QUESTION

Should a resuscitation strategy comprising cardiopulmonary resuscitation (ventilations and compressions) vs. compression only resuscitation be used for adults and children in cardiac arrest following drowning?	
POPULATION:	adults and children in cardiac arrest following drowning
INTERVENTION:	compression-only CPR
COMPARISON:	Standard CPR (ventilations and compressions)
MAIN OUTCOMES:	Critical: Survival to discharge or 30 days with favourable neurological outcome and survival to discharge or 30 days. Important: Return of spontaneous circulation (ROSC)
SETTING:	out-of-hospital
PERSPECTIVE:	Cardiac arrest from drowning is due primarily to anoxia. [Bierens 2016 147; Vanden Hoek 2010 e405; Soar 2010 1407] Therefore, as with pediatric out-of-hospital cardiac arrest where asphyxia is the predominant etiology [Atkins 2009 1484; Young 2004 157; Sirbaugh 1999 174; Kuisma 1995 141], providing ventilation in OHCA due to drowning is important. [Szpilman 2004 25]
BACKGROUND:	There have been no previous systematic reviews of this question.
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	Drowning is the third leading cause of unintentional injury related deaths around the world. Morbidity after initially successful resuscitation is high with many survivors experiencing unfavourable neurological outcomes due to brain hypoxia. Developing evidence-based treatment recommendations to aid those attempting to resuscitate people following drowning is therefore a high priority.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large	Only two studies were found that addressed the question.[Fukada 2019 166; Tobin 2020 1]. Patients who received bystander CPR were compared by the type of	Both studies were retrospective and subject to high risk of bias.

○ Varies ○ Don't know	CPR they received (compression-only or convention CPR with rescue breaths) For **survival with a favourable neurological outcome at discharge/30-days,** there was no statistical difference in either study. **For the critical outcome of survival to hospital discharge/30-days,** Fukada et al [2019 166] reported no statistical difference between groups for survival 30 days. Tobin et al [2020 1], 71 (29.7%) in the conventional CPR group and 56 (18.1%) in the compression-only CPR group **survived to hospital discharge** (aOR=1.54; 95% CI, 1.01 to 2.36, p=0.046). **For the critical outcome of survival (return of spontaneous circulation) to hospital admission,** there was no statistical difference in either study for this outcome.	The cause of arrest in a drowned person includes cardiac etiologies.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	A post-hoc subgroup analysis by Tobin et al. [2020 1] showed conventional CPR was associated with greater adjusted odds of **favourable neurological outcome** in children aged 5 to 15 years (aOR=2.68; 95% CI, 1.10 to 6.77; p= 0.03).	A previous systematic review on all OHCAs supports the concept that conventional CPR may offer a greater chance for neurologically favorable survival than CO-CPR in children aged <1 year. (Ashoor 2017 112) A multicentered European study showed increased survival to hospital discharge when bystanders had performed ventilation [Ashoor 2017 112; Grässner 2019 218]
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 was assessed as very low certainty evidence due to very serious risk of bias, serious inconsistency and serious imprecision.	The significant finding in the subgroup data in children in the study by Tobin must be interpreted with caution due to the small sample size.
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	COSCA has confirmed importance of these outcomes. (Haywood 2018 147)	
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	Existing evidence is insufficient to favor one from of CPR over another. The Task Forces discussed the impact of one standard of basic life support training and the simplification using a single approach for teaching, learning and recalling how to perform CPR. Bystanders are more likely to be willing to perform compression-only CPR (Bray 2017 58) and familiarity with chest compression-only CPR has become widespread in some parts of the world (Grassner 2019). It is simple to teach, learn, remember, and perform (Sayre 2008 2162, Nishiyama 2008 90, Iwami 2015 415, Fukuda 2016 2060). Nevertheless, conventional CPR with compressions and ventilations (CV-CPR) is preferred when the bystander is capable and trained. Compression-only CPR should be considered only if ventilations are not possible.	Unknown undesirable effects, particularly with regard to training, implementation, and infectious disease exposure risks to rescuers.
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	Unknown.	

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.	

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	Compression-only CPR and conventional CPR are already included in training programs.	

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Bystanders are more likely to be willing to perform compression-only CPR (Bray 2017 58) and familiarity with chest compression-only CPR has become widespread in some parts of the world (Grassner 2019). It is simple to teach, learn, remember, and perform (Sayre 2008 2162, Nishiyama 2008 90, Iwami 2015 415, Fukuda 2016 2060). Nevertheless, conventional CPR with compressions and ventilations (CV-CPR) is preferred when the bystander is capable and trained.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Compression-only CPR and conventional CPR are already included in training programs and no additional infrastructure is needed.	

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

	JUDGEMENT						
			or the comparison				
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 lay responders, the treatment recommendation for CPR in drowned OHCA patients who have been removed from the water remains consistent with CPR for all patients in cardiac arrest [Maconochie 2020 S410; Olasveengen 2020 S41] (Good Practice Statement):

Adults:

We recommend that bystanders perform chest compressions for all patients in cardiac arrest[Olasveengen 2020 S41].

We suggest that bystanders who are trained, able, and willing to give rescue breaths and chest compressions do so for adults in cardiac arrest[Olasveengen 2020 S41].

Children:

We suggest that bystanders provide CPR with ventilation for infants and children younger than 18 years with OHCA[Maconochie 2020 S410].

We recommend that if bystanders cannot provide rescue breaths as part of CPR for infants and children younger than 18 years with OHCA, they should at least provide chest compressions[Maconochie 2020 S410].

For healthcare professionals and those with a duty to respond to drowning (e.g. lifeguards), we recommend providing ventilations in addition to chest compressions if they have been trained and are able and willing to do so (Good Practice Statement).

Justification

In making the decision to follow standard BLS treatment recommendations, the review group and Task Force considered the following:

- Cardiac arrest from drowning is due primarily to anoxia (Bierens 2016 147; Vanden Hoek 2010 e405; Soar 2010 1407). Therefore, as with pediatric out-of-hospital cardiac arrest where asphyxia is the predominant etiology (Atkins 2009 1484, Young 2004 157, Sirbaugh 1999 174, Kuisma 1995 141), providing ventilation in OHCA due to drowning is important (Szpilman 2004 25).
- Whilst no randomized clinical trial (RCT) was found, the two observational studies that examined the effect of conventional versus compression-only CPR in OHCA due to drowning were subject to a high risk of bias and were considered very low certainty of evidence.
- The significant finding in the subgroup data in children in the study by Tobin must be interpreted with caution due to the small sample size.
- As noted in the 2020 CoSTR publication, simulation and observational studies favor commencing CPR with compressions over airway and breathing, including two of three simulation RCTs reporting faster times to commencement of rescue breaths when starting with compressions. (Olasveengen 2020 S41)
- A previous systematic review supports the concept that conventional CPR may offer a greater chance for neurologically favorable survival than CO-CPR in children aged <1 year; while a multicentered European study showed increased survival to hospital discharge when bystanders had performed ventilation (Ashoor 2017 112; Grässner 2019 218).
- The impact of one standard of basic life support training and the simplification using a single approach for teaching, learning and recalling how to perform CPR.
- Bystanders are more likely to be willing to perform compression-only CPR (Bray 2017 58) and familiarity with chest compression-only CPR has become widespread in some parts of the world (Grassner 2019). It is simple to teach, learn, remember, and perform (Sayre 2008 2162, Nishiyama 2008 90, Iwami 2015 415, Fukuda 2016 2060). Nevertheless, conventional CPR with compressions and ventilations (CV-CPR) is preferred when the bystander is capable and trained.

Subgroup considerations

Most cardiac arrest in children is hypoxic in nature. Further analysis and future studies should include specific evaluation of children, adolescents, and the aged as distinct subgroups. The two observational studies had significantly different populations. The mean age for Fukada [Fukada 2019 166] was 72.4 years with a standard deviation of 21.6 years. Once propensity matched, then the mean age in the conventional CPR group was 65 years (SD=26.29) and 65.9 years (SD= 26.7) for the compression only group. Tobin [Tobin 2020 1] had an average age of 23.72years (SD = 25.12) in the conventional CPR group and 32.02 years (SD=26.38) in the compression only CPR Group.

Implementation considerations

Public education, training, instruction, and public health messaging materials should reflect the most appropriate method for performing CPR.

Monitoring and evaluation

N/A

Research priorities

High-quality evidence is required to examine the impact of the type of CPR on OHCA patient outcomes overall and in subgroups (e.g. children).

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QUESTION

Should CPR by rescuers wearing PPE vs. CPR by rescuers not wearing PPE be used for survival, quality and fatigue of providers delivering Basic Life Support?

POPULATION:	Providers delivering Basic Life Support
INTERVENTION:	CPR by rescuers wearing PPE
COMPARISON:	CPR by rescuers not wearing PPE
MAIN OUTCOMES:	Survival; CPR quality such as compression depth, compression rate, target depth, target rate, hands-off time, target release; rescuer's fatigue; time to procedure of interest; neurocognitive performance
SETTING:	Adults and children in any setting of cardiac arrest including simulated 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	The COVID-19 pandemic has infected 624 million people globally with nearly 6.5 million deaths as of Oct. 2022. CPR is one of the possible procedures leading to aerosol generation and is associated with a risk of transmission of infection to rescuers. Therefore, healthcare providers have been using personal protective equipment (PPE) including various types of gowns and masks. Several studies suggest that PPE might impair CPR performance and increase rescuer fatigue. However, other studies suggest that PPE including masks with and without valves do not impair the quality of CPR. In addition, masks were found to cause rescuer's breathing discomfort, heat and humidity build-up. Other theoretical side effects include increased CO2 partial pressure and decreased oxygen levels in the blood due to rebreathing.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Wearing PPE has a desirable effect on decreasing the possible transmission of infection from cardiac arrest patients. Studies report the transmission of diseases such as severe acute respiratory syndome (SARS) and middle east respiratory syndrome (MERS) during CPR. Therefore, international CPR guidelines recommend that providers should wear PPE when performing CPR. However, wearing PPE does not improve the quality of CPR (17 studies) or increase the survival (1 studies) of cardiac arrest patients, though it may reduce transmission of infection from healthcare providers to vulnerable patients. Therefore, direct patient benefits are limited. Among included studies, there was only 1 patient-centric outcomes such as survival. A retrospective study compared conventional PPE (before period, n=73) vs enhanced PPE (after period, n=57) including PAPR (powered air-purifying respirator) in emergency department setting (Ko 2021 1291). The use of enhanced PPE affected the performance of CPR to some extent but did not alter patient outcomes compared to the conventional PPE group. The rate of ROSC in the ED (49.3% vs. 43.8%; p = 0.597) and 1-month survival (8.2% vs. 3.5%; p = 0.465) were all lower in the enhanced PPE group, although the difference was not statistically significant. In multivariable logistic regression analyses, using enhanced PPE was not associated with the ROSC rate (OR = 0.79, 95% CI: 0.38–1.67; p = 0.542) or 1 month survival (OR = 0.38, 95% CI: 0.07–2.10; p = 0.266).	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Wearing PPE may increase rescuer fatigue, which could theoretically influence CPR quality and patient outcomes. The Borg score (a measure of fatigue) after 2- min of chest compressions was significantly higher in the N95-mask group than in the surgical mask group (16 vs. 14, p = 0.027; Tian 2021 434). However, the pooled effect did not show any significant difference in CPR quality between PPE vs no PPE. Very low-quality evidence from 2 observational simulation studies showed significantly higher fatigue (VAS score) in the PPE group. All studies varied substantially in the procedures used, including the type of PPE used, the design of simulated scenarios, the duration of CPR performed, and the measures of CPR quality used.	

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 included studies examining CPR quality provide indirect evidence as they are manikin simulation studies. However, among 9 outcomes (6 from RCT, 3 from observational study), 7 outcomes assessed have very low and 2 outcomes assessed to low certainty of evidence.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CPR by rescuers not wearing PPE	Risk with CPR by rescuers wearing PPE				
compression depth (comp depth) assessed with: mm	The mean compression depth was **0** mm	MD **1.75 mm lower** (4.31 lower to 0.81 higher)	-	356 (5 RCTs)	⨁◯◯◯ Very low [a,b,c,d]	
compression rate (rate) assessed with: /min	The mean compression rate was **0** /min	MD **1.03 /min lower** (5.79 lower to 3.72 higher)	-	356 (5 RCTs)	⨁◯◯◯ Very low [a,b,c,d]	
target depth assessed with: %	The mean target depth was **0** %	MD **6.54 % lower** (25.29 lower to 12.21 higher)	-	228 (4 RCTs)	⨁◯◯◯ Very low [a,b,c,e]	
target rate assessed with: %	The mean target rate was **0** %	MD **3.67 % lower** (18.26 lower to 10.91 higher)	-	160 (3 RCTs)	⨁◯◯◯ Very low [a,b,c,e]	
hands-off time assessed with: sec	The mean hands-off time was **0** sec	MD **5.06 sec higher** (1.69 lower to 11.81 higher)	-	80 (2 RCTs)	⨁◯◯◯ Very low [a,b,c,e]	
target release assessed with: %	The mean target release was **0** %	MD **4.3 % higher** (0.83 higher to 7.78 higher)	-	116 (2 RCTs)	⨁◯◯◯ Very low [a,b,c,e]	
compression depth assessed with: mm	The mean compression depth was **0** mm	MD **4.43 mm lower** (8.9 lower to 0.04 higher)	-	504 (4 observational studies)	⨁◯◯◯ Very low [a,f,g,h]	
compression rate assessed with: /min	The mean compression rate was **0** /min	MD **2.35 /min lower** (5.88 lower to 1.18 higher)	-	504 (4 observational studies)	⨁◯◯◯ Very low [a,f,g]	
fatigue assessed with: VAS (10 points)	The mean fatigue was **0**	MD **2.68 higher** (1.38 higher to 3.97 higher)	-	248 (2 observational studies)	⨁◯◯◯ Very low [a,f,g]	

a. manikin simulation studies
b. incomplete outcome data
c. possible selective reporting
d. insufficient sample
e. random sequence generating and allocation concealment
f. confounding bias
g. Bias in classification of interventions
h. 2 studies favor no PPE, while 2 studies non-significant

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 patient outcome was survival, and neurologically intact survival. Core outcome set for cardiac arrest (COSCA) has confirmed importance of these outcomes to patients. High quality CPR is vital to survival.	

