.	

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 availability of vasopressin and corticosteroids across all health settings is unknown, particularly in low and middle-income countries.	Though steroids are cheap and readily available, it is unclear if Vasopressin is readily available in all countries and all environments outside of ICUs. Potentially this might have a negative effect on health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	PATIENTS: The combination of corticosteroids and vasopressin is likely to be acceptable to patients if it improves outcomes that are important to patients. The combination of corticosteroids and vasopressin is likely to be acceptable to patients if it improves outcomes that are important to patients. CLINICIANS: Current resuscitation guidelines prioritise the development of straightforward treatment processes that be easily implemented in care. The addition of vasopressin and corticosteroids to standard resuscitation treatment would add a degree of complexity to current care. This is particularly the case for systems where corticosteroids are only available in powder form & require reconstitution prior to administration. For in-hospital settings in such systems, higher numbers of clinical personnel mean that it is likely that the team would be able to safely reconstitute drugs. However, the added complexity may be a barrier to implementation in some settings. Vasopressin ideally requires refrigeration prior to use , though in some circumstances this may not be essential.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Key challenges to implementation include: - In some systems corticosteroids need to be reconstituted prior to administration, - Ideally vasopressin in recommended to be stored in a refrigerator These issues might add complexity to resuscitation care. Whilst likely feasible in the hospital setting, implementation in the out-of-hospital setting may be more challenging in some systems.	

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	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

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

Recommendation

We suggest against the use of the combination of vasopressin and corticosteroids in addition to usual care for adult in-hospital cardiac arrest, due to low confidence in effect estimates for critical outcomes. (weak recommendation, low to moderate-certainty evidence)

Justification

Overall justification

For in-hospital cardiac arrest, there is moderate evidence that vasopressin and corticosteroids given during cardiac arrest, increase ROSC. However, this does not appear to translate into improvement in survival +/or survival with good neurological outcome.

Detailed justification

Balance of effects

For IHCA, there appears to be moderate evidence that the addition of vasopressin and corticosteroids to usual care improves ROSC. However, this does not seem to translate into a meaningful increase in survival +/or survival with good neurological outcome, therefore the overall value of the intervention is unclear.

Subgroup considerations

Prespecified subgroup analyses were conducted according to age , witnessed status, the initial rhythm (shockable or not), time from cardiac arrest to administration of trial drug and cause of cardiac arrest. There was no effect measure modification for any of these outcomes.

Implementation considerations

Corticosteroids are generally cheap and readily available, but in some systems come in a powdered from which requires reconstitution - this may be challenging in cardiac arrest settings.

Vasopressin is less readily available and is ideally kept in a fridge, which may add complexity to its widespread use.

Monitoring and evaluation

Research priorities

There is need for a large randomised control trial to compare outcomes between cardiac arrest victims in hospital treated with standard care, and those treated with vasopressin and corticosteroids in addition to standard care.
Post-ROSC treatment should also be standardised between groups, ideally with the addition of hydrocortisone to those with post-ROSC hypotension, as this was used in the Mentzelopoulos studies.

QUESTION

Should Vasopressin and Corticosteroids vs. usual care without vasopressin and corticosteroids be used for Adults in OHCA?	
POPULATION:	Adults in OHCA
INTERVENTION:	Vasopressin and Corticosteroids
COMPARISON:	usual care without vasopressin and corticosteroids
MAIN OUTCOMES:	Return of spontaneous circulation (assessed with: Spontaneous circulation with no need for further chest compressions sustained for > 15 mins); Survival to Hospital Discharge ; Survival to Hospital Discharge with Good Neurological Outcome ; Health Related Quality of Life ; Health Related Quality of Life (follow-up: range 30 days to 180 days; assessed with: EuroQol 5 Dimension 5 Level (EQ-5D-5L) Index: Scale from: 0 to 100);
SETTING:	Out of Hospital
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Across the world, sudden cardiac arrest is an important cause of premature death and morbidity. Survival rates are low. Optimising outcomes from cardiac arrest is a key international priority.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The anticipated effects are very substantial if the intervention improves ROSC and even more so if it improves survival with good neurological outcome. The effect of the intervention on return of spontaneous circulation is substantial (relative effect- odds ratio 2.09, 95% CI 1.54 to 2.09; absolute effect 181 more per 1,000, 95% CI 108 more to 250 more). The evidence is categorised as low certainty. Even at the lower end of the 95% confidence interval, this would still represent a substantial benefit.	

	This improvement in return of spontaneous circulation does not translate in to a benefit in survival or survival with good neurological outcome across the three eligible studies. As such, there is uncertainty as to whether the intervention improves these longer-term outcomes that are considered important by patients.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	There was no evidence that the intervention might cause direct harm. However, an intervention that improves ROSC but not overall survival might be viewed as undesirable, depending on cultural norms. There are potential side-effects that may be associated with use of vasopressin and steroids (e.g. infection, hyperglycaemia, peripheral ischaemia). However, these effects are likely to be considered acceptable by patients and clinicians if the outcome improves patient outcomes, such as survival.	

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	Overall, evidence certainty was categorised as low or very low to reflect indirectness and imprecision.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The current evidence shows that the interventions improves rates of return of spontaneous circulation, but this does not translate in to improvements in survival. For some, any intervention that improves ROSC may be viewed as valuable. Obtaining ROSC is an essential step in the pathway to overall survival, but even in patients who do not survive, it might be	

	viewed as providing an opportunity for organ donation or for the patient's relatives to spend time with them while they are alive. The consequences of this include increased burden on the healthcare system (particularly ICU beds). This might be a particular challenge in systems where there is limited ICU capacity. It is also known that post-arrest/ ICU interventions may be painful or distressing for the patient, even if they appear to be adequately sedated. The balance of these values likely varies across cultures.	

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 balance between desirable and undesirable effects likely depends on a value judgement, based on the importance of obtaining ROSC where this does not translate in to an effect on overall survival	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	There are no studies directly addressing this. Corticosteroids are relatively cheap and readily available across most systems. In some systems they may only be available in powder form , requiring reconstitution before use, which might have an effect on how rapidly they can be available for use. Vasopressin is relatively expensive. For integration in to resuscitation care, many systems may require that vasopressin be made available in pre-filled syringes which would further increase its costs. Vasopressin also ideally requires refrigeration until use, potentially creating additional costs. Access to refrigeration is unlikely to be available in many EMS systems. Aside from drugs and refrigeration costs, there are likely to be no other significant costs.	

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	We identified no relevant studies.	

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	We did not identify any studies that addressed the cost effectiveness of the addition of vasopressin and corticosteroids to standard care during cardiac arrest. An increase in ROSC without associated increase in improved functional recovery would likely increase healthcare costs through increased demand on ICU beds.	

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 availability of vasopressin and corticosteroids across all health settings is unknown, particularly in low and middle-income countries.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	PATIENTS: The combination of corticosteroids and vasopressin is likely to be acceptable to patients if it improves outcomes that are important to patients. CLINICIANS: Current resuscitation guidelines prioritise the development of straightforward treatment processes that be easily implemented in care. The addition of vasopressin and corticosteroids to standard resuscitation treatment would add a degree of complexity to current care. This is particularly the case for systems where corticosteroids are only available in powder form & require reconstitution prior to administration. For in-hospital settings in such systems, higher numbers of clinical personnel mean that it is likely that the team would be able to safely reconstitute drugs. However, the added complexity may be a barrier to implementation in some settings. Vasopressin ideally requires refrigeration prior to use , though in some circumstances this may not be essential.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Key challenges to implementation include: - In some systems corticosteroids need to be reconstituted prior to administration, - Ideally vasopressin in recommended to be stored in a refrigerator: but this is not always essential. These issues will add complexity to resuscitation care. Whilst likely feasible in the hospital setting, implementation in the out-of-hospital setting may be more challenging in many systems.	

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

	JUDGEMENT						
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

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

Recommendation

We suggest against the use of the combination of vasopressin and corticosteroids in addition to usual care for adult out-of-hospital cardiac arrest (weak recommendation, very low to low-certainty evidence).

Justification

Overall justification

For Out-of-Hospital cardiac arrest , the level of evidence is very low, since there have been no RCTs done in this setting comparing the effects of the addition of vasopressin and corticosteroids to usual standard of care. Therefore all the evidence is indirect , extrapolated from studies involving patients with in-hospital cardiac arrest, and it is therefore of low certainty.

Subgroup considerations

Implementation considerations

Corticosteroids may need to be reconstituted before administration and vasopressin is ideally stored in a fridge.
Both of these facts suggest that implementing this regime in the out-of-hospital setting may be challenging.

Monitoring and evaluation

Research priorities

There is need for a large randomised control trial to compare outcomes between OHCA arrest victims treated with standard care, and those treated with vasopressin and corticosteroids in addition to standard care. Post-ROSC treatment should also be standardised between groups, ideally with the addition of hydrocortisone to those with post-ROSC hypotension, as this was used in the Mentzelopoulos studies.

QUESTION

Should Emergent or early CAG with PCI if indicated vs. Delayed CAG or no CAG be used for Unresponsive adults (> 18 years old) with return of spontaneous circulation (ROSC) after cardiac arrest without ST-segment elevation on ECG?	
POPULATION:	Unresponsive adults (> 18 years old) with return of spontaneous circulation (ROSC) after cardiac arrest
INTERVENTION:	Emergent or early CAG with PCI if indicated
COMPARISON:	Delayed CAG or no CAG
MAIN OUTCOMES:	Survival at 24 hours-RCTs; Survival to hospital discharge-RCTs; Survival to hospital discharge-no STEMI-RCTs; Survival to hospital discharge-shockable-RCTs; Survival at 30 days-NRCTs; Survival at 90 days-RCTs; Survival at 1 -3 years-NRCTs; Favorable Neurologic Outcome at ICU discharge -RCTs; Favorable Neurologic Outcome at hospital discharge-NRCTs; Favorable Neurologic Outcome at hospital discharge-noSTEMI-NRCTs; Favorable Neurologic Outcome at hospital discharge-shockable-NRCTs; Favorable Neurlogic Outcome at 90 days-RCTs; Favorable Neurologic Outcome at 90 days-noSTEMI-RCTs; Favorable Neurologic Outcome at 90 days-shockable-RCTs; PCI ITT-RCTs; PCI PP-RCTs; Successful PCI ITT-NRCTs; Successful PCI PP-NRCTs; CABG ITT-RCTs; Stroke-ICH-NRCTs; Stroke-ICH-RCTs; Recurrent arrest; Sepsis; Pneumonia; Bleeding; Renal replacement therapy; Acute renal failure; Brady arrhytmias-Pacing; Shock; Survival to hospital discharge-STEMI-NRCTs; Favorable Neurologic Outcome at hospital discharge-STEMI-NRCTs;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival from cardiac arrest is low (~10%). The majority of cardiac arrests are of presumed cardiac etiology amendable to cardiac intervention. Specifics around the use of coronary angriography such as timing, patient populations etc. are not well defined. Patients without ST-segment elevation on ECG are less likely to have a lesion amendable to coronary angiography and percutaneous coronary intervention, compared to patients with ST-segment elevation on ECG. There are, however, patients within this group who require CAG.	Stable, non-cardiac arrest patients suffering a myocardial infarction without ST-segment elevation on ECG do not require urgent coronary angiography.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Improving patient outcomes after cardiac arrest is of utmost importance. The impact of urgent coronary angiography, however, appears to vary by population. While urgent angiography may be most important in post-cardiac arrest patients with STE on ECG we did not find improved survival or neurological outcome in patients without STE on ECG or with initial shockable cardiac arrest rhythms.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	We did not find any evidence of adverse events including, rearrest, bleeding, infection with early coronary angiography compared to delayed coronary angiography.	Coronary angiography for post-cardiac arrest patients requires considerable resource utilization, cost and may detract from other important intervetnsions such as TTM in undifferentiated post-cardiac arrest patients.

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	The certainty of evidence is low for post-cardiac arrest patients with no STEMI on ECG. The effect estimate for survival at 30-days comes from two RCTs [Desch 2021, Kern 2020], one of which was stopped early for futility (OR 0.93 95% CI 0.49 to 1.76). Similarly, one RCT [Lemkes 2019] and a subgroup of Desch 2021 examine patients with no STEMI and an initial shockable rhythm. The certainty of evidence for this population is again low for survival at hospital discharge / 30 days (OR 0.90, 95% CI 0.66 to 1.28). All reported outcomes have confidence intervals for the effect estimate that span 1.00. Further, similar results are noted for functional survival at 30-days [Desch 2021, Kern 2020] (OR 0.88 (95% CI 0.51 to 1.52).	

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	Survival and neurological outcome are both patient-oriented outcomes that are considered highly important for cardiac arrest research. COSCA statement [Haywood 2018] include these as core outcomes for reporting of cardiac arrest.	

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	While the outcome of survival would be valued more than the undesirable effects the effect estimate and certainty of evidence suggests no benefit for early CAG for cardiac arrest patients, patients without STEMI on ECG, and patients with VF as an initial presenting rhythm. This evidence, however, comes from a single RCT where unstable patients were excluded.	

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	Costs were not evaluated in this systematic review. Resource costs, however, are substantial for this intervention and will most likely vary across countries. This would include both costs to the prehospital system and in-hospital system.	

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	We did not include any studies to determine the certainty of evidence around the cost associated with early CAG.	

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	We did not include any studies that examined 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	There is no evidence to suggest benefit for early over delayed coronary angiography for patients without ST-segment elevation on post-ROSC ECG. We therefore recommend either early or delayed angiography for these patients. Recommending either option for post-cardiac arrest patients would not impact health equity	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is widely accepted in non-cardiac arrest patients and in post-cardiac arrest patients with ST-segment elevation no ECG. We did not find evidence to suggest that urgent CAG should also be applied to other groups of post-cardiac arrest patients.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes	Feasibility of this intervention may vary between jurisdictions. While the intervention is a common treatment for both post-cardiac arrest and non-cardiac arrest patients the feasibility of early angiography for post-cardiac arrest patients would depend on system resources to transport patients	

● Varies ○ Don't know	to a centre capable of performing the intervention and on the accessibility of a PCI centre. This will vary across regions.	

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	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

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

Recommendation

When coronary angiography is considered for comatose post-arrest patients without ST elevation, we suggest that either an early or a delayed approach for angiography is reasonable. (weak recommendation, low certainty of evidence)

Justification

In making the above recommendations, the taskforce weighed the fact that we did not find sufficient evidence to demonstrate improved outcomes with early angiography for post cardiac arrest patients without ST-segment elevation regardless of presenting cardiac arrest rhythm (shockable or non-shockable). Patients in cardiogenic shock post arrest were excluded from all studies and there is unlikely to ever be sufficient clinical equipoise to support a randomized trial of delayed intervention in the shock cohort. There may be subgroups of patients without ST-segment elevation with high-risk features that would benefit from earlier coronary angiography.

Importantly this review examined the timing of coronary angiography if it was done, and did not compare to no coronary angiography. It may be that survival and functional survival may not be the right outcomes to measure harm or benefit from an intervention that adjusts the timing of PCI in post arrest patients. We know that the majority of patients admitted to hospital after cardiac arrest do not die from cardiac complications and most die as a result of neurologic injury. There are no significant differences in adverse event rates with either time interval.

Subgroup considerations

Implementation considerations

The ability to implement coronary angiography for post-cardiac arrest patients will vary across systems. It will depend on prehospital resources, distance to cath lab and ability of hospitals to perform intervention. Regional variations may also differ in terms of whether patients are transported directly from the field (“Bypass directive”) or if they are transported to local hospitals and then transferred to a cardiac centre at a later time (“inter-facility transfer”).

Monitoring and evaluation

Research priorities

- Heterogeneity precluded performing a meta-analysis for the majority of studies
- Timing of coronary angiography (definition of early/urgent) inconsistent across studies
- Little data on successful percutaneous coronary intervention
- No studies identified that evaluated this question in the in-hospital setting.
- No RCTs compared intervention with standard care in any patient population
- Only short term/surrogate outcomes were evaluated, future studies should document survival/neurologically intact survival to hospital discharge/30 days.
- There may be alternative endpoints that may show a benefit with timing of coronary angiography such as functional or biochemical endpoints.

QUESTION

Should [Emergent or early CAG with PCI if indicated] vs. [Delayed CAG or no CAG] be used for [Unresponsive adults (> 18 years old) with return of spontaneous circulation (ROSC) after cardiac arrest with ST-segment elevation (STEMI) on ECG]?	
POPULATION:	[Unresponsive adults (> 18 years old) with return of spontaneous circulation (ROSC) after cardiac arrest]
INTERVENTION:	[Emergent or early CAG with PCI if indicated]
COMPARISON:	[Delayed CAG or no CAG]
MAIN OUTCOMES:	Survival at 24 hours-RCTs; Survival to hospital discharge-RCTs; Survival to hospital discharge-no STEMI-RCTs; Survival to hospital discharge-shockable-RCTs; Survival at 30 days-NRCTs; Survival at 90 days-RCTs; Survival at 1 -3 years-NRCTs; Favorable Neurologic Outcome at ICU discharge -RCTs; Favorable Neurologic Outcome at hospital discharge-NRCTs; Favorable Neurologic Outcome at hospital discharge-noSTEMI-NRCTs; Favorable Neurologic Outcome at hospital discharge-shockable-NRCTs; Favorable Neurlogic Outcome at 90 days-RCTs; Favorable Neurologic Outcome at 90 days-noSTEMI-RCTs; Favorable Neurologic Outcome at 90 days-shockable-RCTs; PCI ITT-RCTs; PCI PP-RCTs; Successful PCI ITT-NRCTs; Successful PCI PP-NRCTs; CABG ITT-RCTs; Stroke-ICH-NRCTs; Stroke-ICH-RCTs; Recurrent arrest; Sepsis; Pneumonia; Bleeding; Renal replacement therapy; Acute renal failure; Brady arrhytmias-Pacing; Shock; Survival to hospital discharge-STEMI-NRCTs; Favorable Neurologic Outcome at hospital discharge-STEMI-NRCTs;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival from cardiac arrest is low (~10%). The majority of cardiac arrests are of presumed cardiac etiology amendable to cardiac intervention.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Improving patient outcomes after cardiac arrest is of utmost importance. Urgent angiography may be most important in post-cardiac arrest patients with STE on ECG. There are no RCTs on urgent coronary angiography specific to this population. We identified two observational studies examining patients with post-ROSC STEMI on ECG. Neither study identified benefit with urgent coronary angiography	Urgent coronary angiography and PCI, when indicated, is recommended for patients who have a ST-segment myocardial infarction without cardiac arrest.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	RCTs of post-ROSC patients (Lemkes, Elfwen) did not identify any risk of adverse events such as bleeding, stroke, or re-arrest with early coronary angiography.	Coronary angiography for post-cardiac arrest patients requires considerable resource utilization, cost and may detract from other important intervetnsions such as TTM in undifferentiated post-cardica arrest patients. Timing of ECG post-ROSC may help to avoid false positive activations (Baldi 2020)

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	The certainty of evidence is very low for post-cardiac arrest patients with ST elevation on ECG. A single observational study (Garcia 2016) met our pre-determined criteria for inclusion and found no improvement in survival [OR 1.89 (95% CI 0.48, 7.43)] or neurological outcome [OR 1.12 (95% CI 0.30, 4.19)] at hospital discharge with urgent coronary angiography.	

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	Survival and neurological outcome are both patient-oriented outcomes that are considered highly important for cardiac arrest research. COSCA statement [Haywood 2018] include these as core outcomes for reporting of cardiac arrest.	

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	While the outcome of survival would be valued more than the undesirable effects the effect estimate and certainty of evidence suggests no benefit for early CAG for post-cardiac arrest STEMI patients. This evidence comes from a single observational study.	

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	Costs were not evaluated in this systematic review. Resource costs, however, are substantial for this intervention and will most likely vary across countries. This would include both costs to the prehospital system and in-hospital system.	

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	We did not include any studies to determine the certainty of evidence around the cost associated with early CAG.	

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	We did not include any studies that examined 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		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention is widely accepted in non-cardiac arrest patients and in post-cardiac arrest patients with ST-segment elevation no ECG and is currently recommended in cardiac arrest guidelines.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes	Feasibility of this intervention may vary between jurisdictions. While the intervention is a common treatment for both post-cardiac arrest and non-cardiac arrest patients the feasibility of early angiography for post-cardiac arrest patients would depend on system resources to transport patients	

● Varies ○ Don't know	to a centre capable of performing the intervention and on the accessibility of a PCI centre. This will vary across regions.	

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	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

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

Recommendation

We suggest early coronary angiography in comatose post-cardiac arrest patients with ST segment elevation. (good practice statement)

Justification

For comatose patients with ST segment elevation there is no randomized clinical evidence for the timing of coronary angiography. The Task Force acknowledges that early coronary angiography, and percutaneous intervention if indicated, is the current standard of care for patients with STEMI who did not have a cardiac arrest. We found no evidence to change this approach in patients with ST segment elevation following cardiac arrest.

Subgroup considerations

Implementation considerations

The ability to implement coronary angiography for post-cardiac arrest patients will vary across systems. It will depend on prehospital resources, distance to cath lab and ability of hospitals to perform intervention. Regional variations may also differ in terms of whether patients are transported directly from the field ("Bypass directive") or if they are transported to local hospitals and then transferred to a cardiac centre at a later time ("inter-facility transfer").

Monitoring and evaluation

Research priorities

- Heterogeneity precluded performing a meta-analysis for the majority of studies
- Timing of coronary angiography (definition of early/urgent) inconsistent across studies
- Little data on successful percutaneous coronary intervention

- No studies identified that evaluated this question in the in-hospital setting.
- No RCTs compared intervention with standard care in any patient population
- Only short term/surrogate outcomes were evaluated, future studies should document survival/neurologically intact survival to hospital discharge/30 days.
- There may be alternative endpoints that may show a benefit with timing of coronary angiography such as functional or biochemical endpoints.

QUESTION

Should Automatic external defibrillators application vs. no application be used for pediatric cardiac arrest by lay rescuers?	
POPULATION:	pediatric cardiac arrest by lay rescuers
INTERVENTION:	Automatic external defibrillators application
COMPARISON:	no application
MAIN OUTCOMES:	CPC 1 or 2 at hospital discharge; CPC 1 or 2 hospital discharge < 1 year of age; CPC 1 or 2 at hospital discharge 1-12 years; CPC 1 or 2 at hospital discharge 13-18 years; Hospital discharge 0-18 years; Hospital discharge < 1 year; Hospital discharge 1-12 years; Hospital discharge 13-18 years; CPC 1-2 at one month 6-17 years; Association of Bystander CPR with Hospital discharge with AED use; Association of bystander CPR with AED with CPC 1-2 at hospital discharge;
SETTING:	out of hospital pediatric cardiac arrest
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Cardiac arrest survival rates are low in infants, children, and adolescents. Although shockable rhythms are less common in children compared to adults, survival (with good neurological outcome) could be improved with the application of an AED.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Survival with favorable neurologic outcome is the optimal outcome of cardiac arrest. If AEDs improve outcomes, then the effect is considerable. A child will be able to resume all activities and continue to grow into adulthood. This effect increases with increasing age as the frequency of shockable rhythms increases with age. If a shockable rhythm is not present, then application of an AED may delay initiation of CPR or	

	increase pause duration. Alternatively, since AEDs can provide CPR instructions, AED application can assist lay rescuers and improve CPR quality.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Application of an AED may delay initiation of chest compressions or contribute to longer pauses in chest compressions and ventilations. This may potentially decrease survival in children with non-shockable rhythms.	

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	All published data are from two large registries. No controlled trials are available. Although both registries are quality-controlled, there is limited ability to assure completeness or accuracy of the data. The number of subjects on whom an AED was applied was very small in all age groups compared to the total number of subjects who had a cardiac arrest. There may be significant selection bias in those children who had the AED applied. The rescuers who applied the AED may be those with a greater skillset and provide higher quality CPR, than those with less experience	

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	Society values survival especially with favorable neurologic outcome.	

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 evidence probably favors the intervention in all age groups except those < 1 year. Although the RR for both age groups > 1 indicates a marked increase in survival, the number of patients included in the intervention group is very small compared to control. Additionally, for children in the 1-12 age group, ventilations remain an important aspect of successful resuscitation. Application of an AED may delay the initiation of CPR or increase the length of pauses. Data on long-term outcmes (>= 30 days after hospital discharge) is minimal. For infants < 1 year, the data are are even more limited (12 patients, 1 survivor), so no recommendation could be made. For patients suffering a cardiac arrest of cardiac origin, the liklihood of an initial shockable rhythm is high and delivery of a shock is required for termination. The risk of a schockable rhythm increases with age even in this population.	

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	The placement of AEDs in locations with few children will increase the overall cost of Public Access Defibrillation programs. Use of pediatric pads will also increase costs. The data may support increased placement of AEDs in locations where young children congregate such as day care centers and all schools, not just high schools. However, risk of pediatric cardiac arrest is low in these locations so cost-effectiveness may be poor. Alternatively, improved survival leads to lower long-term medical costs and decreases premature loss of life.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies on the required resources or the cost. Pediatric pads are not required by current guidelines. Data on effectiveness and safety of pediatric vs adult pads in OHCA are not available.	

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 published data on cost effectiveness in children. Cost effectiveness has been shown for adult programs. Succesful neurologic outcomes promotes cost effectiveness. Placement of AEDs in locations with few children or where the risk of a cardiac arrest is low would lower cost-effectiveness.	

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	Equity may be reduced for locations of lower socioeconomic status sites which are not equipped with AEDs.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	AEDs have wide acceptability and there is increasing use in children. Favorable neurologic outcomes are highly desirable. Trained rescuers may hesitate to use an AED when liklihood of a shockable rhythm is considered to be low.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	AEDs are readily available in many locations. Use of an AED when available is highly feasible.	

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	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

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

Recommendation

We suggest the use of an AED by lay rescuers for all children over age 1 year suffering a non-traumatic out-of-hospital cardiac arrest *(weak recommendation, very low certainty evidence)*.

We cannot make a recommendation for or against the use of an AED by lay rescuers for all children below age 1 year suffering a non-traumatic out-of-hospital cardiac arrest

Justification

Overall justification

The available data suggest a benefit of the use of an AED in OHCA of children. However, data are of very low certainty and there is a substantial imbalance between intervention and control groups suggesting possible selection bias. For children > 1 year suffering an out-of-hospital cardiac arrest, the effect is considered strong enough in favor of the intervention to recommend for use of an AED by lay rescuers. Considering the existing evidence in adults and the presumed higher incidence of shockable rhythms in primary cardiac arrest, the writing group made a best practice statement for cardiac arrest of presumed cardiac origin such as for sudden witnessed collapse.

For children younger than 1 year of age, the data preclude any conclusion. Not only does the confidence interval cross "0", the intervention group only included 12 infants with only 1 survivor. There is a risk of delaying CPR while applying an AED in a population in whom respiratory causes of cardiac arrest predominate. Infants who do have a shockable rhythm may benefit from application of an AED.

Detailed justification
Desirable Effects
Survival and survival with favorable neurologic outcome were improved in all age groups > 1 y ears.

Subgroup considerations

The children and adolescents who suffer a sudden witnessed a cardiac arrest, which may indicate a primary cardiac origin, are more likely to have an initial shockable rhythm and delivery of a shock is the only effective therapy. In this population, early defibrillation is highly desirable.

Implementation considerations

Placement of AEDs continues to increase. and in many locations, such as schools and youth sports venues, is required by law. In locations where an AED already exists, it is appropriate to apply the AED to a child in cardiac arrest.

Monitoring and evaluation

Research priorities

There are no randomized controlled trials of AED application in children, only observational trials.

There are limited data on the interaction between high-quality CPR with and without AED application This is particularly y important in light of the importance of rescue breaths with chest compressions in pediatric cardiac arrest.

There are limited data on whether AED application alters outcomes based on the type of CPR provided, i.e. chest compression only or standard CPR with compressions and rescue breathing.

Only short term/surrogate outcomes were evaluated, future studies should document survival/neurologically intact survival to beyond 30 days.

Is there a difference in survival following AED application in children with primary cardiac arrest compared to those in whom a primary cardiac etiology is not suspected.

If AEDs are placed where there are children age 1-12, does the use of the pediatric pads which attenuate the energy dose, increase survival and safety?

Does the AED aid lay rescuers in providing CPR?

There is no information about possible advantages of using the pediatric modifications for the younger children, especially those < 8 years or 25 kg. The application of an AED may be beneficial beyond shock delivery, such as directing the rescuer to the appropriate actions and performing AED. The mechanisms potential human factors and behavioral change are not understood.

QUESTION:

DO PEDIATRIC EARLY WARNING SYSTEMS REDUCE MORTALITY AND SIGNIFICANT CLINICAL DETERIORATION? (A SYSTEMATIC REVIEW)	
POPULATION:	Children born term (gestation ≥37 weeks) to ≤18 years old in the inpatient setting, including emergency departments
INTERVENTION:	Pediatric early warning systems (PEWS) with or without rapid response teams (RRTs)
COMPARISON:	No pediatric early warning systems (PEWS) and no rapid response teams (RRTs)
MAIN OUTCOMES:	A significant clinical deterioration event, including but not limited to: (1) Unplanned/crash tracheal intubation, (2) Unanticipated fluid resuscitation and inotropic/vasopressor use (3) Cardiopulmonary resuscitation (CPR) or Extracorporeal Membrane Oxygenation (ECMO) (4) Death in patients (all-cause mortality) without a Do Not Resuscitate (DNR) order.
SETTING:	In-patient setting, including emergency departments
PERSPECTIVE:	
BACKGROUND:	While there is limited evidence that pediatric early warning system interventions result in a reduction in in-hospital clinical deterioration, some effectiveness studies, with significant methodological limitations, appear to show clinical benefits. The use of pediatric early warning systems (PEWS) should decrease clinically important deteriorations on the wards in non-tertiary care / community hospitals. There was sufficient evidence to warrant a systematic review based on the scoping review performed in 2020.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Recognizing early clinical deterioration and responding clinically in a timely manner in pediatrics is important in improving clinical care and outcome for potentially ill and seriously ill children. There is good evidence that pediatric early warning systems (PEWS) help identify early deterioration with many studies conducted validating the various pediatric early warning scores developed as well as pediatric rapid response teams (RRTs).	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large	The patient-centric outcomes of reduction in mortality, reduction in cardiopulmonary arrest events in hospital paediatric patients are highly desirable. If proven to be effective through early recognition triggering early intervention, pediatric early warning systems can be	

○ Varies ○ Don't know	instrumental in saving lives and improving functional outcomes for children at risk of clinical deterioration.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	No substantial undesirable anticipated effects were seen in studies published.	

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	The systematic review and meta-analysis demonstrated trends of pediatric early warning systems decreasing in-hospital mortality, cardiopulmonary arrest events, and significant clinical deterioration events, although not to statistically significant levels. Based on observational studies, it did show a significant decrease in code events. However, there were significant limitations in the studies. Parshuram 2018 (which is the only RCT) was limited by the variation in the effector arm. The pediatric early warning system observational studies all used before-and-after study-designs, with the inherent limitations of unaccounted or confounding variables and contemporaneous trends and the inability to develop a comparable control group with the potential for risk of bias. The studies that used mortality as an outcome had a very low event rate and studies that used clinical deterioration had varying definitions including cardiopulmonary arrest.	Many studies focus on the derivation and validation of various pediatric early warning systems. These studies demonstrated that pediatric early warning systems were able identify a sick child early, with robust performance. Demonstrating a statistically significant effect after a new implementation is difficult given the limitations. Quality improvement methodology could be used to regulate the impact of pediatric early warning systems that requires a series of changes that include educational processes, documentation review with feedback systems, and modification of other factors thought to improve the delivery of care. While this systematic review and meta-analysis as a whole did not demonstrate a statistically significant decrease in critical outcomes of mortality, cardiopulmonary arrest events and

		significant clinical deterioration events, it does not necessarily show a lack of clinical benefit or value of pediatric early warning systems. This systematic review and meta-analysis suggest that more randomized controlled trials with an efferent arm should be undertaken to validate current findings.