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 terms of survival or CPR quality (outcomes of this PICO), wearing PPE has a moderate desirable effect and a small undesirable effect. PPE is recommended to protect healthcare providers from the transmission when performing CPR in patients with suspected infection. Combining the available evidence, PPE does not significantly affect the quality of CPR, but increases the fatigue of rescuers. Therefore, if an infection is suspected or uncertain, PPE should be worn as indicated. There is a possibility of early fatigue, so replacing the rescuer at an appropriate time is recommended.	

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 for PPE may vary in terms of PPE type from simple mask to PAPR, and on the location where CPR is performed.	

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 identified describing the resource and economic impact of using PPE especially in the cardiac arrest setting.	

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	A study from Kenya indicated that investing in adequate PPE to protect all healthcare workers would result in a 10-fold cost return and prevent over 70% of infections among HCWs. An extra investment of USD 1.56 million will be required to achieve the reduced number of HCW cases and deaths under the adequate PPE scenario. With this investment, an average of 30,041 healthcare worker cases and 416 healthcare worker deaths will be averted. Overall, the return on investment (ROI) from productivity gains is estimated to be USD 170.64 million, translating into a 11.04 times ROI (Kazungu 2021 992). However, the cost-effectiveness may vary according to the country.	

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 were no studies identified describing the health equity of using PPE especially in the cardiac arrest setting.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Wearing various levels of PPE is being implemented in most countries during the global COVID-19 pandemic.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Wearing various levels of PPE is being implemented in most countries during the global COVID-19 pandemic.	

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 monitoring the fatigue of rescuers when performing CPR while wearing PPE (Weak recommendation, Very low certainty of evidence).

Justification

In making this treatment recommendation, we put a high value on protecting healthcare providers from potential infection transmission and consistency with current recommendations on the use of PPE. Although studies indicate an increased incidence of rescuer fatigue with CPR while wearing PPE, there was no effect on CPR quality. Furthermore, there was a lack of clinical studies examining the impact of PPE on patient outcomes. The Task Force considered a treatment recommendation that included an option to shorten CPR cycles while wearing PPE; however, we decided against this as there was no evidence that PPE influenced CPR quality. A shorter CPR cycle may also increase hands-off-chest time. A recent systematic review (BLS #346: Timing of CPR cycles) also suggested against pausing chest compressions at intervals other than every two minutes to assess the cardiac rhythm.
The studies included in this review were predominately simulation manikin-based studies and varied significantly in the procedures used, including the type of PPE, the design of simulated scenarios, the duration of CPR performed, and the measures of CPR quality used. As such, results should be interpreted carefully and may not be generalisable to clinical setting.

Subgroup considerations

In this analysis, RCT and non-RCT were analyzed separately. If there are more studies in the future, subgroup analysis according to PPE level (level C or D), type of respirator (N95, PAPR), adult or children, and CPR time (prolonged or not) are necessary.

Implementation considerations

Wearing PPE is already widely implemented in most countries during the global COVID-19 pandemic.

Monitoring and evaluation

If PPE is worn during CPR, appropriate monitoring should be done to prevent deterioration of CPR quality due to rescuer fatigue.

Research priorities

1. Clinical studies examining the effect of PPE on patient outcome
2. Clinical studies examining the effect of PPE on CPR quality
3. Examine the relationship between PPE use, CPR duration and rescuer fatigue.
4. Clinical studies should consider the best type of PPE or appropriate modification strategies to mitigate rescuer fatigue.

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QUESTION

ECPR Versus Manual or Mechanical Cardiopulmonary Resuscitation (CPR) in Adult Cardiac Arrest

POPULATION:	Adults (≥ 18 years) with cardiac arrest in any setting (out-of-hospital or in-hospital)
INTERVENTION:	ECPR including extracorporeal membrane oxygenation or cardiopulmonary bypass during cardiac arrest
COMPARISON:	Manual or mechanical CPR
MAIN OUTCOMES:	Any clinical outcome, including short-term survival and neurological outcomes (e.g., hospital discharge, 28-days, 30-days, and 1-month) and long-term survival and neurological outcomes (e.g., 3-months, 6-months, 1-year)
SETTING:	Any Setting
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	Survival for refractory cardiac arrest is low.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate	Based on the evidence (primarily RCTs), there is a potential for large benefit in highly selected patients.	The Task Force discussed the potential that ECPR could provide societal benefit by allowing initial survivors who subsequently meet criteria for brain

● Large ○ Varies ○ Don't know		death or withdrawal of life-sustaining treatment to be considered potential organ donors.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know		The risk of harm with the provision of ECPR likely depends on the scenario in which the intervention is applied. The risk of harm would be minimal or negligible if ECPR is provided in a patient who has already received prolonged advanced life support management and where no other treatment options are available. Conversely, if ECPR is provided early in the course of the cardiac arrest, then the risk of harm would include the possibility that ROSC and survival could have occurred without requiring ECPR since ECPR is known to have complications including but not limited to hemorrhage and death. Moreover, transportation to facilitate ECPR might reduce CPR quality. From a resource-allocation standpoint, the risks in applying ECPR to a non-selected population may be the provision of life support to patients who will inevitably not survive (e.g., elderly patient with comorbidities). The Task Force discussed the potential that ECPR could disadvantage individuals if ECPR increases probability of survival without good neurological recovery.

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 for out-of-hospital cardiac arrest. Very low for in-hospital cardiac arrest.	

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 importance of neurologically intact survival is generally agreed upon with recognition that survival without neurological recovery is an undesirable outcome for most 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	See systematic review and CoSTR.	

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 provision of ECPR followed by the management of patients with ongoing veno-arterial ECMO is resource intensive. This intervention is currently unavailable for most OHCA settings and only available in select emergency departments and in-hospital 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		

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 has been no comprehensive cost-effectiveness analysis based on effectiveness data from RCTs.	

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 relevant studies have been identified; however logic would dictate that resource poor areas may not have local centers capable of providing this intervention.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know		This is not formally known, but the acceptability of this intervention to key stakeholders would likely depend on their available resources.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Some are already poised to provide ECPR, but most centers and hospitals would require substantial additional resources and training to be capable of performing it.

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 extracorporeal cardiopulmonary resuscitation (ECPR) may be considered as a rescue therapy for selected patients with out-of-hospital cardiac arrest when conventional cardiopulmonary resuscitation is failing to restore spontaneous circulation in settings where this can be implemented (weak recommendation, low certainty of evidence).

We suggest extracorporeal cardiopulmonary resuscitation (ECPR) may be considered as a rescue therapy for selected patients with in-hospital cardiac arrest when conventional cardiopulmonary resuscitation is failing to restore spontaneous circulation in settings where this can be implemented (weak recommendation, very low certainty of evidence).

QUESTION: Calcium During Cardiac Arrest

POPULATION:	Adults and children with cardiac arrest
INTERVENTION:	Administration of calcium (intravenous or intraosseous) during cardiac arrest
COMPARISON:	No administration of calcium during cardiac arrest
MAIN OUTCOMES:	Any clinical outcome, including return of spontaneous circulation, short-term survival and neurological outcomes (e.g., hospital discharge, 28-days, 30-days, and 1-month) and long-term survival and neurological outcomes (e.g., 3-months, 6-months, 1-year)
SETTING:	Any setting (in-hospital or out-of-hospital)

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival for refractory cardiac arrest remains low with limited pharmacological intervention. Calcium has a theoretically important role through its inotropic effect and smooth muscle contraction that could potentially benefit cardiac arrest patients.	Despite previous recommendations against administering calcium during cardiac arrest management, it continues to be routinely used during resuscitation.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large	Evidence from a recent randomized trial demonstrated no benefit to routine calcium administration during cardiac arrest.	The Task Force discussed the potential effect that calcium administration could have in subpopulations during cardiac arrest, but that there is no evidence to support this (e.g

○ Varies ○ Don't know		hyperkalemia).
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The single high-quality trial available showed a possible decrease in ROSC with calcium administration, although this did not achieve statistical significance.	Longer-term outcomes also had point estimates suggesting worse outcomes with calcium, although numbers were small and confidence intervals included both possible harm and possible benefit.
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	Moderate for out-of-hospital cardiac arrest. Low for in-hospital cardiac arrest	All trials to date have included OHCA patients only.
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	The importance of neurologically intact survival is generally agreed upon with recognition that survival without neurological recovery is an undesirable outcome for most patients.	

○ 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	The available evidence does not show any benefit from the intervention, and suggests possible harm.	

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		Cost of calcium is low in most 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		Cost of calcium is low in most 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 has been no comprehensive cost-effectiveness analysis based on effectiveness data from the randomized trials..	

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 relevant studies have been identified. However, calcium is low cost and widely available in most prehospital and hospital 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 acceptability of calcium administration to key stakeholders would likely depend on the patient subpopulation.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Calcium is widely available in most settings and can be administered intravenously or intraosseously during cardiac arrest.

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
●	○	○	○	○

QUESTION

Should Double Sequential Defibrillation vs. Standard defibrillation be used for Adult cardiac arrest patients with a shockable (VF/pVT) cardiac arrest rhythm?

POPULATION:	Adult cardiac arrest patients with a shockable (VF/pVT) cardiac arrest rhythm
INTERVENTION:	Double (dual) Sequential Defibrillation (DSED)
COMPARISON:	Standard defibrillation
MAIN OUTCOMES:	Good Neurological Outcome at Discharge; Survival to Hospital Discharge; Survival to Hospital Admission; Return of Spontaneous Circulation; Termination of VF;
SETTING:	Any 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 sudden cardiac arrest is low. Patients who present in an initial cardiac rhythm of ventricular fibrillation (VF) have a higher rate of good outcome. Approximately 20% of VF patients, however, will remain in VF despite standard resuscitation interventions. Patients in refractory VF have significantly lower rates of survival than patients who respond to standard resuscitation treatments.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Improvement in survival to discharge and neurologic outcome is substantial.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	It is not currently known if there are undesirable effects of double sequential defibrillation. Excess defibrillation energy may cause myocardial stunning and prevent return of organised rhythm post-defibrillation [Crampton 1980 167]. This was not seen in the current trial.	Damage to defibrillators from DSED has been raised as a concern. The trial was designed so that defibrillations were done in rapid sequence and not simultaneously, and no damage to defibrillators was reported.

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 around the evidence for DSED compared to standard defibrillation is low. The new randomized trial is the first of its kind, and shows a benefit from DSED compared with standard defibrillation (SD). The certainty of evidence was downgraded for concern for risk of bias due to the unavoidable lack of blinding on the part of the treating paramedics, and because of the cluster randomization, with a paramedic service being aware of the treatment group at the time of enrolment and treatment. Evidence was also downgraded for imprecision as the optimal information size, based on the author's own sample size calculations, was not met due to the trial being terminated early.	Sensitivity analyses showed some variability in results.

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 little uncertainty around the value that people put on the main outcome of neurological survival and/or survival to hospital discharge.	

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	Although the certainty of evidence is low, the existing evidence suggests a beneficial effect with DSED compared with SD on all included outcomes.	

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 research examined costs associated with the intervention.	There are most likely costs associated with double dispatching multiple units in order to perform DSED or having two defibrillators available. The extent of the costs associated with this intervention will vary from service to service. In some systems it is already standard for two ambulances (and thus two defibrillators) to be dispatched to every cardiac arrest, but this is not the case in all systems. In the in-hospital setting there is also considerable variation in the number and location of defibrillators present.

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 research examined the resource requirements for the intervention	There are costs associated with the intervention as it requires multiple defibrillators to perform. The resource requirements to carry out the intervention will vary across different healthcare 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	Not known. No included studies	

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	Implementation of DSED could be challenging in settings with lower resources, including rural areas, due to the cost of having two defibrillators available for use.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Stakeholders are likely to accept the benefit vs risk. If effective, the benefit is high, while the associated risks would be low.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies	There is no research examining the feasibility of this intervention. It is likely that the feasibility will be dependent on the setting.	Feasibility will depend on dispatching procedures, availability of units with defibrillators and training of personnel. Feasibility may also depend on the setting, rural vs. urban vs. remote settings. May also depend on low vs high resource settings.

○ 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
○	○	○	•	○

CONCLUSIONS

Recommendation

We suggest that a double sequential defibrillation strategy (weak recommendation, low certainty of evidence) or a vector change defibrillation strategy (weak recommendation, very low certainty of evidence) may be considered for adults with cardiac arrest who remain in ventricular fibrillation or pulseless ventricular tachycardia after 3 or more consecutive shocks.