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	There is no uncertainty or variability in using mortality as a key outcome. In the pediatric early warning system studies, mortality is a common outcome marker. A major limitation to evaluation of these systems is the low rate of pediatric cardiopulmonary arrest and mortality (especially outside the intensive care unit setting), including within the hospitals from which the data in this analysis originate. As such, demonstrating a statistically significant effect after a new implementation is difficult. There is paucity of studies looking at uncertainty about or variability in how people value using clinical outcomes other than mortality and cardiopulmonary arrest and instead use other clinical deterioration events as clinical outcomes in pediatric early warning system studies.	In measuring effectiveness of pediatric early warning systems, other critical and important outcomes like critical deterioration events and code blue events should be used in future 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	In this systematic review and meta-analysis, mortality, cardiopulmonary arrest outside of intensive care, significant clinical deterioration, and code events were used as clinical outcome markers. Most studies demonstrated that these clinical events were generally low frequency (especially outside the critical care setting). However, in any systems that have inpatient monitoring systems (whether specifically pediatric early warning systems or otherwise) with ongoing process-improving initiatives, these would likely result in decrease frequency in these events. There was a demonstrated significant decrease in codes events and trend towards decreased in-hospital mortality, cardiopulmonary arrest events and significant clinical deterioration. While it is not certain that pediatric early warning systems are superior to no pediatric early warning systems in decreasing these, the critical outcomes of interest, the absence of clinical benefit does not necessarily show its lack of benefit or value. Future specific research will need to focus on prospective evaluation of different pediatric early warning systems with efferent arms for predicting, identifying, and providing early intervention for patients at risk for different forms of decompensation, including primary respiratory, circulatory, and neurologic etiologies. Additional outcome measures apart from cardiopulmonary arrest rate or hospital mortality are required. Future studies using the incidence of significant clinical deterioration as key clinical outcomes should be undertaken.	Our taskforce reaffirms that the implementation of pediatric early warning systems should be part of an overall clinical response system, with the task force placing a higher value on improving healthcare provider ability to recognize and intervene for patients with deteriorating illness over the expense incurred by a healthcare system committing significant resources to implement pediatric early warning systems. The task force also noted that the complex process of optimizing patient care is likely to include both the implementation of pediatric early warning systems and ongoing healthcare provider education.

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 paucity of studies looking at resources required using pediatric early warning scores and pediatric early warning systems with or without rapid response teams. Furthermore, these further studies should look not only at the health economic impact and benefits of pediatric early warning systems in resource-rich healthcare institutions but also in healthcare institutions in resource-limited countries.	Our taskforce agreed that the decision to use pediatric early warning systems or other validated inpatient monitoring systems should be balanced between use of existing resources and capabilities of the healthcare setting to adapt to its use and the consequences of its use.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	There is paucity of studies looking at required resources required to develop and sustain pediatric early warning scores and pediatric early warning systems with or without rapid response teams in healthcare institutions. These further studies should look not only at pediatric early warning systems in resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries. Many studies, while not describing cost per se, did provide details into the training, staffing and implementation resources required for pediatric early warning systems. These are variable across sites depending on: 1) Existing infrastructure, including level of care (e.g., tertiary pediatric center, intensive care unit); 2) Resource-availability (24/7 specialist availability, respiratory technicians, etc.); 3) Need and duration of training.	Our taskforce placed a higher value on the potential to recognize and intervene for patients with deteriorating illness over the expense incurred by a healthcare system committing significant resources to implement pediatric early warning systems or validated inpatient monitoring systems. We recognize that the decision to use these inpatient monitoring systems should include staff education, workflows, and audits. This should be balanced by the existing resources and capabilities of the institution.

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 is paucity of studies looking at cost effectiveness of pediatric early warning scores and pediatric early warning systems with or without rapid response teams in healthcare institutions. However, if implementation of a pediatric early warning systems does decrease mortality and morbidity, it would prevent downstream patient morbidity and mortality. As such it would likely be cost-effective. Future studies should be undertaken to evaluate cost-effectiveness of pediatric early warning systems in resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries.	

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	There is paucity of studies looking at equity of pediatric early warning scores and pediatric early warning systems with or without rapid response teams in healthcare institutions. These further studies should look not only at PEWS in resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries. When powered with more analyzable data, these should be stratified by resource-availability e.g., Gross National Income or Sociodemographic Index status of the country.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is paucity of studies looking at acceptability of pediatric early warning scores and pediatric early warning systems with or without rapid response teams in healthcare institutions. These further studies should look not only at pediatric early warning systems in resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is paucity of studies looking at feasibility of pediatric early warning scores and pediatric early warning systems with or without rapid response teams in healthcare institutions. These further studies should look not only at pediatric early warning systems in resource-rich healthcare institutions but also in healthcare institutions from resource-limited countries.	

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	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

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

Recommendation

Treatment Recommendations

We suggest using pediatric early warning systems to monitor hospitalized pediatric patients with the aim of identifying those who may be deteriorating (weak recommendation, low quality evidence).

Justification

The PLS Task Force concluded that the implementation of pediatric early warning systems should be part of an overall clinical response system, with the task force placing a higher value on improving healthcare provider ability to recognize and intervene for patients with deteriorating illness over the expense incurred by a healthcare system committing significant resources to implement pediatric early warning systems. The task force also noted that the complex process of optimizing patient care is likely to include both the implementation of pediatric early warning systems and ongoing healthcare provider education. The PLS Task Force agreed that the decision to use pediatric early warning systems should be balanced between use of existing resources and capabilities of the healthcare setting to adapt to its use and the consequences of its use.

In making these recommendations, the PLS Task Force considered the following:

Values, Preferences, and Task Force Insights

The evidence is equipoised to justify the use of pediatric early warning systems to significantly decrease in-hospital pediatric mortality, significant clinical deterioration, and cardiopulmonary arrest events. However, in systems with available resources that prioritize and value the potential to decrease the incidence of code events for inpatient pediatric patients, there was very weak evidence to support the use of pediatric early warning systems in this context.

The taskforce recognized the significant limitations of available evidence in its treatment recommendations, but also the importance and the potential value of improving healthcare providers' ability to recognize and intervene for patients with deteriorating illness. The use of pediatric early warning systems should be balanced with the expense incurred by a healthcare system committing significant resources to implement pediatric early warning systems. This complex process of optimizing patient care is likely to include both the implementation of pediatric early warning systems as part of a system and ongoing healthcare provider education. The PLS Task Force agreed that the decision to use pediatric early warning systems should be balanced between use of existing resources and capabilities of the healthcare setting to adapt to its use, and the consequences of its use.

For existing systems using pediatric early warning systems, local validation, site-specific adaptation of its use, and longitudinal evaluation of its effectiveness are important.

Knowledge Gaps & Recommendations

• The amount and quality of evidence in children compared with adults for the role of Early Warning Systems or Scores in the inpatient setting is very low. In the pediatric early warning system studies, mortality is a common outcome marker. A major limitation to evaluation of these systems is the low rate of pediatric cardiopulmonary arrest and mortality (especially outside the intensive care unit setting), including within the hospitals from which the data in this analysis originate. As such, demonstrating a statistically significant effect after a new implementation is difficult. We recommend that a workgroup should be set up to recommend & standardize important clinical outcomes that should be tracked and measured following implementation of pediatric early warning systems in hospitals and healthcare systems.

• The other major limitation in our analysis is the use of before-and-after studies, with the inherent limitations of unaccounted or confounding variables and inability to develop a comparable control group associated with the problems of confounding variables and contemporaneous trends. Future studies should not be limited to RCTs but include comparative study approaches as well as Quality Improvement (QI) and longitudinal studies. Quality improvement methodology could be used to regulate the impact of a series of changes that include educational processes, documentation review with feedback systems, and modification of other factors thought to improve the delivery of care.

• Further studies for pediatric early warning systems should focus on controlled trials evaluating RRT compared to no RRT and various compositions of efferent arms and look into specific pediatric subgroups including pediatric patients in the emergency department setting

and specific subgroups of pediatric disease populations – e.g. pediatric oncology and prospectively evaluate different pediatric early warning systems for predicting, identifying, and provide early intervention for patients at risk for different forms of decompensation, including primary respiratory, circulatory, and neurologic etiologies.

• Other future studies should look at pediatric patients in the out-of-hospital setting as well as pediatric patients in resource-rich countries and patients from resource-limited countries and these studies should be powered with more analyzable data and be stratified by resource-availability e.g., Gross National Income or Sociodemographic Index status of the country.

• With regards to pediatric early warning systems implementation considerations, studies should look into staff training/education methodology for pediatric early warning systems implementation, resourcing; feasibility; cost-effectiveness; equity and acceptability of pediatric early warning systems into the existing healthcare systems.

Subgroup considerations

- Pediatric patients in the emergency department setting
- Pediatric inpatients
- Specific subgroups of pediatric disease populations – e.g., pediatric oncology etc.
- Pediatric patients in the out-of-hospital setting
- Pediatric patients in resource-rich countries and patients from resource-limited countries

Implementation considerations

- Resourcing
- Feasibility
- Cost-effectiveness
- Equity and
- Acceptability

Monitoring and evaluation

Research priorities

- Future studies should not be limited to RCTs but include comparative study approaches as well as Quality Improvement (QI) and longitudinal studies. Quality improvement methodology could be used to regulate the impact of a series of changes that include educational processes, documentation review with feedback systems, and modification of other factors thought to improve the delivery of care.
- Further studies for pediatric early warning systems should focus on controlled trials evaluating RRT compared to no RRT and various compositions of efferent arms and look into specific pediatric subgroups including pediatric patients in the emergency department setting and specific subgroups of pediatric disease populations – e.g. pediatric oncology and prospectively evaluate different pediatric early warning systems for predicting, identifying, and provide early intervention for patients at risk for different forms of decompensation, including primary respiratory, circulatory, and neurologic etiologies.
- Other future studies should look at pediatric patients in the out-of-hospital setting as well as pediatric patients in resource-rich countries and patients from resource-limited countries and these studies should be powered with more analyzable data and be stratified by resource-availability e.g., Gross National Income or Sociodemographic Index status of the country.
- With regards to pediatric early warning systems implementation considerations, studies should look into staff training/education methodology for pediatric early warning systems implementation, resourcing; feasibility; cost-effectiveness; equity and acceptability of pediatric early warning systems into the existing healthcare systems.

QUESTION

Should a room temperature at 23ºC vs. room temperature at 20ºC be used for late preterm and term neonates (≥ 34 weeks' gestation, or equivalent birth weight) immediately after birth?	
POPULATION:	Late preterm and term neonates (≥ 34 weeks' gestation or equivalent birth weight) immediately after birth
INTERVENTION:	Room temperature at 23ºC
COMPARISON:	Room temperature at 20ºC
MAIN OUTCOMES:	Survival until hospital discharge, Normothermia on admission to neonatal unit or postnatal ward; body temperature; hypoglycemia; moderate hypothermia (temperature <36ºC); hyperthermia (temperature >37.5ºC); receipt of respiratory support
SETTING:	All
PERSPECTIVE:	Population perspective
BACKGROUND:	ILCOR has previously recommended room temperatures of 23-25ºC for the births of preterm infants <32 weeks' gestation to prevent hypothermia. {Perlman 2015 S204} ILCOR also recommended, for newborn infants ≥30 weeks' gestation born in low-resourced settings, the use of skin to skin contact and use of a plastic bag or wrap, (while noting the absence of evidence for these practices in this gestation group). {Perlman 2015 S204} However, optimal room temperatures for births of late preterm and term infants were not examined in a systematic review.
CONFLICT OF INTERESTS:	None for this worksheet

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A systematic review conducted for ILCOR concluded that "For the critical outcome of mortality, there is evidence from 36 observational studies of increased risk of mortality associated with hypothermia at admission (low-quality evidence but upgraded to moderate-quality evidence due to effect size, dose-effect relationship, and single direction of evidence)". {Perlman 2015 S204} The same systematic review concluded that "There is evidence of a dose effect on mortality, suggesting an increased risk of at least 28% for each 1° below 36.5°C body temperature at admission and dose-dependent effect size". {Perlman 2015 S204} Although the size of effect in this estimate was influenced by inclusion of studies that enrolled very preterm infants, there was also evidence of adverse effects of hypothermia on survival in late preterm and term infants. A systematic review estimated that hypothermia was common in infants born in hospitals (prevalence range, 32% to 85%) and homes (prevalence range, 11% to 92%), even in tropical environments. {Lunze 2013 24}	WHO has recommended ambient temperatures for birthing rooms of 25ºC {World Health Organization (WHO) 1996 }

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 found one cluster-randomized trial that examined operating room temperatures. The study was considered at overall, high risk of bias. However, the risk of bias was only due to concerns about the lack of blinding of the allocation sequence and of the clinicians involved. It showed that for **an operating room temperature 23ºC vs an operating room temperature of 20ºC**:

- For the (critical) primary outcome **survival to hospital discharge,** there were no data.
- For the (important) primary outcome of **normothermia** on admission, there was **possible benefit**

Among important secondary outcomes:

- For **mean temperature** on admission, there was **possible benefit**
- For **moderate hypothermia**, there was **possible benefit**

The rationale for considering the effect moderate was that mean temperatures on admission were higher by 0.3ºC, a difference that was considered clinically significant. Furthermore, for every 1000 infants exposed to an operating room temperature of 23ºC compared to a temperature of 20ºC

- from 55 more to 209 more were normothermic
- 109 fewer to 158 fewer were moderately hypothermic.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with an operating room temperature 20ºC	Risk difference with an operating room temperature at 23ºC
Normothermia on admission to neonatal unit or postnatal ward	825 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	**RR 1.26** (1.11 to 1.42)	Study population	
				499 per 1,000	**130 more per 1,000** (55 more to 209 more)
Body temperature	825 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	-	The mean body temperature was **36.40** ºC	MD **0.3 ºC higher** (0.23 higher to 0.37 higher)
Hypoglycemia	825 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,c]	**RR 0.69** (0.20 to 2.42)	Study population	
				14 per 1,000	**4 fewer per 1,000** (11 fewer to 20 more)
Moderate hypothermia (temperature <36ºC)	825 (1 RCT)[1]	⨁◯◯◯ Very low[a,b,d]	**RR 0.26** (0.16 to 0.42)	Study population	
				189 per 1,000	**140 fewer per 1,000** (158 fewer to 109 fewer)
Receipt of respiratory support	825 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	**RR 2.06** (0.63 to 6.80)	Study population	
				10 per 1,000	**10 more per 1,000** (4 fewer to 55 more)

[1] {Duryea 2016 505.e1}

a. The only RCT reporting on this outcome had a high risk of overall bias
b. Indirectness related to patient population as only c-section neonates were included
c. 95% CI crosses the clinical decision threshold

Maternal temperatures at the time of delivery and on admission to the post-operative care area were also slightly improved (p<0.001)

	With room temp. 20ºC	With room temp. 23ºC
At time of delivery	36.2±0.6ºC	36.6ºC±0.6C
At admission to post-operative care area	36.1±0.6ºC	36.2ºC±0.6C
Maternal hypo-thermia (P=0.008)	77%	69%

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	d. OIS not satisfied e. 95% CI crosses the clinical decision threshold with the possibility of harm as well as benefit and OIS not satisfied due to low event rate	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	The systematic review found that from the one trial of **an operating room temperature 23ºC vs an operating room temperature of 20ºC, clinical benefit or harm could not be excluded**	Measures to prevent hypothermia may increase risk for hyperthermia, because preterm or very ill neonates may have deficient thermoregulation and their capacity to maintain normothermia is limited. The 2015 ILCOR NLS CoSTR stated that; "A by-product of [these] interventions to prevent hypothermia is more-frequent hyperthermia (temperature greater than 37.5°C). Hyperthermia (temperature greater than 37.5°C) also increases the risk for neonatal mortality and morbidity in both term and preterm infants".{Perlman 2015 S204} A recent study in a low resource setting found that "mortality rate was estimated to be at minimum at admission temperature of 37.5 °C" with higher mortality above and below that level. {Cavallin 2020 722} Of particular relevance to late preterm and term infants, the adverse outcomes of hypoxic ischaemic encephalopathy (which are mitigated by controlled, therapeutic hypothermia) are exacerbated by hyperthermia. While it is possible that some of these effects are confounded by the presence of infection (e.g chorioamnionitis, sepsis) there are plausible reasons why hyperthermia may itself compound brain injury. {Kasdorf 2013 379}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with an operating room temperature 20ºC	Risk difference with an operating room temperature at 23ºC
Hyperthermia	825 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,c]	**RR 4.13** (0.88 to 19.32)	Study population	
				5 per 1,000	**15 more per 1,000** (1 fewer to 87 more)

[1] {Duryea 2016 505.e1}

a. The only RCT reporting on this outcome had a high risk of overall bias
b. Indirectness related to patient population as only c-section neonates were included
c. 95% CI crosses the clinical decision threshold with the possibility of harm as well as benefit and OIS not satisfied due to low event rate

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	The certainty of evidence for all outcomes was very low, with downgrading for very serious risk of bias, and serious indirectness and imprecision in the one included RCT.	The single trial examined only operating room temperatures, but the results were thought likely to also apply to other birthing rooms.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The outcome of survival to hospital discharge (or its converse, mortality) have been judged by both care givers and parents to be the highest ranked outcomes of importance. {Strand 2020 F328, Webbe 2020 425}	Other outcomes such as admission temperatures or presence of various degrees of hypothermia have not been ranked. However, they are likely to be ranked as important because of their potential effect on mortality. Cold stress is common, particularly among late preterm infants and has been associated with higher rates of NICU admission. {Laptook 2006 24}

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 review found evidence of benefit for four outcomes (normothermia, temperatures on admission, hypothermia and moderate hypothermia), without evidence of harm. Although in this single trial, more infants became hyperthermic, (a result that was not statistically significant) a much higher number avoided moderate hypothermia.	The balance of effects may be influenced by other concurrent interventions. For example, if other effective measures such as skin to skin care and use of a plastic bag or wrap are routine, a higher room temperature may make less difference, or may increase the risk of hyperthermia to unacceptable levels.

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 was no description of costs incurred when increasing the temperature in the operating theatres.	Maintaining any defined temperature for birthing rooms and operating rooms in most locations will require air conditioning, which is not available in all settings. The extent to which room-by-room adjustment of temperatures is available in settings that have air conditioning may vary.

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	The single study to address this comparison did not provide an estimate of costs or resources required.	The costs may be site specific, and depend on prevailing temperatures and availability and design of air conditioning systems.

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 were no studies addressing cost-effectiveness.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No studies addressed health equity.	The effect on health equity may depend on the costs and feasibility of changing operating room or birthing room temperatures in lower vs higher-resourced settings, which are unknown.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Operating room temperatures between 20 and 23.9ºC have been recommended {Association of Operating Room Nurses 2018 }, although the preferred range of temperatures for individual operating room staff may differ. {Joseph 2018 137}	The ambient temperature of operating theatres is often determined by the need to provide a safe, comfortable working environment for theatre personnel.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	The operating room temperature was able to be altered for the cited study. {Duryea 2016 505.e1} Maintaining temperatures 23º to >25ºC in operating theatres and birthing rooms was also a focus of five quality improvement (observational) studies that were included in the review. {Aley-Raz 2020 476, Datta 2017 e000183, Patodia 2021 277, Shaw 2018 126, Sprecher 2021 270} All five included multiple interventions, none fully documented the extent of adherence to this component and none provided data in a form that allowed assessment of the specific effects of maintaining higher temperatures in theatres and birthing rooms. However, these studies suggest that the intervention is feasible in some locations in both high income and middle income countries.	Controlling ambient temperatures is likely to be difficult or impossible in low resourced settings.

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	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**

	JUDGEMENT						
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

Recommendation

In late preterm and term infants (≥34 weeks' gestation), we suggest the use of room temperatures of 23ºC compared to 20ºC at birth in order to maintain normal temperature (weak recommendation, very low certainty evidence).

Justification

- In the included study, raising operating room temperature to 23ºC appeared to be safe for most infants born by caesarean section, improved their body temperatures and reduced the risk of hypothermia, when compared to 20ºC. However, the certainty of evidence is very low.
- Although more infants became hyperthermic in the higher operating room group in the one included study (not statistically significant), hypothermia was avoided in many more. Maternal hypothermia was also reduced. The balance of effects is likely to favour operating room temperatures of 23ºC vs 20ºC.
- Because of the location and selection criteria for the one included study, the effects on infants other than those born by caesarean section are unknown. Although only operating room temperatures were studied, the NLS Task Force considered the effects were likely to apply to other birth locations.
- Although only a small increment in body temperature was noted, it was considered clinically significant, because maintaining normothermia may take a combination of interventions, each making a small contribution. Raising delivery room temperatures to 23ºC to 25ºC has been recommended among a combination of interventions to maintain normothermia for preterm newborn infants <32 weeks' gestation. {Perlman 2015 S204}
- Several included quality improvement studies confirmed feasibility, but the resources required, and effects on equity have not been assessed.

Subgroup considerations

There were insufficient data to undertake any subgroup analyses. In the one included study, which was performed in a high income country (USA) the timing of umbilical cord clamping was not stated.

Implementation considerations

Raising the operating room or delivery room temperature appears feasible, in that it has been used as an intervention not only in the RCT analysed in this systematic review, but also as a component of multifaceted interventions in 5 included observational studies (using quality improvement models). {Aley-Raz 2020 476, Datta 2017 e000183, Patodia 2021 277, Shaw 2018 126, Sprecher 2021 270} However, feasibility may be location specific.

Monitoring and evaluation

Ongoing monitoring of temperatures is recommended to assess the balance of benefits and risks, which may vary by location and depending on other concurrent interventions to maintain normal temperature. {Perlman 2015 S204}

Research priorities

- The balance of risks and benefits when combined with other measures to maintain normothermia (e.g. skin to skin care, plastic bag or wrap).
- The effect of other set temperatures (besides 20ºC or 23ºC) for operating rooms or birthing rooms.
- The effect of measures to control room temperatures in various settings on risk of airborne diseases.
- Whether the results found for operating room temperatures are applicable to other birthing locations.
- The effect of maternal hypothermia or hyperthermia on newborn infants' temperatures.

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QUESTION

Should skin to skin care vs. no skin to skin care (routine hospital care as defined by study authors) be used for late preterm and term infants (≥ 34 weeks' gestation, or equivalent birth weight) immediately after birth?	
POPULATION:	Late preterm and term infants (≥ 34 weeks' gestation or equivalent birth weight), immediately after birth
INTERVENTION:	Skin to skin care
COMPARISON:	No skin to skin care (routine hospital care as defined by study authors)
MAIN OUTCOMES:	Survival to hospital discharge; normothermia on admission to neonatal unit or postnatal ward; body temperature; hypoglycemia; admission to neonatal intensive or special care unit; any hypothermia < 36.5º C; cold stress/mild hypothermia (temperature 36.0 – 36.4ºC); moderate hypothermia (temperature 32.0-35.9ºC); severe hypothermia (temperature <32.0ºC);
SETTING:	Any
PERSPECTIVE:	Population perspective
BACKGROUND:	ILCOR 2015 {Perlman 2015 S204} NRP 793 Maintaining Infant Temperature During Delivery Room Resuscitation (which focused on newborn infants ≥30 weeks' gestation) made the following treatment recommendations: • There are no data examining the use of plastic wrap during resuscitation/stabilization. To maintain body temperature or prevent hypothermia during transition (birth to 1–2 hours of life), we suggest that after a well newborn infant of greater than 30 weeks of gestation has been dried, his or her trunk and limbs may be put in a clean food-grade plastic bag and swaddled compared with open crib or cot and swaddling (weak recommendation, very-low-quality evidence). • There are no data on skin-to-skin contact during resuscitation/ stabilization. To maintain normal body temperature or prevent hypothermia during transition (birth to 1–2 hours after delivery), we suggest well newborns of greater than 30 weeks of gestation be nursed with skin-to-skin contact or kangaroo mother care compared with a cot/open crib and swaddling or incubator (weak recommendation, very-low-quality evidence).
CONFLICT OF INTERESTS:	None for this worksheet

ASSESSMEN

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A systematic review conducted for ILCOR concluded that "For the critical outcome of mortality, there is evidence from 36 observational studies of increased risk of mortality associated with hypothermia at admission (low-quality evidence but upgraded to moderate-quality evidence due to effect size, dose-effect relationship, and single direction of evidence)". {Perlman 2015 S204} The same systematic review concluded that "There is evidence of a dose effect on mortality, suggesting an increased risk of at least 28% for each 1° below 36.5°C body temperature at admission and dose-dependent effect size". {Perlman 2015 S204} Although the size of effect in this estimate was influenced by inclusion of studies that enrolled very preterm infants, there was also evidence of adverse effects of hypothermia on survival in late preterm and term infants. A systematic review estimated that hypothermia was common in infants born in hospitals (prevalence range, 32% to 85%) and homes (prevalence range, 11% to 92%), even in tropical environments. {Lunze 2013 24}	
Desirable Effects		

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	This systematic review found that that **for skin to skin care, when compared to no skin to skin care for late preterm and term infants**: • For the critical primary outcome of **survival to hospital discharge**, clinical benefit or harm cannot be excluded. • For the important primary outcome of **normothermia on admission** to a neonatal unit or postnatal ward, clinical benefit or harm cannot be excluded Among secondary outcomes: • **Mean body temperature on admission** was 0.32 ºC higher • For **hypoglycemia**, there was possible clinical benefit • For **admission to a neonatal special or intensive care unit**, there was possible benefit **The rationale for considering the effect moderate was that** although no difference was found in primary or several of the secondary outcomes, mean temperatures on admission were higher by 0.32ºC, a difference that was considered clinically significant. For every 1000 infants exposed to skin to skin care compared to routine hospital care, • from 153 fewer to 309 fewer were hypoglycemic • from 12 fewer to 60 fewer were admitted to a neonatal intensive or special care unit.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard hospital care	Risk difference with skin to skin care
Survival to hospital discharge	203 (1 RCT)[1]	⊕◯◯◯ Very low[a,b]	**RR 1.00** (0.99 to 1.01)	Study population	
				1,000 per 1,000	**0 fewer per 1,000** (10 fewer to 10 more)
Normothermia on admission to neonatal unit or postnatal ward	551 (3 RCTs)[1,2,3]	⊕◯◯◯ Very low[c,d,e,f]	**RR 1.39** (0.91 to 2.12)	Study population	
				614 per 1,000	**239 more per 1,000** (55 fewer to 688 more)
Body temperature assessed with: digital or mercury or contactless thermometer, axillary, rectal or other defined site	1048 (8 RCTs)[1,2,3,4,5,6,7,8]	⊕◯◯◯ Very low[c,g,h,i,j]	-	The mean body temperature was **36.5** ºC	MD **0.32 ºC higher** (0.10 higher to 0.54 higher)
Hypoglycemia				Study population	

	100 (1 RCT)[6]	⊕◯◯◯ Very low[b,k,l]	**RR 0.16** (0.05 to 0.53)	326 per 1,000	**273 fewer per 1,000** (309 fewer to 153 fewer)
Admission to neonatal intensive or special care unit	512 (3 RCTs)[1,7,9]	⊕◯◯◯ Very low[c,d,i]	**RR 0.34** (0.14 to 0.83)	Study population	
				70 per 1,000	**46 fewer per 1,000** (60 fewer to 12 fewer)
Any hypothermia < 36.5º C	197 (1 RCT)[8]	⊕⊕⊕◯ Moderate[c]	**RR 0.54** (0.28 to 1.06)	Study population	
				210 per 1,000	**97 fewer per 1,000** (151 fewer to 13 more)
Cold stress/mild hypothermia (temperature 36.0 – 36.4ºC)	443 (2 RCTs)[1,2]	⊕◯◯◯ Very low[c,d,i,m]	**RR 0.10** (0.00 to 557.45)	Study population	
				214 per 1,000	**192 fewer per 1,000** (214 fewer to 118,878 more)
Moderate hypothermia (temperature 32.0-35.9ºC)	626 (4 RCTs)[1,10,3,6]	⊕◯◯◯ Very low[c,d,i,o]	**RR 0.54** (0.20 to 1.52)	Study population	
				309 per 1,000	**142 fewer per 1,000** (247 fewer to 161 more)
Severe hypothermia (temperature <32.0ºC)	203 (1 RCT)[1]	⊕◯◯◯ Very low[a,b,p]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

[1] {Ramani 2018 492} [2] {Srivastava 2014 22} [3] {Safari 2018 32} [4] {Christensson 1992 488} [5] {Huang 2019 68} [6] {KoÇ 2017 1} [7] {Kollmann 2017 e0168783} [8] {Carfoot 2005 71} [9] {Marín Gabriel 2010 1630} [10] {Johanson 1992 859}

a. Infants born by caesarean section and those at risk for needing resuscitation were excluded
b. The only included study had a high risk of overall bias
c. 95% CI crosses the clinical decision threshold
d. All studies were at high risk of overall bias
e. I^2 = 90% but the high value might be due to differences between small and large magnitude of effect
f. Most of the studies included only well term newborns
g. All but one of the studies were judged to be at high risk of bias
h. I^2 = 95%
i. Studies excluded all or most infants who needed resuscitation
j. Most studies only included vaginal births, some included only caesarean births
k. Single study underpowered for this outcome
l. All vaginal births, infants excluded if they developed a health problem during skin to skin care
m. I^2 = 87%
n. I^2 = 84%
o. No events in either study group

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	The current review found no studies that reported whether skin to skin care, when compared to standard hospital care, altered rates of hyperthermia or other adverse outcomes.	Measures to prevent hypothermia may increase risk for hyperthermia, because preterm or very ill neonates may have deficient thermoregulation and their capacity to maintain normothermia is limited. The 2015 ILCOR NLS CoSTR stated that; "A by-product of [these] interventions to prevent hypothermia is more-frequent hyperthermia (temperature greater than 37.5°C). Hyperthermia (temperature greater than 37.5°C) also increases the risk for neonatal mortality and morbidity in both term and preterm infants".{Perlman 2015 S204} A recent study in a low resource setting found that "mortality rate was estimated to be at minimum at admission temperature of 37.5 C" with higher mortality above and below that level. {Cavallin 2020 722} Of particular relevance to late preterm and term infants, the adverse outcomes of hypoxic ischaemic encephalopathy (which are mitigated by controlled, therapeutic hypothermia) are exacerbated by hyperthermia. While it is possible that some of these effects are confounded by the presence of infection (e.g., chorioamnionitis, sepsis) there are plausible reasons why hyperthermia may itself compound brain injury. {Kasdorf 2013 379}

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	The certainty of evidence for all outcomes was very low except 'any hypothermia' which was moderate. Of the 9 studies that reported results for the comparison between skin to skin care and routine hospital care, 6 included only normal vaginal births, {Christensson 1992 488, KoÇ 2017 1, Marín Gabriel 2010 1630, Ramani 2018 492, Safari 2018 32, Srivastava 2014 22} 2 included only caesarean births, {Huang 2019 68, Kollmann 2017 e0168783} and all but 2 {Johanson 1992 859, Ramani 2018 492} excluded infants who needed, or were at increased risk of needing resuscitation. Only one study enrolled infants ≥34 weeks	The review focused on the effects of skin to skin care from birth or very soon after, so studies commencing skin to skin care 20 min after birth were not included. Furthermore, other well established benefits of skin to skin care commenced during and continued after hospital

	{Johanson 1992 859} , one ≥35 weeks {Marín Gabriel 2010 1630} , two ≥36 weeks {Carfoot 2005 71, KoÇ 2017 1}, and the remainder only term infants. Thus, of the infants the systematic review intended to include, many of those at risk of hypothermia and other adverse outcomes are not represented in the data. The likely effect of these selection criteria on effect sizes was considered in judging risk of bias and indirectness. The different ways that studies reported temperature (e.g., different cut-off points) limited the opportunities for meta-analysis. This could have resulted in underestimation of beneficial effects.	care were not assessed in this review. These include benefits for mother-infant bonding, decreased maternal pain profiles and stress levels, establishing a normal microbiome, establishment of breast feeding, and on survival of preterm infants.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The outcome of survival to hospital discharge (or its converse, mortality) have been judged by both care givers and parents to be the highest ranked outcomes of importance. {Strand 2020 F328, Webbe 2020 425}	Other outcomes such as admission temperatures or presence of various degrees of hypothermia have not been ranked. However, they are likely to be ranked as important because of their potential effect on mortality. Cold stress and hypothermia are common, particularly among late preterm infants and have been associated with higher rates of NICU admission. {Laptook 2006 24}
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 review found evidence of benefit for three outcomes (temperatures on admission, decreased risk of hypoglycemia as well as that of neonatal special or intensive care unit admission) with skin to skin care. None of the outcomes suggested the likelihood of harm.	The task force noted the possibility of unmeasured risks of skin to skin care. These could include accidental newborn suffocation. {Bartick 2020 11, Bass 2018 104, Steinhorn 2020 7} However the risks of uncommon or rare serious life-threatening events (sudden unexpected postnatal collapse {Matzner 2020 344}) have not been compared in sufficient-sized studies to determine whether the rate is higher with skin to skin care or routine hospital care.
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	None of the studies provided estimates of costs or resources required, (except in some cases, to specify training of staff in correct methods for the study). Several of the studies took place in low income countries with limited healthcare resources, and noted that skin to skin care was considered a low-cost intervention.	The use of skin to skin care could reduce the need for multiple use or disposable equipment such as warming devices.