If a double sequential defibrillation strategy is utilized, we suggest an approach similar to that in the available trial, with a single operator activating the defibrillators in sequence. (good practice statement)

Justification

Existing data provides low certainty evidence of improved ROSC, VF termination, survival to discharge and favorable neurologic outcome (mRS 0-2) with DSED compared with SD for refractory VF. These data also provide low certainty evidence for improvement in VF termination and survival to discharge with VC compared with SD. Benefits from VC compared with SD on ROSC and favorable neurologic outcome at hospital discharge did not reach statistical significance. However, it is not possible to conclude with the data available whether DSED is superior to VC for this patient population.

Subgroup considerations

None

Implementation considerations

Implementation of DSED would require training of frontline staff as well as ensuring that there were defibrillators that were available to provide the intervention. Implementation of a VC strategy would require training, but would not necessarily require additional defibrillators.

Monitoring and evaluation

It is important to monitor the intervention, not just to determine effectiveness but to track any adverse events such as harm to the patient, defibrillator damage, the increase in resource utilization etc.

Research priorities

-Comparison of the effectiveness of DSED and VC in this patient population
-Optimal timing of either of these defibrillation strategies
-Whether pad placement with SD affects efficacy

Reference

Crampton R. Accepted, controversial, and speculative aspects of ventricular defibrillation. Progress in Cardiovascular Diseases. Volume 23, Issue 3, 1980, 167-186

QUESTION

Should Vector Change Defibrillation vs. Standard defibrillation be used for Adult cardiac arrest patients with a shockable (VF/pVT) cardiac arrest rhythm?

POPULATION:	Adult cardiac arrest patients with a shockable (VF/pVT) cardiac arrest rhythm
INTERVENTION:	Vector change (anterior-posterior pad placement, VC) defibrillation
COMPARISON:	Standard defibrillation (SD)
MAIN OUTCOMES:	Good Neurological Outcome at Discharge; Survival to Hospital Discharge; Survival to Hospital Admission; Return of Spontaneous Circulation; Termination of VF;
SETTING:	Any 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 sudden cardiac arrest is low. Patients who present in an initial cardiac rhythm of ventricular fibrillation (VF) have a higher rate of good outcome. Approximately 20% of VF patients, however, will remain in VF despite standard resuscitation interventions. Patients in refractory VF have significantly lower rates of survival than patients who respond to standard resuscitation treatments.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Improvement in survival to discharge and neurologic outcome is substantial.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	It is not currently known if there are undesirable effects of VC defibrillation. Whether changing the orientation of pad placement during resuscitation would have any negative effect, such as interrupting CPR or delaying defibrillation, is not known.	

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 around the evidence for VC compared with SD is low to very low. The new randomized trial is the first of its kind, and shows a benefit from VC compared with SD for VF termination and survival to discharge. Point estimates also suggested possible benefit for ROSC and survival with favorable neurologic outcome, but statistical significance was not achieved for those outcomes. The certainty of evidence was downgraded for risk of bias due to the unavoidable lack of blinding on the part of the treating paramedics, and because of the cluster randomization, with a paramedic service being aware of the treatment group at the time of enrolment and treatment. Evidence was also downgraded for imprecision as the optimal information size, based on the author's own sample size calculations, was not met due to the trial being terminated early. Certainty was downgraded additionally for imprecision for ROSC and favorable neurologic outcome, due to a confidence interval spanning both benefit and harm.	

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 little uncertainty around the value that people put on the main outcome of neurological survival and/or survival to hospital discharge.	

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	Although the certainty of evidence is low to very low, the existing evidence suggests a beneficial effect with VC compared with SD on all included outcomes.	

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 research examined costs associated with the intervention.	Changing pad orientation could require some cost for training.

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 research examined the resource requirements for the intervention	

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	Not known. No included studies	

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	While no studies addressing the effect on equity were identified, changing the pad placement should be feasible in any setting where a defibrillator is already available, and thus we do not anticipate that a VC strategy would affect equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Stakeholders are likely to accept the benefit vs risk. If effective, the benefit is high, while the relative risks would be low.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies	There is no research examining the feasibility of this intervention. It is likely to be feasible as no additional equipment would be required.	

○ 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
○	○	○	•	○

CONCLUSIONS

Recommendation

We suggest that a double sequential defibrillation strategy (weak recommendation, low certainty of evidence) or a vector change defibrillation strategy (weak recommendation, very low certainty of evidence) may be considered for adults with cardiac arrest who remain in ventricular fibrillation or pulseless ventricular tachycardia after 3 or more consecutive shocks.

If a double sequential defibrillation strategy is utilized, we suggest an approach similar to that in the available trial, with a single operator activating the defibrillators in sequence. (good practice statement)

Justification

Existing data provides low certainty evidence of improved ROSC, VF termination, survival to discharge and favorable neurologic outcome (mRS 0-2) with DSED compared with SD for refractory VF. These data also provide low certainty evidence for improvement in VF termination and survival to discharge with VC compared with SD. Benefits from VC compared with SD on ROSC and favorable neurologic outcome at hospital discharge did not reach statistical significance. However it is not possible to conclude with the data available whether DSED is superior to VC for this patient population. There are no trials on either intervention in IHCA, but the TF opinion is that this evidence could be applied to the IHCA, with additional downgrading for indirectness.

Subgroup considerations

None

Implementation considerations

Implementation of DSED would require training of frontline staff as well as ensuring that there were defibrillators that were available to provide the intervention. Implementation of a VC strategy would require training, but would not necessarily require additional defibrillators.

Monitoring and evaluation

It is important to monitor the intervention, not just to determine effectiveness but to track any adverse events such as harm to the patient, defibrillator damage, the increase in resource utilization etc.

Research priorities

-Comparison of the effectiveness of DSD and VC in this patient population
-Optimal timing of either of these defibrillation strategies
-Whether pad placement with SD affects efficacy

Reference

Crampton R. Accepted, controversial, and speculative aspects of ventricular defibrillation. Progress in Cardiovascular Diseases. Volume 23, Issue 3, 1980, 167-186

QUESTION

Glascow Coma Scale motor score for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Glasgow Coma Scale motor score evaluated within 96h after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 3 or at 6 months after cardiac arrest.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. The majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on the high likelihood of severe hypoxic brain injury and prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy. Identifying patients with a likely good outcome based on clinical examination could facilitate the	

	continuation of care in some unconscious patients. The Glasgow Coma Scale motor score less than three is an integral part of the prognostication algorithm for predicting poor outcome.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The Glasgow Coma Score (GCS) motor score was investigated in two observational studies [Hifumi, 2015 2201; Moseby-Knappe, 2020 1852]. According to bias assessments the overall bias was moderate in one study [Moseby-Knappe 2020 1852] and high in one study [Hifumi 2015 2201]. In both studies the clinical examination was done off-sedation. In one study [Moseby-Knappe, 2020 1852] GCS motor score of > 3 on a day three or four (72–96h) after cardiac arrest predicted good outcome at 6 months with specificity of 84% (95% CI 79-83%) and sensitivity of 77% (95% CI 67-85%). In the same study GCS motor score 3–5 on day 4 predicted good outcome with 72% (95% CI 66-77%) specificity and 96% (95% CI 93-97%) sensitivity. In one study [Hifumi, 2015 2201] GCS motor score 4–5 evaluated on ICU admission predicted good outcome at 3 months after cardiac arrest with specificity of 98% (95% CI 93-99%)and sensitivity of 12% (95% CI 7-17%).	Sedation may interfere with clinical examination potentially reducing its accuracy for predicting good neurological outcome. In the study with motor response evaluated on hospital admission [Hifumi, 2015 1852] GCS motor score 4–5 was a relatively uncommon but highly specific (98%) predictor of good neurological outcome. If confirmed by further studies, this sign may be considered to screen patients destined to neurological recovery early after arrest and potentially rationalise post-resuscitation interventions

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small	Cardiac arrest patients with prolonged unconsciousness are the population in whom prognostic uncertainty is maximal in the intensive care unit (ICU), and who are the target of currently recommended prognostic algorithms. In these patients, combining multiple prognostic tests may reduce uncertainty. Continuing care and conducting more confirmatory tests with signs of a possible good outcome based on	

● Trivial ○ Varies ○ Don't know	a test result of GCS motor score higher than three is not likely to have undesirable effects as it may increase the certainty of the patients' prognosis.	

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 from GCS motor score is very low because of the small number of studies, the risk of bias (high to moderate), and the risk of interference related to the use of sedation and pain medication.	Similarly to other predictors based on clinical examination, GCS motor score cannot be concealed from the treating team. GCS motor score is prone to confounding due to sedation. The performance of the painful stimulus eliciting the motor response is not standardized.

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	It is common to define CPC scores of 1–2 as a favorable neurological outcome after cardiac arrest. There is limited data available regarding whether some people value a CPC of 3 as a favorable 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	Assessment of the GCS motor score is an integral part of prognostication in patients after cardiac arrest. It is already recommended as a way to identify those unconscious patients who have a GCS motor score less than 3, and who should undergo further testing for hypoxic brain injury. Using the GCS motor score in order to identify those with a better motor response, is not likely to have undesirable effects. On the other hand the effect of administered sedation and pain medication may influence the assessment of the GCS motor score and the adequate time for achieving a reliable test result may vary between patients.	

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 for the assessment of GCS motor score are negligible.	No study assessing savings from prognostication based on GCS motor score was identified in our review. Using the GCS instead of other means of prognostication could lead to saving but no such studies were found.

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	Assessing the GCS motors score is not costly, but we did not identify any studies specifically assessing costs of GCS motor score.	

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 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	Considering the negligible costs of GCS motor score, a problem of inequity is unlikely.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	We have not identified any study assessing acceptability, but acceptability is likely.	

● Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of GCS motor score does not require special skills or equipment. Nevertheless, the examiner needs to be familiar with the basics of clinical neurological examination.	

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 assessing the Glasgow Coma Scale motor score in the first four days after cardiac arrest to identify patients with a score higher than three, which may indicate an increased likelihood of favourable outcome (weak recommendation, very low certainty of evidence).

Justification

The evidence is limited, but the assessment of GCS is without cost and is an integral part of intensive care. The need to ensure that the assessment is not influenced by sedation is likely to be a problem that clinicians are somewhat familiar with. We note that the admission GCS motor score also was specific for predicting outcome but since the evidence was of such low certainty, its value is unclear.

Subgroup considerations

The data are exclusively from patients with OHCA and those with a cardiac cause of the arrest.

Implementation considerations

Monitoring and evaluation

Research priorities

Larger studies on the use of the GCS in cardiac arrest patients at various time-points are needed. In addition, there is a need to include in-hospital cardiac arrest patients as well as those with a non-cardiac cause of the arrest.

The clinical course and the need for further prognostic tests in patients with a GCS motor score of three (flexion) is currently unclear.

Studies comparing the use of GCS motor score to other means of assessing the prognosis are needed. This includes studies assessing costs and cost-effectiveness.

Studies on whether there is inter-rater variability between different health care professionals assessing the GCS motor score.

References:

Hifumi T, Kuroda Y, Kawakita K, et al. Effect of Admission Glasgow Coma Scale Motor Score on Neurological Outcome in Out-of-Hospital Cardiac Arrest Patients Receiving Therapeutic Hypothermia. Circ J. 2015;79(10):2201-8.

Moseby-Knappe, M., Westhall, E., Backman, S. et al. Performance of a guideline-recommended algorithm for prognostication of poor neurological outcome after cardiac arrest. Intensive Care Med 46, 1852–1862 (2020).

QUESTION

Brain computed tomography (CT) for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Grey matter/white matter ratio (GWR), QRA, and ASPECTS-b on brain computed tomography (CT)), assessed within three hours after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 1 month after cardiac arrest.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The ability of brain CT performed at one to three hours after ROSC to predict good neurological outcome was assessed in one study [Lee, 2017]. Hypoxic-ischaemic changes due to cardiac arrest were quantified using the density ratio between the grey and white matter (GWR), the quantitative regional attenuation (QRA) score and the Alberta Stroke Program Early CT (ASPECTS-b) score. **A GWR ≥ 1.25 or a QRA ≤ 5** predicted good neurological outcome at 1 month with **77% specificity and 25% sensitivity**. **ASPECTS- b≥15** predicted good neurological outcome with **89% specificity and 75% sensitivity.** Kyu Sun Lee, Sung Eun Lee, Jun Young Choi, et al. Useful Computed Tomography Score for Estimation of Early Neurologic Outcome in Post-Cardiac Arrest Patients With Therapeutic Hypothermia, Circulation Journal, 2017, Volume 81, Issue 11, Pages 1628-1635 **Grey matter to white matter ratio (GWR)** is the ratio between the densities (measured in Hounsfield units) of the grey matter and the white matter on brain CT. In the normal brain, the grey matter has a higher density than the white matter. The occurrence of brain oedema reduces GWR. **QRA (Quantitative regional abnormality)** is the sum of hypoattenuations in 12 parenchymal areas on brain CT and is calculated bilaterally (lower scores indicate fewer hypoattenuation, maximum score of 24). **ASPECTS-b** (The Alberta Stroke Program Early CT Score) provides a semiquantitative assessment of early ischemic changes on brain CT in the middle cerebral artery territory, bilaterally. ASPECTS-b score is calculated by subtracting 1 per each change from the maximum score of 20 points. Lower scores indicate more abnormalities.	In the study from Lee, 2017 CT was performed early, when the discriminative value of GWR for post-CA brain injury is low. The ASPECTS-b score, was more accurate than GWR or QRA in that study [Lee, 2017]. However, ASPECTS-b has been designed for assessing ischaemic injury from stroke, which is usually unilateral. Brain damage after CA is usually bilateral, which deprives the reader of the CT scan of a contralateral reference when detecting ischaemic changes. The feasibility of the ASPECT-b score after CA is thus uncertain.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ●Small ○Trivial ○ Varies ○ Don't know	Brain CT implies exposure to ionizing radiation. Brain imaging is usually not available at the bedside and requires transportation to a Radiology department. Patients after cardiac arrest are often hemodynamically unstable, and intra-hospital transport may carry additional risk.	A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to therapeutic obstinacy.