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 studies provided sufficient detail about costs to determine the certainty of evidence for required resources.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No studies included in the review examined cost effectiveness, noting that the focus of the review was on initiating skin to skin care within minutes after birth, and not on its use for subsequent hospital care.	A study has assessed the cost effectiveness of "Kangaroo ward care" compared with "Intermediate Intensive Care" in the context of a randomised controlled trial. {Sharma 2016 64} The study, conducted in India, found statistically significant, substantial cost savings for parents and hospital with the use of Kangaroo Mother Care, of which skin to skin care with the mother was a critical component.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably	Skin to skin care is likely to be an intervention applied equally easily in low-resourced settings as in high-resourced settings. The included studies were	

reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	done in high-income countries (Sweden, Austria, UK, Spain), middle-income countries (Turkey, India, China, Iraq) and low-income countries (Zambia). Use of skin to skin care to reduce the need for equipment that may be unaffordable (or should be prioritised to the smallest and sickest infants) in low resource settings may improve equity.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Three included studies provided information about acceptability of skin to skin care. {Carfoot 2005 71, Huang 2019 68, Nissen 2019 1} Carfoot et al. reported that a larger proportion of mothers were very satisfied with their assigned study treatment in the skin to skin care group (90%) than in the control group (59%) and expressed that they would prefer to receive the same care in the future (86% vs 30%). {Carfoot 2005 71} Huang et al. (in a study of fathers providing skin to skin care in circumstances where the mother could not) reported significantly lower scales of anxiety and depression and better role attainment than those in the control group. {Huang 2019 68} Nissen at al. reported in an observational study that before the intervention, no mothers undertook 1 hour's uninterrupted skin to skin contact with their newborns, compared to 54.8% after an educational and promotional intervention. {Nissen 2019 1} In a qualitative study that aimed "to identify barriers and enablers to conducting safe uninterrupted skin-to-skin contact (SSC) in the first hour after birth in a low-resource setting and to evaluate how health care professionals coped with the identified barriers after completion of an intervention package", Mbalinda et al identified various factors. Of note, when the mother and infant had to move to the post-natal ward within one hour after birth there were difficulties maintaining skin to skin care during transportation. A few mothers were considered unwilling to keep the infant skin to skin. {Mbalinda 2018 95}	There is a larger literature supporting the use of skin to skin care at later time points, for a variety of maternal, and neonatal outcomes. Studies report some barriers to use, but overall, it is judged to be acceptable for use in postnatal care. {Gill 2021 1407, Gupta 2021 2310, Ionio 2021 4695} It is likely that this acceptability applies to use immediately after birth.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Some of the included studies documented withdrawal of infants from the study at rates ranging from 2.4% to 16.9% because of reasons including that the infant required resuscitation, or the mother was unable to commence or continue to provide skin to skin care. {Huang 2019 68, Johanson 1992 859, Kollmann 2017 e0168783, Ramani 2018 492, Safari 2018 32, Srivastava 2014 22} The range of circumstances in which skin to skin care cannot be utilised effectively might have been underestimated because many of the studies specifically included only well mothers and newborns. In an observational study in Uganda that was included in the review and which examined the effects of skin to skin care, an educational and promotional intervention resulted in 54.8% of eligible infants receiving 1 hour of uninterrupted skin to skin care from immediately after birth after the intervention vs none before the intervention. {Nissen 2019 1}	There may be cultural values that encourage or present barriers to skin to skin care.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
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

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

Recommendation

In late preterm and term infants (≥34 weeks' gestation) at low risk of needing resuscitation, we suggest the use of skin to skin care immediately after birth rather than no skin to skin care to maintain normal temperature (weak recommendation, very low certainty evidence).

Justification

Overall justification

- Skin to skin care is simple, appears to be safe for most infants and improves their body temperatures, when compared to no skin to skin care. However, because of the selection criteria of included studies, there is insufficient evidence to make a recommendation for infants at high risk of needing resuscitation.
- Skin to skin care, when compared with no skin to skin care, increased body temperatures on admission to a neonatal unit or postnatal ward, and reduced the risk of hypoglycemia, and NICU admission. No benefits were found for other outcomes of the review, but small samples, study selection criteria and the limited range of outcomes reported by several of the included studies may have limited the detection of benefits.
- No undesirable effects were identified. None of the included studies reported hyperthermia.
- Most of the evidence is of very low certainty. Importantly, most studies excluded mothers who were not well, and infants who had needed or were at risk of needing resuscitation. Infants 34-36 weeks' gestation were under-represented among the included studies.
- The balance of effects is likely to favour skin to skin care commenced within minutes after birth over other care, which in most studies consisted of drying and wrapping the infant and placing the baby in a hospital cot. There are other well-described benefits of skin to skin care for the ongoing care of neonates.
- The task force noted the possibility of unmeasured risks of skin to skin care. These could include accidental newborn suffocation. However, the risks of uncommon or rare serious life-threatening events have not been compared in sufficient-sized studies to determine whether the rate is higher with skin to skin care or no skin to skin care.
- Skin to skin care from immediately after birth is likely to be cost-effective, acceptable and feasible in high-, middle- and low-income countries.

Subgroup considerations

There were insufficient data to undertake meaningful subgroup analyses. Some studies specified early umbilical cord clamping and none specified that delayed umbilical cord clamping was routinely performed, or provided a breakdown by timing of cord clamping. For setting, since only one outcome was reported by sufficient studies to consider a subgroup analysis by income of country, a subgroup analysis was not considered meaningful. There were no studies that involved outborn infants.

Implementation considerations

Skin to skin care has been widely applied for ongoing care of well newborns, and as part of neonatal intensive or special care. Depending on location, practice change strategies may be required to promote skin to skin care within minutes after birth.

Monitoring and evaluation

Neonate's temperatures on admission to post-natal wards or neonatal intensive or special care units should continue to be monitored, as an important indicator of the quality of care. {Perlman 2015 S204}

Research priorities

- The role of skin to skin care in maintaining normal temperature in infants requiring resuscitation: (a) Can some resuscitation manoeuvres be performed during skin to skin care and (b) for infants who have required some resuscitation interventions, when can skin to skin care be safely commenced?
- The role of skin to skin care in maintaining normal temperature in the setting of delayed umbilical cord clamping.
- The balance of risks and benefits of skin to skin care in the setting of various ambient temperatures.

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QUESTION

Should a plastic bag or wrap vs. no plastic bag or wrap be used for late preterm and term neonates (≥34 weeks' gestation, or equivalent birth weight), immediately after birth?	
POPULATION:	Late preterm and term neonates (≥34 weeks' gestation, or equivalent birth weight), immediately after birth
INTERVENTION:	A plastic bag or wrap
COMPARISON:	No plastic bag or wrap Note that in the studies identified for this comparison; • Studies that provided drying or no drying prior to the application of the plastic bag or wrap were combined. • Care in the control group included care under a radiant warmer or an incubator or a cot with or without drying and swaddling with a blanket and with or without a head covering.
MAIN OUTCOMES:	Survival to hospital discharge; normothermia on admission to neonatal unit or postnatal ward; body temperature; hypoglycemia; any hypothermia <36.5ºC; hypothermia <35ºC; moderate hypothermia (temperature 32.0-35.9ºC); hyperthermia (temperature >37.5ºC)
SETTING:	All
PERSPECTIVE:	Population perspective
BACKGROUND:	ILCOR 2015 {Perlman 2015 S204} NRP 793 Maintaining Infant Temperature During Delivery Room Resuscitation (which focused on newborn infants ≥30 weeks' gestation) Treatment Recommendations: There are no data examining the use of plastic wrap during resuscitation/stabilization. To maintain body temperature or prevent hypothermia during transition (birth to 1–2 hours of life), we suggest that after a well newborn infant of greater than 30 weeks of gestation has been dried, his or her trunk and limbs may be put in a clean food-grade plastic bag and swaddled compared with open crib or cot and swaddling (weak recommendation, very-low-quality evidence). The current systematic review found a small number of studies in late preterm and term infants examining the use of a plastic bag or wrap to prevent hypothermia, enabling metanalysis.
CONFLICT OF INTERESTS:	None for this worksheet

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A systematic review conducted for ILCOR concluded that "For the critical outcome of mortality, there is evidence from 36 observational studies of increased risk of mortality associated with hypothermia at admission (low-quality evidence but upgraded to moderate-quality evidence due to effect size, dose-effect relationship, and single direction of evidence)". {Perlman 2015 S204} The same systematic review concluded that "There is evidence of a dose effect on mortality, suggesting an increased risk of at least 28% for each 1° below 36.5°C body temperature at admission and dose-dependent effect size". {Perlman 2015 S204} Although the size of effect in this estimate was influenced by inclusion of studies that enrolled very preterm infants, there was also evidence of adverse effects of hypothermia on survival in late preterm and term infants. A systematic review estimated that hypothermia was common in infants born at hospitals (prevalence range, 32% to 85%) and homes (prevalence range, 11% to 92%), even in tropical environments. {Lunze 2013 24}	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	This systematic review found that **for use of a plastic bag or wrap versus no plastic bag or wrap:** • For the primary (critical) outcome of **survival to hospital discharge, clinically significant benefit or harm cannot be excluded** (**very low certainty of evidence** • For the primary (important) outcome of **normothermia on admission**, there was **possible benefit** Among secondary outcomes: • **Body temperature** was higher • For any **hypothermia <36.5ºC**, there was **possible benefit** • For **hypothermia <35ºC**, there was **possible benefit** • For **moderate hypothermia (temperature 32.0-35.9ºC)** **The rationale for considering the effect moderate was that** mean temperatures on admission were higher by 0.29ºC, a difference that was considered clinically significant. Furthermore, for every 1000 infants exposed to a plastic bag or wrap (with or without prior drying) compared to no plastic bag or wrap, • from 81 more to 362 more were normothermic • from 128 fewer to 261 fewer had hypothermia <36.5ºC • from 4 fewer to 48 fewer had hypothermia <35ºC	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard hospital care (other care)	Risk difference with a plastic bag or wrap with either prior drying or no drying
Survival to hospital discharge	305 (2 RCTs)[1,2]	⊕◯◯◯ Very low[a,b,c,d]	**RR 0.95** (0.60 to 1.51)	Study population	
				981 per 1,000	**49 fewer per 1,000** (392 fewer to 500 more)
Normothermia on admission to neonatal unit or postnatal ward	305 (2 RCTs)[1,2]	⊕◯◯◯ Very low[a,c,e]	**RR 1.50** (1.20 to 1.89)	Study population	
				406 per 1,000	**203 more per 1,000** (81 more to 362 more)
Body temperature	425 (3 RCTs)[1,2,3,f]	⊕◯◯◯ Very low[g,h]		The mean body temperature was **36.3ºC**	MD **0.29ºC higher** (0.2 higher to 0.38 higher)
Hypoglycemia	201 (1 RCT)[1]	⊕◯◯◯ Very low[c,d,i]	**RR 0.99** (0.48 to 2.03)	Study population	
				130 per 1,000	**1 fewer per 1,000** (68 fewer to 134 more)

Any hypothermia <36.5ºC	425 (3 RCTs)[1,3,f]	⊕◯◯◯ Very low[e,g,h]	**RR 0.57** (0.45 to 0.73)	Study population	
				474 per 1,000	**204 fewer per 1,000** (261 fewer to 128 fewer)
Hypothermia <35ºC	400 (2 RCTs)[1,4]	⊕◯◯◯ Very low[c,e,h]	**RR 0.21** (0.05 to 0.91)	Study population	
				50 per 1,000	**40 fewer per 1,000** (48 fewer to 4 fewer)
Moderate hypothermia (temperature 32.0-35.9ºC)	199 (1 RCT)[1]	⊕◯◯◯ Very low[d,j]	**RR 0.96** (0.66 to 1.38)	Study population	
				370 per 1,000	**15 fewer per 1,000** (126 fewer to 141 more)

[1] {Shabeer 2018 1324} [2] {Leadford 2013 e128} [3] {Cardona-Torres 2012 129} [4] {Johanson 1992 859}.

a. Two studies had high risk of overall bias
b. I^2 = 98%
c. Though the mean gestational age of enrolled neonates was >34 weeks, some neonates of lesser gestational age were also enrolled in one study
d. 95% CI crosses clinical decision threshold
e. OIS not satisfied
f. One trial had one control group, with two experimental groups
g. Though mean gestational age of the enrolled neonates was > 34 weeks, studies enrolled some neonates of gestational age less than 34 weeks
h. All RCTs had high risk of bias
i. 1 study had a high risk of bias
j. Indirectness related to patient population as only vaginal births were included

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	For **hyperthermia**, benefit or harm could not be excluded (very low certainty evidence from 3 RCTs enrolling 425 participants, downgraded for very serious risk of bias, serious indirectness and very serious imprecision). The event rate was sufficiently low that an absolute risk difference was not calculable.	Measures to prevent hypothermia may increase risk for hyperthermia, because preterm or very ill neonates may have deficient thermoregulation and their capacity to maintain normothermia is limited. The 2015 ILCOR NLS CoSTR stated that; "A by-product of [these] interventions to prevent hypothermia is more-frequent hyperthermia (temperature greater than 37.5°C). Hyperthermia (temperature greater than 37.5°C) also increases the risk for neonatal mortality and morbidity in both term and preterm infants". {Perlman 2015 S204}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with standard hospital care (other care)	Risk difference with a plastic bag or wrap with either prior drying or no drying
Hyperthermia (temperature >37.5ºC)	425 (3 RCTs)[1,2,a]	⊕◯◯◯ Very low[b,c,d]	**RR 15.91** (0.17 to 1448.75)	Study population	
				Not applicable	Not applicable

[1] {Cardona-Torres 2012 129} [2] {Shabeer 2018 1324}

a. One trial had one control group, with two experimental groups
b. Though mean gestational age of the enrolled neonates was > 34 weeks, both Shabeer 2018 and Cardona-Torres 2012 studies enrolled some neonates who were of gestational age less than 34 weeks

	c. Very low event rate and not satisfying OIS ; with 95% CI indicating substantial benefit and harm d. All RCTs had high risk of bias	A recent study in a low resource setting found that "mortality rate was estimated to be at minimum at admission temperature of 37.5 °C" with higher mortality above and below that level. {Cavallin 2020 722} Of particular relevance to late preterm and term infants, the adverse outcomes of hypoxic ischaemic encephalopathy (which are mitigated by controlled, therapeutic hypothermia) are exacerbated by hyperthermia. While it is possible that some of these effects are confounded by the presence of infection (e.g chorioamnionitis, sepsis) there are plausible reasons why hyperthermia may itself compound brain injury. {Kasdorf 2013 379}
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	The certainty of evidence was very low for all primary and secondary outcomes. All four studies included in this comparison included births <34 weeks as well as late preterm and term infants ≥34 weeks' gestation, but did not provide data in a form that allowed exclusion of infants <34 weeks. The likely effect of these selection criteria on effect sizes was considered in judging risk of bias and indirectness.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The outcome of survival to hospital discharge (or its converse, mortality) have been judged by both care givers and parents to be the highest ranked outcomes of importance. {Strand 2020 F328, Webbe 2020 425}	Other outcomes such as admission temperatures or presence of various degrees of hypothermia have not been ranked. However, they are likely to be ranked as important because of their potential effect on mortality. Cold stress is common, particularly among late preterm infants and has been associated with higher rates of NICU admission. {Laptook 2006 24}

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 review found evidence of benefit for the outcomes of normothermia, temperatures on admission, hypothermia <36.5ºC and hypothermia <35º with use of a plastic bag or wrap. None of the outcomes suggested the likelihood of harm.	The task force considered that there might be unmeasured adverse effects, including potential effects on promotion of early and successful breast feeding. There was concern that although hyperthermia was not demonstrated in the included studies with the use of a plastic bag or wrap, there might be increased risk of hyperthermia in the setting of care with a radiant warmer or in an incubator. There was concern that use of a plastic bag or wrap might be regarded as a substitute to encouraging skin to skin care.

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	A clean food-grade plastic bag or wrap suitable for a newly born infant is likely to be of very low cost. In two studies included in this systematic review, the cost was estimated at USD 0.03 in 2013. {Belsches 2013 e656, Leadford 2013 e128} Purpose-designed sterile bags packaged for clinical use are more expensive, and wraps are intermediate in cost.	The task force also considered the environmental impact of recommending widespread use of plastic bags or wraps. However, this must be weighed against benefits, and also compared with the widespread use of other disposables in clinical care. While the cost of plastic bags or wraps may be low for individual babies, the cost to clinical services may be high if they are used for a high proportion of late preterm and term-born infants.
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 studies estimated resource requirements.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies included in the review examined cost effectiveness.	The effects of use of a plastic bag or wrap in increasing rates of normothermia on admission to a neonatal unit or postnatal ward may offset the minimal costs of the plastic bags or wraps themselves.

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 four included studies were from low- or middle-income countries (Zambia, India, Mexico and Nepal).	Plastic bags or wraps are likely to be available in both low and high income countries, and in low resource settings, may offset the lack of availability of more expensive devices and equipment. In low-resourced settings, there is a possibility that the use of plastic bags or wraps for late preterm and term infants might divert their use from very preterm infants who might derive greater benefit.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	The authors of one study in the review commented that; “The wrap procedure was well accepted by the neonatal staff and did not interfere with resuscitation in the delivery room”. {Travers 2021 55}	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The included studies were performed in low or middle income countries.	Plastic bags or wraps have been recommended for use in more preterm infants for more than a decade.

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	Large	Moderate	Small	Trivial		Varies	**Don't know**

	JUDGEMENT						
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

Recommendation

The NLS Task Force considered that in late preterm and term infants ≥34 weeks' gestation, for routine use of a plastic bag or wrap vs no plastic bag or wrap, the balance of desirable and undesirable effects was uncertain and the certainty of evidence was very low. Furthermore, cultural values and maternal preferences in relation to this specific intervention and cost implications are not known, and therefore no treatment recommendation for routine use can be formulated. The NLS Task Force considered it important to promote skin to skin care. In some situations where skin to skin care is not possible, it is reasonable to consider the use of a plastic bag or wrap, among other measures to maintain normal temperature (weak recommendation, very low certainty evidence).

Justification

- The systematic review found evidence to support the use of a plastic bag or wrap in the setting of standard hospital care to improve rates of normothermia and reduce risk of hypothermia in late preterm or term newborn infants (≥34 weeks' gestation, or equivalent birth weight) without evidence of adverse effects. Because of a low number of studies and enrolled infants, studies in with and without prior drying were combined. The certainty of evidence was very low for all outcomes.
- Because of a low number of studies and enrolled infants, studies with and without prior drying were combined in the meta-analysis.
- The Task Force was concerned that there may be unmeasured adverse effects, such as adverse effects on establishment of a normal neonatal microbiome and on promotion of early breast feeding.
- There was also concern that the plastic bag or wrap might be regarded as a substitute to encouraging skin to skin care.
- The resources required are likely to be inexpensive, but costs may be large if the intervention is applied to all newborn infants. A clean, food-grade plastic bag or wrap is necessary, but costs may increase if purpose-designed sterile bags packaged for clinical use are used. Cost-effectiveness is unknown, but could be positive if improved rates of normothermia and avoidance of hypothermia results in avoidance of any admissions to a neonatal special or intensive care unit.
- Use of this low-cost fairly simple intervention may improve equity. The four studies suggesting benefit were conducted in middle- or low-income countries, suggesting feasibility in these settings. However, the overall effect on equity remains unknown. Equity could be adversely affected if use of plastic bags or wraps was diverted from more preterm infants for who potential to benefit is greater.

Subgroup considerations

There were insufficient data to conduct subgroup analyses. Although the included studies enrolled both late preterm and term infants, no breakdown of data by gestation were provided. None of the studies provided any information about timing of umbilical cord clamping. All were from middle- or low-income countries (Zambia, India, Mexico, Nepal) but overall sample sizes for the various comparisons were insufficient to allow meaningful subgroup analysis by country income.

Implementation considerations

Neither of the included studies reported any problems with adherence to the use of a plastic bag or wrap in addition to other care. Practice change strategies may be required to promote the use of a plastic bag or wrap within minutes after birth.

Monitoring and evaluation

Neonate's temperatures on admission to post-natal wards or neonatal intensive or special care units should continue to be monitored, as an important indicator of the quality of care. {Perlman 2015 S204}

Research priorities

- The balance of risks and benefits of plastic bag or wrap in the setting of various ambient temperatures and maternal temperatures, and in the setting of combinations of measures to maintain normothermia.
- Is there a role for adding a plastic bag or wrap as a serial or supplementary intervention, if other measures are insufficient?
- The role of plastic bags or wraps for out-of-facility births.
- The acceptability to parents and caregivers.

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QUESTION

Should a plastic bag or wrap combined with skin to skin care vs. skin to skin care alone be used for late preterm and term neonates (≥34 weeks or equivalent birth weight)?	
POPULATION:	Late preterm and term neonates (≥34 weeks or equivalent birth weight)
INTERVENTION:	A plastic bag or wrap combined with skin to skin care
COMPARISON:	Skin to skin care
MAIN OUTCOMES:	Survival to discharge; normothermia on admission to neonatal unit or postnatal ward; body temperature; admission to neonatal intensive or special care unit; any hypothermia < 36.5 ºC; cold stress/mild hypothermia (temperature 36.0-36.4ºC); moderate hypothermia (temperature 32.0-35.9ºC); hyperthermia (temperature >37.5ºC);
SETTING:	All
PERSPECTIVE:	Population perspective
BACKGROUND:	ILCOR 2015 {Perlman 2015 S204} NRP 793Treatment Recommendations: There are no data examining the use of plastic wrap during resuscitation/stabilization. To maintain body temperature or prevent hypothermia during transition (birth to 1–2 hours of life), we suggest that after a well newborn infant of greater than 30 weeks of gestation has been dried, his or her trunk and limbs may be put in a clean food-grade plastic bag and swaddled compared with open crib or cot and swaddling (weak recommendation, very-low-quality evidence). There are no data on skin-to-skin contact during resuscitation/ stabilization. To maintain normal body temperature or prevent hypothermia during transition (birth to 1–2 hours after delivery), we suggest well newborns of greater than 30 weeks of gestation be nursed with skin-to-skin contact or kangaroo mother care compared with a cot/open crib and swaddling or incubator (weak recommendation, very-low-quality evidence). The current systematic review found a small number of studies that compared the use of a plastic bag or wrap with no plastic bag or wrap for term and late preterm infants who were receiving skin to skin care, enabling metaanalysis.
CONFLICT OF INTERESTS:	None for this worksheet

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A systematic review conducted for ILCOR concluded that "For the critical outcome of mortality, there is evidence from 36 observational studies of increased risk of mortality associated with hypothermia at admission (low-quality evidence but upgraded to moderate-quality evidence due to effect size, dose-effect relationship, and single direction of evidence)". {Perlman 2015 S204} The same systematic review concluded that "There is evidence of a dose effect on mortality, suggesting an increased risk of at least 28% for each 1° below 36.5°C body temperature at admission and dose-dependent effect size". {Perlman 2015 S204} Although the size of effect in this estimate was influenced by inclusion of studies that enrolled very preterm infants, there was also evidence of adverse effects of hypothermia on survival in late preterm and term infants. A systematic review estimated that hypothermia was common in infants born at hospitals (prevalence range, 32% to 85%) and	

homes (prevalence range, 11% to 92%), even in tropical environments. {Lunze 2013 24}

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

The systematic review found that **using a plastic bag or wrap, compared to no plastic bag or wrap for late preterm and term infants who are receiving skin to skin care:**

- For the critical primary outcome **survival to hospital discharge,** the effect of the intervention could not be evaluated because all infants survived in the one RCT enrolling 271 participants that reported this outcome.
- For the important primary outcome of **normothermia** on admission, there was **possible benefit**

Among secondary outcomes:

- For **mean temperature** on admission there was **possible benefit**
- For **hypothermia <36.5ºC** there was **possible benefit**
- For **moderate hypothermia**, there was **possible benefit**

The rationale for considering the effect moderate was that for every 1000 infants exposed to a plastic bag or wrap with skin to skin care, compared to skin to skin care alone

- from 18 more to 174 more were normothermic
- 23 fewer to 148 fewer were hypothermic <36.5ºC
- 83 fewer to 200 fewer were moderately hypothermic.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with skin to skin care alone	Risk difference with a plastic bag or wrap combined with skin to skin care
Survival to discharge	271 (1 RCT)[1]	⨁⨁◯◯ Low[a,b]	**RR 1.00** (0.99 to 1.01)	Study population	
				Not applicable	
Normothermia on admission to neonatal unit or postnatal ward	692 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,c]	**RR 1.39** (1.08 to 1.79)	Study population	
				221 per 1,000	**86 more per 1,000** (18 more to 174 more)
Body temperature	692 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,b,c]	-	The mean body temperature was **36.0** ºC	MD **0.2 ºC higher** (0.1 higher to 0.3 higher)
Admission to neonatal intensive or	275 (1 RCT)[1]	⨁⨁◯◯ Low[c,d]	**RR 0.26** (0.03 to 2.26)	Study population	
				29 per 1,000	**21 fewer per 1,000**

ADDITIONAL CONSIDERATIONS

special care unit					(28 fewer to 36 more)
Any hypothermia < 36.5 ºC	692 (2 RCTs)[1,2]	⊕⊕◯◯ Low[a,c]	**RR 0.89** (0.81 to 0.97)	Study population	
				777 per 1,000	**85 fewer per 1,000** (148 fewer to 23 fewer)
Cold stress/mild hypothermia (temperature 36.0-36.4ºC)	692 (2 RCTs)[1,2]	⊕⊕◯◯ Low[a,b]	**RR 1.19** (0.98 to 1.44)	Study population	
				341 per 1,000	**65 more per 1,000** (7 fewer to 150 more)
Moderate hypothermia (temperature 32.0-35.9ºC)	692 (2 RCTs)[1,2]	⊕⊕◯◯ Low[a,b,e]	**RR 0.66** (0.54 to 0.81)	Study population	
				436 per 1,000	**148 fewer per 1,000** (200 fewer to 83 fewer)

[1] {Belsches 2013 e656} [2] {Travers 2021 55}

a. There was indirectness related to the neonates enrolled as one study enrolled neonates born via vaginal delivery while there was no information for the other.
b. Optimal information size not met
c. 95% confidence interval crosses decision threshold
d. Belsches 2013 has not provided information on whether both vaginal and c-section neonates were enrolled
e. Though I^2 value is >50%, the high value might be due to differences between small and large magnitude of effect. The point estimates and the 95% CI are overlapping as well. Hence, the certainty of evidence was not downgraded for inconsistency.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know

RESEARCH EVIDENCE

For **hyperthermia, benefit or harm could not be excluded**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with skin to skin care alone	Risk difference with a plastic bag or wrap combined with skin to skin care
Hyperthermia (temperature >37.5ºC)	692 (2 RCTs)[1,2]	⊕◯◯◯ Very low[a,b]	**RR 1.02** (0.08 to 12.85)	Study population	
				3 per 1,000	**0 fewer per 1,000** (3 fewer to 34 more)

[1] {Belsches 2013 e656} [2] {Travers 2021 55}

a. There was indirectness related to the neonates enrolled as one study enrolled neonates born via vaginal delivery while there was no information for the other.

ADDITIONAL CONSIDERATIONS

Measures to prevent hypothermia may increase risk for hyperthermia, because preterm or very ill neonates may have deficient thermoregulation and their capacity to maintain normothermia is limited. The 2015 ILCOR NLS CoSTR stated that; "A by-product of [these] interventions to prevent hypothermia is more-frequent hyperthermia (temperature greater than 37.5°C). Hyperthermia (temperature greater than 37.5°C) also increases the risk for neonatal mortality and morbidity in both term and preterm infants".{Perlman 2015 S204}

A recent study in a low resource setting found that "mortality

	b. Very low event rate with wide 95% CI consistent with either appreciable harm or benefit	rate was estimated to be at minimum at admission temperature of 37.5 °C" with higher mortality above and below that level. {Cavallin 2020 722} Of particular relevance to late preterm and term infants, the adverse outcomes of hypoxic ischaemic encephalopathy (which are mitigated by controlled, therapeutic hypothermia) are exacerbated by hyperthermia. While it is possible that some of these effects are confounded by the presence of infection (e.g, chorioamnionitis, sepsis) there are plausible reasons why hyperthermia may itself compound brain injury. {Kasdorf 2013 379}

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	The GRADE certainty of evidence for all outcomes was **low or very low**. The two included studies enrolled only term infants, {Belsches 2013 e656, Travers 2021 55} and both excluded some high risk infants so there is indirectness of evidence with respect to preterm infants and those at high risk of adverse outcomes. The likely effect of these selection criteria on effect sizes was considered in judging risk of bias and indirectness.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The outcome of survival to hospital discharge (or its converse, mortality) have been judged by both care givers and parents to be the highest ranked outcomes of importance. {Strand 2020 F328, Webbe 2020 }	Other outcomes such as admission temperatures or presence of various degrees of hypothermia have not been ranked. However, they are likely to be ranked as important because of their potential effect on mortality. Cold stress is common, particularly among late preterm infants and has been associated with higher rates of NICU admission. {Laptook 2006 24}

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	There was low certainty evidence of benefit for one primary and two secondary outcomes of the review, although for most	The Task Force considered that there might be unmeasured

○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	outcomes, there was insufficient data or clinically significant benefit or harm could not be excluded.	adverse effects, including potential effects on establishment of a normal neonatal microbiome, and on promotion of early and successful breast feeding. On the other hand, if skin to skin care is not succeeding in maintaining normothermia, the addition of a plastic bag or wrap might be beneficial for the mother baby pair when compared to transferring the baby to a radiant warmer or cot. The question of safety was also considered, as a baby in a plastic bag or wrap might be more at risk of unsafe positioning or falling. However, there are no data to estimate this risk. Unclean bags might also pose an infection risk.

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	A clean food-grade plastic bag or wrap suitable for a newborn infant is likely to be of very low cost. In two studies included in this systematic review, the cost was estimated at USD 0.03. {Belsches 2013 e656, Travers 2021 55} Purpose-designed sterile bags packaged for clinical use are more expensive, and wraps are intermediate in cost.	The Task Force also considered the environmental impacts of recommending widespread use of plastic bags or wraps. However, this must be weighed against benefits, and also compared with the widespread use of other disposables in clinical care. While the costs of plastic bags or wraps may be low for individual babies, the costs to clinical services may be high if they are used for a high proportion of late preterm and term-born babies.

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 studies estimated resource requirements.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies formally assessed cost effectiveness, and for the outcome of admissions to a neonatal intensive or special care unit benefit or harm could not be excluded on the basis of the available data.	A study has assessed the cost effectiveness of "Kangaroo ward care" compared with "Intermediate Intensive Care" in the context of a randomised controlled trial. {Sharma 2016 64} The study, conducted in India, found statistically significant, very substantial cost savings for parents and hospital with the use of Kangaroo Mother Care, of which skin to skin care with the mother was a critical component. If the additional, temporary use of a plastic bag or wrap in addition to skin to skin care in approximately the first hour after birth had a positive effect on this balance by preventing hypothermia it could improve confidence in skin to skin care and its subsequent uptake, and thereby could have an indirect beneficial effect on cost-effectiveness.
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 two included studies were conducted in a low-income country (Zambia).	Plastic bags or wraps are likely to be available in both low and high income countries, and in low resource settings, may offset the lack of availability of more expensive devices and equipment. The use of a plastic bag or wrap with skin to skin care in the interval immediately after birth might have benefits in improving confidence in subsequent skin to skin care, thereby reducing barriers to its use. In low-resourced settings, there is a possibility that the use of plastic bags or wraps for late preterm and term infants might divert their use from very preterm infants who might derive greater benefit.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No study specifically reported acceptability to all stakeholders. However, in one of the included studies, Belsches et al reported that the plastic bag was readily accepted by the labor and delivery staff after demonstrating that term infants frequently develop hypothermia and that it did not interfere with neonatal resuscitation. {Belsches 2013 e656} The other study reported that decreased compliance with polyethylene bags over time may have been related to soiled bags or cultural norms of dressing infants in new baby clothes. In addition, lack of masking (of the trial) may have encouraged mothers to remove the polyethylene bag when infants were no longer hypothermic. {Travers 2021 55}	There may be cultural concerns about the use of plastic bags or wraps compared to clothing.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The included studies were both performed in a low income country. Rates of withdrawal due to inability to continue study treatment were low. Plastic bags or wraps have been recommended for use in more preterm infants for more than a decade.	

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	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**

	JUDGEMENT						
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

Recommendation

The Task Force considered that in late preterm and term infants ≥34 weeks' gestation, for routine use of a plastic bag or wrap in addition to skin to skin care immediately after birth compared to skin to skin care alone, the balance of desirable and undesirable effects was uncertain. Furthermore, the cultural values and maternal preferences in relation to the use of plastic bags or wraps and the cost implications are not known, and therefore no treatment recommendation can be formulated.

Justification

- The systematic review found evidence to support the use of a plastic bag or wrap as an adjunct to skin to skin care to improve rates of normothermia and reduce risk of any hypothermia or moderate hypothermia in late preterm or term newborn infants (≥34 weeks' gestation, or equivalent birth weight) without evidence of adverse effects. However, the overall balance of risks and benefits was considered to be uncertain.
- The certainty of the evidence was low or very low for all analysable outcomes.
- Despite the findings of the review, the Task Force remained uncertain about the balance of effects. There was concern plastic bags or wraps might impair the acceptability or safety of skin to skin care, and thereby cause harm.
- The resources required are likely to be inexpensive for individual babies, but costs may be a barrier if the intervention is applied to a high proportion of births. The cost-effectiveness is unknown, but could be positive if any admissions to a neonatal special or intensive care unit are prevented, or if confidence in and uptake of skin to skin care is improved.
- Use of this low-cost fairly simple intervention could improve equity. The two studies suggesting benefit were conducted in low-income countries, and suggested feasibility in these settings. However, the full range of effects on equity is unknown.

Subgroup considerations

There were insufficient data to conduct subgroup analyses. Neither study provided any information about timing of umbilical cord clamping. Both were from a single hospital in a low income country (Zambia).

Implementation considerations

Practice change strategies may be required to promote the use of a plastic bag or wrap as an adjunct to skin to skin care within minutes after birth.

Monitoring and evaluation

Neonate's temperatures on admission to post-natal wards or neonatal intensive or special care units should continue to be monitored, as an important indicator of the quality of care. {Perlman 2015 S204}

Research priorities

- The balance of risks and benefits of plastic bag or wrap in combination with skin to skin care in the setting of various ambient temperatures, and depending on the use of other concomitant measures to maintain normothermia in late preterm and term infants.
- Is there a role for adding a plastic bag or wrap as a serial or supplementary intervention, if skin to skin care alone is insufficient to maintain normothermia, with the goal of sustaining skin to skin care?
- The acceptability to mothers and clinicians of addition of a plastic bag or wrap, in the setting of provision of skin to skin care.

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Question

Should initial suctioning of the nose and mouth vs. no initial suctioning be used for neonates who are born through non-meconium-stained amniotic fluid?	
POPULATION:	neonates who are born through non-meconium-stained amniotic fluid
INTERVENTION:	initial suctioning of the nose and mouth
COMPARISON:	no initial suctioning
MAIN OUTCOMES:	Receipt of assisted ventilation; Advanced resuscitation and stabilization interventions (intubation, chest compressions, epinephrine (adrenaline) in the Delivery Room (DR); Saturations at 5 minutes; Saturations at 9 minutes; Saturations at 10 minutes; Time to 86% saturation; Adverse effects of intervention - time to 92% saturations; Unanticipated admission to the NICU; Heart rate at 5 minutes; Apgar Score of 10 at 5 minutes; Subgroup analysis saturations at 5 minutes - vaginal births; Subgroup analysis saturations at 5 minutes - c/s; Respiratory Rate (any RR>60 in first 24 hours of life);
SETTING:	Any
PERSPECTIVE:	Population
BACKGROUND:	This question has not been addressed in a systematic review nor subjected to a GRADE analysis of certainty of evidence by ILCOR previously. A Scoping Review (NLS 596) conducted in 2019 found sufficient evidence to justify conducting a systematic review. {Wyckoff 2020 S185}
CONFLICT OF INTERESTS:	• Author Ersdal has published observational studies on use of resuscitation maneuvers including suctioning in low resource settings and was excluded from decisions about inclusion or bias assessment for these studies {Ersdal 2012 869, Ersdal 2018 171, Haug 2020 68, Størdal 2020 e0240520, Mduma 2019 e030572, Msemo 2013 353}. • Author Rüdiger has published an observational study about suctioning immediately after birth {Konstantelos 2015 777} and was excluded from decisions about inclusion or bias assessment for this study.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Suctioning of clear amniotic fluid is a very important topic worldwide as it affects many newly born infants including those not requiring/receiving resuscitation. It is very important to know if there is any evidence of benefit or harm as this has traditionally been a part of worldwide neonatal care which has not been assessed. Transition from fetus to newborn involves the infant clearing lung fluid and expanding their lungs with air. Longstanding historical practice has been to use oro/nasopharyngeal suctioning at birth routinely to remove fluids. There have been	This question was prioritized by ILCOR because although it is a widespread practice, it has not been addressed in a systematic review nor subjected to a GRADE analysis of certainty of evidence by ILCOR previously. A Scoping Review (NLS 596) conducted in 2019 and found sufficient evidence to justify a systematic review. {Wyckoff 2020 S185} Because a systematic review had not yet been performed, the treatment recommendation in 2020

	increasing concerns that this practice may not confer benefit and may have undesirable consequences. This has led ILCOR to recommend that ***"Suctioning immediately after birth, whether with a bulb syringe or suction catheter, may be considered only if the airway appears obstructed or if PPV is required"***. {Wyckoff 2015 543 } The World Health Organisation (WHO) reviewed 3 studies included in this systematic review {Gungor 2006 9, Gungor 2005 453, Waltman 2004 32} which examined the effect of oral and nasal suctioning at birth on oxygen saturation (SpO2) levels at 5 minutes of life. They graded the quality of evidence for this outcome as high. The pooled mean difference (MD) in oxygen saturation levels was 9.8% lower (95% CI -10.2% to -9.4%) in those who underwent oropharyngeal or nasopharyngeal suctioning. There was a significant reduction in the proportion of infants with normal Apgar scores in the suctioning group compared to the group with no suctioning (RR 0.54, 95% CI 0.29 to 1.00, p=0.049). {WHO 2012} The WHO said ***"In neonates born through clear amniotic fluid who start breathing on their own after birth, suctioning of the mouth and nose should not be performed."*** (strong recommendation, high quality of evidence) they also say ***"In neonates born through clear amniotic fluid who do not start breathing after thorough drying and rubbing the back 2-3 times, suctioning of the mouth and nose should not be done routinely before initiating positive pressure ventilation. Suctioning should be done only if the mouth or nose is full of secretions."*** (strong recommendation, GDG consensus in absence of published evidence). (WHO strong recommendation, based on high quality evidence of lower oxygen saturation and low quality evidence of lower Apgar scores). {WHO 2012} An ILCOR scoping review **Suctioning clear amniotic fluid during resuscitation in the delivery room (#NLS596)** found sufficient evidence to justify a systematic review of suctioning clear amniotic review at delivery. {Wyckoff 2020 S185} This systematic review found 9 RCTs and 2 prospective observational studies all of whom note that suctioning of clear amniotic fluid from the mouth and / or nose has been a common or routine	was that "*This treatment recommendation is unchanged from 2010. Routine intrapartum oropharyngeal and nasopharyngeal suctioning for newborn infants with clear or meconium-stained amniotic fluid is no longer recommended*". {Perlman 2010 S516, Wyckoff 2020 S185} The ILCOR scoping review (#NLS596) found that nasopharyngeal suctioning may have serious risks and has been associated with irritation to mucous membranes and increased risk for iatrogenic infection {Gungor 2006 9, Gungor 2005 453}, bradycardia {Cordero 1971 441, Gungor 2006 9}, apnea {Cordero 1971 441}, hypoxemia and arterial oxygen desaturation {Carrasco 1997 832, Gungor 2005 453, Kohlhauser 2000 270}, hypercapnea {Skov 1992 389}, impaired cerebral blood flow regulation {Perlman 1983 329} and increased intracranial pressure {Fisher 1982 416 }. Fluctuations in cerebral blood flow have been shown to cause intraventricular haemorrhage in premature infants and neonatal animals. It is possible that nasopharyngeal suction produces vagal-induced bradycardia and increased risk of infection. {McCartney 2000 217} The procedure may take a long time {Konstantelos 2015 777}, and newborns who received suctioning compared with the control group had significantly lower oxygen saturation levels through the first 6 minutes of life and took longer to reach a normal range {Carrasco 1997 832, Gungor 2006 9, Gungor 2005 453, Konstantelos 2015 777}. Suctioning was commonly applied outside of resuscitation guidelines. {Konstantelos 2015 777}

	historical practice. A prospective observational study {Konstantelos 2015 777} showed that resuscitation guidelines are often not followed and oral, nasal or oronasopharyngeal suctioning is carried out outside of current resuscitation guidelines. It also showed that suctioning can take a long time which raises the potential for a delay in other resuscitation measures if these were required.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For **unanticipated admission to the NICU** one RCT included 448 infants of ≥35 weeks' gestation, **clinical benefit or harm cannot be excluded** (Relative risk [RR], 1.50; 95% CI, 0.96, 2.30 p=0.07) absolute risk increase 91 more per 1000 with no suctioning vs. suctioning (95% CI, 8 fewer per 1000 to 238 more patients per 1000 patient receiving no suctioning). Evidence was of very low certainty (downgraded for serious risk of bias and indirectness and very serious imprecision) {Kelleher 2013 326}. For the outcomes of receipt of assisted ventilation, need for advanced resuscitation, no studies reporting analysable data were found.	The ILCOR NLS Task Force were concerned that data about NICU admissions in the Kelleher study was either an underpowered secondary outcome or a type 1 error. There was not a pathophysiological explanation for this finding given the other saturation and heart rate data. The authors of the Kelleher study advised caution in interpreting this outcome. {Kelleher 2013 326} One observational (case control) study reported that immediate postnatal oronasopharyngeal suctioning did not compromise cerebral and muscle tissue oxygenation. {Pocivalnik 2015 153}

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	This systematic review found 9 randomized controlled trials and 2 observational studies comparing suctioning vs no suctioning. Two RCTs {Gungor 2005 453, Gungor 2006 9} have very similar results and very low standard deviations around their oxygen saturation measurements. Clarification about the data has been sought and where relevant outcome data with and without these 2 RCTS are presented. **Outcomes related to oxygen saturations:** For the important secondary outcome of of **oxygen saturations at 5 minutes** 5 RCTs including 560 participants found for suctioning vs. no suctioning	Some case series (ineligible for the review) described serious consequences (including bradycardia and apnoea and in one case post suctioning cardiac arrest. {Cordero 1971 441} Repeated use of suction devices may have potential infection risks, if methods for ensuring sterility are insufficient. This could apply in some settings with low or very low healthcare resources.

	possible harm (mean difference (MD) -9.08% (95%CI -9.51 to -8.66% p<0.001)). Evidence was of **very low certainty** (downgraded for serious risk of bias, serious inconsistency, very serious indirectness). {Bancalari 2019 271, Gungor 2005 453, Gungor 2006 9, Modarres Nejad 2014 400, Takahashi 2009 261}. Analysis without the two Gungor studies found for suctioning vs no suctioning, **clinical benefit or harm could not be excluded** (MD -0.26% (95%CI -1.77 to 1.26%) p=0.74). The evidence was of very low certainty, (downgraded for serious risk of bias, serious inconsistency and very serious indirectness). {Bancalari 2019 271, Modarres Nejad 2014 400, Takahashi 2009 261} For the important secondary outcome of of **oxygen saturations at 9 minutes** 3 RCTs including 280 participants, for suctioning vs no suctioning found **possible harm (**MD -1.52% 95% CI -2.69 to -0.35% p=0.01). This finding was statistically significant but of unclear clinical significance. Evidence was of **very low certainty** (downgraded for serious risk of bias, serious inconsistency, very serious indirectness) {Bancalari 2019 271, Modarres Nejad 2014 400, Takahashi 2009 261} For the important secondary outcome of of **oxygen saturations at 10 minutes** 2 RCTs including 110 participants found **clinical benefit or harm could not be excluded** with no significant difference in saturations in infants receiving suction (MD -0.14 (95%CI -1.17, 0.89) p=0.78]. Evidence was of **very low certainty** (downgraded for serious risk of bias, serious inconsistency, very serious indirectness) {Bancalari 2019 271, Takahashi 2009 261}. For the important secondary outcome of **oxygen saturations over the first 10 minutes of life** the data were presented in different ways in different studies, precluding a comprehensive meta-analysis of all studies that reported data on this outcome. For the important secondary outcome of of **oxygen saturations over the first 10 minutes from birth** 3 RCTs {Bancalari 2019 271, Carrasco 1997 832, Gungor 2006 9} including 254 participants provided evidence of **very low certainty** (downgraded for serious risk of bias, serious imprecision and very serious indirectness) and 1 prospective observational study {Konstantelos 2015} including 346 participants gave graphical representations of saturations over time from birth. All show a trend	The NLS task force discussed whether the oxygen saturation data should be analysed using a random or fixed effects model. The more commonly used fixed effects model gave greater weight to studies with smaller standard deviations including the two Gungor studies which are surprisingly similar in their results. A random effects model gave more even weighting across studies however, this was felt to be methodologically inappropriate as other unaccounted for random effects were not present. Consequently, a fixed effects model was used. The studies that reported oxygen saturations at set time points all showed either no difference or lower saturations in infants receiving suctioning vs. no suction. The pooled mean difference narrows over the first few minutes of life with little difference from 10 minutes of age onwards. This pattern was the same whether a fixed or random effects model was used. Three RCTs {Bancalari 2019 271, Carrasco 1997 832, Gungor 2006 9} and 1 prospective observational study {Konstantelos 2015 777} gave graphical representations of saturations over time from birth. All show slightly higher oxygen saturations over the first 5-10 minutes of life in babies who had no suctioning. One RCT including 20 healthy term participants reported slightly lower saturations in those receiving suctioning at 5 minutes but slightly higher saturation readings at 10 and 15 minutes Evidence was of **very low certainty** (downgraded for very serious risk of bias, very serious indirectness and very serious imprecision). {Waltman 2004, 32}

	to slightly lower oxygen saturations (suctioning vs. no suctioning) although by 10 minutes of age saturations were very similar in infants who did and did not receive suctioning at birth. One RCT including 20 healthy term participants reported slightly lower saturations in those receiving suctioning at 5 minutes but a trend to slightly higher saturation readings at 10 and 15 minutes. Evidence was of **very low certainty** (downgraded for very serious risk of bias, very serious indirectness and very serious imprecision). {Waltman 2004, 32} **For the important secondary outcome of time to reach target oxygen saturations of 86% or 92%** Some studies {Gungor 2005 453, Gungor 2006 9, Modarres Nejad 2014 400} reported the proportion of infants that received suctioning or no suctioning who achieved target saturations at certain time points whilst another {Carrasco 1997 832} reported mean (SD) time to achieve target saturations. The target saturations reported are those selected by studies included in this systematic review. Two RCTs {Modarres Nejad 2014 400, Carrasco 1997 832} provided data in a form that could not be meta-analysed. In one RCT including 170 participants all infants with suctioning achieved 92% saturations by 11 minutes vs. 9 minutes in the group receiving no suction. {Modarres Nejad 2014 400} The authors noted that no babies in the suctioned group achieved 92% saturations before 8 minutes. In one RCT including 30 participants, mean (SD) time to achieve saturations of 86% was 8.2 +/- 3.3 minutes (suctioning) and 5.0 minutes +/- 1.2 (no suction). For 92% saturations the times (suctioning vs. no suctioning) were 10.2 +/-3.3 minutes and 6.8 +/- 1.8 minutes respectively. {Carrasco 1997 832} Two RCTs {Gungor 2005 453, Gungor 2006 9} including 280 participants (all healthy, term infants) found 140 infants with no suctioning all achieved oxygen saturations of 86% by 5 minutes and 92% by 6 minutes. In contrast only 2.9% of the 140 infants with suctioning achieved saturations of 86% by 5 minutes and none achieved saturations of 92% by 6 minutes. In the suctioning group the maximum time to achieve saturations of 86% and 92% were 8 and 11 minutes, respectively. Evidence was of **very low certainty** (downgraded for serious imprecision and very serious indirectness).	

	One prospective observational study {Konstantelos 2015 777} including 346 participants reported 1 episode of severe desaturation to <75% following suctioning. **Outcomes relating to Apgar scores** Insufficient data on the important secondary outcome of low Apgar scores (<7) was available for analysis. For the secondary outcome of **Apgar scores** (score of 10 at 5 minutes) 3 RCTs including 450 participants showed **possible harm** (Relative risk [RR], 0.63; 95% CI 0.57, 0.70 p<0.001) ARD (suctioning vs. no suctioning) 370 fewer (95% CI 430 fewer to 300 fewer per 1000 patients) with suctioning). This finding was statistically significant but of unclear clinical significance. Evidence was of **very low certainty** (downgraded for serious indirectness) {Gungor 2005 453, Gungor 2006 9, Modarres Nejad 2014 400}. Analysis without the two Gungor studies showed no significant difference in Apgar scores (score of 10 at 5 minutes) [MD 1.00 (0.98, 1.02) p=1] so in this analysis **clinical benefit or harm could not be excluded**. **Other outcomes** One study reported that suctioning took between 2 and 154 seconds. {Konstantelos 2015 777} In this study, suctioning was performed a median of 2.5 time per infant with the median time for each suctioning episode being 9 seconds, which has potential to delay other resuscitation measures if these are required.	

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	For the important outcome of **assisted ventilation,** the **certainty of evidence was very low** downgraded for very serious risk of bias, serious inconsistency, very serious indirectness and very serious imprecision. For the critical outcome of **advanced resuscitation,** the **certainty of evidence was very low** downgraded for very serious risk of bias, serious inconsistency, very serious indirectness and very serious imprecision.	The results of 2 RCTs {Gungor 2005 453, Gungor 2006 9}, (one including infants born by caesarean section and the other vaginal births) for oxygen saturation and heart rate levels are almost identical and have much smaller standard deviations than other studies. The task force has sought clarification from the authors about the data. Outcome

	Data was available for the important outcome of **adverse effects of intervention**. • Evidence on **oxygen saturation at 5 minutes** was of **very low certainty** • Evidence on time to reach **oxygen saturations of 86%** was of **very low certainty** • Evidence on time to reach **oxygen saturations of 92%** was of **very low certainty** • Evidence on **heart rate at 5 minutes** was of **very low certainty** Insufficient data were available to be able to report on the important outcome of **receipt or duration of supplemental oxygen**. Insufficient data was available to be able to report on the important outcome of **soft tissue injury or infection or bradycardia.**	data with and without these 2 RCTS are presented.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The extent to which parents and clinicians value the outcomes selected for this review have not been assessed comprehensively or with any rigor. However, the outcomes were selected by consensus of the NLS Task Force as important. Although most outcomes represent only transient benefit or harm, they were considered significant because of the implications for nearly every birth worldwide.	

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	Intervention is receiving suctioning and the comparison is no suctioning. There was little evidence of desirable effects and some evidence of undesirable effects including: • Lower oxygen saturations at 5 minutes of age in infants who had received initial suction of the mouth or nose although this finding is not present in the analysis without the Gungor studies. • The increased time to reach saturations of 86% and 92% • Potential for harm (soft tissue injury and case reports of severe bradycardia) • Fewer infants who had received suctioning compared with no suctioning achieved an Apgar score of 10 at 5 minutes although this finding is not present in the analysis without the Gungor studies. • Potential delay in initiating resuscitation measures if these were needed, however the group noted that the babies in this systematic review were predominantly healthy term babies • Concerns over carrying out an invasive procedure if there is no evidence of benefit Overall, undesirable effects reported in studies outweighed desirable effects.	The Task Force considered that for a very small proportion of infants, there is unsuspected obstruction of the airway (e.g., by mucous or vernix) even in the presence of clear amniotic fluid.

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	No studies were identified that addressed resource utilization. Suction devices are commonly available in delivery settings and would need to remain in order to manage the rare situations where the airway is obstructed by particulate matter. If suctioning of clear amniotic fluid was not required then a reduction in suctioning consumable equipment (e.g. suction catheters) might be achieved.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There were no studies that reported the impact of suctioning clear amniotic fluid vs. not suctioning on resources. As the comparison is removal of an intervention it is unlikely that additional staffing or equipment costs would be incurred. However, there may be costs involved in training and practice change strategies.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies were found that compared the cost-effectiveness of suctioning clear amniotic fluid vs. not suctioning clear amniotic fluid in the delivery room.	Reduction in the use of suctioning may reduce consumable costs. That reduction in cost may be of much greater importance in low resource settings.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No studies were found that considered the equity of recommendations on suctioning clear amniotic fluid vs. no suctioning of clear amniotic fluid in the delivery room.	We speculate that not suctioning clear amniotic fluid is an option in all settings and may increase health equity globally. However, training to update practice may vary in availability especially in low resource settings.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Suctioning of clear amniotic fluid is widely practiced. ILCOR and WHO recommendations have advised against routine suction of clear amniotic fluid. The influence of longstanding historical practice and the perceived need to actively manage newborn babies drives persistence in suctioning of clear fluid. A prospective observational study that adherence to a resuscitation guideline that recommended no suctioning showed poor adherence, with 66% of preterm infants and 23% of term infants born through clear amniotic liquid still receiving suctioning. {Konstantelos 2015 777} In contrast, an Australian population-based study reported declining rates of suctioning over a 10-year period from approximately 25% to 10% of all liveborn infants, which was presumed to be in response to changes in guidelines. {Kapadia 2020 126 }	Suctioning of clear amniotic fluid is a long standing, well established clinical practice. This weight of historical practice is evident in the persistence of suctioning practices despite increasingly stated recommendations against this. There may be a perception that suction provides a stimulus to breathe. In settings with a lack of training this provides a strong incentive to suction in the hope that further intervention will not be necessary. An emphasis on mechanical suction in historic guidelines may have contributed to this {WHO 1998}. All of the papers in this review commented on suctioning of clear amniotic fluid remaining a common practice.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Removing a currently practiced intervention should be feasible from a resource perspective. Teaching to update practice to current recommendations will be more feasible in some health settings than others. Longstanding historical practice may influence the human factors aspect of feasibility.	

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	Large	**Moderate**	Small	Trivial		Varies	Don't know

	JUDGEMENT						
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

Recommendation

We suggest that suctioning of clear amniotic fluid from the nose and mouth should not be used as a routine step for newborn infants at birth (weak recommendation, very low certainty of evidence). Airway positioning and suctioning should be considered if airway obstruction is suspected (good practice statement).

Justification

Overall justification

In making this recommendation, the Newborn Life Support Task Force noted that studies that reported oxygen saturations at set time points up to 10 minutes all showed either no difference or lower saturations in babies receiving suctioning vs. no suctioning. The pooled mean difference in oxygen saturations (MD -9.08% (95%CI -9.51, -8.66) p<0.001) at 5 minutes narrowed over the first 10 minutes of life with little difference from 10 minutes of age onwards. Studies that reported saturations at fixed time points and studies that displayed saturation data as a graph all showed a pattern of lower saturations over the first few minutes of life in infants receiving suctioning. This was supported by studies that looked the time taken to achieve target saturations, these found that infants that received suctioning at birth took longer to achieve those target saturations.

The Task Force concluded that no benefit from routine suctioning of clear amniotic fluid was found. They were hesitant to conclude possible harm from lower saturations in the first 10 minutes of life because the data consisted of graphical trends, although it was noted that this was a consistent trend to lower oxygen saturation in those with suctioning. The statistically significant reduction in oxygen saturations at 5 minutes was not seen in all analyses and the statistically significant reduction in oxygen saturations at 9 minutes may not be clinically significant.

The Task Force considered that it was not justified to routinely use an intervention such as oral and nasal suctioning in the absence of benefit. Although the participants included in studies included in this systematic review were predominantly healthy term newborn infants, the potential for delay in resuscitation for those who required it was also a concern.

It was also noted that fewer babies receiving suctioning achieved a 5 minute Apgar score of 10 (RR 0.63; 95% CI, 0.57 to 0.70 p<0.001; ARD 370 fewer per 1000 95% CI 430 fewer to 300 fewer per 1000).

Subgroup analysis suggested an interaction by delivery type (vaginal delivery vs. caesarean section) and found high heterogeneity. The interaction and the heterogeneity were not evident when the Gungor studies were removed, an analysis that was conducted to explore the high heterogeneity.

This systematic review recommendation does not apply to situations where there are concerns regarding airway obstruction.

Detailed justification
Balance of effects
Undesirable effects of suctioning clear amniotic fluid outweighed the desirable effects

Subgroup considerations

The following subgroup analyses were predefined in the protocol.

Gestational age categories (gestational age is used define categories and birthweight is only used in studies that only used birthweight)

- ≥34 +0 weeks or >2000g

- 28 +0 - 33 +6 weeks or 1000-2000g
- <28 +0 weeks or <1000g

Route and method of delivery (Vaginal vs Caesarean section)
Suction device used (Bulb vs Catheter Suction)

Gestational age

Insufficient data were available for this subgroup analysis as the studies included in this systematic review were predominantly in term babies. Only one prospective observational study {Konstantelos 2015 777} and one RCT {Kelleher 2013 326} included both preterm and term infants.

The Kelleher study included infants ≥35 weeks although the median (IQR) gestation was 39 (38–40) weeks for the no suction (wipe) group and 39 (38–40) for suction group. {Kelleher 2013 326} The majority of the infants in the Konstantelos study were born at term. {Konstantelos 2015 777}

Vaginal vs Caesarean section

Insufficient data were available for a subgroup analysis of the following outcomes: receipt of assisted ventilation, advanced resuscitation, receipt of supplemental oxygen, unanticipated NICU admission.

For the outcome of oxygen saturations at 5 minutes there is a difference favoring no suction in both vaginal delivery and caesarean section subgroups with high heterogeneity within subgroups (I^2 =97%) and evidence of an interaction by delivery type (test for subgroup differences 0.03) also with high heterogeneity between subgroups (I^2=78.6%). Given the very high heterogeneity, despite almost identical results in two studies {Gungor 2005 453, Gungor 2006 9}, a sensitivity analysis was carried out. With the two Gungor studies removed from both subgroups there was no difference in saturations in either subgroup with no interaction (p=0.86) and heterogeneity reduced (I^2=0%).

Among the two methodologically identical RCTs, {Gungor 2005 453, Gungor 2006 9} one studied vaginally born infants and the other those born by caesarean section, each included 140 participants and found identical time to achieve saturations of 86% or 92%.

Suction device used (Bulb vs Catheter Suction)

Two RCTs {Kelleher 2013 326, Waltman 2004 32} studied infants receiving bulb suction vs. no suction or wiping. No studies compared bulb suction to catheter suction. Outcomes in the Kelleher and Waltman studies were reported differently, hence comparison could not be made and subgroup analysis was not possible.

Implementation considerations

One study {Konstantelos 2015 777} showed poor adherence to guidelines whilst another {Kapadia 2020 126} suggested reduced rates of suctioning over time possibly in response to changing guidelines. Clearly worded, unambiguous recommendations may help with implementation.

Monitoring and evaluation

Auditing of when and why suctioning is performed may support practice change and provide valuable information for research.

Research priorities

- The role of suctioning of clear amniotic fluid at birth for infants at higher risk of needing resuscitation or respiratory support
- The role of suctioning of clear amniotic fluid at birth for preterm infants
- Adherence to resuscitation guidelines in relation to the practice of suctioning clear amniotic fluid

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QUESTION

NLS 5140- Tactile stimulation for resuscitation immediately after birth	
POPULATION:	Term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations
INTERVENTION:	Any tactile stimulation performed within 60 seconds after birth and defined as one or more of the following: rubbing the chest/sternum; rubbing the back; rubbing the soles of the feet; flicking the soles of the feet; combination of these methods. This intervention should be done in addition to routine handling with measures to maintain temperature.
COMPARISON:	Routine handling with measures to maintain temperature, defined as care taken soon after birth, including positioning, drying and additional thermal care.
MAIN OUTCOMES:	Spontaneous breathing without positive pressure ventilation (yes or no); time to the first spontaneous breath or crying from birth; and time to heart rate ≥100 bpm from birth.
SETTING:	Delivery room or any other place of birth
PERSPECTIVE:	
BACKGROUND:	Tactile stimulation has been suggested in the initial steps of stabilization of the newborn infant in the treatment recommendations from ILCOR in 1999, 2006, 2010, 2015 and 2020 {Kattwinkel 1999 1927; ILCOR 2006 e-978; Perlman 2010 S516; Perlman 2015 S204; Wyckoff 2020 S185}. These recommendations are largely based on many years of experience and expert opinion. Because the effectiveness of tactile stimulation to facilitate breathing at birth has never been systematically evaluated by ILCOR, this PICOST was prioritized by the Neonatal Life Support Task Force.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Each year approximately 10% of 140 million neonates born globally are delivered with absent or poor respiratory effort and need some degree of support to achieve cardiopulmonary stability {Ersdal 2012 869}. Basic resuscitation interventions immediately after birth in these infants are essential in preventing progression to circulatory collapse and death. One of the most common interventions to stimulate breathing at birth is tactile stimulation. For decades, tactile stimulation has been suggested in the initial steps of stabilization of the newborn infant {Wyckoff 2020 s185}, but its effectiveness was never systematically assessed.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Based on the systematic review, the very limited available data suggest a benefit to tactile stimulation in decreasing the need of tracheal intubation in preterm infants, but the certainty of evidence is very low {Dekker 2017 61}. Observational studies showed that, although the methods of stimulating were variable, infants that received tactile stimulation responded with crying, grimacing and body movements {Katheria 2016 75; Gaertner 2018 F132; Pietravalle 2018 306; Van Henten 2019 F661}. A single center RCT compared single vs. repetitive tactile stimulation in preterm infants immediately after birth. Patients in the repetitive stimulation group had higher oxygen saturation levels and lower oxygen requirements at the start of transport to the NICU {Dekker 2018 37}. A single center RCT compared two different techniques of tactile stimulation (back rubbing vs foot flicking). Among 186 infants >1500g who did not cry at birth, 77% presented with spontaneous breathing without PPV. No differences were found between the techniques {Cavallin 2021 137}. In studies that analyze a bundle of procedures to stimulate respiratory transition at birth in low resource settings, tactile stimulation together with upper airway suction triggered the initiation of spontaneous respirations {Ersdal 2012 869; Msemo 2013 e353}.	Tactile stimulation has the potential to trigger respiratory movements in apneic newly born infants and to increase the depth and the frequency of respirations in infants with irregular or shallow breathing {Dekker 2019}. If this is true, an important percentage of the 14 million newborns that need help to initiate breathing at birth each year globally would benefit from a non-invasive procedure available in all settings, but there are no randomized controlled studies to affirm this potential beneficial effect. This assumption would be correct only if the method (type, number, body region, duration) of tactile stimulation is an evidence-based recommendation. However, there are no data on the optimal means by which to deliver tactile stimulation. In a systematic review of 15 studies on tactile stimulation to terminate or to prevent apnea of prematurity, tactile stimulation, manual or mechanical, has been shown to shorten the duration of apnea, hypoxia, and or bradycardia or even prevent an apnea, although the review did not assess the tactile stimulation in delivery-room resuscitation just after birth. This provides indirect evidence that tactile stimulation may be effective to stimulate breathing in newborn infants with absent, intermittent or shallow respiration immediately after birth {Cramer 2018 45}.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Based on a narrative review, there are some concerns related to possible adverse effects of tactile stimulation in delaying the initiation of ventilation beyond 60 seconds after birth, which may then compromise the efficacy of the overall resuscitation {Cavallin 2021 137; KC 2021 235; Pietravalle 2018 306}. Also, there is a report of soft tissue trauma after tactile stimulation {Kalaniti 2017 84]. Pietravalle et al observed 150 term newborn infants with apnea, hypotonia or both at birth in a single center in Mozambique. Tactile stimulation was performed in 68% of these infants. First stimulation was provided at a median of 134 seconds (IQR 53-251) after birth. Only 9 (9%) infants who received tactile stimulation responded with spontaneous breathing without need for PPV {Pietravalle 2018 306}. KC et al observed 22,752 births in Nepal, Bangladesh and Tanzania, and 5,330 did not cry within 1 minute after birth. Among them, 2,055 (39%) received tactile stimulation, 1,907 (36%) were suctioned immediately after birth, and 677 (13%) received bag and and mask ventilation. Most newborns (71–95%) who did not respond to stimulation did receive bag and mask ventilation, but only 1% within the recommended 1 minute after birth {KC 2021 235}. Cavallin et al observed 186 infants >1500g who did not cry at birth in a single center in Uganda. Among the 42 infants	Possibly, the adverse effects depend on the training and expertise of health care providers.

	who did not demonstrate spontaneous breathing after tactile stimulation, the median time to initiate PPV was 60 seconds, i.e. in half of the infants PPV was delayed (started after 60 seconds). No skin lesions were reported in these infants {Cavallin 2021 137}. A case report of soft tissue trauma, with bruises and scratches to the infant's back, has been reported during/after tactile stimulation {Kalaniti 2017 84}. No studies systematically report possible adverse outcomes of tactile stimulation in newborn infants with absent, intermittent or shallow respiration immediately after birth in relation to admission to a neonatal special unit or intensive care unit, neurodevelopment or survival.	