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 brain CT is very low because of lack of blinding and it is based on only one retrospective study ([Lee, 2017] on 67 participants) investigating good outcome. That study included only patients with CT scan performed within six hours after CA (potential selection bias) A source of confounding for GWR is represented by the different available methods and sites of measurement.	Unlike other predictors, such as those based on clinical examination, imaging is not affected by sedation or paralysis and can be assessed blindly. There is no consensus on what the normal levels for GWR are. ASPECT-b score has been designed to assess ischemic injury after stroke.

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	Almost all prognostic studies included in our review defined good outcome as CPC 1–2.	There may be interindividual variations on how good neurological outcome is perceived.

Balance of effects

Does the balance between desirable and undesirable effects favor 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 ○ Don't know	A high GWR or QRA or ASPECT-b score is associated with good neurological outcome after cardiac arrest. However, evidence is limited to one study, and both sensitivity and specificity are probably too low to make clinical decisions based on brain CT.	

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 addressing this question were identified.	The costs of imaging assessment are higher when compared with those of clinical examination. In addition, the measurement of GWR/QRA/ASPECTS-b requires additional calculations and skills. On the other side, undergoing brain CT is routine for most patients who are unconscious after resuscitation and are scheduled for coronary angiography and/or treatment with anticoagulants.

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 any studies specifically assessing costs of imaging for prognostication after cardiac arrest.	

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 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 addressing this question were identified.	A problem of inequity is possible, since prognostic assessment using imaging implies resources and skills that may not be universally available.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any studies assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review.	Imaging studies used for neuroprognostication after cardiac arrest cannot be performed at the bedside and require transportation to a Radiology Department, with additional clinical and safety risks. A CT scan is likely available in every hospital, at least in high-income countries, but the skills to assess the severity of HIBI on brain CT may not be universally available.

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 using GWR, QRA, or ASPECTS-b on brain CT to predict good neurological outcome in patients who are comatose after cardiac arrest (weak recommendation, very-low certainty of evidence).**

Justification

Evidence showing that a high grey matter to white matter ratio (GWR), a low quantitative regional attenuation (QRA) score or a high Alberta Stroke Program Early CT (ASPECTS-b) score predict good neurological outcome after cardiac arrest is limited to one study, and the certainty of evidence is very low. There is a wide heterogeneity of measurement techniques (sites and calculation methods) for GWR.

Subgroup considerations

None

Implementation considerations

Prognostication based on imaging requires technology and skills that may not be universally available.

Monitoring and evaluation

Research priorities

A consistent GWR threshold for predicting good neurological outcome after cardiac arrest should be identified.

A standardisation of the methods for GWR calculation is warranted.

The optimal timing for prognostication using brain CT after cardiac arrest is still unknown. Studies assessing serial brain CT after cardiac arrest are desirable.

None

QUESTION

Diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI) for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Diffusion-weighted imaging (DWI) on brain magnetic resonance imaging (MRI), assessed within eight days after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1–2 at 6 months after cardiac arrest.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data, are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest was necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post-cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	DWI was investigated in five observational studies [Park, 2020; Oh, 2019; Jang, 2019; Mlynash, 2010, Wouters, 2021] Park JS, In YN, You YH, et al. (2020) Ultra-early neurologic outcome prediction of out-of-hospital cardiac arrest survivors using combined diffusion-weighted imaging find- ings and quantitative analysis of apparent diffusion coefficient. Resuscitation 148:39–48 Oh SH, Park KN, Choi SP, et al. (2019) Beyond dichotomy: patterns and amplitudes of SSEPs and neurological outcomes after cardiac arrest. Crit Care 23:224 Jang J, Oh SH, Nam Y, et al. BS (2019) Prognostic value of phase information of 2D T2*-weighted gradient echo brain imaging in cardiac arrest survivors: A preliminary study. Resuscitation 140:142–149 Mlynash M, Campbell DM, Leproust EM, et al. (2010) Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. Stroke 41:1665–1672 Wouters A, et al., Added Value of Quantitative Apparent Diffusion Coefficient Values for Neuroprognostication After Cardiac Arrest, Neurology, 2021. 96(21): p. e2611. In one study [Oh, 2019] on MRI immediately after rewarming, **absence of restricted diffusion** on DWI predicted good outcome with specificity of **95% (sensitivity 72%),** and the **presence of a single area of restricted diffusion** predicted good outcome with **92% specificity (sensitivity 94%)**. In one study [Park, 2020], **the absence of restricted diffusion** was assessed at 3.1 h and 77.6 h after ROSC. Earlier MRI assessment predicted good outcome at six months with **specificity of 60% (sensitivity 100%)** and later MRI assessment with **specificity of 93% (sensitivity 100%)**. In another study [Jang 2020], the MRI was assessed around 70 hours (74.5 h) after ROSC. In that study, **absence of DWI lesions** predicted good outcome at six months **with specificity of 93% (sensitivity 92%).** In one study (Jang, 2019, 142) on 39 patients, the **absence of restricted diffusion** on MRI at 77.6 (75.9–80) h after ROSC predicted good outcome at 6 months with **93.3 [68.1–99.8] specificity** and **100 [86.7–100] sensitivity** (very-low certainty of evidence). One study [Milnash, 2010] assessed **the absence of DWI or fluid-attenuated inversion recovery (FLAIR) lesions** within 8 days from ROSC at cortex, deep grey nuclei, and cerebellum and pons. Accuracy for predicting good outcome at six months was **specificity 80%, sensitivity 79%** for **absence of lesions in the cortex, specificity 87%, sensitivity 50%,** for **absence of lesions in the deep grey nuclei,** and **specificity 20%, sensitivity 100%** for **absence of lesions in the brainstem and cerebellum.** One study [Wouters, 2021] determined the predictive accuracy for good outcome at six months of **average apparent diffusion coefficient (ADC)** value and **percentage of brain voxels with an ADC value <450 x 10^{-6} mm^2/s**. The thresholds for average ADC and percentages of ADC< 450 x 10^{-6} mm^2 were	Acute PCABI is characterised by cytotoxic oedema, cellular swelling, and restriction of water diffusion in affected brain areas which appears as a hyperintensity on DWI with corresponding low apparent diffusion coefficient (ADC). The absence of DWI changes is a potentially valuable predictor of good clinical The development of brain oedema after CA is time-dependent, and the extent of changes may not be evident before 3–7 days after CA .The only study we included that assessed MRI serially showed that the accuracy of MRI was higher at 77.6h vs 3.1h after ROSC. The spatial distribution of brain injury is also of relevance, due to the selective vulnerability of specific brain areas to post CA brain injury.

	determined according to 100% sensitivity to predict good outcome. **The average ADC value** to predict good outcome **with 100% sensitivity was >931 x 10^{-6} mm^2/s (specificity 38%).** The threshold of **<6.5% of brain voxels with an ADC value <450 x 10^{-6} mm^2/s predicted good outcome with 100% sensitivity and 26% specificity.** The certainty of evidence was very low for all studies.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Brain imaging is usually not available at the bedside. Patients after cardiac arrest are often hemodynamically unstable, and intra-hospital transport may carry additional risk.	A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to therapeutic obstinacy.

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 the evidence for DWI-MRI is very low because of the lack of blinding and the lack of established criteria of DWI or ADC thresholds to define a 'positive' MRI. An additional issue is selection bias. All DWI-MRI studies investigating good outcome prediction were small retrospective studies. Apparent diffusion coefficient (ADC) allows a quantification of the diffusion changes on brain MRI. However, the evidence is limited to one study, and no ADC threshold for prediction of good neurological outcome has been established.	Unlike other predictors, such as those based on clinical examination, imaging is not affected by sedation or paralysis and can potentially be assessed blindly. The interpretation of quantitative imaging results is operator dependent. However, as far as poor outcome prediction is concerned, at least one study showed that expert neuroradiologists' visual assessment of brain CT

		provided an accurate prediction. Similarly, we feel that an expert neuroradiologist should be able to detect the absence of pathological findings on MRI. Variations in the measurement methods (e.g., location of the region of interest) and differences in MRI scanners and scanning protocols might exist. Standardisation and normalisation of imaging techniques are of value.

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	A good outcome was defined as CPC 1-2 in all but one study (Mlynash, 2010, 1665), in which good outcome was defined as CPC 1-3.	There may be interindividual variations in how good neurological outcome is perceived.

Balance of effects

Does the balance between desirable and undesirable effects favor 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 ○ Don't know	The absence of restricted diffusion on MRI is associated with good outcome after cardiac arrest. In two studies [Park, 2020; Jang 2020] the absence of restricted diffusion in DWI-MRI assessed at around three days after CA predicted good outcome with high sensitivity and specificity (92-100% and 93%, respectively).	

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 study assessing costs or savings related to prognostication based on imaging has been included in our review. However, the costs of MRI are higher when compared with those of clinical examination.	

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 any studies specifically assessing costs of imaging for prognostication after cardiac arrest.	

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 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	We did not find any studies addressing this question.	A problem of inequity is possible, since prognostic assessment using imaging implies resources and skills that cannot be available anywhere anytime.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	Feasibility was not specifically addressed in any of the studies included in this review.	MRI cannot be performed at the bedside, which is a major limitation, and it carries

○ Yes ○ Varies ○ Don't know		additional risks due to the magnetic field, which makes it incompatible with most standard monitoring equipment and with some implanted devices, such as pacemakers/defibrillators. In addition, MRI recording is a relatively long procedure. An MRI is available in most hospitals in high-income countries, but the skills to assess the severity of HIBI on brain MRI may not be universally available.

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 using the absence of diffusion restriction on cortical MRI between 72h and 7 days after ROSC, in combination with other tests, for predicting good neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).

We suggest against using ADC on brain MRI to predict good neurological outcome in patients who are comatose after cardiac arrest (weak recommendation, very-low certainty of evidence).

Justification

Evidence from five studies consistently suggests that the absence of visible cytotoxic oedema, assessed as the absence of cortical DWI changes on brain MRI, predicts good neurological outcome with high specificity at 72h or later after cardiac arrest.
Apparent diffusion coefficient (ADC) allows quantifying diffusion changes on brain MRI. However, the evidence is limited to one study, and no ADC threshold for prediction of good neurological outcome has been established.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

Research priorities

The criteria for defining a normal MRI after cardiac arrest must be standardized.

The spatial distribution of DWI MRI changes due to HIBI varies widely. The best area of the brain to be assessed for predicting good outcome after cardiac arrest is currently unknown.

QUESTION

Neuron Specific Enolase (NSE) for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Neuron specific enolase (NSE), assessed within 72 h after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at ICU discharge or at 6-12 months after cardiac arrest.
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. A systematic review was published in 2021 identified three studies that evaluated the use of NSE for prediction of good functional outcome and an updated search conducted in May 2022 identified one more study.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. The majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on the high likelihood of severe hypoxic brain injury are the results of the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy. Identifying patients with a likely good outcome based on prognostication results could facilitate the continuation of care in some unconscious patients.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○Moderate ○ Large ○ Varies ○ Don't know	NSE was investigated in four observational studies [Zellner, 2013; Moseby-Knappe, 2021; Streitberg 2017, Wihersaari]. In two studies [Zellner, 2013; Moseby-Knappe, 2021] blood NSE values within the upper limit of the normal range (17–18 µg/L) at 24h predicted good neurological outcome at 6 months with specificities of 85% and 89%, respectively (sensitivities 46% and 26%, respectively). At 48h normal NSE values predicted good neurological outcome with specificities of 84% and 89% (corresponding sensitivities 58% and 41%). certainty of evidence low or moderate One study [Moseby-Knappe, 2021] reported that normal NSE blood levels (=<17 µg/L) at 72h predicted good neurological outcome at 6 months after cardiac arrest with specificity of 80% and sensitivity of 75%. certainty of evidence low or moderate In one study [Streitberger, 2017] normal blood NSE levels (=< 17 µg/L) at 72h predicted good neurological outcome at ICU discharge determined as CPC scores 1–3 with specificity of 87% and sensitivity of 33%. (certainty of evidence low or moderate) In one study [Wihersaari, 2022] normal NSE values (=< 17 µg/L) at 48 hours predicted favorable functional outcome at 12 months with a specificity of 54% and sensitivity of 90%.	All three studies determined the specificity for the normal upper limit of blood NSE levels. At 48h normal NSE blood level predicted good outcome with good specificities (84–89%) but only moderate sensitivity (41–58%). Patients dying from non-neurological causes may influence the neuronal biomarkes' ability to predict good outcome

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○Varies ○Don't know	False positive prediction occurring in patients having serum NSE levels below the upper limit of normal range (17 µg/L) may lead to falsely optimistic prediction, inappropriate continuation of life sustaining therapy and falsely optimistic information provided for relatives in patients destined to poor recovery. This is possible with the reported cut-off of 17 µg/L for blood NSE given the specificity less than 90% to predict good outcome reported in all three studies.	NSE has confounding sources (red blood cells;haemolysis, neuroendocrine tumours), however, this is more of a problem in poor outcome prediction. Method for NSE determination vary between laboratories and can

		influence levels measured in the clinical/experimental 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	The certainty of evidence for NSE in predicting good outcome is very low. There is imprecision given the wide variation in the sensitivities and specificities of NSE less than the upper limit of normal for the prediction of good outcome. In addition, there is the problem of indirectness as most studies have included only patients included in interventional randomized controlled trials with strict inclusion criteria. There is a clear risk of bias based on the use of NSE in clinical practice to withdraw care in case of high levels, i.e. a self-fulfilling prophecy.	Differently from other predictors, like those based on clinical examination, NSE is not affected by sedation or paralysis, and it can be assessed blindly. However, in the studies we evaluated, results of NSE measurement were not concealed from the treating team. An additional source of confounding is represented by the different available methods of measurement.