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	Overall, the certainty of evidence was very low or absent. For the important outcome of tracheal intubation in the delivery room, evidence of very low certainty (downgraded for risk of bias, indirectness, and imprecision, and upgraded by the strong association) from 1 observational trial {Dekker 2017 61} involving 245 preterm newborns showed possible benefit from receiving tactile stimulation in addition to routine handling with measures to maintain temperature compared to routine handling (RR 0.41, 95%CI 0.20-0.85). There are concerns related to: Indirectness: All studied infants (n=245) were put on CPAP before tactile stimulation in contrast to the common practice of tactile stimulation before CPAP or positive pressure ventilation. Selection bias: A total of 673 infants were video recorded, of whom only 321 recordings were complete and of good quality. From these, 245 recordings included stabilization at birth of infants born with a gestational age <32 weeks and were included in the analysis. Confounding: the indication of tactile stimulation was retrospectively assessed and not clear. Among the 81 infants that did not receive tactile stimulation, 72 presented apnea/irregular breathing, hypoxia and/or braycardia immediately after birth. Among the 164 infants that received tactile stimulation, it was not possible to determine the number of infants that had indication for the procedure. The authors report that these 164 infants received 585 episodes of tactile stimulation, but in 198 (34%) episodes the clinical indications for the procedure could not be retrieved.	One study that could not be included in the systematic review due to a critical risk of bias did not find a beneficial effect of tactile stimulation. In a single center in Austria, Baik-Schneditz et al reported that respiratory support in the first 15 minutes after birth was applied in 24/43 (56%) neonates who received tactile stimulation and in 31/57 (54%) of non-stimulated infants {Baik-Schneditz 2018 952}. For the important primary outcomes of establishment of spontaneous breathing without PPV, time to the first spontaneous breath or crying, and time to heart rate ≥100 bpm, no data were reported. For the critical secondary outcomes of survival, neurodevelopmental outcomes, and intraventricular hemorrhage in preterm infants <34 weeks, no data were reported. For the important secondary outcomes of admission to a neonatal special or intensive care unit and oxygen and/or respiratory support at admission, no data were reported.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The valuation of the main outcomes is consistent with the values assigned by the ILCOR NLS task force and a larger group of neonatal resuscitation experts. {Strand 2020 328}.	

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	We have considered the balance between the evidence supporting a possible reduction in the risk of tracheal intubation and the lack of evidence of benefit or harm for other outcomes.	Although there are some concerns related to delaying the initiation of positive pressure ventilation and possible trauma in depressed newly born infants, the possible benefit of decreasing the need of invasive procedures, such as tracheal intubation in preterm infants {Dekker 2017 61}, that require specialized equipment and trained personnel, influenced our judgement. Also studies that show that a bundle of procedures including tactile stimulation provided to infants who do not adequately breathe immediately after birth may trigger the initiation of respirations in around 50% of them without further need for resuscitation {Ersdal 2012 869} influenced our judgement.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	There are no published cost data on tactile stimulation immediately after birth	The procedure per se (tactile stimulation) does not require financial investments, except for training health care providers. There are potential savings if tactile stimulation reduces the need for positive pressure ventilation and tracheal intubation, and the progression to circulatory collapse. These considerations may be applied in both low and high resource settings.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No data available. No studies were found that estimate the costs of applying tactile stimulation vs. not applying tactile stimulation for term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No data available. No studies were found that estimate the cost effectiveness of applying tactile stimulation vs. not applying tactile stimulation for term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations.	Although there are no published cost-effectiveness data, it is possible that tactile stimulation will decrease the cost of delivery room supplies used to offer positive pressure ventilation at birth. There could be a cost if there are (as yet unmeasured) adverse effects.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No data available.	The use of tactile stimulation in term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations may increase health equity. If a simple and inexpensive procedure that can be equally used in low and high resource settings, without additional resource requirements beyond providers' training, can decrease the need for positive pressure ventilation at birth, this procedure may increase opportunities to offer adequate resuscitation globally. This assumption would be correct only if the method (time of initiation, type of stimulus, body region, number of stimuli, total duration) of tactile stimulation is an evidence-based recommendation. However, there are no data on the optimal method of tactile stimulation.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tactle stimulation is probably acceptable, since it is recommended for newly born infants with inadequate respiratory effort at birth in several neonatal resuscitation guidelines and recommendations across the world for decades {Kattwinkel 1999 1927; International Liaison Committee on Resuscitation 2006 978; Perlman 2010 S516; Perlman 2015, S204; Wyckoff 2020 S185; Aziz 2020 S524; Madar 2021 291; Liley 2017 621; Hosono 2020 128; WHO 2012 1}.	Dekker et al, reported that "colleagues of the neonatal team are very reluctant to not stimulate infants as tactile stimulation is one of the most basic interventions during neonatal resuscitation" {Dekker 2018 37}. Lee et al reported that the quality of evidence for stimulation at birth is low, partly because it is considered the standard of care {Lee 2011 S12}.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Tactile stimulation is a feasible intervention to implement. Training of health care providers will be necessary in order to avoid delays in the initiation of positive pressure ventilation and tissue trauma in term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations.	

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	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

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

Recommendation

We suggest it is reasonable to apply tactile stimulation in addition to routine handling with measures to maintain temperature in newborn infants with absent, intermittent, or shallow respirations during resuscitation immediately after birth (weak recommendation, with very low certainty due to risk of bias, indirectness, and imprecision). Tactile stimulation should not delay the initiation of positive pressure ventilation for newborns who continue to have absent, intermittent, or shallow respirations after birth.

Justification

In making these recommendations, the Neonatal Life Support Task Force acknowledges the following:

- The very limited available data suggest a possible benefit to tactile stimulation in decreasing the need for tracheal intubation in preterm infants, but the certainty of evidence is very low. This benefit was found in a single retrospective cohort study {Dekker 2017 61} involving 245 preterm newborns <32 weeks of gestational age. The results of this study should be analyzed with caution due to indirectness (all 245 infants were put on CPAP before tactile stimulation in contrast to the common practice of tactile stimulation before CPAP or positive pressure ventilation), possible selection bias (among 673 infants who were video recorded immediately after birth, 245 (36%) were included in the study), and confounding (the clinical indication of tactile stimulation was retrospectively assessed and it could not be determined in 34% of the 585 tactile stimulation episodes).
- Observational studies showed that, in general, infants who received tactile stimulation responded with crying, grimacing and body movements, although the methods of stimulation were variable and the outcomes analyzed were not exactly the same among the studies {Gaertner 2018 F132; Katheria 2016 75; Pietravalle 2018 306; Van Henten 2019 F661}. These studies could not be included in the systematic review due the lack of control groups who did not receive tactile stimulation.
- A single center RCT compared single vs. repetitive tactile stimulation in preterm infants immediately after birth. Patients in the repetitive stimulation group had higher oxygen saturation levels and lower oxygen requirements at the start of transport to the NICU {Dekker 2018 37}. This study could not be included in the systematic review due to the lack of control group who did not receive tactile stimulation.
- A single center RCT compared back rubbing vs. foot flicking to provide tactile stimulation in preterm and term infants with birthweight >1500g who did not cry at birth. There was no difference between both techniques in achieving effective crying to prevent the need of PPV {Cavallin 2021 137}. This study could not be included in the systematic review due to the lack of a control group who did not receive tactile stimulation.
- In studies that analyze a bundle of procedures to stimulate respiratory transition at birth in low resource settings, tactile stimulation together with upper airway suction triggered the initiation of spontaneous respirations {Ersdal 2012 869; Msemo 2013 e353}. These studies could not be included in the systematic review due to the inability to isolate the effects of tactile stimulation as well as the lack of a control group.

Despite the possible benefits outlined above, there are some concerns related to possible adverse effects of tactile stimulation in delaying the initiation of ventilation beyond 60 seconds after birth, which may then compromise the efficacy of the overall resuscitation {Cavallin 2021 137; KC 2021 235; Pietravalle 2018 306}. Also, there is a report of soft tissue trauma after tactile stimulation {Kalaniti 2017 84].

Subgroup considerations

No data were reported regarding subgroups of interest: gestational age (<34 weeks, 34-36 6/7 weeks, and ≥37 weeks), cord management (early and delayed/cord milking), settings (high and low resource), and method of stimulation (type, number and/or duration of stimuli).

Implementation considerations

Implementation will require a decison on the optimal methods of tactile stimulation: time of initiation, type of stimulus, body region, number of stimuli, total duration. Once an evidence-based technique is recommended, training should be available to health care providers.

Monitoring and evaluation

As the recommendation for tactile stimulation is very weak and is based on very low certainty evidence, continued monitoring and evaluation is highly recommended.

Research priorities

In order to make evidence-based recommendations on the use of tactile stimulation for term or preterm newborn infants immediately after birth with absent, intermittent, or shallow respirations, it is important that research covers the following knowledge gaps:

- Effect of tactile stimulation on the main outcomes: breathing without PPV; time to the first spontaneous breath or crying from birth; and time to heart rate ≥100 bpm from birth
- Effect of tactile stimulation on secondary outcomes: death in the delivery room, hospital death; neurodevelopmental outcomes; intraventricular hemorrhage only in preterm infants; oxygen and/or respiratory support at admission to a neonatal special unit or intensive care unit; and admission to a neonatal special or intensive care unit for those not admitted by protocol.
- Effects of tactile stimulation in different gestational ages.
- Effects of tactile stimulation with different cord management strategies.
- Which patients benefit from tactile stimulation (all, patients with apnea, irregular breathing or other): what is the indication of tactile stimulation
- Efficacy of different methods of tactile stimulation (rubbing, flicking or other)
- Efficacy of stimulation in different parts of the body (soles of the feet, back, chest or other)
- When to start tactile stimulation after birth and when to stop
- Duration of each stimulus (seconds)
- Optimal number of stimuli
- Optimal duration of stimulation before providing respiratory support (seconds)
- Adverse effects of tactile stimulation

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QUESTION

Should use of additional modalities for heart rate assessment: ECG, doppler device, digital stethoscope, photoplethysmography, video plethysmography, dry electrode technology vs. COMPARISON: Compared with 1. Pulse oximetry with or without auscultation 2. Auscultation alone 3. In between intervention comparison be used for Newly born infants in the delivery room?

POPULATION:	Newly born infants in the delivery room
INTERVENTION:	Use of additional modalities for heart rate assessment: ECG, doppler device, digital stethoscope, photoplethysmography, video plethysmography, dry electrode technology
COMPARISON:	COMPARISON: Compared with 1. Pulse oximetry with or without auscultation 2. Auscultation alone 3. In between intervention comparison
MAIN OUTCOMES:	Unanticipated admission to neonatal intensive care unit (I) Death before hospital discharge (C) Duration of positive pressure ventilation (PPV) in delivery room from the start of PPV (I) Tracheal intubation in delivery room (I) Chest compressions or epinephrine (adrenaline) in delivery room (I) Time from birth to heart rate ≥100 bpm as measured by ECG (I) Resuscitation team performance in the delivery room (I)
SETTING:	Delivery Room
PERSPECTIVE:	Population perspective
BACKGROUND:	
CONFLICT OF INTERESTS:	VK has authored one of the studies included in the systematic review but did not participate in the decision to include the study or RoB assessment of the study.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	- Annually 140 million neonates are born worldwide and up to 5% of term neonates will not initiate adequate respiratory effort after stimulation by drying and warming. More than 7 million newborn infants will require positive pressure ventilation (PPV) every year for heart rate below 100 beats per minute (bpm) or gasping or apnea. Rising heart rate (HR) is the most important indicator of effective positive pressure ventilation in initially bradycardic newborns. [Wyckoff 2020 S185] HR is critical to decision-making in the delivery room, and therefore accurate assessment of HR is a priority. -Although there have been multiple studies investigating latency and accuracy of various modalities for HR determination in the delivery room (DR), there is limited evidence to date of what the impact of the methodology of heart rate assessment on clinical outcomes might be {Kamlin 2008 758;	- Fast, accurate and continuous HR estimation is desirable during neonatal resuscitation as it allows the team to make decisions and determine effectiveness of the resuscitation efforts. - Underestimating HR can lead to interventions when not indicated, such as PPV, intubation, chest compressions and epinephrine administration. This may lead to harm. On the other hand, overestimation of HR may result in a delay of necessary critical interventions, such as PPV, intubations, chest compressions and potentially result in adverse outcomes. [Phillipos 2016 130] -Recommendation for method of HR assessment varies across the different resuscitation councils of the world.

	Dawson 2013 957 958; van Vonderen 2015 51; Iglesias 2018 F236; Henry 2020 75}	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	-The evidence suggests that ECG is faster in acquiring HR in the delivery room compared to auscultation with pulse oximeter {Murphy 2018 F490}. Auscultation with pulse oximeter is less accurate compared to ECG in estimating HR in the delivery room for the first few minutes after birth {Kamlin 2006 320; Murphy 2018 F491}. - Pulse oximeter is less accurate than ECG {Kamlin 2008 758; Dawson 2013 957; Van Vonderen 2015 51; Abbey 2021 6; Henry 2020 75} as it was shown in 28,211 observations [Mean Bias -1.2; LoA (95%CI): -17.9 to 15.5 (-32.8, 30.4)]. - Single cohort study with 48 newborns and 755 data pairs {Van Vonderen 2015 51} showed that pulse oximeter is less accurate than ECG to detect heart rate below 100 bpm up to 300 seconds. - Single RCT {Abbey 2021 4} with 51 premature newborns infants showed no difference in the duration of PPV between ECG and pulse oximeter (ECG: 345s (120,558) vs. PO: 196s (150,273); p=0,37). -Single before-after observational study {Shah 2019 15} involving 632 newborn infants showed association of decrease in delivery room tracheal intubations with ECG use (aOR 0.65, 95% CI 0.45-0.94]. In small randomized controlled trials involving 91 newborns no decrease in endotracheal intubation was noted with ECG use in the delivery room (RR 1.34, 95% CI 0.69-2.59) {Katheria 2017 6; Abbey 2021 4}.). The certainty for this evidence remains low due to risk of bias and imprecision.	-ECG allows for continuous HR assessment compared to auscultation, which offers intermittent HR assessment. - ECG allows continuous visualization of HR while auscultation relies on a team member who needs to count audible heart beats over a period of time using a stethoscope. - There have been no studies examining the impact of ECG use in the delivery room on resuscitation team performance. - Randomized controlled trial evidence of the impact of HR assessment method on outcomes for very low birth weight (VLBW) infants and infants needing intubation or cardiopulmonary resuscitation (CPR) in the delivery room remain extremely limited {Katheria 2017 6 ; Abbey 2021 4}. Additional studies are needed to assess effect of ECG use for HR assessment in the DR on these important subgroups of infants.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	• One before-after observational study including 632 infants showed increased incidence of chest compressions with ECG monitoring [(aOR 3.59, 95% CI 1.36-9.46)] {Shah 2021 15}. This study had a higher baseline rate of chest compressions (3%) when compared to previously described incidence of chest compressions in newly born infants. Authors did not assess compliance with NRP guidelines in infants receiving chest	• It is also important to note that the appropriate HR threshold for chest compressions in newly born infant remains a knowledge gap. • It remains unclear if the timing of cord clamping, especially in relation to the aeration of the lungs, impacts rate of bradycardia in newly born infants at birth. Immediate cord clamping may result in drop in left ventricular output and may result in bradycardia at the time of birth. Recognition of such bradycardia by tools that measure HR faster than auscultation with/without pulse oximeter may result in an increase

	compressions. It remains unclear if temporal trends and other confounders played a role in increase in chest compressions with the use of ECG monitoring in DR. Interestingly, the incidence of epinephrine use in the delivery room was no different between two groups {Shah 2021 15}. • Small randomized controlled trials did not show any change in the incidence of chest compressions with ECG use in the delivery room {Katheria 2017; Abbey 2021 4}. These studies were not powered to find a difference in incidence of chest compressions.	in resuscitation interventions. It remains unclear if this is beneficial or harmful. • There is limited data on use of ECG for delivery room resuscitation of VLBW infants. Application of leads to very/extremely premature skin may cause skin damage or may result in increased incidence of hypothermia if the plastic wrap used for thermoregulation is being repeatedly undone. • It remains unclear if the use of ECG will result in delay or non-recognition of pulseless electrical activity in a newly born infant. • It remains unclear if underestimation or overestimation of heart rate by pulse oximetry or auscultation will result in inappropriate interventions or delay in critical interventions such as positive pressure ventilation during neonatal resuscitation.

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	• There was low certainty of evidence of decrease in the important outcome of tracheal intubation in the delivery room from 1 observational study, but benefit or harm could not be excluded for the same outcome from low certainty evidence obtained from 2 RCTs. • Similarly, there was low certainty of evidence of increase in chest compressions in the DR from 1 observational study, but benefit or harm could not be excluded for the important outcome of chest compressions in the DR from 2 RCTs as event rate was zero in both studies. • For important outcomes of duration of PPV and time from birth to HR ≥ 100 bpm, certainty of evidence was very low due to risk of bias and serious imprecision. • For the critical outcome of death before discharge, evidence was of a low certainty downgraded for risk of bias and imprecision.	

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	• There is probably no important uncertainty or variability in how much people value death before discharge and unanticipated admission to the neonatal intensive care unit as outcomes. • Other outcomes are process outcomes or surrogate outcomes. For other outcomes, there is possibly important uncertainty or variability.	Outcome ratings were adopted from the following publication: [Strand 2020 328]

	• We included outcomes that were previously judged to be critical or important by an expert panel and thus are likely to influence healthcare providers to use one method of HR monitoring over another in the DR.	

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	Certainty of current evidence is low. The desirable and undesirable effects of use of ECG in the delivery room remain unclear.	

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	Costs of ECG monitoring in the delivery room are context-dependent. Many centers are able to re-allocate monitors from existing resources; others providers will need to allocate resources to buy additional monitors. Beyond the ECG monitor, the cost of using disposable leads (gel electrodes) and costs associated with training may be considered. As such, it is deemed a moderate cost.	It is possible that the routine use of ECG for heart rate assessment in infants receiving positive pressure ventilation immediately after birth may reduce the need for further neonatal resuscitation interventions and long-term undesirable outcomes. There is no current evidence to support that use of ECG will alter need for resuscitation interventions or clinical outcomes in newly born infants.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There is no evidence currently available to answer this question.	

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 is no evidence currently available to answer this question.	

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	There are no data available to inform the answer to this question.	A preponderance of neonatal asphyxia occurs in resource-limited areas. We speculate that an affordable heart rate assessment tool that provides rapid and accurate data may positively impact outcomes in areas where neonatal asphyxia is more prevalent. We speculate that equipment and adequately trained personnel to perform the intervention may not always be available, especially in low-resource settings.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	• Stakeholders have variable acceptance of this intervention • We speculate this is predominantly due to the lack of evidence of impact on outcomes and cost-effectiveness.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Multiple studies have demonstrated feasibility of use of ECG in newly born infants in various settings {Perlman 2015 S207}.	Number of infants needing tracheal intubations or CPR {Katheria 2017 6 ; Shah 2019 15; Abbey 2021 4} and number of VLBW infants (Iglesías 2016 272) included in the studies are limited.

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	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
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

Recommendation

- Where resources permit, we suggest that the use of ECG for heart rate assessment of a newly born infant requiring resuscitation in the delivery room is reasonable (weak recommendation, low certainty of evidence).
- Where ECG is not available, auscultation with pulse oximetry is a reasonable alternative for heart rate assessment but the limitations of these modalities should be kept in mind (weak recommendation, low certainty of evidence).
- There is insufficient evidence to make a treatment recommendation regarding use of digital stethoscope, audible or visible Doppler US, dry electrode technology, reflectance-mode green light photoplethysmography and or transcutaneous electromyography of the diaphragm for heart rate assessment of a newborn in the delivery room.
- Auscultation with or without pulse oximetry should be used to confirm the heart rate when ECG is unavailable, not functioning or when pulseless electrical activity is suspected.

Justification

- Low certainty evidence from 3 studies inform this recommendation {Katheria 2017; Abbey 2021; Shah 2019}.
- Evidence from a recent ILCOR COSTR suggests that ECG does provide more rapid and more accurate assessment of heart rate in the delivery room than any of the alternative methods. However, it remains unclear if this level of speed and precision translates to clinically relevant differences in resuscitation interventions or clinical outcomes for newly born infants.
- One needs to balance the desire to have a rapid, continuous and accurate heart rate assessment in newly born infants needing resuscitation with the potential cost of ECG monitoring in the delivery room. This is especially true in the face of a lack of high certainty data regarding clinical impact of routine ECG use for heart rate assessment in newly born infants in the delivery room. Individual councils should take into account the available resources, values and preferences while creating local guidelines for recommended modalities for HR assessment in the delivery room.

Subgroup considerations

Implementation considerations

Acquiring ECG monitors in the delivery room: many centers might be able to re-allocate monitors from existing resources; others providers will need to allocate resources to buy additional monitors. Use of ECG for HR assessment for newly born infants will require training of resuscitation team personnel.

Monitoring and evaluation

Continued monitoring and evaluation of resuscitation team performance and clinical outcomes, including resuscitation interventions is recommended.

Research priorities

- Does use of ECG or other modalities for heart rate assessment improve neonatal outcomes (unanticipated admission to neonatal intensive care unit, death before hospital discharge, duration of PPV in delivery room from the start of PPV, tracheal intubation in delivery room, chest compressions or epinephrine (adrenaline) in delivery room, time from birth to heart rate ≥100 bpm as measured by ECG)?
- Impact of ECG or other modalities for HR measurement on resuscitation team performance
- Impact of ECG and other modalities for HR assessment on equity
- Cost effectiveness of different modalities for HR assessment in the delivery room
- Should the HR assessment method in the delivery room be different for vigorous versus non-vigorous newly born infants?
- HR assessment method for a subgroup of infants who require intubation and/or CPR in the delivery room
- HR assessment method for VLBW infants
- Prevalence of bradycardia in a newly born infant after change in ILCOR recommendations for delayed cord clamping
- Prevalence of pulseless electrical activity for newly born infants in the DR

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QUESTION

NLS 5312- CPAP versus No CPAP for Term Respiratory Distress in Delivery Room	
POPULATION:	In spontaneously breathing newly born ≥34+0 weeks gestation infants with respiratory distress and/or low oxygen saturations during transition after birth.
INTERVENTION:	Continuous positive airway pressure (CPAP) (at different levels with or without supplemental oxygen)
COMPARISON:	Compared with no CPAP (with or without supplemental oxygen)
MAIN OUTCOMES:	Admissions to neonatal intensive care unit (NICU) or higher level of care receiving any positive pressure support [primary outcome]; receiving tracheal intubation or chest compressions in the delivery room; use and duration of respiratory support in NICU; air-leak syndromes including pneumothorax and pneumomediastinum; death at hospital discharge; length of hospital stay; moderate-severe neurodevelopmental impairment (>18 months)
SETTING:	Delivery room
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	At birth, the newly born infant rapidly undergoes major and complex physiologic changes. Failure to establish and maintain air breathing from the fluid-filled environment of the womb leads to impaired transition. Resultant respiratory distress is common, affecting up to 7% of all term newborns (Edwards 2013 29), and is even more prevalent in late preterm infants. Further, respiratory distress is responsible for 30-40% of admissions to the neonatal intensive care units (NICU) (Guha DK, editor Neonatology - Principles and Practice, 1st ed. 1998). Fifteen percent of term infants and 29% of late preterm infants admitted to the NICU develop significant respiratory morbidity (Hibbard 2010 419). The etiology of respiratory distress among term and late preterm newborn infants is heterogeneous and includes transient tachypnea of newborn, respiratory distress syndrome (surfactant deficiency), pneumonia, and meconium aspiration syndrome. These conditions present similarly in a non-specific manner, with signs such as tachypnea, nasal flaring, retractions, and grunting, making precise diagnosis difficult. Symptoms may progress to respiratory failure and death if not readily recognized and managed appropriately (Warren 2010 487). In infants with progressive respiratory failure, mechanical ventilation (MV) with or without surfactant has been the usual treatment. This approach is invasive and may contribute to airway and lung injury. Therapy for respiratory distress traditionally consisted of oxygen given via headbox, low-flow nasal prong or cannula, or face mask. Continuous positive airway pressure (CPAP), a non-invasive form of respiratory support, has also been used for the prevention and treatment of respiratory distress. CPAP devices apply a positive pressure to the airways of a spontaneously breathing baby throughout the respiratory cycle. Extrapolated from evidence in preterm babies that CPAP applied early after birth improves survival without	

	bronchopulmonary dysplasia (BPD) (Schmölzer 2013 f5980 and Subramaniam 2016 1465), there has been progressively increased use of CPAP among term and late preterm newly born infants (Smithhart 2019, Hishikawa 2016 1).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	In preterm infants less than 32 weeks, early CPAP use decreases the need for mechanical ventilation and decreases the risk of death or chronic lung disease (Subramaniam 2016 1465). The effect of CPAP applied in the delivery room in term and late preterm infants with respiratory distress has been less clear. In the literature search for the current review, two randomized controlled trials (RCTs) were available in this population. In these studies, the RR of NICU admission was 0.27 (0.11, 0.66) when CPAP was applied to infants delivered by cesarean section with or without respiratory distress. One RCT used CPAP as treatment for babies with respiratory distress; another RCT with a larger sample size used prophylactic CPAP. On average, 94/1000 fewer infants treated with CPAP in the delivery room (DR) were admitted to the NICU than infants not treated with CPAP. These RCTs were small (totaling 323 subjects) and included only infants delivered by cesarean section. Therefore, conclusions should be considered with caution. If the outcomes are confirmed in larger trials, the impact on infants in this population would be substantial. The magnitude of effect from the included trials leads to a number needed to treat of 10.8 with a 95% CI of 8.7 to 22.7; for every ~11 infants treated with CPAP, 1 fewer infant will be admitted to the NICU. However, since the two RCTs included only newborns born by caesarean section, CPAP should be evaluated among vaginally delivered newborns in a randomized fashion. Of the two observational studies included in this systematic review, one studied only a cohort of NICU admissions and therefore cannot be evaluated for main outcome of NICU admission. The other before-after observational study with a larger sample that included vaginal and cesarean deliveries found the opposite effect on NICU admissions, when compared with RCTs. There was also a positive association between CPAP use and NICU admissions. To summarize, we cannot exclude benefit or harm for CPAP use in the delivery room due to the scarcity and heterogeneity of the available evidence.	In preterm infants, CPAP increases transpulmonary pressure and functional residual capacity (FRC) and improves lung compliance. It also prevents alveolar collapse (atelectrauma), decreases intrapulmonary shunt, and provides progressive alveolar recruitment. In addition, CPAP conserves surfactant and prevents pharyngeal wall collapse. It also stabilizes the chest wall and decreases thoracoabdominal asynchrony and work of breathing if there is respiratory distress (Elgellab 2001 1782). Moreover, it splints the diaphragm and stimulates lung growth (Zhang 1996 1471). Finally, bubble CPAP adds high-frequency ventilation (Lee 1998 69) and stochastic resonance effects (Pillow 2005 826). Hence, CPAP use may improve respiratory distress in the newborn and reduce the NICU admissions and the need for MV and hence its sequelae, including airway and lung injury.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	The RCTs available for this review comparing 168 subjects with CPAP of 5 cm H_2O versus 155 subjects with no CPAP reported no cases of pulmonary air leak, but they have a small sample size and one study used CPAP prophylactically. Two observational studies included in this review found a positive association between CPAP use and occurrence of air leak syndromes, including pneumothorax. The RR for pneumothorax/air leak in these infants was 4.92 (4.13, 5.87). These studies are limited by significant selection bias. Similarly, CPAP use was associated with an increase in NICU respiratory support with the RR 7.78 (4.25, 14.24) and length of hospital stay with the MD 1 (0.31, 1.69) in a single-center observational cohort studying term newborn infants. However, NICU respiratory support was reported in two RCTs and length of hospital stay was reported in	CPAP may introduce ongoing risk during transition after birth and beyond (in NICU). In preterm human observational studies, apnea was seen after applying the interfaces used to provide CPAP. Hence, it is speculated that interfaces used to provide CPAP could stimulate the receptors of the trigeminal nerve and provoke the diving reflex, with resultant apnea and bradycardia (Kuypers 2020 60). Pulmonary air leak syndromes, including pneumothorax, may be more common with CPAP treatment and may require invasive interventions, such as thoracentesis or thoracostomy tube, and lead to further complications (Morley 2008 700). Higher levels of CPAP may lead to increased dead space ventilation and cause retention of carbon dioxide. Excessive CPAP can increase intrathoracic pressure, resulting in diminished venous return to the heart and reduced cardiac output, decreased pulmonary perfusion, and

	one RCT. No statistically significant differences were reported between newborns who received CPAP and those who did not receive CPAP in RCTs enrolling late preterm and term newborn infants born via cesarean deliveries.	enhanced ventilation-perfusion mismatch. Gastric distension and decreased gastrointestinal blood flow may occur with the application of CPAP (Jaile 1992 125). Nasal obstruction from secretions or improper application of nasal prongs has been described (Wung 1975 76). The approach may cause local drying, cracking, irritation, or trauma, resulting in nasal septum erosion, necrosis, or deformities. If the infant breathes with the mouth widely open, it may lead to fluctuations in oxygenation. There may be a subgroup of as-yet-unidentified babies that may benefit from the CPAP and another subgroup in which the CPAP increases the risk of undesirable effects. Further investigations should address these questions.

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	Despite a large effect size with a robust confidence interval for the main outcome of NICU admission from two RCTs, the certainty of evidence was downgraded to low, recognizing serious risk of bias (not blinded), serious imprecision (small sample size), and serious indirectness (only cesarean deliveries; Celebi 2016 also included newborn infants without respiratory distress with prophylactic CPAP). Neither RCT specified the criteria for NICU admissions, thereby introducing risk for assessment bias. These RCTs found a statistically significant decrease in NICU respiratory support with CPAP when compared with no CPAP with a large magnitude of effect, which may be considered a proxy for a higher level of care. The certainty of evidence is very low for the main outcome of NICU admission from one observational study (Hishikawa 2016), which is moderately limited by confounding, classification of interventions, deviations from intended interventions and missing data, and seriously limited by measurement of outcomes and overall bias. The certainly of evidence was very low for the secondary outcome of pulmonary air leak from two RCTs, and low from two observational studies due to a strong positive association between CPAP and air leak syndromes. The certainty of evidence ranged from low to very low for the secondary outcomes of length of hospital stay and death at hospital discharge.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The group places value on both harm avoidance (increase in pulmonary air leak syndromes) and the potential benefit (decrease in NICU admissions and respiratory support) of CPAP with or without supplemental oxygen. Despite available studies that were considered to have a high risk of bias, and the certainty of evidence ranging from low to very low for the considered outcomes, the reduction in NICU admission is an outcome that would be valued by most stakeholders. Similarly, pneumothorax or air leak syndromes is an important outcome and if CPAP were confirmed to be causative in the pathogenesis of disease, avoidance of this outcome would be valued by most stakeholders.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	There are discrepancies in the direction of effect in benefit versus harm among the RCTs and the observational studies included in this review. While we put slightly more value on the RCTs over the observational studies, the observational studies included a large number of subjects, which contributes to that overall uncertainty. The RCTs reviewed suggest a benefit of CPAP after cesarean section in reducing NICU admission. One study applied CPAP to all babies, regardless of signs of respiratory distress. The other study included only babies with signs of respiratory distress. It is unknown whether this effect would be similar in infants delivered vaginally. The observational studies identified a potential risk of pneumothorax. There is lack of precision in this finding, given that one study focused only on NICU admissions, and both compared populations inherently different from each other in that the decision to initiate CPAP was not based on a randomized approach.	It is important to consider that the balance of effects of using CPAP in the delivery room could be different depending on gestational age (late preterm vs term), mode of delivery (vaginal vs c-section), presence of labor before a c-section or if CPAP is used in symptomatic patients vs using it as prophylactic CPAP.