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	It is common to define CPC scores 1–2 as good neurological outcome after cardiac arrest. One found study [Streiberger, 2017] used CPC scores 1–3 as the definition for good neurological recovery. There is limited data available regarding if some people value a CPC 1-3 as the same way as a CPC 1-2.	

○ 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	NSE is recommended for the prediction of poor outcome in cardiac arrest patients Therefore the result will be available in many patients, and in case of a low level will favour prolonging care until other means of prognostication can be completed or the patient´s clinical status changes.	

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 costs of biomarkers' assessment are higher when compared with prognostication without biomarkers. No study assessing cost from prognostication based on NSE has been included in our review.	NSE is widely available in clinical laboratories

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 any studies specifically assessing costs of NSE for prognostication after cardiac arrest.	

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 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	A problem of inequity is possible, since assessment of biomarkers is a resource that cannot be universally available.	However, NSE is rather widely available in clinical laboratories

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	We have not identified any study assessing acceptability, but acceptability is likely as the use of NSE is already part of a multimodal approach to determine the prognosis after cardiac arrest.	

○ Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Assessment of biomarkers requires resources that may not be universally available. However, NSE is already included as a means to identify patients with poor outcome as part of a multimodal approach. In addition, NSE is routinely measured in many hospitals and clinics as a tumour biomarker. The most important caution required during withdrawing and managing the blood sample is avoiding haemolysis.	

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 using normal NSE (<17 µg/L) within 72 hours after ROSC, in combination with other tests, for predicting favorable neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

Four studies including more than 1000 patients suggest that a normal NSE value at 48 hours has some accuracy to predict good functional outcome.

Subgroup considerations

The studies have included mainly patients with OHCA, a cardiac origin and those who have undergone TTM.

Implementation considerations

Monitoring and evaluation

Research priorities

- Larger studies including heterogenous samples of cardiac arrest including those with a non-cardiac cause of the arrest and in-hospital cardiac arrest
- The use of NSE together with other recommended modalities for predicting good outcome

References:

Moseby-Knappe M, Mattsson-Carlgren N, Stammet P, Backman S, Blennow K, Dankiewicz J, Friberg H, Hassager C, Horn J, Kjaergaard J, Lilja G, Rylander C, Ullen S, Unden J, Westhall E, Wise MP, Zetterberg H, Nielsen N, Cronberg T (2021) Serum markers of brain injury can predict good neurological outcome after out-of-hospital cardiac arrest. Intensive Care Med 47:984–994

Zellner T, Gärtner R, Schopohl J, Angstwurm M NSE and S-100B are not sufficiently predictive of neurologic outcome after therapeutic hypothermia for cardiac arrest, Resuscitation 84. 1382–1386

Streitberger KJ, Leithner C, Wattenberg M, et al. Neuron-Specific Enolase Predicts Poor Outcome After Cardiac Arrest and Targeted Temperature Management: A Multicenter Study on 1,053 Patients

Wihersaari L, Reinikainen M, Furlan R, Mandelli A, Vaahersalo J, Kurola J, Tiainen M, Pettilä V, Bendel S, Varpula T, Latini R, Ristagno G, Skrifvars MB.Neurofilament light compared to neuron-specific enolase as a predictor of unfavourable outcome after out-of-hospital cardiac arrest. Resuscitation. 2022 May;174:1-8

QUESTION

GFAP, serum tau protein, and NFL for prediction of good neurological outcome in adults after cardiac arrest	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Blood levels of biomarkers (GFAP, serum tau protein, NFL), assessed within 72 hours after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 6 or 12 months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was conducted in May 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. The vast majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy. Identifying patients with a likely good outcome based on prognostication results could facilitate the continuation of care in some unconscious patients.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**<u>Glial fibrillary acid protein (GFAP)</u>** GFAP was investigated in two observational studies [Moseby-Knappe 2021, Humaloja 2021]. **24h:** One study [Moseby-Knappe 2021] used the normal value for GFAp (<22 pg/mL) at 24h to predict good outcome after cardiac arrest and reported **specificity of 97% and sensitivity of 41%.** **48h:** One study [Moseby-Knappe 2021] used the normal value for GFAp (<22 pg/mL) at 48h to predict good outcome after cardiac arrest and reported specificity **of 97% and sensitivity of 35%.** One study [Humaloja 2021] determined the cut-off to predict good neurological outcome with **100% and 95% specificities (210 and 439 pg/mL, respectively) with sensitivities of 43% and 75% respectively**. **72h:** One study [Moseby-Knappe 2021] used the normal value for GFAp (<22 pg/mL) at 72h to predict good outcome after cardiac arrest and reported **specificity of 95% and sensitivity of 44%.** One study [Humaloja 2021] determined the cut-off to predict good neurological outcome with **100% and 95% specificities (187 and 359 pg/mL, respectively) with sensitivities of 44% and 73%, respectively**. **<u>Serum Tau Protein</u>** Serum Tau was investigated in two observational studies [Moseby-Knappe 2021, Humaloja 2021] **24h:** One study [Moseby-Knappe 2021] used the normal value for Tau-protein (<1.55 pg/mL) at 24h to predict good outcome after cardiac arrest and reported **specificity of 94% and sensitivity of 28**%. **48h:** One study [Moseby-Knappe 2021] used the normal value for Tau-protein (<1.55 pg/mL) at 48h to predict good outcome after cardiac arrest and reported **specificity of 95% and sensitivity of 41%.** One study [Humaloja 2021] determined the cut-off to predict good neurological outcome with **95% specificity (3.28 pg/mL) with sensitivity of 53%.** **72h:** One study [Moseby-Knappe 2021] used the normal value for Tau-protein (<1.55 pg/mL) at 72h to predict good outcome after cardiac arrest and reported specificity of 93% and sensitivity of 52%. One study [Humaloja 2021] determined the cut-off to predict good neurological outcome **with 100% and 95% specificities (2.10 and 3.37 pg/mL, respectively) with sensitivities of 21% and 52%,** respectively. **<u>Serum Neurofilament Light Chain (NFL)</u>** **24 h**: Serum NfL was investigated in three observational studies [Moseby-Knappe 2021, Wihersaari 2021, WIhersaari 2022] at 24 h. Two studies [Wihersaari 2021, Wihersaari 2022] determined the NfL cut-off to predict good outcome with **100% specificity (12.5 and 30 pg/mL) with sensitivity ranging between 12–79%.** One study [Wihersaari 2022] determined the cut-off to predict good outcome with **95% specificity**	NfL is investigated in three studies, whereas both GFAP and tau protein are investigated in two studies. UHC-L1 is only investigated in one study. Cut-off values, specificities and sensitivities for GFAp, tau, and NfL are varying between the studies.

	(21.5 pg/mL) with sensitivity of 37%. One study [Moseby-Knappe, 2021]used the normal value for NfL (55 pg/mL) as the cut-off, and it predicted good outcome with **specificity of 95% and sensitivity of 65%.** **48h**: Serum NfL was investigated in three observational studies [Moseby-Knappe 2021, Wihersaari 2021, WIhersaari 2022] at 48h. Two studies [Wihersaari 2021, Wihersaari 2022] determined the NfL cut-off to predict good outcome with **100% specificity (8 and 30 pg/mL) with sensitivity ranging between 6–74**%. One study [Wihersaari 2022] determined the cut-off to predict good outcome with **95% specificity (29 pg/mL) with sensitivity of 39%.** One study [Moseby-Knappe, 2021] used the normal value for NfL (55 pg/mL) as the cut-off, and it predicted good outcome with specificity of **96% and sensitivity of 54%.** **72h**: Serum Nfl was investigated in two observational studies [Moseby-Knappe 2021, Wihersaari 2021] at 72h. One study [Wihersaari, 2021] determined the cut-off to predict good outcome **with 100% specificity (27 pg/mL) with corresponding sensitivity of 67%.** One study [Moseby-Knappe, 2021] used the normal value for NfL (55 pg/mL) as the cut-off, and it predicted good outcome with **specificity of 97% and sensitivity of 51%.** **Ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1**) Serum UCH-L1 was investigated in one observational study [Moseby-Knappe 2021]. They used the normal value of UHC-L1 (<327 pg/mL) at **24, 48 and 72 hours** after cardiac arrest as cut-off and it predicted good neurological outcome with **specificities of 85%, 82%, and 70%,** respectively with corresponding sensitivities of 64%, 74%, and 88%, respectively.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○Varies ○Don't know	Falsely positive prediction occurring in patients having serum levels of a given biomarker below the identified cut-off with 100% specificity are not likely to occur with the biomarkers included, since their investigation is still in the explorative phase and none of them has been adopted as a criterion for WLST.	None of these biomarkers are currently **widely** available for clinical use.

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 GFAP, serum tau protein, NFL, and UHC-L1 is very low because of the very limited number of studies and varying cut-offs reported between studies.	Differently from other predictors, like those based on clinical examination, biomarkers are not affected by sedation or paralysis, and can be assessed blindly. A specific advantage of NFL is the fact of originating only in neurons. However, the range of thresholds for 100% specificity is wide.

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	It is common to define CPC scores 1–2 as good neurological outcome after cardiac arrest. One found study [Streiberger, 2017] used CPC scores 1–3 as the definition for good neurological recovery. There is limited data available regarding whether some people value a CPC 1-3 in the same way as a CPC 1-2.	

Balance of effects

Does the balance between desirable and undesirable effects favor 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 ○ Don't know	Considering the small amount of evidence supporting their use, the balance of effects suggests against using these biomarkers, or not favouring either option. Outside of the context of studies, these biomarkers are not currently widely available and there are too few studies to support their use.	

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 costs of biomarker assessment are higher when compared with those of clinical examination. No study assessing savings from prognostication based on GFAP, serum tau protein, or NFL was identified in our review.	

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 any studies specifically assessing costs of GFAP, serum tau protein, NFL, or UHC-L1 for prognostication after cardiac arrest.	

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 addressing cost-effectiveness of these biomarkers.	

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	A problem of inequity is possible, since assessment of biomarkers implies resources that could not be universally available.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Assessment of biomarkers requires resources that may not be universally available. More specifically, GFAP, serum tau protein, NFL, UHC-L1 have been assessed from thawed samples that were previously frozen in highly specialised centres for research purposes and are not currently routinely available for clinical use in most hospitals.	

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 suggest against using serum levels of glial fibrillary acidic protein, serum tau protein, or neurofilament light chain in clinical practice for predicting favorable neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low- certainty evidence).

Justification

The cut-offs used for predicting good outcome with the these biomarkers vary to a great degree making it difficult to provide recommendations.

Subgroup considerations

Most studies have been conducted in OHCA with a cardiac cause of the arrest.

Implementation considerations

All studies conducted thus far have been done in specialised centres with the biomarker assessed outside clinical practise. No study has used a commercially available assay that would facilitate biomarker assessment in clinical practice.

Monitoring and evaluation

These tests are currently not widely available.

Research priorities

Further studies on GFAP, serum tau protein, and NFL are needed to confirm their predictive value after cardiac arrest, to assess their reproducibility, and to identify consistent thresholds for 100% specificity.