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	Although there are no published data on resource utilization, it is likely that CPAP use increases the cost of delivery room supplies. CPAP may be provided in several ways, requiring different types of resources that have variable associated costs. Use of CPAP requires resources, including equipment and team training in the labor and delivery room. It may include gas sources, especially if oxygen is supplemented. These resources may already be in place in many settings. Disposable costs will be increased if CPAP is recommended in all age groups. This may be challenging in some resource-limited settings.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There were no studies that stated or reported the resources requirement, including costs, personnel, and infrastructure.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies were found that compared the cost-effectiveness of use of CPAP vs. no CPAP for respiratory distress among term and late preterm infants.	Decreasing NICU admissions would likely decrease the overall cost of care, including length of stay, and have the potential for some savings, despite the increased cost associated with CPAP use. There was a positive association between the CPAP use and air leaks from the observational data. The external validity of this weak evidence with low certainty data from single center remains purely speculative. If this speculation proves to be true in future RCTs, there may be increased costs in a subset of newborn infants (for example, babies born vaginally or without respiratory distress) with symptoms requiring intensive care monitoring, evaluation and management, including mechanical ventilation and/or needle or tube thoracentesis. It may be worth performing cost-effectiveness analysis on putting resources into CPAP availability, which could lead to overall reduced costs.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No data available.	We speculate that equipment and adequately trained personnel to perform the intervention may not be always available, especially in low-resource settings. An intervention that does not include CPAP with or without supplemental oxygen may be more likely to increase health equity globally, including in low-resource settings. The implementation of CPAP in low-resource settings may decrease NICU admissions, thereby making care more efficient and affordable. On the other hand, if the positive association between CPAP use and pneumothoraces found in the observational studies were to be true in randomized trials, CPAP use may reduce the health equity in a subset of symptomatic newborn infants who may be admitted to special care nursery and/or require invasive treatment. Caution should be exercised since we do not know how even a large observational data set from a high-resource single NICU setting would translate to populations in high- or low-resource settings, even within countries that generally have good resources.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	CPAP is widely used internationally. It is likely to be accepted by stakeholders in settings where the resources are available.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	From a practical point of view, CPAP is feasible, especially with t-piece resuscitator availability in labor and delivery rooms. CPAP may not be feasible where equipment is limited or unavailable.	In considering the feasibility to implement the use of CPAP, training of staff is very important.

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	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

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

Recommendation

For spontaneously breathing late preterm and term newborn infants in the delivery room with respiratory distress, there is insufficient evidence to suggest for or against routine use of CPAP compared with no CPAP.

Justification

In making this recommendation, the Neonatal Life Support Task Force acknowledges the following:

- The use of CPAP in the delivery room (DR) has been recommended for babies with persistent signs of respiratory distress, labored breathing, or cyanosis after the initial steps of resuscitation. This has been mainly extrapolated from evidence in preterm patients. The benefits and risks in late preterm and term babies had not previously been systematically reviewed.
- The two RCTs included only 323 subjects, who were all delivered by cesarean section (one RCT enrolled 259 newborns used prophylactic CPAP).
- Within the observational studies we identified a positive association between the use of CPAP and the presence of air leak syndromes (one nested cohort study included only babies admitted to the NICU).
- Therefore, in making this recommendation, we integrate the values placed on avoidance of potential harm as noted by the positive association between CPAP use and air leak syndromes and potential benefit as noted by the reduction in NICU admission among infants born by cesarean section.

Subgroup considerations

For subgroup of spontaneously breathing late preterm and term infants born by cesarean section, use of CPAP may be considered compared with no CPAP to reduce the likelihood of NICU admission (weak conditional recommendation, very low-certainty evidence).

Implementation considerations

From a practical point of view, CPAP is feasible especially with t-piece resuscitator availability in labor and delivery rooms. Despite inclusion of 2 randomized controlled trials, this review shows that the certainty of evidence remains very low.

Monitoring and evaluation

Rates of NICU admissions and pulmonary air-leak syndromes should be monitored with or without CPAP use in the delivery room among late preterm and term newborns with respiratory distress.

Research priorities

Large multicenter RCTs are needed to evaluate the effects of early CPAP use in the delivery room for term and late preterm infants with respiratory distress.

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QUESTION

Should Supraglottic airways vs. face mask be used for PPV among newborn infants 34 0/7 weeks' or more gestation during resuscitation immediately after birth?

POPULATION:	PPV among newborn infants 34 0/7 weeks' or more gestation during resuscitation immediately after birth
INTERVENTION:	supraglottic airways
COMPARISON:	face mask
MAIN OUTCOMES:	Failure to improve with device; Endotracheal intubation during resuscitation; Chest compressions during resuscitation; Adrenaline administration during resuscitation; Time to heart rate > 100 bpm; Duration of positive-pressure ventilation; Admission to NICU; Air leak during initial hospital stay; Soft tissue injury; Survival to hospital discharge; Neurodevelopmental impairment at >/= 18 months;
SETTING:	Delivery room or any other place of birth.
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. During neonatal resuscitation, face masks and endotracheal tubes are the most frequently used interfaces, but both have limitations. Proficiency using a face mask rapidly declines after training. Furthermore, the efficacy of face mask ventilation may be compromised by leak around the mask or upper airway obstruction resulting in inadequate tidal volumes. Achieving proficiency in endotracheal intubation requires training and experience. Even with training, neonatal intubation is associated with low first attempt success rates and adverse events. Supraglottic airways (SGAs) have been used for many years as alternative interfaces for providing routine PPV in the operating room and for the management of difficult airways in adults, children, and neonates outside the delivery room. The SGA is a flexible airway tube attached distally to a small, soft, elliptical mask. The tube and mask are inserted orally and advanced into the hypopharynx without laryngoscopy or other instruments. Once properly inserted, the mask fits over the laryngeal inlet and the proximal end of the airway tube is connected to a PPV device. Variations on the SGA design include devices with a pre-curved airway tube and devices with or without an inflatable cuff/rim around the mask. Given the importance of effective PPV and the limitations of using either a face mask or endotracheal tube, the ILCOR NLS Task Force prioritized evaluation of SGAs for PPV. In 2015, the NLS Task Force conducted a systematic review focused on using an SGA compared with endotracheal intubation as the secondary device for PPV if initial ventilation with a face mask failed. For this review, the Task Force aimed to compare the use of an SGA with a face mask as the initial device for administering PPV during resuscitation immediately after birth and to determine if use of an SGA would decrease the probability of failing to improve with initial PPV.
CONFLICT OF INTERESTS:	One author (GMW) was co-author of one of the included observational studies. He was excluded from bias assessment of this study. One author (DT) was co-author of 3 included randomized trials and both included observational studies. He was excluded from bias assessment of these studies. Both acknowledged their potential intellectual conflicts of interest and participated in the Task Force discussion of the consensus on science and treatment recommendations

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	In this review, 14% of infants who received PPV immediately after birth failed to improve and 6% went on to receive endotracheal intubation. A more effective interface, such as a supraglottic airway, could	Establishing effective, spontaneous breathing is critical for successful transition at birth, including lung aearation and

○ Probably yes ● Yes ○ Varies ○ Don't know	improve short- and long-term outcomes for newborn infants who received PPV.	perfusion, and oxygenation. Newborn infants who have apnoea or ineffective breathing are given positive pressure ventilation (PPV) to facilitate establishment of breathing and to prevent ischaemic injury and cardiac arrest. This occurs in about 5% of all births. Endotracheal intubation is an advanced resuscitation skill not available to many first responders. Therefore, a simple and effective oropharyngeal interface is required to deliver PPV. Face masks are used most commonly, but tidal volumes are frequently inadequate due to mask leak, and delivery of gas flow to the lungs may be limited by upper airway obstruction or glottic closure, which is common in neonatal apnoea.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For every 10 infants who initially received PPV by supraglottic airway, compared with a face mask, one fewer infant failed to improve in response to PPV. For every 20-25 infants who initially received PPV by supraglottic airway, compared with a face mask, one infant avoided endotracheal intubation. The average time until the newborn's heart rate was greater than 100 bpm was 65 s shorter and the duration of PPV was nearly 20 s shorter with a supraglottic airway. Although these are clinically important benefits, the overall desirability of effects was judged to be moderate, given that few data were available for the critical outcome of survival at hospital discharge and no data were available for the critical outcome of neurodevelopmental impairment.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Although no difference in harm was identified, including air leak or soft tissue injury, when comparing the supraglottic airway and face mask, the available evidence was insufficient to make a judgement about undesirable effects. Overall, the rate of adverse events was very low, raising concern about incomplete ascertainment, particularly as most of the included studies did not report on methods for ascertaining and classifying adverse events.	Adverse effects should be assessed more closely in future studies. Some adverse effects reported by children and adults, such as sore throat, are difficult to assess in neonates.

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	There was moderate certainty evidence of benefit for the important outcome of failure to improve with the assigned device but low certainty of evidence of benefit for the important outcomes of endotracheal intubation during resuscitation, time to heart rate > 100 bpm, and duration of positive pressure ventilation. Among outcomes for which there was no statistically significant effect, the certainty of evidence was either very low (air leak, admission to NICU) or low (survival to hospital discharge, chest compressions during resuscitation, adrenaline administration during resuscitation, soft tissue injury). We assessed imprecision in relation to the optimal information size (OIS), calculated for each outcome. Imprecision was judged to be serious for all outcomes except for duration of PPV. Thus, the overall certainty of evidence of was judged to be low.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	We included key outcomes relating to clinical improvement on receipt of PPV and prevention of short and long-term morbidity. We limited outcomes to those that were previously judged to be critical or important by an expert panel, and thus are likely to influence healthcare providers to use one device in preference to another.	Outcome ratings were adopted from the following publication: Strand ML, Simon WM, Wyllie J, Wyckoff MH, Weiner G. Consensus outcome rating for international neonatal resuscitation guidelines. Arch Dis Child Fetal Neonatal Ed. 2020;105(3):328-30.

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	Infants appear to be more likely to improve with PPV and less likely to require endotracheal intubation when PPV is provided by a supraglottic airway compared with face mask. Effect sizes were moderately large. However, the overall certainty of evidence was low to moderate and few or no data were available for several critical outcomes (survival to hospital discharge, neurodevelopmental impairment, adrenaline during resuscitation) and important outcomes (air leak during initial hospital stay, time to HR > 100 bpm). Furthermore, there was concern about incomplete ascertainment of adverse effects.	The balance of desirable and undesirable effects could be different in different clinical settings.

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	The included studies did not provide any cost data.	Given that about 5% of all newborns receive PPV and that ventilation equipment needs to be widely available in birthing environments, the cost of supraglottic devices is an important consideration. Costs may vary by device and location. If supraglottic devices can be reused, then costs may be similar to face masks.

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	The included studies did not provide any cost data.	

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	The included studies did not provide any cost-effectiveness data.	

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	Adverse outcomes may be reduced, especially in settings where access to tracheal intubation is limited. The included studies were predominatly undertaken in low resource settings, where resuscitation was largely initiated by midwives or primary providers. The supraglottic airway was able to be used after a short duration of training. This review has demonstrated the feasibility and potential benefit in such settings. It should be noted that supraglottic airways were not routinely available in many of the settings in which the studies were conducted, and acquisition of the device was supported by a grant or the device was provided by the manufacturer.	Cost and availability of supraglottic airways will influence the extent to which potential benefits are realised and whether health equity is increased or decreased.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Once health providers became aware and were trained to use the supraglottic airway, it appeared to be an acceptable method for providing PPV.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The included studies have demonstrated that it is feasible to use a supraglottic airway to commence PPV after birth.	

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	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
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

Recommendation

Where resources and training permit, we suggest that a supraglottic airway may be used in place of a face mask for newborn infants 34 0/7 weeks' or more gestation receiving intermittent positive-pressure ventilation during resuscitation immediately after birth.

Justification

- Although “failure to improve with device” was variously defined by authors, and studies often allowed cross-over to the alternative device if the newborn failed to improve with the assigned device, there was a strong inverse association between the use of a supraglottic airway and risk of endotracheal intubation. This may reflect a greater likelihood of achieving effective ventilation using the supraglottic airway. Given that the interventions were not blinded, and ability to intubate in the largest trial was dependent on physician availability, there are risks of differential co-interventions and other biases. Furthermore, optimal information size was not achieved for any of the critical or important pre-specified outcomes except duration of positive-pressure ventilation. Therefore, further trials are needed before stronger recommendations can be made about use of a supraglottic airway as the initial device for positive-pressure ventilation.
- Although the training provided was incompletely documented in several studies and no study compared the effectiveness of different training programs, successful insertion of the supraglottic airway was high among midwives and primary providers despite apparently short duration training using a manikin.
- While the individual studies had limited power to establish the safety of the supraglottic airway, there were a relatively large number of newborns reported across all studies and very few adverse events reported.
- Neither the cost of supplying supraglottic airways in the delivery room nor the cost-effectiveness of providing positive-pressure ventilation with a supraglottic airway compared with a face mask has been studied. In several studies, the device was provided as part of the study. The availability of resources and economic considerations may influence the decision whether to use a supraglottic airway or face mask. Given the large number of infants worldwide who receive positive-pressure ventilation after birth, it is important to evaluate the cost-effectiveness of the supraglottic airway as the initial device for positive-pressure ventilation.

Subgroup considerations

No data were reported to perform subgroup analyses by gestational age (term vs. late preterm).

For the outcome “failure to improve”, the only outcome with sufficient data to perform a subgroup analysis based on device design (cuffed device vs. uncuffed (i-Gel™) device), there was no evidence of interaction ($p = 0.29$, $I2 = 10\%$).

Implementation considerations

Within the context of research trials, use of an SGA in the delivery room appears to be feasible even in resource limited settings. Despite the relatively large number of newborns enrolled in published trials, the certainty of evidence remains low. Implementation will remain dependent upon training requirements and resource utilization.

Monitoring and evaluation

As the recommendation is weak and is based on low certainty evidence, continued monitoring of the safety and efficacy of SGAs for initial PPV immediately after birth is recommended.

Research priorities

The training requirements to achieve and maintain competency with supraglottic airway insertion, including different types of device.

The effectiveness and safety of supraglottic airways as the initial device for positive-pressure ventilation in high resource settings.

The effectiveness and safety of supraglottic airways compared with face masks during chest compressions.

The effectiveness and safety of supraglottic airways compared with face masks for newborns with orofacial anomalies.

The effectiveness and safety of different supraglottic airway designs.

The effectiveness and safety of supraglottic airways for positive-pressure ventilation among newborns less than 34 weeks' gestation.

The resource utilization and cost-effectiveness of using supraglottic airways compared with face masks as the initial device for positive-pressure ventilation in different settings.

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

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	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	**Face-mask leak**: The direction in two studies towards benefit in reducing mask leak is consistent with training simulation studies, whereby using

○ Large ○ Varies ○ Don't know	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; I^2 = 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; I^2 = 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; I^2 = 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; I^2 = 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; I^2 = 0%). For the important outcome of ***bronchopulmonary dysplasia/chronic lung disease (any),*** evidence of	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}.

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 low[a,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]	⨁⨁◯◯ Low[a,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]	⨁⨁◯◯ Low[a,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]	⨁⨁◯◯ Low[a,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]	⨁⨁◯◯ Low[a,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]	⨁⨁◯◯ Low[a,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]	⨁⨁◯◯ Low[a,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}

a. 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
b. Moderate - I^2 = 61%
c. Wide confidence interval
d. Wide confidence interval / Small sample size
e. Wide confidence interval, small sample size, single study, remote outcome

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; I^2 = 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						
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

	JUDGEMENT						
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

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).

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.

Subgroup considerations

No subgroup analyses were pre-planned or performed.

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).

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).

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?

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QUESTION

Should a clinical decision rule be used to diagnose chance of surviving a cardiac arrest among hospitalized patients at risk of cardiac arrest?	
POPULATION:	Hospitalized adults and children experiencing an in-hospital cardiac arrest.
INTERVENTION:	Any pre-arrest clinical prediction rule.
PURPOSE OF THE TEST:	Predict survival or survival with favorable neurological outcome following in-hospital cardiac arrest.
ROLE OF THE TEST:	Facilitate do-not-attempt cardiopulmonary resuscitation (DNACPR) discussions with patients/ families and inform decisions on which patients who should not be resuscitated.
LINKED TREATMENTS:	Cardiopulmonary resuscitation
ANTICIPATED OUTCOMES:	Prediction of survival to hospital discharge and survival with favorable neurological outcome.
SETTING:	In-hospital cardiac arrest.
PERSPECTIVE:	A reliable test can predict survival outcomes and could be implemented in clinical practice to facilitate DNACPR discussions with patients and decide which patients that should not be attempted resuscitated.
BACKGROUND:	CPR is started in only 6-12% of all hospital deaths in some settings, this is mainly to a pre-existing DNACPR at the time of the cardiac arrest. In cases where CPR is initiated for in-hospital cardiac arrest, only 15-30 % will survive to hospital discharge and some of these patients will survive in a state of health they would not have desired. Thus, the ability to predict which patients that are likely, or unlikely, to achieve a meaningful survival outcome from CPR is important to patients, their families, and caregivers.
SUBGROUPS:	Adults and children.
CONFLICT OF INTERESTS:	Theresa Djärv has published studies on pre-arrest prediction scores and was excluded from bias assessment.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Only 15-30 % of in-hospital cardiac arrest patients will survive to hospital discharge and some of these patients will survive with unfavorable neurological outcome with a cerebral performance category of 3 or 4. Thus, the ability to predict which patients that are likely, or unlikely, to benefit from CPR is important to patients and caregivers.	• Hospitalized patients are normally at risk of physiological deterioration and cardiac arrest. For these patients, a key decision is whether CPR should be attempted if they experience a cardiac arrest. • Decisions regarding resuscitation have important implications. If CPR is attempted in a patient in whom it would be futile or does not align with their values and preferences, the individual will be subjected to a medical intervention that would not be in their best interests. If resuscitation is not attempted where it might be in the patient's best interests, the patient will inevitably die. • Identifying patients in whom CPR is appropriate is clinically challenging and requires careful discussion with the patient or their family to elicit their values and preferences. A key concern is that such discussions and linked decisions may be unduly influenced by the healthcare provider's and patient's subjective assessment of the likely success of CPR. Prediction scores provide an attractive solution to inform these challenging discussions. However, current scores are rarely used in practice and there is a need to synthesize evidence on their test performance.

Test accuracy

How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ● Varies	We identified 23 studies investigating 13 different pre-arrest prediction rules of survival following in-hospital cardiac arrest. • For the outcome of predicting survival to hospital discharge, we identified very low certainty evidence from seven historical cohort studies {Ebell 1997 171, O'Keeffe 1994 21, Bowker 1999 89, Ohlsson 2014 294, Limpawattana 2018 1231, George 1989 28, Cohn 1993 347} investigating the pre-arrest morbidity (PAM) score (downgraded for risk of bias, indirectness, imprecision, and inconsistency) and four of these studies investigated the	All studies predicted survival outcomes for cardiac arrest patients only. All studies were based on historical cohorts and there were no prospective validation or prospective

○ Don't know	prognosis after resuscitation (PAR) score (downgraded for risk of bias, indirectness, imprecision, and inconsistency), Table 2. The studies identified various cut-off values for the score to predict no chance of survival to hospital discharge. Due to clinical heterogeneity in study cohorts, no meta-analysis was conducted. The outcomes of the PAM score and PAR score are presented in Table 1 and Table 2 respectively. Limpawattana et al., {Limpawattana 2018 1231} did not report data to calculate sensitivity, specificity, NPV, and PPV with 95% confidence intervals (CI). However, they reported an area under the curve (AUC) of 0.65 (95% CI: 0.56-0.74) for the PAM score and self-calculated outcome measures without confidence intervals for the prediction of death (as opposed to survival) with a PPV of 92.2, a specificity of 87.8, a sensitivity of 39.2, and a NPV of 28.1. For the PAR score, they reported an AUC of PAR 0.6 (95% CI: 0.52-0.70). **Table 1:** Predictive values of historical cohort studies using the pre-arrest morbidity (PAM) score to predict survival to hospital discharge (presented with 95% CI). NPV negative predictive value; PPV positive predictive value. Table 2: Predictive values of historical cohort studies using the prognosis after resuscitation (PAR) score to predict survival to hospital discharge (presented with 95% CI) • For the outcome of predicting survival to hospital discharge, we identified very low certainty evidence from two historical cohort studies {Bowker 1999 89, Limpawattana 2018 1231} investigating the modified pre-arrest morbidity (MPI) score (downgraded for risk of bias, indirectness, imprecision, and inconcistency). Bowker et al. showed a sensitivity of 100 (95% CI: 87.7-100), a specificity 22.5 (95% CI: 17.3-28.3), a NPV of 100 (95% CI: 93.3-100), and a PPV of 13.3 (95% CI: 9.0-18.6) for a MPI score >6. Limpawattana et al. did not report data to calculate sensitivity, specificity, NPV, and PPV with 95% CIs. However, they reported self-calculated outcome measures without confidence intervals for the prediction of death (as opposed to survival) with a PPV of 92.2, a specificity of 87.8, a sensitivity of 39.2, and a NPV of 28.1 for a MPI score >5. • For the outcome of predicting survival to hospital discharge, we identified very low certainty evidence from one historical cohort study investigating the modified early warning score (MEWS) {Stark 2015 916}, two historical cohort studies investigating the National Early Warning Score (NEWS) {Haegdorens 2020 4594, Roberts 2017 1601}, one historical cohort study investigating the Clinical Frailty Scale {Ibitoye 2021 147}, and one historical cohort study investigating the APACHE III score {Ebell 1997 171}. The level of evidence for all scores was downgraded for downgraded for risk of	implementation of the scores. Use of historical cohorts may introduce the risk of creating 'self-fulfilling prophesies' as resuscitative efforts may have been terminated early on some patients due to clinician bias.

Study	Cut-off	Sensitivity	Specificity	NPV	PPV
Ebell 1997	PAM >8	100 (90.0-100)	1.8 (0.9-3.1)	100 (71.5-100)	5.4 (3.8-7.5)
O'Keeffe 1994	PAM >8	100 (86.3-100)	2.0 (0.6-4.5)	100 (47.8-100)	9.1 (6.0-13.2)
Bowker 1999	PAM >6	100 (92.5-100)	12.9 (8.7-18.1)	100 (87.7-100)	19.9 (15.0-25.6)
Ohlsson 2014	PAM >7	96.6 (88.1-99.6)	10.9 (7.2-15.7)	92.6 (75.7-99.1)	21.5 (16.7-27.0)
George 1989	PAM >8	100 (89.7-100)	22.6 (15.1-31.8)	100 (85.8-100)	29.3 (21.2-38.5)
Cohn 1993	PAM >8	100 (92.0-100)	25.0 (12.7-41.2)	100 (69.2-100)	59.5 (47.4-70.4)

Study	Cut-off	Sensitivity	Specificity	NPV	PPV
Ebell 1997	PAR >8	97.6 (94.8-99.1)	30.6 (26.2-35.4)	95.4 (90.3-98.3)	46.1 (41.8-50.5)
O'Keeffe 1994	PAR >5	100 (86.3-100)	22.8 (17.8-28.4)	100 (93.9-100)	11.1 (7.3-16.0)
Bowker 1999	PAR >7	100 (87.7-100)	28.8 (23.1-35.0)	100 (94.7-100)	14.3 (9.7-20.0)
Ohlsson 2014	PAR >10	98.3 (90.8-100)	10.5 (6.8-15.2)	96.0 (79.6-99.9)	21.8 (16.9-27.2)

bias, indirectness, imprecision, and inconsistency. Ibitoye et al. showed a sensitivity of 100 (95% CI: 75.3-100), a specificity of 51.9 (95% CI: 40.3-63.5), a NPV of 100 (95% CI: 91.2-100), and a PPV of 26.0 (95% CI: 14.6-40.3) for a Clinical Frailty Scale >4. Haegdorens et al. showed a sensitivity of 57.9 (95% CI: 33.5-79.7), a specificity of 71.4 (95% CI: 41.9-91.6), a NPV of 55.6 (95% CI: 30.8-78.5), and a PPV of 73.3 (95% CI: 44.9-92.2) for a NEWS ≥5 and Roberts et al. showed a sensitivity of 89.3 (95%CI: 80.1-95.3), a specificity of 31.7 (95% CI: 25.6-38.2), a NPV of 89.7 (95% CI: 80.8-95.5), and a PPV of 30.7 (95%CI: 24.7-37.3) for a NEWS ≥7. Stark et al. did not report data to calculate sensitivity, specificity, NPV, and PPV with 95% CIs. However, they reported self-calculated outcome measures without confidence intervals for the prediction of death (as opposed to survival) with a PPV of 76, a specificity of 80, a sensitivity of 47, and a NPV of 53 for a Modified Early Warning Score of 7. Ebell et al. did not report data to calculate sensitivity, specificity, NPV, and PPV with 95% CIs. However, they reported an area under the curve of 0.59 for the APACHE III score to predict survival to hospital discharge.

- For the outcome of predicting survival to hospital discharge with favorable neurological outcome, we identified low certainty evidence from seven historical cohort studies {Ebell 2013 1872, Piscator 2018 63, Rubins 2019 2530, Cho 2020 36, Thai 2019 140, Ohlsson 2016 294, Hong 2021 10631} investigating the Good Outcome Following Attempted Resuscitation (GO-FAR) score to predict survival with a cerebral performance category (CPC) of 1 (downgraded for risk of bias, indirectness, and imprecision). The outcomes are presented in Table 3. Hong et al. did not report data on survival with CPC of 1 but the authors provided data showing a sensitivity of 94.1 (95% CI: 87.6-97.8), a specificity of 11.7 (95% CI: 8.5-15.6), a NPV of 87.0 (95% CI: 73.7-95.1), and a PPV of 24.1 (95% CI: 20.0-28.6) for the GO-FAR score to predict survival to hospital discharge.

Study	Cut-off	Sensitivity	Specificity	NPV	PPV
Ebell 2013	≥24	99.3 (99.0-99.5)	10.4 (10.1-10.7)	99.2 (98.9-99.5)	11.4 (11.1-11.7)
Piscator 2018	≥24	99.3 (96.1-100.)	9.7 (6.9-13.1)	97.4 (86.2-99.4)	28.9 (24.9-33.1)
Rubins 2019	≥24	95.7 (88.0-99.1)	17..1 (13.2-21.6)	95.0 (86.1-99.0)	19.5 (15.5-24.1)
Cho 2020	≥24	99.4 (96.6-100)	11.4 (9.4-13.8)	99.0 (94.4-100)	17.6 (15.2-20.3)
Thai 2019	≥24	99.2 (99.0-99.4)	8.2 (7.9-8.4)	98.4 (97.9-98.7)	16.1 (15.8-16.4)
Ohlsson 2016	≥24	97.8 (88.2-99.9)	10.3 (6.8-14.9)	96.2 (80.4-99.9)	16.9 (12.5-22.0)

Table 3: Predictive values of historical cohort studies using the good outcome following attempted resuscitation (GO-FAR) score to predict survival to hospital discharge with a cerebral performance category (CPC) of 1 (presented with 95% CIs). NPV negative predictive value; PPV positive predictive value.

- For the outcome of predicting survival to hospital discharge with favorable neurological outcome, we identified low certainty evidence from one historical cohort study {George 2020 162} investigating the Good Outcome Following Attempted Resuscitation 2 (GO-FAR 2) score, one historical cohort study {Piscator 2019 92} investigating the Prediction of Outcome for In-hospital Cardiac Arrest (PIHCA) score, and two classification and regression tree models (CART 1, CART 2) {Ebell 2013 2688 , Guilbault 2017 333}. The CART models {Ebell 2013 2688, Guilbault 2017 333} aimed to predict survival with a CPC=1 whereas the GO-FAR 2 score and the PIHCA score investigated survival with CPC ≤2. The outcomes are summarized in Table 4. All scores were downgraded for risk of bias and imprecision.

Study	Model	Sensitivity	Specificity	NPV	PPV
Ebell 2013	CART 1	96.0 (94.9-96.9)	24.1 (23.3-24.8)	97.8 (97.2-98.3)	14.6 (13.9-15.2)
Guilbault 2017	CART 1	95.6 (84.9-99.5)	28.5 (22.9-34.6)	97.2 (90.2-99.7)	19.9 (14.8-25.9)
Ebell 2013	CART 2	94.1 (92.9-95.2)	29.5 (28.8-30.3)	97.5 (97.0-98.0)	14.7 (14.1-15.4)
Guilbault 2017	CART 2	95.6 (84.9-99.5)	36.4 (30.3-42.8)	97.8 (92.2-99.7)	21.8 (16.3-28.3)
George 2020	GO-FAR 2	98.9 (98.6-99.1)	6.7 (6.4-6.9)	95.7 (94.9-96.4)	21.8 (21.4-22.2)
Piscator 2019	PIHCA	99.4 (96.8-100)	8.4 (6.0-11.3)	97.4 (86.5-99.9)	29.4 (25.7-33.2)

	Table 4: Predictive values of historical cohort studies using different scores than the GO-FAR score to predict survival to hospital discharge with favorable neurological outcome (presented with 95% CIs).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	We identified no evidence on the desirable effects of using a pre-arrest clinical decision rule.	There are many potentially beneficial effects of a reliable pre-arrest clinical decision rule: A) The tool can be used to aid DNACPR discussions with patients and next of kin, B) Use of the tool may result in fewer patients receiving CPR when it is futile or does not align with their values and preferences, C) A reliable tool may also result in fewer patients that do not receive CPR when it is an appropriate clinical intervention (i.e. realistic chance of patient achieving outcome that is valued by them) D) Patients that should be resuscitated will be resuscitated

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	We identified no evidence on the undesirable effects of using a pre-arrest clinical decision rule. However, implementation of a clinical decision rule that does not have a perfect negative predictive value could result in patients not being resuscitated following cardiac arrest where they may have achieved an outcome that is valued by them.	

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence was very low for all the identified clinical decision rules. We found no prospective studies applying a clinical decision rule in clinical practice. There were serious concerns regarding risk of bias and imprecision for all of the scores. Moreover, there were applicability concerns regarding most of the scores and many studies were based on selected patient cohorts, single center studies, and/ or cohorts from the 1980'ies and 1990'ies that cannot be directly compared to contemporary resuscitation practices. Thus, there were concerns regarding indirectness for several of the studies.	The task force valued narrow confidence intervals not crossing 99% for the negative predictive value as it is important not to miss potential survivors when applying a clinical decision rule.

Certainty of the evidence of test's effects

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	As there were no prospective studies implementing any of the pre-arrest clinical decision rules, there is no direct evidence regarding the direct benefits, adverse effects or burdens of the tests.	

Certainty of the evidence of management's effects

What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies on the management's effects.	

Certainty of the evidence of test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies on the link between the test results and the management decisions.	It is likely that a reliable test implemented in clinical practice would be used to facilitate DNACPR discussions with the patients.

Certainty of effects

What is the overall certainty of the evidence of effects of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○Low ○ Moderate ○ High ●No included studies	No prospective studies and no randomized studies were identified. Thus, the effect of clinical implementation of a pre-arrest decision rule is unknown.	The evidence suggests that none of the decision rules can reliably predict no chance of surviving or surviving with favorable neurological outcome. Thus, implementation may result in patients not being resuscitated although they could have survived.

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	No included research examining patient values or provider values. However, the value placed on different outcomes (e.g. survival, survival with good neurological outcome, health related quality of life) will likely vary across individuals, communities, and cultures.	

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 clinical decision rules misclassified several patients as non-survivors/ not surviving with favorable neurological outcome even though they did survive. Thus, implementation could lead to an unacceptable number of patients not being offered resuscitation even though they could have survived.	The EIT Task Force values a very high negative predictive value over the positive predictive value as the most important thing would be not to miss potential survivors.

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	No studies evaluated the cost associated with implementing a pre-arrest clinical decision rule.	Correct use of the clinical decision rule may require training of all healthcare providers of unknown duration and frequency. It is unknown how implementation of a pre-arrest clinical decision rule would affect the number of DNACPR discussions and number of patients being resuscitated/ attempted resuscitated.

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 studies evaluated cost and/or resource requirements. There may be concerns that some of the scores may be difficult to calculate for the clinicians without technological aid, although the increasing use of electronic health records may facilitate integration of a score within that system	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No studies evaluated cost and/or resource requirements. There may be concerns that some of the scores may be difficult to calculate for the clinicians without technological aid and that training would be required. It is unknown whether implementation would affect rates of resuscitation attempts.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No included studies examined health equity. However, implementation of a successful pre-arrest prediction rule may result in more patients receiving the same chance of resuscitation without e.g. racial bias.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No studies investigated acceptability.	Implementing a clinical decision rule with a high likelihood of misidentifying patients as non-survivors will likely not be accepted by key stake holders, such as clinicians and patients/ relatives.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No studies investigated implementation or feasibility of pre-arrest clinical decision rules. There may be concerns that some of the scores may be difficult to calculate for the clinicians without technological aid which may be of particular concern in low-resource settings.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		**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 THE EVIDENCE OF TEST ACCURACY	**Very low**	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	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**

	JUDGEMENT						
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
	○	○	○	○

Deleted: •

CONCLUSIONS

Recommendation

We recommend against using any currently available pre-arrest prediction rule as a sole reason to not resuscitate an adult with in-hospital cardiac arrest (strong recommendation, very low certainty evidence).

We are unable to make a recommendation about using pre-arrest prediction rules to facilitate do-not-attempt CPR discussions with adult patients, pediatric patients, or their substitute decision maker as there are no studies investigating the clinical implementation of such a score for this indication.

We are unable to provide any recommendation for pediatric patients as no studies on children were identified.

Justification

In making this recommendation, the task force valued a perfect negative predictive value (i.e. no chance of classifying a survivor as a non-survivor). None of the existing pre-arrest prediction rules were able to reliably predict no chance of survival to hospital discharge or survival with favorable functional outcome. The task force also noted that most studies on the PAM, PAR, APACHE III and MPI scores were based on cohorts before 2000, when survival rates were lower. The PAM score and the PAR scores did not perform consistently across cohorts.
Some studies were based on selected patient cohorts or patients from a single center, raising concerns about generalizability. All studies were based on historical cohorts, and concern for bias and unaccounted for confounding was high. As there were no prospective studies identified on clinical implementation of a pre-arrest prediction model to facilitate do-not-attempt cardiopulmonary resuscitation (DNACPR) discussions, it is unknown whether the clinical implementation of such a score would influence the rate of DNACPR discussions, the rate of DNACPR orders, survival outcomes, or patient perspectives.

- All scores predicting survival with favorable neurological outcome included variables such as hypotension, respiratory insufficiency, or sepsis before the arrest that may change during the hospital admission. Thus, there are concerns regarding applicability of these models.
- The GO-FAR score identifies the chance of survival with good neurological outcome (i.e. CPC of 1) although patients and relatives may value survival with a CPC > 1.

- Scores that can predict a very low chance of survival with favorable functional outcome may be used to facilitate DNACPR discussions with patients, although the score may not be able to predict no chance of survival or survival with favorable neurological outcome.

Subgroup considerations

We found no evidence concerning the pediatric population.

Implementation considerations

We found no clinical evaluation of any implementation strategies of such pre-arrest clinical decision rule.

Monitoring and evaluation

It is important to measure compliance and survival rates and continuously reassess the criteria if considering implementation of any pre-arrest clinical decision rule.

Research priorities

We identified several knowledge gaps in the published literature.

- There are no clinical decision tools to predict return of spontaneous circulation and several scores did not predict survival to hospital discharge.
- We found no studies assessing long term outcomes beyond hospital discharge or outcomes assessing quality of life.
- No studies were found on in-hospital pre-arrest clinical prediction of survival for pediatric patients.
- No studies were found on in-hospital pre-arrest clinical prediction of survival in low-resource settings.
- No studies were found on in-hospital pre-arrest clinical prediction of survival on patient values of survival outcomes, either among at-risk patients or cardiac arrest survivors
- We did not identify any score predicting survival with favorable neurological outcome that did not include physiological deterioration before cardiac arrest.
- There is a lack of prospective clinical validation studies and randomized trials investigating the use of a in hospital pre-arrest clinical prediction rule to be used for do-not-attempt cardiopulmonary resuscitation discussions and/ or making DNACPR orders.
- How the use of clinical decision tools affects resuscitation practices, cost-benefit, or survival outcomes.
- It is unknown how the use of a clinical decision tool affects resuscitation practices, cost-benefit, or how it affects survival outcomes.

QUESTION

Is targeting basic life support (BLS) training to the likely rescuers of those at high-risk of out-of-hospital arrest (OHCA) effective?	
POPULATION:	For Adults and children at high-risk of OHCA
INTERVENTION:	Focused BLS training of likely rescuers (e.g. family or care-givers)
COMPARISON:	no such BLS training targeting
MAIN OUTCOMES:	Patient outcomes: Good neurological outcome at hospital discharge/30-days; Survival at hospital discharge/30-days; Return of spontaneous circulation (ROSC); Rates of bystander CPR; Bystander CPR quality during an OHCA (any available CPR metrics); Rates of automated external defibrillator (AED) use. Educational outcomes at the end of training and within 12 months: CPR quality (chest compression depth and rate; chest compression fraction; full chest recoil, ventilation rate, overall CPR competency) and AED competency; CPR and AED knowledge; Confidence and willingness to perform CPR; and secondary training.
SETTING:	Lay person BLS training
BACKGROUND:	Significant numbers of out of hospital cardiac arrest (OHCA) occur in the home. Targeting basic life support (BLS) training to bystanders who are most likely to witness an OHCA may be a promising intervention to improve patient outcomes.
CONFLICT OF INTERESTS:	The following Task Force members declared an intellectual conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committees: Janet Bray and Judith Finn.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Out-of-hospital cardiac arrest (OHCA) is a significant cause of death. Bystander CPR rates are low. ILCOR last reviewed the evidence for this question in 2015 and there have been 11 studies conducted since that time.	Institutions treating CA-patients have the opportunity to reach these group and can teach them CPR with low effort

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	There are now 43 studies reporting relevant outcomes for this PICO –including 12 new studies since the 2015 ILCOR review. In brief, there is insufficient evidence on subsequent use of BLS skills and patient outcomes following the training of family members and significant others at high-risk of cardiac arrest. Existing evidence suggest likely rescuers are unlikely to seek training on their own, but are willing to receive training. Most studies examining educational outcomes following training demonstrate improvements to skills and knowledge. Those trained were also likely to share training with others. ***For the critical patient outcomes of survival with favorable neurologic outcome at discharge/30 days, survival at discharge/30 days, return of spontaneous circulation (ROSC), rates of bystander CPR, bystander CPR certainty during an OHCA and rates of automated external defibrillator,*** the certainty of evidence from 12 studies (3 RCTS) for these outcomes remains very low to low with too few OHCA events in individual studies during follow-up to be confident in the direction of effect. ***For the important outcome of BLS skills at completion of training,*** the low to moderate certainty of evidence from 23 studies (3 RCTS) for these outcomes supporting the previous COSTR findings that providing BLS training improve skills and knowledge in these groups. ***For the important outcomes of BLS skills and knowledge retention to one-year,*** we identified six non-RCTs of very low certainty evidence which were subject to high risk of bias due to high loss-to-follow-up. Overall, there was some degradation in some skills compared to post-training, but an improvement in skills and knowledge compared to most baseline measurements ***For the important outcome of willingness to provide CPR,*** all 10 studies (2 RCTs, moderate certainly of evidence) showed an increase in willingness to provide CPR following training F***or the new important outcome of confidence to perform CPR,*** we identified very low certainty of evidence from five non-RCTs studies reporting an increased confidence to perform CPR following training. ***For the important outcome of secondary training*** we identified a low certainty of evidence from 9 studies. All studies with reported sharing of training materials with others.	These groups are willing to be trained and are unlikely to have any or recent BLS training. They are also unlikely to seek training on their own.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Some studies showed CPR skills were not at guideline standards 6-months after training, particularly with training without a manikin (e.g. Blewer 2016 740; Blewer 2020 28).	No increase in anxiety after training (Macken 2017 572). Degradation in BLS skills and knowledge is seen in all trained groups without further training.

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		Most studies were downgraded due to loss to follow-up (>95%) for both short and long term outcomes. Most non-RCTs did not adjust for differences in characteristics and confounders (e.g. prior CPR training) at baseline between groups. Studies of video only education (compared to CPR kits with a manikin, or instructor-led training) showed inferior educational outcomes. The overall Judgement was upgraded for consistency.

Outcome	Certainty of evidence	
Patient outcomes	Very low	⊕
Educational outcomes immediate to one-month	Low to Moderate	⊕⊕⊕
Educational outcomes to one-year	Very low	⊕
Willingness to provide CPR	Moderate	⊕⊕⊕
Confidence to perform CPR	Low	⊕⊕
Secondary training	Low	⊕⊕

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is survival, and neurologically intact survival. COSCA has confirmed importance of these outcomes. COSCA: Haywood K, Whitehead L, Nadkarni VM, Achana F, Beesems S, Bottiger BW, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation. 2018;127:147-63. Educational outcomes were decided and prioritised by the EIT Task Force.	

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	Balance of effect favours BLS training in these groups. Higher value on: • the improvements in BLS skills when compared to baseline data or no training groups; • the potential benefits of patients receiving early CPR/BLS by a family-member or caregiver in the case of OHCA; • the willingness of this group to be trained and to use skills if required. • The multiplier effect of trainees training others.	BLS training in high-risk groups is already adopted.

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	Varies. There are a number of resources required to set-up CPR training and refresh BLS skills (e.g. personnel, equipment). These costs are potentially reduced with self-instruction (e.g. CPR-kits self-training).	In one study recommendation by a healthcare professional to attend CPR training was an important contributing factor in prompting persons to participate. Encouragement, rational and providing direction or resources to refresh skills during initial training may support BLS skill and knowledge refreshment.

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	Low quality evidence.	Self-training kits are now reasonably priced.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No evidence was found that examined the cost-effectiveness of this intervention in this group.	

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	Varies. Could be incorporated into existing programs and sites (e.g. cardiac rehabilitation, hospital discharge education, hospital out-patients) to reduce inequality. There are known BLS training inequities –training high-risk groups may help to reduce these inequities.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	High proportions of eligible participants took up training. Patients, family members and/or staff have positive feedback about the training.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Varies. Likely to require a local champion until integrated into practice.	Referral to BLS training alone is unlikely to increase training in these groups.

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	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

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
○	○	○	○	•

Recommendation	We recommend BLS training for likely rescuers of populations at high-risk of out-of-hospital cardiac arrest (strong recommendation, low-to-moderate certainty of evidence). We recommend health care professionals encourage and direct likely rescuers of populations at high-risk of cardiac arrest to attend BLS training (ungraded, good practice statement).
Justification	In making this recommendation, the EIT Task Force placed higher value on: • the improvements or competency in BLS skills and confidence when compared to baseline data or guideline standards; • the improvements in confidence; • the multiplier effect of trained individuals training others. • the high proportion of OHCA that occur in the home and the potential benefits of patients receiving CPR by a family-member or caregiver in the case of OHCA; • the willingness of this group to be trained and to use skills if required; • CPR training doesn't increase anxiety in trainees; and • that these groups are unlikely to see training on their own. Given these facts we considered it important to recommend that health care professionals encourage and direct these groups to attend BLS training even though they may not take up training (Greenberg 2011, 166). We placed lesser value on the associated costs, and the potential that performance of some skills may not be to guideline standard and may not be retained without refresher CPR training.
Subgroup considerations	• The majority of the research is in cardiac patients or high-risk infants.
Implementation considerations	• It is important that opportunity to practice BLS skills is provided with training.
Monitoring and evaluation	• N/a
Research possibilities	• Long term follow-up through cardiac arrest registries may resolve the loss to follow-up.

Evidence to decision table for EIT 4000 Resuscitation courses and patient outcome

Updated ALS EtD

QUESTION

Should ALS vs. no ALS be used for health problem or population?	
POPULATION:	Adult in-hospital patients who have a cardiac arrest
INTERVENTION:	Prior participation of one or more members of the resuscitation team in an accredited advanced cardiac life support course (e.g. AHA ACLS, RC(UK)/ERC ALS)
COMPARISON:	No such participation
MAIN OUTCOMES:	ROSC; Survival to Discharge or 30-day survival; 1 year survival;
SETTING:	**IN-HOSPITAL**
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	Janet Bray is a member of the Australian Resuscitation Council – who provide ALS training. Andy Lockey is a Trustee of the Resuscitation Council UK – who provide ALS training.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Attendance of participants on an advanced cardiac life support course comes at a cost - both financial and time - to stakeholders including participants themselves and their institutions. It is therefore important to show whether this participation has any meaningful impact upon	Likely to be a lack of recent data as advanced cardiac life support training is generally widespread.

	patient outcomes.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The original systematic review, with a search date of 6 March 2018, identified 8 studies (Lowenstein 1986 512, Sanders 1994 56, Makker 1995 116, Camp 1997 529, Pottle 2000 45, Dane 2000 83, Moretti 2007 458, Sodhi 2011 209). One additional study was identified in an updated search run in May and October 2021 (Pareek et al., 2018), For the critical outcome of "return of spontaneous circulation" we have identified very low quality evidence (downgraded for risk of bias, inconsistency, indirectness and imprecision) from seven observational studies (Lowenstein, Sabyan, Lassen, & Kern, 1986; Makker, Gray-	No studies were found that examined the impact of advanced cardiac life support training on good neurological outcomes. All except the latest study (Pareek et al., 2018) were conducted prior to the current available evidence for post-resuscitation care (e.g. targetted temperature management). More contemporary studies found consistently better outcomes for the intervention (Pareek et al., 2018; Sodhi et al., 2011). One study reported a statistically significant improvement in time to ROSC following the introduction of advanced cardiac life support training (mean 11.5 minutes vs 30.0 minutes). This study reported no change in duration of attempted resuscitation in patients who did not achieve ROSC (Moretti 2007 458) One study reported the probablity of achieving ROSC was associated with number of resuscitating team members who were trained in ACLS (Moretti 2007 458). One study reported a decrease treatment errors, such as incorrect rhythm assessment, in IHCA following the implementation of ALS training (Makker 1995, 116). Studies were not able to identify which components of training contributed to outcomes. Advanced cardiac life support training provides the opportunity to update health care professionals on changes in resuscitation practice as new evidence emerges and is integrated into resuscitation guidelines and algorhythms.

	Siracusa, & Evers, 1995; Moretti et al., 2007; Pareek et al., 2018; Pottle & Brant, 2000; Sanders et al., 1994; Sodhi, Singla, & Shrivastava, 2011) enrolling 2093 patients showing benefit for advanced cardiac life support training (OR 1.66 95% CI 1.24 – 2.21). For the critical outcome of "survival to hospital discharge" or "survival to 30 days" we have identified very low quality evidence (downgraded for risk of bias, inconsistency, indirectness and imprecision) from eight (Camp, Parish, & Andrews, 1997; Dane, Russell-Lindgren, Parish, Durham, & Brown Jr, 2000; Lowenstein et al., 1986; Moretti et al., 2007; Pareek et al., 2018; Pottle & Brant, 2000; Sanders et al., 1994; Sodhi et al., 2011) observational studies (Lowenstein 1986 512,	

	Sanders 1994 56, Camp 1997 529, Pottle 2000 45, Dane 2000 83, Moretti 2007 458, Sodhi 2011 209) enrolling 1667 patients showing possible benefit for advanced cardiac life support training (OR 2.48 95% CI 1.21 – 5.09). For the critical outcome of "survival to 1 year" we have identified very low quality evidence (downgraded for risk of bias, inconsistency, and imprecision) from two observational studies (Pottle 2000 45, Moretti 2007 458) enrolling 455 patients showing no benefit (OR 3.61 95% CI 0.11 – 119.42). One study had very high loss to followup (25%) in the ALS training period (Pottle 2000 46).	

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Some studies reported increased rates of attempted resuscitation following the introduction of advanced cardiac life support training, but do not report on the appropriateness of this change. [Lowenstein 1986 512, Camp 1997 529]	
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	ROSC (7 studies - (Lowenstein et al., 1986; Makker et al., 1995; Moretti et al., 2007; Pareek et al., 2018; Pottle & Brant, 2000; Sanders et al., 1994; Sodhi et al., 2011)) & Survival to discharge and 30 days (8 studies - (Camp et al., 1997; Dane et al., 2000; Lowenstein et al., 1986; Moretti et al., 2007; Pareek et al., 2018; Pottle & Brant, 2000; Sanders et al., 1994; Sodhi et al., 2011)) -	Advanced cardiac life support courses have evolved over time.

	downgraded for risk of bias, inconsistency, indirectness and imprecision 1 year survival (2 studies - Pottle 2000 45, Moretti 2007 458) - downgraded for risk of bias, inconsistency and imprecision The certainty of evidence is very low. Existing evidence is old and of very poor quality – mostly retrospective, single-centre studies, using historical controls, with poor reporting on patient characteristics. Only one study adjusted outcomes for possible confounding – but only adjusted for rhythm (Dane 2000 83). Some studies were conducted with small sample sizes, and are likely to be underpowered. The most recent studies reporting data post-2000 which is when international guidelines were first introduced, ((Pareek et al., 2018; Sodhi et al., 2011))	

	showed a significant benefit to the addition of advanced cardiac life support training to staff already trained in basic life support. One study is subject to significant confounding, as the authors only reported unadjusted outcomes and provided very limited data on patient and arrest characteristics between the two periods (Sodhi et al., 2011). The other study was limited to nursing staff in one institution in India (Pareek et al., 2018). Most effect estimates favoured advanced cardiac life support training.	
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	Patients value survival with good neurological outcome (Haywood 2018 e783). It is expected that health care professionals	No studies examined the critical outcome of good neurological function.

	are trained to treat medical emergencies. Standardised advanced cardiac life support training is likely to improve the care provided during cardiac arrest, and thus improve outcomes for patients.	
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	Whilst the positive effects are presented with very low evidence, they likely offset the potential negative effect of inappropriate attempted resuscitations.	
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 has been no formal cost effectiveness analysis in the studies identified.	The costs of running advanced life support courses include: 1) costs to the overseeing Resuscitation Council (e.g. manual production, e-learning platforms) 2) costs to the course centre (e.g. faculty costs, facility costs, equipment purchase and maintenance) 3) costs to the employers (e.g. course fees, covering study and professional leave time for candidates and faculty) 4) costs to the employees (e.g. course fees in some cases) These costs can be mitigated by alternative methods of course delivery, including hybrid courses consisting of e-learning modules.

		There may also be costs incurred in low resource settings in terms of other educational interventions that may suffer if advanced cardiac life support training were to be prioritised.
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	Costs are likely to vary between different health care settings.	
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	The potential for lives saved by health care professional's participation in these courses outweighs the costs of candidates attending these courses.	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	The associated resources and costs may prohibit advanced cardiac life	

● Varies ○ Don't know	support training in some health care settings. If advanced cardiac life support courses were to be prioritised, this may come at the expense of other healthcare educational interventions in low resource settings.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The potential for lives saved by participation in these courses outweighs the costs of candidates attending these courses. There is an expectation from the public and healthcare institutions that employees will be trained to deal with this important critical condition, so this evidence supports the fact that these courses are fit for purpose.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes	This is an intervention that has been	

● Yes ○ Varies ○ Don't know	well established in healthcare education in high resource settings. But its provision may not be feasible or appropriate in in some health care settings.	

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	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

	JUDGEMENT						
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

Recommendation

We recommend the provision of accredited adult advanced cardiac life support training for health care professionals who provide advanced life support care for adults (strong recommendation, very low quality of evidence).

Justification

Adult advanced cardiac life support training improves resuscitation knowledge and skills and it is likely to ensure best practice is applied in these emergency situations.

We recognize that the evidence in support of this recommendation comes from observational studies of very low quality. However, pooling of the available evidence consistently favours advanced cardiac life support training, and having advanced cardiac life support trained staff present during an attempted adult resuscitation has been found to reduce treatment errors such as incorrect rhythm assessment (Makker 1995, 116) and time to ROSC (Moretti 2007 458). We recognise that the provision of accredited adult advanced cardiac life support training may not be feasible or appropriate in low resource settings.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Similar review needed for other life support courses (e.g. PALS).

Recommended CoSTR:

- We recommend the provision of accredited adult advanced cardiac life support training for health care professionals who provide advanced life support care for adults (strong recommendation, very low quality of evidence).
- Values and preferences statement: In making this recommendation we recognize that the evidence comes from observational studies of very low certainty. However pooling of the available evidence consistently favours ACLS/ALS training.
- The provision of accredited ACLS/ALS training may not be feasible or appropriate in some low resource settings.
- Knowledge gaps: impact of blended learning approaches, ideal recertification intervals, impact of modifications necessitated by COVID pandemic.

Neonatal Resuscitation Training (NRT) EtD

QUESTION

Are cardiac arrest outcomes improved as a result of a member of the resuscitation team attending an accredited advanced life support course?	
POPULATION:	Patients requiring in-hospital cardiac arrest resuscitation of any age - NEWBORN
INTERVENTION:	Prior participation of one or more members of the resuscitation team in an accredited advanced life support course NEONATAL RESUSCITATION TRAINING (NRT)
COMPARISON:	No such participation
MAIN OUTCOMES:	ROSC; Survival to Discharge or 30-day survival; 1 year survival; survival with favourable neurological outcome; stillbirth rate; neonatal mortality; perinatal mortality
SETTING:	**HOSPITAL SETTING**
CONFLICT OF INTERESTS:	Andy Lockey is a Trustee of Resuscitation Council UK – who provide NLS training.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	Neonatal survival rates are globally poor, in particular in low and middle income settings. The potential for number of lives saved is more impactful for newborn than it is with adults.	Attendance of participants on an NRT course comes at a cost - both financial and time - to stakeholders including participants themselves and their institutions. It is therefore important to show whether this participation has any meaningful impact upon patient outcomes. All studies were from low-income or middle-income countries.
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 20 studies. 2 studies were RCTs (Bang 1999, Gill 2011) and the remainder were pre-post studies. 4 studies covered community settings (Bang 1999, Ariawan 2006, Carlo 2010, Gill 2011), and the remainder covered hospital settings. **NRT verses control** All stillbirths: RR 0.79, 95% CI 0.44 to 1.41; participants=5661; studies=2; I2=67% 7-day neonatal deaths: RR 0.53, 95% CI 0.38 to 0.73; participants=5518; studies=2; I2=0% 28-day neonatal deaths: RR 0.50,	No evidence presented for high-income settings. Hospital based studies show more consistency in direction of effect. This may be due to more consistent implementation of training and more accurate data acquisition when compared with community settings. Pre-post studies lack concurrent control group, therefore confounding factors are present. Lack of consistency of settings, duration of training, varying study designs, and lack of consistent outcomes contribute to substantial heterogeneity. Despite the heterogeneity of evidence, all analyses show a coniststent treatment effect for this training with potential for many lives saved.

	95% CI 0.37 to 0.68; participants=5442; studies=2; I2=0% perinatal deaths: RR 0.63, 95% CI 0.42 to 0.94; participants=5584; studies=2; I2=68% The effect was significant for 7-day neonatal mortality , 28-day neonatal mortality and perinatal mortality. Significant heterogeneity was observed in analysis of total stillbirths and perinatal mortality. **Post-NRT verses pre-NRT** All stillbirths: RR 0.88, 95% CI 0.83 to 0.94; participants=1 425 540; studies=12; I2=47% Fresh stillbirths: RR 0.74, 95% CI 0.61 to 0.90; participants=296 819; studies=8; I2=84% 1-day neonatal mortality: RR 0.58, 95% CI 0.42 to 0.82; participants=280 080; studies=6; I2=89% 7-day neonatal mortality: RR 0.82, 95% CI 0.73 to 0.93; participants=360 383; studies=7; I2=71% 28-day neonatal mortality: RR 0.86, 95% CI 0.65 to 1.13; participants=1 116 463; studies=7; I2=95%	

	Perinatal mortality: RR 0.82, 95% CI 0.74 to 0.91; participants=1 243 802; studies=6; I2=90% The changes were significant in all the outcomes; except 28-day neonatal mortality. Heterogeneity was significant in all outcomes except all stillbirths. A funnel plot for all stillbirths showed asymmetry, thereby indicating a publication bias. **Extracting and analysing data for hospital based studies only gives the following results:** All studies were Post-NRT verses pre-NRT (no RCTs containing hospital data) All Stillbirths: RR 0.88, 95% CI 0.82-0.94; participants 1 334 307; 9 studies; I2=48% Fresh Stillbirths: RR 0.71, 95% CI 0.54-0.93; participants 231 455; 6 studies; I2=88% 1-day neonatal mortality: RR 0.58, 95% CI 0.38-0.90; participants 216 373; 5 studies; I2=89% 7-day neonatal mortality: RR 0.78, 95% CI 0.63-0.97; participants 296 300; 5 studies; I2=79%	

	28-day mortality: RR 0.89, 95% CI 0.65-1.22; participants 1 090 594; 6 studies; I2=96% Perinatal mortality: RR 0.78, 95% CI 0.70-0.87; participnts1 178 446; 4 studies; I2=83% The changes were significant in all the outcomes; except 28-day neonatal mortality. Statistical and clinical heterogeneity was significant in all outcomes except all stillbirths. Hospital based studies only therefore showed even more consistency in direction of effect.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small •Trivial ○ Varies ○ Don't know	Nil identified.	Potential for diverting resource away from other public health initiatives in low income settings
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	**Post-NRT verses pre-NRT (Hospital settings only)** The quality of evidence for post-NRT verses pre-NRT was very low for all outcomes.	

	Downgraded for risk of bias, indirectness, 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	Patients value survival with good neurological outcome (Haywood 2018 e783). It is expected that health care professionals are trained to treat medical emergencies. Standardised NRT training is likely to improve the care provided during cardiac arrest, and thus improve outcomes for patients.	No studies examined the critical outcome of longer term outcomes or good neurological function. No studies explored the values of key stakeholders or family members.
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	Yes - no undesirable effects identified.	
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	There has been no formal cost effectiveness analysis.	All studies covered low-income and middle-income countries only. There may be significant resource implications if manikins are required for training.

○ Varies ○ Don't know		
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 evidence was identified	Costs are likely to vary between different health care settings.
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 is no evidence surrounding the actual costs, although the cost-benefit analysis is likely to favour the intervention	The potential for lives saved by health care professional's participation in these courses outweighs the costs of providing these courses.
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	Variable evidence.	The associated resources and costs may prohibit NRT training in some health care settings, although some kind of training may be provided at low costs. If advanced NRT courses were to be prioritised, this may come at the expense of other healthcare educational interventions in low resource settings. However this should be balanced against the benefits of improving patient outcomes with potentially very little cost or resource needed.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no • Probably yes ○ Yes	Whilst there is no evidence surrounding the acceptability for	The potential for lives saved by participation in these courses outweighs the costs of candidates attending these courses.

○ Varies ○ Don't know	key stakeholders, it is reasonable to expect that it would be an acceptable intervention.	There is an expectation from the public and healthcare institutions that employees will be trained to deal with this important critical condition, so this evidence supports the fact that these courses are fit for purpose.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	This is an intervention that has been well established in healthcare education in low-income and middle-income settings.	

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	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

	JUDGEMENT						
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

Recommendation

We recommend the provision of accredited NRT life support training for health care professionals who provide advanced life support care for newborns and babies (strong recommendation, very low-certainty evidence).

Justification

- A quarter of global neonatal deaths are due to birth asphyxia. The majority of these deaths occur in lo
- Neonatal resuscitation training (NRT) of birth attendants using mannequins result in improved knowle
- Translation of NRT into improved neonatal outcomes and the effect estimates of improvements are in updated.
- NRT resulted in significant reduction in stillbirths and early neonatal mortality. However, continuum o day 7 to 28

Subgroup considerations

- HBB addressed in separate ETD.

Implementation considerations

- Published evidence only covers low and middle income settings.
- This provides evidence of where the impact of this intervention is particularly beneficial

Monitoring and evaluation

Research priorities

- Future studies need to establish the best combination of settings, trainee charecteristics and training frequency to sustain the existing effect on perinatal mortality reduction.
- Studies addressing longer term outcomes including favourable neurological outcomes
- Studies of courses in high income settings needed as well

NRT recommendation:

- We recommend the provision of accredited NRT life support training for health care professionals who provide advanced life support care for newborns and babies (strong recommendation, very low-certainty evidence).
- Values and preferences statement: In making this recommendation we recognize that the evidence in support of this recommendation comes from studies of very low quality and relate to a range of NRT courses run in different low and middle resource settings around the world over a large time period.
- The provision of accredited NRT training is feasible in low and middle resource settings.
- Knowledge gaps: best combination of settings, trainee charecteristics and training frequency to sustain the existing effect on perinatal mortality reduction.

Helping Babies Breath (HBB) EtD

QUESTION

Is perinatal mortality reduced as a result of a member of the resuscitation team attending a helping babies breathe (HBB) course?	
POPULATION:	Newborns in low-income settings requiring in-hospital cardiac arrest resuscitation
INTERVENTION:	Prior participation of one or more members of the resuscitation team in a Helping Babies Breathe (HBB) intervention
COMPARISON:	No such participation
MAIN OUTCOMES:	ROSC; Survival to Discharge or 30-day survival; 1 year survival; survival with favourable neurological outcome; stillbirth rate; neonatal mortality; perinatal mortality
SETTING:	**HOSPITAL SETTING**
PERSPECTIVE:	Data on the effectiveness of a certified teaching program to improve survival might justify allocation of resources and stimulate further dissemination.
BACKGROUND:	In 2015, a UN-inter-agency group for child mortality estimated about 2.6 million neonates die each year in their first month of life, 98% in low-resource settings. The American Academy of Pediatrics initiated the “Helping Baby Breath” program in 2010 as an evidence-based neonatal resuscitation program to save newborns’ lives in resource limited settings. This simulation-based training of healthcare providers in postnatal resuscitation and care was adopted by WHO and implemented in a variety of countries.
CONFLICT OF INTERESTS:	none

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	Neonatal survival rates are globally poor, in particular in low income settings. The potential for number of lives saved is more impactful for newborn than it is with adults.	Attendance of participants on an HBB course comes at a cost - both financial and time - to stakeholders including participants themselves and their institutions. It is therefore important to show whether this participation has any meaningful impact upon patient outcomes. All studies were from low-income countries.
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 by Versantvoort 2020 identified 7 studies. All studies were pre/post studies. Our search identified one additional study (Innerdal 2020) All studies were conducted in low-resource settings focusing on the association between HBB and intrapartum related stillbirths and/or neonatal mortality. **Post-HBB versus pre-HBB**	No evidence presented for middle or high-income settings. Pre-post studies lack concurrent control group, therefore confounding factors are present. Lack of consistency of settings, duration of training, varying study designs, and lack of consistent outcomes contribute to substantial heterogeneity. Despite the heterogeneity of evidence, all analyses show a coniststent treatment effect for this training with potential for many lives saved.

	No meta-analysis was performed Significant decreases were found after the implementation of HBB in one of two studies describing **perinatal mortality (all dealths in the first week after birth including intrapartum still births)** (n=25 108, RR 0.75 p<0.001) one study described a reduction in **perinatal mortality (FSR + 1 day neonatal mortality**) (n=9769, RR 0.27 p<0.0001) four out of six studies related to **intrapartum still births (fresh still births)** (n=135 489, RR 0.31-0.76) five out of six studies focusing on **1 day neonatal mortality** (n=121 058, RR 0.12-0.67) one out of three studies regarding **7 day neonatal mortality** (n=4 390, RR 0.32) The changes were significant in all outcomes. No changes were seen in the late (28-day	

	neonatal mortality. All included studies were predominantly of moderate quality. There was a single high quality study (Arabi 2018)	
Undesirable Effects **How substantial are the undesirable anticipated effects?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small •Trivial ○ Varies ○ Don't know	Nil identified.	Potential for diverting resource away from other public health initiatives in low income settings. Teaching material developed in high income countries and supported by charities and international health organisations
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	HBB training was performed differently in the selected studies eg. duration of training and follow-up was not identical. Because of clinical and statistical heterogeneity, meta-analysis was not performed. Downgraded for risk of bias 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	No studies examined the critical outcome of longer term outcomes or good neurological function. No studies explored the values of key stakeholders or family members.	Patients value longterm survival with good neurological outcome (Haywood 2018 e783). It is expected that health care professionals are trained to treat medical emergencies. Additional interventions in the postnatal period that focus on other causes of mortality such as neonatal infections, convulsions, hypothermia and feeding difficulties may be needed to increase overall neonatal survival rate.
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	Yes - no undesirable effects identified.	
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 has been no formal cost effectiveness analysis in the included studies. A separate cost effectiveness analysis was conducted at the Haydom Luteran Hospital in rural	Cost effectiveness analysis including government owned institutions, urban hospitals and district facilities would be desirable for a more diverse analysis to explore cost-driving factors and predictors of enhanced cost-effectiveness. All studies covered low-income countries only.