References:

Moseby-Knappe M, Mattsson-Carlgren N, Stammet P, Backman S, Blennow K, Dankiewicz J, Friberg H, Hassager C, Horn J, Kjaergaard J, Lilja G, Rylander C, Ullen S, Unden J, Westhall E, Wise MP, Zetterberg H, Nielsen N, Cronberg T (2021) Serum markers of brain injury can predict good neurological outcome after out-of-hospital cardiac arrest. Intensive Care Med 47:984–994

Wihersaari L, Ashton NJ, Reinikainen M, Jakkula P, Pettila V, Hastbacka J, Tiainen M, Loisa P, Friberg H, Cronberg T, Blennow K, Zetterberg H, Skrif- vars MB, Comacare Study G (2021) Neurofilament light as an outcome predictor after cardiac arrest: a post hoc analysis of the COMACARE trial. Intensive Care Med 47:39–48

Wihersaari L, Reinikainen M, Furlan R, et al. Neurofilament light compared to neuron-specific enolase as a predictor of unfavorable outcome after out-of-hospital cardiac arrest, Resuscitation174:1–8

Humaloja J, Lahde M, Ashton N J, et al. GFAp and tau protein as predictors of neurological outcome after out-of-hospital cardiac arrest: A post hoc analysis of the COMACARE trial, Resuscitation 170: 141–149

QUESTION

Full-montage EEG with continuous or nearly continuous background without discharges or seizures for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Full-montage EEG assessed within five days after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 3 or 6 months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Twelve studies (Admiraal, 2019; Backman 2018; Beretta, 2019; Carrai, 2016; Carrai, 2021; Duez, 2019; Hofmeijer, 2015; Rossetti, 2017; Scarpino, 2021; Sivaraju 2015; Sondag, 2017; Westhall, 2016) investigated the ability of a **benign EEG pattern** recorded **during the first five days after ROSC** to predict good outcome. The benign EEG pattern consisted of a **continuous or nearly continuous background without** superimposed **abundant/generalized periodic discharges or seizures**. In all 12 studies, the 2012 American Clinical Neurophysiology Society (ACNS) standardized terminology for use in critical care was adopted, or the pattern definitions were consistent with ACNS. Twelve studies (Admiraal, 2019; Backman 2018; Beretta, 2019; Carrai, 2016; Carrai, 2021; Duez, 2019; Hofmeijer, 2015; Rossetti, 2017; Scarpino, 2021; Sivaraju 2015; Sondag, 2017; Westhall, 2016) investigated the ability of a **benign EEG pattern** recorded **during the first five days after ROSC** to predict good outcome. The benign EEG pattern consisted of a **continuous or nearly continuous background without abundant/generalized discharges or seizures**. In all 12 studies, the 2012 American Clinical Neurophysiology Society (ACNS) standardized terminology for use in critical care was adopted, or the pattern definitions were consistent with ACNS. The criteria for both the superimposed discharges and the background varied slightly across studies. In six studies (Admiraal, 2019; Backman, 2018; Duez, 2018; Hofmeijer, 2015; Sondag, 2017; Westhall, 2016), the definition of background was consistent (continuous or nearly continuous, normal voltage), with minor variations (see below), while criteria for superimposed discharges were different: four of these studies (Admiraal 2019; Backman 2018; Duez 2019; Westhall 2016) used the absence of abundant (> 50% of the record) periodic discharges or abundant spike-wave as a criterion (**definition A1a** in the systematic review), while two studies (Duez, 2019; Hofmeijer 2015; Sondag, 2019) used the absence of generalized periodic discharges as a criterion (**definition A1b** in the systematic review). One study (Duez, 2019) assessed the predictive value of both criteria. Two of the four studies using definition A1a (Backman 2018; Westhall 2016) used an additional criterion (normal anteroposterior EEG gradient) to define a benign pattern. Two of these four studies (Westhall, 2016; Duez, 2019) also investigated a more restrictive definition by further adding reactivity. Concerning background, besides the continuous or nearly continuous normal voltage, four studies (Carrai, 2016; Carrai, 2021; Rossetti 2017; Scarpino 2021) also included a low-voltage background among benign EEGs (**definition A2** in the systematic review). In one of these studies [Rossetti, 2017], reactivity was	One reason for higher specificity for good outcome prediction in the most restrictive definitions of favorable EEG could be the inclusion of EEG reactivity. This was observed across different populations [Admiraal, 2019, 17; Duez, 2019], different subpopulations of the same study cohort [Backmann, 2018; Westhall, 2016], and in the same dataset when EEG reactivity was not considered [Westhall, 2016]. However, the assessment of EEG reactivity was not standardized in the studies.

	required to define EEG as favorable. Two studies (Beretta 2018); Sivaraju 2015), besides the continuous or nearly continuous normal voltage, alos included a discontinuous background (**definition A3** in the systematic review), provided that the voltage was normal [Sivaraju 2015] or that the background was reactive [Beretta 2018). In the six studies using the A1a and A1b definitions (**continuous or nearly continuous, normal-voltage background without abundant/generalized periodic discharges or seizures**), sensitivity and specificity for good outcome prediction ranged from 51 to 63% and from 82% to 88% at 12h, respectively. At 24h, these were 39–78% and 67–100%. The highest specificities for good outcome (90-100%) were observed in studies using the most restrictive definition of benign EEG (A1a, reactive, normal gradient). In studies assessing the EEG at multiple time points (Admiraal, 2019; Duez, 2019; Hofmeijer 2015) the specificities decreased, and the sensitivities increased over time. In the four studies using the A2 definition [Carrai, 2021, 133; Carrai, 2016, 940; Scarpino 2021, 162; Rossetti, 2017, e674], at an early time window (<6 hours to 24 h after ROSC), specificities ranged between 87% to 98% and sensitivities ranged between 57% to 100% [Carrai, 2021, 133; Carrai 2016, 940; Scarpino, 2021, 162] At a later time window (48–72 h after ROSC) in two studies (Carrai 2016; Rossetti 2017) specificities were 83% and sensitivities 91% and 100%. In one of the two studies [Beretta, 2019, 106374] using the A3 definition, the specificity to predict good outcome was 77% (sensitivity 77%) at 0-5 days from ROSC. In the other study [Sivaraju, 2015, 1264], the specificity for good outcome was 97% (sensitivity 72) within 72 hours after ROSC. This specificity decreased remarkably (84%) if the EEG record included discharges. The overall certainty of the evidence for the use of the separate EEG modalities included was very low. Most studies had a moderate risk of bias, due to lack of blinding that may have caused a self-fulfilling prophecy. Imprecision was also an issue, due to the small sample size and the heterogeneity in timing of assessment and – partly – in definitions, which prevented pooling. Admiraal MM, van Rootselaar AF, Hofmeijer J, et al. (2019) Electro- encephalographic reactivity as predictor of neurological outcome in postanoxic coma: a multicenter prospective cohort study. Ann Neurol 86:17–27. Backman S, Cronberg T, Friberg H, et al. (2018) Highly malignant routine EEG predicts poor prognosis after cardiac arrest in the target temperature management trial. Resuscitation 131:24–28 Beretta S, Coppo A, Bianchi E, et al. (2019) Neurological outcome of postanoxic refractory status epilepticus after aggressive treatment. Epilepsy Behav E&B 101:106374 Carrai R, Spalletti M, Scarpino M, et al. (2021) Are neurophysiologic tests reliable, ultra-early prognostic indices after cardiac arrest? Neurophysiol Clin (Clinical neurophysiology) 51:133–144 Carrai R, Grippo A, Scarpino M, et al. (2016) Time- dependent and independent neurophysiological indicators of prognosis in post-anoxic coma subjects treated by therapeutic hypothermia. Minerva Anestesiol 82:940–949	

	Duez CHV, Johnsen B, Ebbesen MQ, Kvaloy MB, Grejs AM, Jeppesen AN, Soreide E, Nielsen JF, Kirkegaard H (2019) Post resuscitation prognostica- tion by EEG in 24 vs 48h of targeted temperature management. Resusci- tation 135:145–152 Hofmeijer J, Beernink TM, Bosch FH, et al., (2015) Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 85:137–143 Rossetti AO, Tovar Quiroga DF, Juan E, et al. (2017) Electroencephalography pre- dicts poor and good outcomes after cardiac arrest: a two-center study. Crit Care Med 45:e674–e682 Scarpino M, Lolli F, Lanzo G, et al. (2021) SSEP amplitude accurately predicts both good and poor neurological outcome early after cardiac arrest; a post-hoc analysis of the ProNeCA multicentre study. Resuscitation 163:162–171 Sivaraju A, Gilmore EJ, Wira CR, et al. (2015) Prognostication of post-cardiac arrescoma: early clinical and electroencephalographic predictors of outcome.Intensive Care Med 41:1264–1272 Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, et al. (2017) Early EEG for outcome predic- tion of postanoxic coma: prospective cohort study with cost-minimiza- tion analysis. Crit Care 21:111 Westhall E, Rossetti AO, van Rootselaar AF, Wesenberg Kjaer T, et al. (2016) Standardized EEG inter- pretation accurately predicts prognosis after cardiac arrest. Neurology 86:1482–1490	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	None known.	A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to the delivery of futile care.

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 for EEG with continuous or nearly continuous background pattern without abundant/generalized periodic discharges or seizures is very low because of bias (mainly due to lack of blinding) and imprecision. Although all studies adopted the ACNS terminology, there were some inconsistencies in the definition of periodic discharges.	The EEG background is affected by sedation and systemic organ dysfunction. How this may affect the ability of EEG to predict good neurological outcome is uncertain.

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	All prognostic studies defined good outcome as CPC 1–2 or mRS 0-3.	Additional outcomes about neurocognitive status and quality of life were not assessed.

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	Evidence from twelve studies shows that a continuous or nearly continuous EEG background with a normal voltage without abundant/generalized periodic discharges or seizures within 72h from ROSC predicts good neurological outcome after cardiac arrest with a specificity >80% and a sensitivity >50% in most studies.	The severity of periodic discharges (generalized vs abundant) is not measured consistently across studies. Sedation might suppress some favorable EEG features, thus reducing the ability of EEG to predict good outcome. However, this remains to be investigated.

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	We did not include any specific studies assessing EEG costs. However, specific equipment and skills are required for assessing EEG.	

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 any studies specifically assessing costs of EEGs.	

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 addressing cost-effectiveness of EEGs.	

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 specific equipment and skills needed to assess EEGs are not available everywhere. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed the acceptability of EEG. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A survey (Friberg, 2015, 158) published in 2015 showed that EEG is the most widely used predictor of neurological outcome after cardiac arrest. However, that survey was conducted in high-income countries. The availability of the equipment and skills required to use EEG for assessing post-cardiac arrest brain injury may be lower in other countries and communities.	Using a standard (ACNS) definition for the EEG patterns is important for their implementation. Most studies used the 2012 ACNS terminology but none used the 2021 ACNS terminology.

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

Recommendations

We suggest using a continuous or nearly continuous normal voltage EEG background without abundant/generalised periodic discharges or seizures within 72h from ROSC to predict good outcome in patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

There is insufficient evidence to recommend for or against using a low voltage or a discontinuous EEG background on days 0-5 from ROSC to predict good neurological outcome after cardiac arrest (weak recommendation, very low-certainty evidence).

We suggest that the American Clinical Electrophysiology Society (ACNS) terminology be used to classify the EEG patterns used for prognostication (good practice statement).

Justification

In making their recommendation in favor of a continuous or nearly continuous, normal-voltage EEG background without abundant/generalized periodic discharges or seizures as a predictor of good neurological outcome in patients who are comatose after cardiac arrest, the TF members considered the consistency of the evidence (12 studies, mostly with >80% specificity and >50% sensitivity) and the consistency of the definition, made using an ACNS or ACNS-compatible terminology.

The background definition was consistent in six of these studies. Although the criteria for periodic discharges varied slightly within this subgroup, this did not affect the prediction accuracy.

Evidence from the remaining six studies confirmed the ability of a continuous or nearly continuous, normal-voltage EEG background without seizures or discharges to predict good neurological outcome. These studies also included a low-voltage or discontinuous EEG background among the 'benign' EEG patterns. These patterns are farther from normal than a continuous or nearly continuous background, and their accuracy could not be assessed separately. The ILCOR TF considered the evidence supporting these patterns insufficient for recommending their use.

Subgroup considerations

None.

Implementation considerations

Monitoring and evaluation

Research priorities

The effects of sedation and systemic organ dysfunction on the predictive value of the EEG background should be investigated.

The value of low-voltage background and discontinuous reactive/normal voltage background fro predicting good outcome should be investigated

The value of EEG reactivity for predicting good outcome deserves further investigation using standardized stimulation and assessment.

It is not clear which aspect of periodic discharges (ie distribution, morphology, prevalence, etc.) has greatest importance in affecting the prognosis of a favorable EEG pattern.

The value of dominant EEG rhythms (e.g. theta) in prognostication after cardiac arrest deserves investigation.

The predictive value of favorable EEG patterns defined according the 2021 ACNS definitions deserves investigation, albeit the differences vs the 2012 definitions regarding the features used for predicting a good outcome are minimal.

QUESTION

Favorable EEG patterns non-ACNS-defined for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Full-montage EEG assessed within 72h after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) on hospital discharge or three or six months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Three studies [Lamartine, 2016; Leao, 2015; Alvarez, 2015] defined favorable EEG patterns using heterogeneous definitions none of which complied with the American Clinical Neurophysiology Society's (ACNS) terminology. Those definitions were mostly based on dominant frequencies of the background activity (theta or alpha vs. delta) and none excluded superimposed discharges. The timing of outcome was hospital discharge in one study [Alvarez, 2015], three months in one study [Lamartine, 2016] and six months in one [Leao, 2015]. In one study [Lamartine, 2016] EEG was assessed at several time-windows within 24 hours after CA (at 0–8h, 8–16h, and 16–24h**) and specificity to predict good outcome ranged between 64% and 77% being highest at the earliest time-window (sensitivities ranged between 86% to 96%).** In another [Alvarex, 2015] study EEG assessed within 24 hours after CA favorable EEG pattern predicted good outcome with specificity of **100% but sensitivity was low 25%.** All three studies assessed EEG approximately **within 24–48 h after CA and the specificities to predict good outcome ranged between 68% and 91% (sensitivities from 75% to 96%)** Lamartine Monteiro M, Taccone FS, Depondt C, et al. (2016) The prog- nostic value of 48-h continuous EEG during therapeutic hypothermia after cardiac arrest. Neurocrit Care 24:153–162 Leao RN, Avila P, Cavaco R, Germano N, Bento L (2015) Therapeutic hypothermia after cardiac arrest: outcome predictors. Revista Brasileira de terapia intensiva 27:322–332 Alvarez V, Reinsberger C, Scirica B, et al. (2015) Continuous electrodermal activity as a potential novel neurophysiological biomarker of prognosis after cardiac arrest—a pilot study. Resuscitation 93:128–135	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies	None known.	A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to the delivery of futile care.

○ Don't know		

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 about varying favorable EEG patterns is very low because of bias (mainly due to lack of blinding), inconsistency of definitions, 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	All studies defined good outcome as CPC 1–2	Additional outcomes about neurocognitive status and quality of life were not assessed.

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	Evidence from three studies showed that heterogeneous, non-ACNS-defined benign EEG patterns mainly based on dominant frequency, are associated with good neurological outcome. However, the evidence was heterogeneous and limited to three studies.	

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	We did not include any specific studies assessing EEG costs. However, specific equipment and skills are required for assessing EEG	

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 any studies specifically assessing costs of EEGs.	

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	We did not identify any studies addressing cost-effectiveness of EEGs.	

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

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 specific equipment and skills needed to assess EEGs are not available everywhere. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of EEGs. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	The equipment and skills required for their assessment may represent an obstacle for their implementation.	

○ 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

	JUDGEMENT						
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

Recommendations

We suggest against using heterogeneous, non-ACNS-defined benign EEG patterns to predict good neurological outcome after cardiac arrest.

Justification

In recommending against using non-ACNS-defined benign EEG patterns to predict good neurological outcome after cardiac arrest, the panel considered the limited evidence and the heterogeneity of pattern definitions.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Studies are needed to identify the role of dominant EEG rhythms in predicting good outcome after cardiac arrest.

QUESTION

Continuous amplitude-integrated EEG (aEEG) or reduced montage EEG for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Amplitude integrated EEG (aEEG) or original EEG using reduced electrode montages assessed within 72 hours after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) on hospital discharge or 6 months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Five studies [Wennevirta, 2009; Jang, 2019; Oh, 2013; Rundgren, 2010; Eertmans, 2019] investigated the predictive value of a **continuous normal-voltage background** defined from quantitative trend analysis using amplitude-integrated EEG (**aEEG**) [Jang, 2019; Oh, 2013] or original **EEG with reduced electrode montages** [Rundgren, 2010; Wennewirta, 2009] at a time ranging from 6 to 72 h after ROSC. Two studies [Rundgren, 2010; Wennewirta, 2009] assessed reduced-montage EEG at two time-windows (within 24h and between 24 and 48h after ROSC) and favorable EEG pattern predicted good outcome at **earlier time window with specificity 56–96% (sensitivities 53–67%) and at later time-window with specificity of 67–79% (sensitivity 95%)**. Two studies [Jang, 2019; Oh, 2013] investigated **aEEG within 72h after ROSC** and specificity to predict good outcome **on hospital discharge** [Oh, 2013] was **96% (sensitivity 57%)** and **at 6 months** [Jang, 2019] **85% (sensitivity 100%)**. One study [Eertmans, 2019] analyzed the original EEG tracing of a bispectral index (BIS) monitor recorded between 6 and 48 h from ROSC from four frontotemporal channels. **A slow diffuse theta and/or delta activity,** as opposed to epileptiform, burst-suppression, or suppression (<5 μV), predicted good neurological outcome with **79% specificity at all time points, with 55%-86% sensitivity.**	aEEG results report voltage and continuity, but do not directly enable a morphological assessment of the original EEG signals making the identification of superimposed activity difficult unless the original EEG channels are also displayed. In one study [Oh, 2013] original EEG was reviewed to exclude epileptical discharges.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	None known.	A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to the delivery of futile care.

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 about favorable aEEG or reduced-montage EEG is very low because of bias (mainly due to lack of blinding) and imprecision.	Strengths of aEEG include bedside investigation, wide availability, and non-invasiveness. aEEG provides a real-time investigation of electrical brain activity. aEEG enables non-s-specialists to intepret EEG

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	Most studies define good outcome as CPC scores 1–2	

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 main disadvantage of aEEG is the limited access to the raw EEG's morphology.

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	We did not include any specific studies. However, specific equipment is required for assessing aEEG.	

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 any studies specifically assessing costs of aEEGs.	

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	We did not identify any studies addressing cost-effectiveness of aEEGs.	

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

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 specific equipment and skills needed to assess aEEGs are not available everywhere. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of aEEGs. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes	The equipment and skills required for their assessment may represent an obstacle for their implementation.	Intepretation of aEEG does not require a specialist

○ Yes ○ Varies ○ Don't know		(compared to full montage EEG)

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

	JUDGEMENT						
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

Recommendations

We suggest against the use of other EEG metrics, including reduced montage or amplitude integrated EEG, BIS, or EEG-derived indices, to predict good outcome in patients who are comatose after cardiac arrest.

Justification

In recommending against using amplitude-integrated EEG, the panel considered that these techniques do not allow or allow only a limited morphological assessment of the original EEG signal. Moreover, the evidence was limited to few studies.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Studies are needed to confirm the consistency of aEEG patterns with those identified by experts on full-montage EEG.

The evidence on aEEG is limited to a few studies, and further studies are needed to ensure the reproducibility of the results.

References:

Eertmans W, Genbrugge C, Haesen J, et al. (2019) The prognostic value of simplified EEG in out-of-hospital cardiac arrest patients. Neurocrit Care 30:139–148

Jang J, Oh SH, Nam Y, et al. BS (2019) Prognostic value of phase information of 2D T2*-weighted gradi- ent echo brain imaging in cardiac arrest survivors: A preliminary study. Resuscitation 140:142–149

Oh SH, Park KN, Kim YM, et al. (2013) The prognostic value of continuous amplitude-integrated electroencephalogram applied immediately after return of spontaneous circulation in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation 84:200–205

Rundgren M, Westhall E, Cronberg T, et al. (2010) Continu- ous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med 38:1838–1844

Wennervirta JE, Ermes MJ, Tiainen SM, et al.P (2009) Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity. Crit Care Med 37:2427–2435

QUESTION

Bispectral index (BIS) for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Bispectral index (BIS) assessed within 24 hours after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) on hospital discharge or 6 months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The predictive value of BIS was evaluated in three studies [Park, 2018; Seder, 2010; Leary, 2010]. In one study [Park, 2018] the outcome was defined at 6 months after CA and in two studies [Seder, 2010; Leary, 2010] on hospital discharge. In two studies, a **BIS value greater than 21 at 1–3 h** [Park, 2018] after ROSC **or 24 at 3–6 h** after ROSC [Seder, 2010] predicted good neurological outcome **with 94% [79.8–99.3] and 86% [73.3–94.2] specificity**, respectively (sensitivities 88% [61.7–98.4] and 94%, [83.1–98.7] respectively). In one study [Leary, 2010], the ability of BIS to predict good neurological outcome **at 24 h** from ROSC was assessed at different BIS thresholds. **Specificity increased from 41% [25.6–56.7] at BIS 30 to 92.9% [80.5–98.5]at BIS 60**. **Sensitivities decreased from 95% [75.1–99.9] to 20% 20 [5.7–43.7],** respectively. Park JH, Oh JH, Choi SP, Wee JH (2018) Neurologic outcome after out-of- hospital cardiac arrest could be predicted with the help of bispectral- index during early targeted temperature management. Scand J Trauma Resusc Emerg Med 26:59 Seder DB, Fraser GL, Robbins T, Libby L, Riker RR (2010) The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive Care Med 36:281–288 Leary M, Fried DA, Gaieski DF, Merchant RM, Fuchs BD, Kolansky DM, Edelson DP, Abella BS (2010) Neurologic prognostication and bispectral index monitoring after resuscitation from cardiac arrest. Resuscitation 81:1133–1137	BIS value greater than 21 or 24 had high specificity at 2-5 h from ROSC in two studies [Park, Seder], but its accuracy was lower at 24 h [Leary], possibly reflecting a partial recovery of EEG background activity in patients with poor outcome. BIS is quantitative trend analysis tool based on a few EEG channels. BIS is based on a proprietary technology that returns a single number from zero (corresponding to an isoelectric EEG) to 100 (‘full consciousness

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	None known.	A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to the delivery of futile care.

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 about favorable BIS threshold is very low because of lack of blinding and low precision.	

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	All prognostic studies defined good outcome as CPC 1–2.	There may be interindividual variations on how good neurological outcome is perceived.

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	High BIS values within 24h from ROSC predict good neurological outcome after cardiac arrest. However, the optimal BIS threshold has yet to be identified. The evidence is limited to three studies.	BIS does not enable a morphological assessment of the original EEG signals, so the identification of superimposed activity is not possible. The interaction of sedation on the reliability of BIS for

		predicting good outcome has yet to be investigated.

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 addressing this question were identified	

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 addressing this question were 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	No studies addressing this question were identified	

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	Specific equipment is needed to assess BIS. This may not be available everywhere, which can reduce equity.	Presumably, using BIS is simpler than using a full - montage EEG

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed the acceptability of BIS. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The equipment required for BIS may represent an obstacle to its implementation.	Interpretation of BIS does not require a specialist compared to full montage EEG.

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

Recommendations

We suggest against the use of other EEG metrics, including reduced montage or amplitude integrated EEG, BIS, or EEG-derived indices, to predict good outcome in patients who are comatose after cardiac arrest.

Justification

In recommending against using BIS, the ALS TF considered that, although aery-low-quality evidence from three studies shows that high BIS values within 24h from ROSC predict good neurological outcome after cardiac arrest, the evidence is limited to three studies. Moreover, the optimal BIS threshold has yet to be identified. BIS analysis is made on a limited number of leads and is based on a proprietary algorithm preventing a direct and more complete EEG morphology analysis, even if the raw EEG signal is displayed.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The interference of sedation on BIS deserves investigation.

A consistent threshold for predicting good outcome using BIS should be identified.

QUESTION

Cerebral recovery index (CRI) for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	Cerebral recovery index (CRI) derived from automated quantitative EEG assessed within 24 hours after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) on hospital discharge or 6 months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented the evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest is necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. Most of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	One study [Tjepkerma-Cloostermans, 2013, R252] investigated the ability of cerebral recovery index (CRI) to predict good outcome at 6 months after CA. In that study, a CRI above 0.57 at 18 h or 0.69 at 24 h predicted good neurological outcome with **100% specificity (sensitivities 65% [44.3–82.8] and 26% [11.1–46.3] respectively).**	CRI is a summary score which represents a combination of five quantitative EEG features derived from automated quantitative EEG analysis. Each feature is combined into CRI, which ranges from 0 to 1 (the higher, the better). The included study showed that the CRI of patients with good outcome improved faster than did those of patients with poor outcome.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		A falsely optimistic prediction in a patient with poor neurological outcome may potentially lead to futile care being provided.

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 about CRI is very low because of lack of blinding and it is based on only one study.	CRI is based on an automated and quantitative EEG analysis, which makes the interpretation simpler and more objective. However, the availability of this technique is still limited, and these results need to be validated in a larger patient cohort.

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	Almost all prognostic studies included in our review defined good outcome as CPC 1–2.	There may be interindividual variations in how good neurological outcome is perceived.

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	A CRI above 0.57 at 18 h or 0.69 at 24 h predicted good neurological outcome with high specificity after cardiac arrest. However, the evidence is limited to one study. The CRI thresholds for 100% specificity change over time. These thresholds need confirmation from further studies by different groups to ensure reproducibility.	The interaction between sedation and CRI has not been investigated.

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 addressing this question were identified.	

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 addressing this question were 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	No studies addressing this question were identified.	

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	CRI is calculated with specific software that is not universally available. The experience in CRI concerns a restricted group of investigators.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	The equipment and skills required for CRI assessment may represent an obstacle for their implementation.	CRI has the advantage of being based on an automated and quantitative EEG analysis, which makes the interpretation simpler and more objective.

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

Recommendations

We suggest against the use of other EEG metrics, including reduced montage or amplitude integrated EEG, BIS, or EEG-derived indices, to predict good outcome in patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Justification

In making the recommendation, the ALS TF considered that although a CRI above 0.57 at 18 h or 0.69 at 24 h predicted good neurological outcome with high specificity after cardiac arrest, the evidence is limited to one study. The CRI thresholds for 100% specificity change over time. These thresholds need confirmation from further studies by different groups to ensure reproducibility. CRI is based on specific software that is not universally available.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

Research priorities

Studies assessing the reproducibility of CRI are warranted.