	Tazania (Vossius 2014), this was based on the Msemo 2013 included in the systematic review Costs per life saved were USD 233, while they were USD 4.21 per life year gained. Costs for maintaining the program were USD 80 per life saved and USD 1.44 per life year gained. Costs per disease adjusted life year (DALY) averted ranged from International Dollars (ID; a virtual valuta corrected for purchasing power world-wide) 12 to 23, according to how DALYs were calculated.	
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	A cost-effectiveness analysis was conducted on the Msemo 2013 study in Tanzania.	

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	The potential for lives saved by birth attendents' participation in these courses outweighs the costs of providing these courses.	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased • Varies ○ Don't know	No evidence identified.	The associated resources and costs may prohibit HBB training in some health care settings. If HBB were to be prioritised, this may come at the expense of other healthcare educational interventions in low resource settings. However this should be balanced against the benefits of improving patient outcomes with potentially very little cost or resource needed.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	No evidence identified.	Whilst there is no evidence surrounding the acceptability for key stakeholders, it is reasonable to expect that it would be an acceptable intervention. The potential for lives saved by participation in HBB outweighs the costs of candidates attending these courses. There is an expectation from the public and healthcare institutions that employees will be trained to deal with this important critical condition, so this evidence supports the fact that these courses are fit for purpose.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes • Yes ○ Varies ○ Don't know	This is an intervention that has been well established in healthcare education in low-income settings.	

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	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**

	JUDGEMENT						
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

Recommendation

We recommend the provision of Helping Babies Breath support training for healthcare providers who provide advanced life support care for newborns and babies (strong recommendation, very low-certainty evidence).

Justification

- A quarter of global neonatal deaths are due to birth asphyxia. The majority of these deaths occur in lo
- HBB resulted in significant reduction in stillbirths and early neonatal mortality. However, continuum o beyond 28 days.

Subgroup considerations

- NRT addressed in separate ETD.

Implementation considerations

- Published evidence only covers low income settings.
- This provides evidence of where the impact of this intervention is particularly beneficial

Research priorities

- Future studies need to establish the best combination of settings, trainee charecteristics and training frequency to sustain the existing effect on perinatal mortality reduction.
- Further cost-effectiveness analyses
- Studies addressing longer term outcomes including favourable neurological outcomes

HBB recommendation:

- We recommend the provision of Helping Babies Breath support training for healthcare providers who provide advanced life support care for newborns and babies (strong recommendation, very low-certainty evidence).
- Values and preferences statement: In making this recommendation we recognize that the evidence in support of this recommendation comes from studies of very low quality and relate to a range of HBB implementations run in different low resource settings around the world over a large time period.
- The provision of HBB training is feasible in low resource settings.
- Knowledge gaps: best combination of settings, trainee charecteristics and training frequency to sustain the existing effect on perinatal mortality reduction.

QUESTION

"Blended learning approach for life support education"	
POPULATION:	Participants undertaking an accredited life support course (e.g. BLS, ACLS/ALS, PALS, ATLS)
INTERVENTION:	Blended learning approach
COMPARISON:	Non blended learning approach (stratified to subgroups of online only and face-to-face only)
MAIN OUTCOMES:	Knowledge acquisition/retention (end of course, 6 months, 1 year), skills acquisition/retention (end of course, 6 months, 1 year), participant satisfaction (end of course), patient survival, implementation outcomes (cost, time needed)
BACKGROUND:	Blended learning is an educational approach that has gained popularity in medical education and professional development. It combines the advantages of both face-to-face and online approaches and gives learners more control over the educational content to be engaged, sequencing, and pace of learning as well as flexibility around when and where learning takes place. (1) Online elements are usually, but not always, delivered prior to the face-to-face element. The ever-increasing demands upon clinical service delivery time have historically been a driver to reduce teaching and study leave time. As a result, there is a need within healthcare education for flexible, tailored, and timely methods of teaching (2) which are also efficient and cost-effective.(3) A blended learning approach has the ability to deliver cost savings for both learners and teaching institutions when compared with conventional classroom learning whilst still maintaining face-to-face contact. (4-6) As an additional rationale, online learning may hold advantages from a learning theory perspective. Learning in such formats may be better tailored to the learner, be it in respect to different levels of pre-knowledge or for different learning styles, pace of learning etc. (7) More recently, the impact of the COVID-19 pandemic on the feasibility of face-to-face interactions and teaching has been profound, making the use of technology to facilitate learning a necessity rather than an option. (8-11) Although a blended learning approach appears to be an obvious solution to some of these challenges and drivers, it is important that this teaching approach is formally evaluated. This is particularly important with regard to specific targeted educational interventions, such as accredited life support courses. The 2020 CoSTR strongly recommended "providing the option of eLearning as part of a blended-learning approach to reduce face-to-face training time in ALS courses (very low- to low-certainty evidence)" (12) This systematic review is designed to look at the impact of all forms of blended learning on all accredited life support courses.
CONFLICT OF INTERESTS:	Andy Lockey is a Trustee of Resuscitation Council UK – who provide blended and non-blended life support training.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The COVID-19 pandemic has significantly impacted upon the ability to deliver pure face-to-face training. The skills needed to be taught mean that pure online learning may not be sufficient. There is evidence of the development of blended learning variants of life support courses to enable training to continue in times of pandemic and potentially in the post-pandemic era as well.	Attendance of participants on accredited life support courses come at a cost - both financial and time - to stakeholders including participants themselves and their institutions. Blended learning offers an opportunity to deliver such training with a requirement for participants and faculty to take a shorter time away from clinical duties. It is important to assess whether this alternative approach to training is effective.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Basic Life Support** The review included 14 studies (13-26). For the outcome of BLS knowledge (post intervention), one study found a statistically significant benefit for blended learning (21), one study found a statistically significant benefit for face-to-face only (17), one study found increased requirements for knowledge remediation in the blended learning group (22), and two studies found no significant difference between the blended learning and control groups (14, 16). There was no significant difference between the groups at any time point between 2 and 12 months (14, 16, 17, 21). All studies were of adult BLS courses. For the outcome of BLS skills (post intervention), three studies found a statistically significant benefit for blended learning (14, 18, 26). One of these studies also found a statistically significant benefit for face-to-face only for total number of chest compressions (18). One study of infant BLS found better performance with blended learning in a range of BLS components, but no analysis was performed for statistical significance (23). The remaining eight studies (including one of infant BLS) found no significant difference between the intervention and control groups (13, 16, 17, 19-22, 24). For BLS skills retention, one study found no significant difference between the groups at 2 months (21). One study found a statistically significant benefit for blended learning at 3 months when compared to online learning only for compression depth, but the opposite for compression rate (26). Two studies found a statistically significant benefit for blended learning at 6 months (14, 26). The remaining four studies found no significant difference between the intervention and control groups (16, 18, 20, 24). There was no significant difference between groups for one study at 9 months (17) and one study at 12 months (16). For the outcome of attitudes, there was evidence of positive attitudes to all forms of training (20, 22, 24, 26). For the outcome of costs, the single cost analysis study found a notable financial benefit for teaching BLS via a blended learning approach (15). **Adult advanced cardiac life support:** The review included eight studies (27-34). For the outcome of ALS knowledge (post intervention), two studies found significantly higher scores in the blended learning group (27, 34), whilst the remainder of the studies found no significant difference between the groups (28, 32, 33). There was no significant difference between groups for one study at 7 months (28). For the outcome of ALS skills (post intervention), one pilot study (33) found significantly higher scores in	Lack of consistency of settings, duration of training, varying study designs and different types of outcome measures contribute to substantial clinical and methodological heterogeneity for both BLS and ALS sub-groups. As such, it is not feasible to perform any meta-analysis for any of the outcomes. For ATLS, only one study was available. Pre-post studies lack concurrent control group, therefore confounding factors are present. Despite the heterogeneity of evidence, the majority of the analyses show no detrimental effect for blended learning and a treatment effect in favour of blended learning in some domains.

	the control group however a subsequent study of the revised version of the same course found significantly higher scores in the blended learning group (34). The remainder of the studies found no significant difference between the groups (27, 28, 30, 32). There was a diversity of attitudes with three studies finding a preference for blended learning (27, 30, 32) and two studies finding a preference for face-to-face learning (28, 31). For the outcome of costs, two studies found a notable financial benefit for teaching ALS via a blended learning approach (29, 33). **Adult trauma life support:** One study found that a blended learning approach for Advanced Trauma Life Support is better in terms of knowledge outcomes (35). Overall pass rates were better but there was no specific description of the breakdown of skills performance as opposed to knowledge outcomes in determining the final result so a conclusion about skills training cannot be made.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Two small studies with a total of 259 participants found no significant difference that favoured the control group for post intervention knowledge scores or requirements for knowledge remediation in Basic Life Support (17, 22). Otherwise, there was no evidence to suggest any other detrimental outcomes from this intervention for BLS. One study of a pilot approach to e-ALS training showed significantly higher skills in the traditional group for immediate knowledge retention (33), but this was not evidenced in the follow up study of the revised course (34).	Despite the heterogeneity of evidence, the majority of the analyses show no detrimental effect for blended learning and a treatment effect in favour of blended learning in some domains.

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	**BLS and adult advanced cardiac life support** • The quality of evidence was very low for knowledge, skills, and attitudes. • Downgraded for risk of bias, indirectness, and inconsistency. **Advanced Trauma Life Support** • The quality of evidence was very low for knowledge, skills, and attitudes. • Non-RCT study downgraded for risk of bias, and imprecision.	

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	Participant and faculty attitudes were assessed, and were on the whole favourable to the intervention of blended learning. No studies examined the critical outcome of patient outcomes or good neurological function. No studies explored the values of key stakeholders or family members.	In respect to the outcomes 'improved patient outcome' and 'good neurologic outcome' it might not be scientifically sound to link the 'type of course format' to outcomes at the patient level given the indirectness of effects with a substantial number of potential confounders.

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	Yes	

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	**BLS** One study (15) demonstrated that initial set up costs of a blended learning programme resulted in a large unspecified net loss. There was however a net profit of €10,530 at 5 years in the blended learning group compared to a loss of €1,754 in the control group. **Adult advanced life support** Results from two studies (29, 33) showed that the blended learning course is superior to the traditional course in terms of cost reductions. A study from Singapore found 61% savings over 5 years if blended-ACLS were to be used instead of traditional-ACLS (29). The estimated annual cost to conduct blended-ACLS and traditional-ACLS were S$43,467 and S$72,793, respectively. Furthermore, one of the UK studies reported more than 50% cost reductions in which the total costs per participant were $438 for blended ALS training and $935 for traditional ALS training (33).	Significant costs may be needed by accrediting institutions to develop and update online materials and host learning management systems to deliver online content. This may vary depending upon the complexity of content needed. Over time these costs may be mitigated for these institutions by the ongoing savings. Other stakeholders (i.e. participants, those funding placements on these courses) are likely to see only a positive cost saving from blended learning courses.

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	High certainty of evidence for BLS and adult advanced cardiac life support. No evidence available for Advanced Trauma Life Support.	Costs may be variable depending upon pre-existing resources within different programs.

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	Evidence shows that following investment in the development of resources, the intervention is cost effective for BLS and adult advanced cardiac life support. No evidence available for Advanced Trauma Life Support.	The potential for lives saved by health care professional's participation in these courses outweighs the costs of providing these courses.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No evidence presented.	Blended learning approaches may improve accessibility to those in remote locations and in times of pandemic for participants otherwise unable to attend traditional courses. Conversely, a blended learning approach may disadvantage those without access to online learning. Individual approaches to learning may vary and a blended learning approach may not suit all participants.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Attitudinal results were favourable for blended learning approaches to BLS and adult advanced cardiac life support. No evidence available for Advanced Trauma Life Support.	There has been considerable pressure from key stakeholders for many years to reduce costs associated with life support courses. In addition, reducing the time needed away from the clinical workforce is a priority for participants and faculty alike. Any strategy that reduces costs and time out is likely to be acceptable to stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes	Requires access to online learning. Therefore may not be feasible in all settings (e.g. low resource settings may not be able to provide online access or various media, and may therefore prefer traditional face-to-face teaching). The costs of programme developers, online support, ongoing data management, and web development may also impact upon the feasibility for developing a blended learning approach in lower resource settings.

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	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

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

Recommendation

We recommend a blended learning as opposed to non-blended approach for life support training where resources and accessibility permit its implementation (strong recommendation, very low quality of evidence).

Justification

- A blended learning approach is grounded in a strong framework from educational theory
- Blended learning approaches result in similar or better educational outcomes for participants
- A blended learning approach can enable ongoing training of life support skills for those in remote locations, lower resource settings, and in times of pandemic
- A blended learning approach may not be feasible in areas where access to online learning is limited or unavailable
- Non-blended learning approaches (i.e. face-to-face only or online only) are an acceptable alternative where resources or accessibility do not permit the implementation of a blended learning approach.
- The majority of the research evidence used 'face-to-face' only as the control group, with very limited evidence for 'online only' as the control group
- Blended learning enables consistent messaging with regard to content which can be particularly beneficial for pre-course preparation.
- Participant and stakeholder costs are reduced with a blended learning approach
- Duration of face-to-face training is reduced, although time is still needed to complete the online component

Subgroup considerations

Implementation considerations

- Set up costs for the development of online teaching materials and learning management systems may be significant for accrediting institutions

Monitoring and evaluation

Research priorities

- Future studies need to establish the elements of instructional delivery that are associated with better educational outcomes
- Are certain levels of blended learning (i.e. how much, what exactly, when used) more beneficial than other when compared with each other
- Does a blended learning approach to life support education result in better patient outcomes
- Do certain sub-groups of participant (e.g. first time vs recertificating) have better educational outcomes from a blended learning approach?
- Further studies are needed for blended learning compared with online only learning.

Recommended CoSTR:

We recommend a blended learning as opposed to non-blended approach for life support training where resources and accessibility permit its implementation (strong recommendation, very low quality of evidence).

Values and preferences statement:

In making this recommendation we recognize that:

- A blended learning approach is grounded in a strong framework from educational theory
- Blended learning approaches result in similar or better educational outcomes for participants
- A blended learning approach can enable ongoing training of life support skills for those in remote locations, lower resource settings, and in times of pandemic
- A blended learning approach may not be feasible in areas where access to online learning is limited or unavailable
- Non-blended learning approaches (i.e. face-to-face only or online only) are an acceptable alternative where resources or accessibility do not permit the implementation of a blended learning approach.
- The majority of the research evidence used 'face-to-face' only as the control group, with very limited evidence for 'online only' as the control group
- Blended learning enables consistent messaging with regard to content which can be particularly beneficial for pre-course preparation.
- Participant and stakeholder costs are reduced with a blended learning approach
- Duration of face-to-face training is reduced, although time is still needed to complete the online component

Knowledge gaps:

- The elements of instructional delivery that are associated with better educational outcomes;

- Are certain levels of blended learning (i.e. how much, what exactly, when used) more beneficial than other when compared with each other;
- Does blended learning life support educational lead to better patient outcomes
- Do certain sub-groups of participant (e.g. first time vs recertificating) have better educational outcomes from a blended learning approach?
- Further studies are needed for blended learning compared with online only learning

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QUESTION

Should a specific recovery position, such as the lateral recumbent position, be used in persons with a decreased level of responsiveness?	
POPULATION:	Adults and children in the first aid setting, with a reduced level of responsiveness of non-traumatic aetiology, who do not require resuscitative interventions
INTERVENTION:	specific positioning (recovery positioning i.e. various semi-prone, lateral recumbent, side-lying or three-quarters prone positions of the body)
COMPARISON:	any other position
MAIN OUTCOMES:	Survival, incidence of cardiac arrest, delayed detection of apnoea and cardiac arrest, need for airway management, incidence of aspiration, hypoxia, likelihood of cervical spine injury, and complications (venous occlusion, arterial insufficiency, arm discomfort/pain, discomfort/pain, aspiration pneumonia).
SETTING:	prehospital first aid settings
PERSPECTIVE:	lay provider and first aid context
BACKGROUND:	The recovery position, (various semi-prone, lateral recumbent, side-lying or three-quarters prone positions of the body), are widely recommended for patients with a decreased level of responsiveness {Handley 2017 A6}. The logic of the recovery position is to reduce the risk or effect of airway obstructions, facilitate drainage of the airways, reduce the risk of aspiration, reduce chest pressure that could impair breathing, limit neck movement, allow for observation of breathing and be of low risk to the subject while being easy to return the subject to a supine position, if required {Handley 1997 2174}. A decreased level of responsiveness represents an abnormal arousability and depressed alertness, on a continuum from sleepiness (somnolence) to unresponsive (comatose). For example, the subject may respond to verbal or mechanical stimulation but quickly return to an unresponsive state when unstimulated. There are many non-traumatic causes including exposure to poisons or intoxicants, hypoglycemia, stroke or seizure. Importantly, the recovery position should not be employed for a subject who is in cardiac arrest, i.e. they are unresponsive and breathing abnormally (gasping or agonal breathing) or not breathing at all (apnea), instead automated external defibrillator (AED) application and cardiopulmonary resuscitation are indicated. Therefore, it is necessary to initially assess and continuously monitor the subject for deterioration and indications for resuscitative interventions. Authors have expressed concern and provided evidence from healthy volunteers simulating apnea using breath holding to suggest that placing individuals in the recovery position may impair the detection of cardiac arrest and that supine positioning with a head-tilt-chin-lift should be adopted instead {Freire-Tellado 2017 173; Navarro-Paton 2019 104}. However, it remains unknown, how well the head-tilt-chin-lift is performed or whether it can be maintained for prolonged periods by first aid providers, including lay persons. The observation of the subject may be more complete when they are supine, but a patent airway and unencumbered breathing may be easier to obtain in the recovery position. Recovery type positioning in sleeping adults as well as sedated children has been reported to reduce apnea, airway obstruction and respiratory disturbance compared to the supine position {Arai 2004 1638; Arai 2005 949; Litman 2005 484; Svatikova 2011 262; Turkington 2002 2037}. The strength and certainty of scientific evidence supporting the use of the recovery position, and agreement on which specific position is best, is very limited.
CONFLICT OF INTERESTS:	none

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There is little evidence on the effectiveness of the recovery position (and various side-lying and lateral recumbent positions) compared to other individual positions (for example the “position found,” rolling the individual supine or prone) for maintaining airway patency, adequate ventilation and preventing cardiac arrest. A 2015 ILCOR Consensus on Science on this topic concluded that first aid providers should position unresponsive patients who are breathing adequately into a recovery position as opposed to leaving them supine, but this was a weak recommendation,	Worldwide, about 500 000 deaths are attributable to drug use. More than 70% of these deaths are related to opioids, with more than 30% of those deaths caused by overdose. According to WHO estimates, approximately 115 000 people died of opioid overdose in 2017. UNODC (2021). {World Drug Report 2021}. Available at:

	from very low certainty evidence. {Singletary 2015 S269; Zideman 2015 e225} Furthermore, it was not possible to identify an optimal recovery position. A 2019 ILCOR scoping review and Consensus on Science on this topic described a diverse knowledge base on the role of positioning in airway patency and the maintenance of breathing, as well as numerous gaps in the understanding. Therefore, we conducted a systematic review on whether the use of the recovery position in adults and children with a non-traumatic decreased level of responsiveness changes outcomes in comparison with other patient positioning strategies, to inform future guidelines. This PICOST was prioritized by the ILCOR First Aid Task Force because of concerns expressed in the medical community for potential missed signs of cardiac arrest among some individuals placed into a lateral recumbent recovery position, and concern for potential airway compromise in persons with a diminished level or responsiveness (such as from an opioid or other substance overdose) who are maintained in a supine position.	https://www.unodc.org/unodc/data-and-analysis/wdr2021.html Aspiration and positional asphyxia are important contributors to opioid related mobidity and mortality {Nicolakis 2020 2121; . Opioid overdoses that do not lead to death are several times more common than fatal overdoses and a major cause of morbidity. The global opioid crisis has been worsened by the COVID19 pandemic. During the COVID-19 pandemic, drug overdose deaths have increased in the US, primarily driven by synthetic opioids. CDC Emergency Preparedness and Response: Increase in Fatal Drug Overdoses Across the United States Driven by Synthetic Opioids Before and During the COVID-19 Pandemic, 17 December 2020. Available at: https://emergency.cdc.gov/han/2020/han00438.asp

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The review identified a lack of comparative studies examining clinical outcomes which precluded comparisons or meta-analyses. Furthermore, the lack of high-certainty comparative studies that support (or oppose) the use of the recovery position, is also very limited. In total, 3 prospective observational studies (n= 1003) {Adnet 1999 745; Julliand 2016 521; Wagner 2020 e037676}; , 4 case series (n=251) {Freire-Tellado 2016 e1; Kloster 1999 439; Ryvlin 2013 966; Verducci 2019 e227} were included. The included papers were published over 24-years (1999 to 2020) and were conducted in 6 different countries (France, Germany, Norway, Spain and USA (two studies), as well as one multinational European and one multinational, multi continent study. ***Observational studies*** The observational studies enrolled a total of 450 adults and 553 children experiencing poisoning, febrile seizures, non-febrile seizure, vasovagal symptoms or out of hospital cardiac arrest resulting in activation of emergency medical services. {Adnet 1999 745; Julliand 2016 521; Wagner 2020 e037676} In an observational descriptive study of body position and suspected aspiration pneumonia in 205 acutely poisoned patients, 112 patients (54%) were found supine, 30 (15%) left lateral decubitus, 25 (12%) prone group, 20 (10%) right lateral decubitus, and 18 (9%) in a semi-recumbent position. The prone position and semi-recumbent positions were associated with a decreased rate of suspected aspiration pneumonia ($p < 0.05$); whereas there was no significant difference between left lateral decubitus, right lateral decubitus, and supine groups with respect to the incidence of pulmonary infiltrates. {Adnet 1999 745} The use of the recovery position in 145 of 553 (26.2%) paediatric patients with a decreased level of responsiveness, cared for at European emergency departments, was associated with deceased admission rate (adjusted odds ratio (aOR= 0.28; 95% CI 0.17 to 0.48, $p<0.0001$). {Julliand 2016 521} In a prospective observational study of 200 cases of out-of-hospital cardiac arrest attended by bystanders, only 64 (32%) patients were found by the emergency services to have been placed in a supine position suitable for the performance of chest compressions. Of the remainder, 37 (18.5%) were found to be in the recovery position, which was more likely to have been the	

	case if bystanders had recently attended a CPR course. Although there was no statistically significant difference in favourable neurological outcome between patients placed in the recovery position compared with those placed in a position suitable for chest compression ($p > 0.05$), it was suggested that knowledge of the recovery position might distract bystanders from performing CPR.{ Wagner 2020 e037676} ***Case series and case reports*** Three included case series (n=244) described the position of persons with sudden unexpected death in epilepsy {Freire-Tellado 2016 e1; Kloster 1999 439; Ryvlin 2013 966; Verducci 2019 e227}, one case series, in the form of a research letter, identified seven cases believed to be missed out of hospital cardiac arrest { Freire-Tellado 2016 e1}, were included. A retrospective analysis of deaths in an outpatient population of a tertiary referral centre identified 140 patients with epilepsy who died between 1965 and 1996, of which 24 patients experienced sudden unexpected death in epilepsy. Of these, 17 (71%) were in the prone position, 1 was supine position (4%) and 6 (25%) were in unclassified positions. When an equal likelihood of prone or the supine positioning is assumed, the difference was found to be statistically significant ($p=0.001$; two tailed test) { Kloster 1999 439}. In a systematic retrospective survey of international epilepsy monitoring units 29 cardiorespiratory arrests were reported by 27 units from 11 countries. Among the 16 sudden unexpected deaths in epilepsy and fatal near sudden unexpected death in epilepsy cases in which the position of the patient could be assessed, 14 were prone at the time of cardiorespiratory arrest, often with the face partly tilted to one side.{Ryvlin 2013 966} A retrospective review including death scene investigation, autopsy and next of kin interviews identified 237 definite and probable cases of sudden unexpected death in epilepsy. The majority (128/186, 69%) were found in the prone position ($p < 0.05$).{ Verducci 2019 e227}	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	One case series {Freire-Tellado 2016 e1} and two observational studies { Adnet 1999 745; Wagner 2020 e037676} were identified describing undesirable effects of a recovering position for persons with decreased responsiveness of non-traumatic etiology, who do not require additional resuscitative maneuvers at the time of assessment. A case series in the form of a research letter to the editor reports seven out of hospital cardiac arrest victims who were initially assessed as unresponsive and breathing by first aid providers prior to being placed in the recovery position, who were later discovered to be in cardiac arrest by emergency medical services providers. {Freire-Tellado 2016 e1} In an observational descriptive study of body position and suspected aspiration pneumonia in 205 acutely poisoned patients, 112 patients (54%) were found supine, 30 (15%) left lateral decubitus, 25 (12%) prone group, 20 (10%) right lateral decubitus, and 18 (9%) in a semi-recumbent position. The prone position and semi-recumbent positions were associated with a decreased rate of suspected aspiration pneumonia ($p <0.05$); whereas there was no significant difference between left lateral decubitus, right lateral decubitus, and supine groups with respect to the incidence of pulmonary infiltrates.{Adnet 1999 745} A prospective observational cohort study covering a community of 400 000 inhabitants over one year reported how bystander cardiopulmonary resuscitation, including individual positioning, related to clinically relevant outcomes.	Identification of CA might differ between FA providers and EMS and do we know anything about the time from FA assessment to EMS assessment, something might have happened between the assessments. Authors of some recent studies suggest a relationship between the recovery position and delayed or missed detection of cardiac arrest. However, at this time, there is inadequate direct evidence to suggest a causal relationship {Freire-Tellado 2017 173; Navarro-Paton 2019 104}.

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	The evidence base enrolling individuals who experienced decreased level of responsiveness of non-traumatic etiology, consists of small observational studies, case series and a case report. There is a lack of certainty of evidence for whether the recovery position contributes meaningfully to desirable or undesirable outcomes. Certainty was downgraded due to risk of bias (position recalled by parents or EMS record), indirectness (aspiration pattern on x-ray) and imprecision since the evidence is from studies that indirectly compare interventions of interest in the population of interest.	

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	There is no important uncertainty about how much people value the use of the recovery position in decreased level of responsiveness of non-traumatic etiology.	It is likely that stakeholders would value clarity and greater certainty regarding individual positioning for persons experiencing decreased level of responsiveness of non-traumatic etiology. There is limited evidence to inform this value statement.

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	No difference in outcomes of critical importance were identified in the included studies, according to body position. As both desirable and undesirable effects are very uncertain, balancing them is not possible.	The use of a recovery position may be best utilized in situations where a sole first aid responder is unable to remain at the side of a casualty with diminished responsiveness. Where a responder can remain with the casualty, the emphasis should be on maintaining an open airway, monitoring breathing, and being prepared to respond to deterioration.

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	No evidence.	The task force believes that teaching and employing positional interventions (such as the recovery position) are low cost, have a low resource requirement, and are employable in most settings. The task force acknowledges that first aid training time is a precious resource and curricula are often crowded with potentially life-saving content. The time and

		resources required to teach the recovery position in first aid courses are likely to be very significant.

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 evidence. There are no important uncertainties regarding the required cost/resources of using the recovery position.	

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	No evidence.	There are no available studies to compare the cost effectiveness of the recovery position. However, it was felt by the task force that positional interventions are a high value and low cost immediately available and universally accessible 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	No evidence. As positional interventions do not require expensive equipment, training or health systems, health equity is not likely to be negatively impacted by positional interventions.	Lower socioeconomic groups experience a disproportionate burden of drug related morbidity and mortality (misuse and abuse) {Rehm 2018 53}. Interventions targeting drug related harm contribute to improved health equity. The task force is sensitive to subgroups of persons experiencing decreased levels of consciousness who may experience worse outcomes and unintended inequity from changes in first aid and positioning guidelines i.e., if the use of the recovery position is optional, will implicit biases result in certain subgroups less first aid.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Without a demonstrable improvement in outcomes using a non-recovery position, recommending the routine abandonment of the recover position is unlikely to be an acceptable strategy for key stakeholders. The First Aid Task Force does not find the current evidence sufficient to recommend against the routine use of the recovery position and encourages further research.	Delayed detection of deterioration and missed detection of cardiac arrest is a significant concern applicable to all individuals with a decreased level of responsiveness, regardless of their position. The task force believes a great emphasis on individual monitoring and the assessment of airway patency and adequacy of breathing should be emphasized for the care of all persons with decreased level of responsiveness.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The feasibility of the recovery position will vary by scene safety, first aid provider and individual characteristics. No evidence was identified to measure the feasibility of the recovery position.	However, the recovery position is a highly feasible intervention to implement.

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	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**

	JUDGEMENT						
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

Recommendation

Treatment Recommendations:

When providing first aid to a person with a decreased level of responsiveness of non-traumatic etiology and who does not require immediate resuscitative interventions, we suggest the use of the recovery position. (Weak recommendation, very low certainty evidence)

When the recovery position is used, monitoring should continue for signs of airway occlusion, inadequate or agonal breathing and unresponsiveness. (Good Practice Statement)

If body position, including the recovery position, is a factor impairing the first aid provider's ability to determine the presence or absence of signs of life, the person should be immediately positioned supine and re-assessed. (Good Practice Statement)

Persons found in positions associated with aspiration and positional asphyxia such as face down, prone, and neck and torso flexion positions should be positioned supine for reassessment. (Good Practice Statement)

Technical remarks:

Resuscitative interventions may include opening and maintaining an open airway, rescue breathing, chest compressions and the application of an automated external defibrillator.

Various recovery positions have been described and there remains little evidence to suggest an optimal position. The recommended recovery position, (lateral recumbent positioning with arm nearest the first aid provider at right angle to the body and elbow bent with palm up and far knee flexed), remains unchanged from the 2015 CoSTR).

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Justification

The task force discussed that normally we would not generate treatment recommendations based on so few studies and a level of evidence of low certainty. However, the opioid crisis and the large increase in the number of individuals requiring first aid, and being treated with the recovery position, has made this an important question for review.

The task force discussed weighing the possible risk of abandoning the recovery position in favour of the supine position and application of the head-tilt-chin-lift; however, but the result of such a change was unclear and not justified by the evidence identified.

In situations where a sole first aid responder is unable to remain at the side of a casualty and monitor their responsiveness and breathing, the task force agreed that the use of a recovery position is appropriate. Likewise, if a sole responder finds it necessary to maintain an open airway while in a supine position and is unable to call for help or perform other immediate first aid, such as administering naloxone for suspected opioid overdose, a recovery position may be useful.

The task force discussed the importance of first aid provider safety when accessing and changing the position of an individual. The difficulty and risk of physically turning the individual may vary based on provider and subject size, depth of unresponsiveness, additional first aid providers immediately available, and settings such as an enclosed space, private and public settings. First aid provider safety was seen as a priority by the task force.

The task force discussed how individual body habitus as well as head, face, spine and other structural characteristics may determine the suitability and effectiveness of different individual positions for the maintenance of airway patency and adequate ventilation. For example, the supine position in an obese person with a decreased level of responsiveness may be associated with airway obstruction and inadequate ventilation, whereas it may be more suitable for a person of lean body habitus. In the balance of these considerations, recommending the recovery position is believed to have the potential to benefit most individuals with a decreased responsiveness in the first aid setting.

Patient deterioration including cardiac arrest can occur after the patient has been put in recovery position (possibly as a result of the ongoing pathophysiological process). Therefore, continuous monitoring or reassessment at fixed interval (e.g. every 2 minutes if continuous monitoring is not possible) after putting the patient in recovery position should be emphasized and included in the education and training.

Subgroup considerations

Evidence does not differ significantly between adult and paediatric individuals, different aetiologies of decreased level of responsiveness (such as seizure, syncope or poisoning), and individual habitus.

Implementation considerations

Additional training/education may be necessary for assessing responsiveness and breathing initially and after putting the subject in the recovery position, , when to use recovery position, when not to use recovery position is necessary.

Monitoring and evaluation

After scene safety and activation of the emergency response system, the careful and continuous monitoring and evaluation of individuals with decreased level of responsiveness is a primary concern for first aid providers.

Research priorities

The Task Force discussed that additional studies would be very useful. These could include randomized controlled trials, prospective cohort studies or even larger case series representing the total experience of a center or centers, or even case reports that report airway patency and ventilation adequacy in persons experiencing opioid toxicity or emergency call takers randomizing callers to place individuals with non-traumatic decreased level of responsiveness to either the recovery position or the supine position. Future studies are also required to understand the role of positioning in patient assessment, how best to monitor for deterioration and what position is best relative to individual characteristics.

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