References:

Tjepkema-Cloostermans MC, van Meulen FB, Meinsma G, van Putten MJ (2013) A Cerebral Recovery Index (CRI) for early prognosis in patients after cardiac arrest. Crit Care 17:R252

QUESTION

High amplitude of the N20 wave of somatosensory evoked potenials (SSEPs) for prediction of good neurological outcome in adults with cardiac arrest (Subsection of Prognostication ETD)	
POPULATION:	Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature management.
INTERVENTION:	A N20 wave voltage of median nerve somatosensory evoked potentials (SSEP), assessed within 96 h after cardiac arrest.
COMPARISON:	*None.*
MAIN OUTCOMES:	Prediction of good neurological outcome defined as Cerebral Performance Categories (CPC) 1-2 at 3 or 6 months after cardiac arrest
STUDY DESIGN:	Prognostic accuracy studies where the 2 x 2 contingency table (i.e., the number of true/false negatives and positives for prediction of good outcome) was reported, or where those variables could be calculated from reported data. are eligible for inclusion. Unpublished studies, reviews, case reports, case series, studies including less than 10 patients, letters, editorials, conference abstracts, and studies published in abstract form were excluded.
TIMEFRAME:	An ILCOR review from 2013 and an update from 2020 presented evidence of predictors of poor neurological outcome after cardiac arrest. More recently, several studies identifying predictors of good neurological outcome after cardiac arrest have been published, therefore, an ILCOR evidence review for predictors of good neurological outcome after cardiac arrest was necessary. The most recent search of this systematic review evidence update on neuroprognostication was launched in October 2022.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Neurologic injury is the most common cause of death in patients with post cardiac arrest syndrome. The vast majority of these deaths occur due to withdrawal of life-sustaining treatment (WLST) based on the prediction of poor neurological outcome. Neurological prognostication after cardiac arrest is of utmost importance to avoid futile treatments for unsalvageable patients but also to minimize the risk of falsely pessimistic prediction and self-fulfilling prophecy.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	SSEPs were investigated in five observational studies [Endisch, 2015; Oh,2019; Glimmerween, 2020; Scarpino, 2021; Benghanem 2022] The amplitude was calculated in microvolts (μV) as the difference between the voltage of the N20 negative wave and the voltage of the following positive P25 wave **(N20–P25**), but in one study [Endisch,2015] the baseline-N20 amplitude was occasionally used if it was larger than the N20–P25 difference. One study [Benghanem, 2022] reported both N20–P25 and **N20–baseline** amplitudes. The largest amplitude of the two sides was used, except in one study [Glimmerween, 2020], where the smallest amplitude was used. In one study (Oh, 2019) an amplitude threshold >2.31 μV at 48-72h after ROSC predicted good outcome at six months with **97% specificity** and **53% sensitivity**. In one study [Benghanem, 2022], an amplitude threshold **>3.2 μV** measured at a median of 3[2-4] days after ROSC predicted good outcome at six months with **93% specificity** and **29% sensitivity**). In one study [Glimmerveen 2020] an amplitude threshold **>3.6 μV** (smallest of the two sides) at 48-72h after ROSC predicted good outcome at six months with **96% specificity and 32% sensitivity**. In one study [Scarpino, 2021], an amplitude threshold > **4 μV at 12 h, 24 h, and 72 h** after ROSC predicted good outcome at six months with **specificities between 86 and 91%, with 48–51% sensitivity**. In one study [Endisch, 2015] an N20 amplitude threshold **>4.2 μV** at 24–96h predicted good outcome at ICU discharge with **92% specificity** and **28% sensitivity.** In three studies [Endisch, 2015; Scarpino, 2021; Oh, 2019] higher amplitude thresholds above 5 μV and up to 10 μV were investigated. Specificities ranged from **93% and 100%**, while **sensitivities** ranged from **6% to 37%.** In one study [Benghanem, 2022], an **N20-baseline amplitude >2 μV** predicted good outcome at six months with **73% specificity (39% sensitivity)** while an **N20 baseline amplitude >2.7 μV** predicted a good outcome at six months with **87% specificity and 28% sensitivity**. The risk of bias was moderate in four studies, and high in one study.	A universally recognised normal range for N20-P25 amplitude has not been established. SSEP recording methods need standardisation. The N20 amplitude is affected by recording parameters, such as the electrode position or montage and how the amplitude is calculated. While most studies measured the N20 amplitude as the difference between the N20 and the P25 peak, two studies calculated it as the N20-baseline difference in some or all patients. This variability may partly explain the variability of the SSEP thresholds. Limited evidence ([Glimmerveen 2020, Scarpino, 2022) suggests that the amplitude of the N20 SSEP wave evolves over time after ROSC. In all but one study (Glimmerveen 2020) the largest amplitude of the two sides was used.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ●Trivial ○ Varies	None known.	A falsely optimistic prediction in a patient with poor neurological outcome

○ Don't know		may potentially lead to therapeutic obstinacy.

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 about SSEP is very low, mainly because of lack of blinding, inconsistent voltage thresholds across studies, and serious imprecision.	While the absence of the N20 SSEPs wave is probably not influenced by sedation and temperature, the effects of these confounders on the N20Amp are less known.

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	All studies defined good outcome as CPC 1–2.	There may be interindividual variations on how good neurological outcome is perceived.

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 shows that a high N20Amp predicts good neurological outcome after cardiac arrest with high specificity. In all but one study included in our review, an N20 amplitude threshold >4.0 µV yielded a specificity above 90%. However, the thresholds varied widely across studies. The methods to calculate the N20 amplitude were inconsistent.	

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	We did not include any specific studies assessing SSEP costs. However, specific equipment and skills are required for assessing SSEPs.	

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 any studies specifically assessing the costs of SSEPs.	

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	We did not identify any studies related to this question.	

○ Favors the intervention ○ Varies ● No included studies		
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	We did not identify any studies related to this question. However, the specific equipment and skills needed to assess SSEPs are not available everywhere. This can create a problem in terms of equity.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify any studies related to this question. However, acceptability of SSEPs is likely.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We did not identify any studies related to this question.	SSEPs have been used for decades and are implemented in many hospitals worldwide. However, the equipment and skills required for their assessment may represent an obstacle for their implementation. The lack of

		consensus about the N20Amp to use for predicting good neurological outcome may represent an issue.

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

Recommendations

We suggest against using the amplitude of the N20 SSEP wave to predict good neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

Although very-low-certainty evidence suggests that a high N20 amplitude predicts good neurological outcome after cardiac arrest with high specificity, the amplitude threshold for this prediction varied widely across studies. The methods to calculate the N20 amplitude were inconsistent. There is observational evidence that sedative agents, especially Midazolam, decrease the N20 amplitude. Finally, the optimal timing for predicting good outcome using SSEP amplitude has not been established yet.

In making their recommendation, the task force members also considered evidence from additional studies, not included in the 2021 review, showing an overlap in the distribution of the highest N20 wave amplitude values in patients with poor and good outcome.

Subgroup considerations

None

Implementation considerations

Monitoring and evaluation

Research priorities

The methods to calculate the N20 SSEP amplitude need to be standardized.

The interrater variability in the assessment of the N20 SSEP amplitude must be investigated

The optimal N20 SSEP amplitude for predicting good outcome needs to be established

The effects of sedation on the N20 SSEP amplitude must be investigated.

There is still limited evidence on the correlation between time after ROSC and the N20 SSEP amplitude.

There is still limited evidence on the added value of the combination of a high N20 SSEP wave amplitude with other predictors of good neurological outcome

QUESTION

Should ECPR vs. no ECPR be used for pediatric cardiac arrest ?	
POPULATION:	pediatric cardiac arrest
INTERVENTION:	ECPR
COMPARISON:	no ECPR
MAIN OUTCOMES:	Survival to hospital discharge; Survival to hospital discharge; Survival to 12 months; Survival to 12 months with VABS II >=70; Survival to 12 months with VABS II >=70.
SETTING:	in hospital setting
PERSPECTIVE:	In the pediatric cardiac population and other select physiologic conditions, conventional CPR may not provide the most optimal means of providing oxygenated perfusion to the cerebral and systemic circulations.
BACKGROUND:	The evidence update in pediatric ECPR conducted from 2018 and 2021 included two systematic reviews {Esangbedo, 2020, e-934; Farhat, 2021, 682} and 15 published studies. Considering the evidence becoming available on this topic both in pediatrics and in adults, the decision was made to update the adult and pediatrics systematic review {Holmberg, 2022 – PROSPERO CRD42022341077}.
CONFLICT OF INTERESTS:	None declared.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Survival and neurologic outcomes from refractory in-hospital cardiac arrest in pediatrics remain poor.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Given the favorable results reported in selected pediatric populations and in institutions with significant resources, there are promising outcomes that deserve to be better understood in order to be replicated. In some physiologic conditions or diseases, conventional CPR with chest compressions may not provide the most optimal means of providing oxygenated perfusion to the cerebral and systemic circulations.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	The transition from delivering CPR to ECPR may alter the quality of resuscitation measures; moreover, the patient transport that may be necessary to move the patient with ongoing CPR to a cannulation-suited location may decrease the quality of CPR measures.	The resources allocated to maintain the system performance (people, equipment) may redirect efforts away from other valuable and necessary care practices and interventions in the organization.

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	Very low certainty of evidence in-hospital cardiac arrest. Insufficient evidence for out-of-hospital cardiac arrest.	

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 field of pediatric resuscitation values survival with good (or favorable) neurological outcome. There is not much variability about its importance. There is variability on how studies analyze or dichotomize categorical neurological outcomes.	There are no comparative studies evaluating health related quality of life outcomes or patient-oriented outcomes.

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	See published updated systematic review.	

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 resources required to deliver ECPR are higher than conventional CPR. There are no cost effectiveness studies published in pediatrics. The cost comparison published {Hamzah, 2021, 2523} reported as secondary outcomes longer lengths of stay and higher inpatient hospital costs in the ECPR group compared to the no ECPR group.	The institutional resources needed to develop and sustain an ECPR system are substantial; these may represent significant incremental additional resources in institutions without cardiac surgery programs.

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	Limited information on cost comparisons is available from a single country (USA) which may or may not be generalizable to other regions.	

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 included studies in pediatrics.	

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 insufficient published evidence to understand if there is equitable access within an institution or between institutions across a system (e.g., either regional or national). However, we speculate that there are wide differences in access in this complex and expensive intervention.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	ECMO and ECPR has been adopted by some institutions. The acceptability has not been formally evaluated but quality networks (e.g., PC4) and registries (e.g., ELSO) report an increasing use of this technology for IHCA resuscitation in pediatrics.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Systems with adequate and committed resources (people, expertise, equipment) have shown this intervention to be feasible to implement in the in-hospital setting.	

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 there is insufficient evidence to change the treatment recommendation from the 2020 & 2021 Pediatric CoSTR (Maconochie 2020 A120, Maconochie 2021 147 Sup 1).

We suggest that ECPR may be considered as an intervention for selected infants and children (e.g., pediatric cardiac populations) with IHCA refractory to conventional CPR, in settings where resuscitation systems allow ECPR to be well performed and implemented (weak recommendation, very low-quality evidence). There is insufficient evidence in pediatric OHCA to formulate a treatment recommendation for the use of ECPR.

Justification

In making this weak recommendation, we note that in select pediatric patient populations (i.e., cardiac arrest with cardiac disease) the practice of using ECPR has become widespread across some institutions with systems that support post operative cardiac surgical ecosystems.

We acknowledge that ECPR is a complex system intervention that requires considerable resources and sustained training that may not be universally available.

Subgroup considerations

The majority of the published literature includes in-hospital pediatric cardiac patients. There is a need to understand which out-of-hospital selected pediatric populations and in-hospital pediatric non-cardiac populations may benefit from ECPR compared to high quality CPR alone.

Implementation considerations

The investment required to implement and sustain a high-quality ECPR program compared to a high-quality CPR program is significant. A high quality ECPR program is more likely to be feasible in organizations that build on the infrastructure and expertise necessary for cardiac surgery or trauma programs. Given the low frequency event and the high performing system required to sustain an ECPR program, organizations must be able to commit significant additional resources for training, simulation, and performance improvement processes to ensure the quality and the expertise are adequate. If these resources are not available, it may be reasonable to consider not using ECPR, as this intervention is not suitable to ad-hoc deployments.

Monitoring and evaluation

The evaluations of processes and patient outcomes are necessary to continue to better understand the impact of ECPR compared to high-quality CPR alone.

Research priorities

The knowledge gaps remain numerous when it comes to comparing the application of ECPR (which involves a first period of conventional CPR) to conventional CPR alone in pediatrics.

- There are no comparative prospective studies nor randomized trials.
- There are insufficient studies in selected IHCA (e.g., non-cardiac) or in OHCA populations.
- It remains unknown how the transition from conventional CPR to ECPR alters the quality of resuscitation measures.

- It remains unknown how best to provide closed chest CPR and transition to a peripheral or to central ECPR cannulation (with or without a sternotomy) or how to best perform open chest CPR in the context of surgical instrumentation for central ECPR.
- It remains unknown how best to provide immediate and early post cardiac arrest care with ECPR (E-PCAC) (temperature targeted management, oxygenation, decarboxylation, perfusion pressure, transfusion therapies).
- Reporting of studies using ECPR is heterogeneous and not standardized; this domain of resuscitation research would benefit from applying core definitions from the Utstein reporting standards and from incorporating pediatric core outcomes for cardiac arrest (P-COSCA) {Topjian 2020 e-246}. Moreover, an update in Utstein reporting definitions would serve to enhance the reporting of resuscitation measures applied during this technique (e.g., temperature applied on reperfusion; total duration of cardiac arrest deconstructed with intervals of conventional compressions, open chest compressions, and interruptions…).

QUESTION

Should presence of pupillary light reflex (PLR) vs. absence be used for predicting good neurological outcomes in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Pupillary light reflex (PLR) present within 10 days after cardiac arrest.
COMPARISON:	Non-reactive pupillary response
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioral scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The predictive ability of presence of pupil reactivity to classify good neurological outcome was evaluated in 8 studies [Abend 2012 32, Anton-Martin 2020 607, Brooks 2018 324, Ducharme-Crevier 2017 452, Fink 2014 664, Topjian 2021 282, Nishisaki 2007 10, Lin 2020 534], in 402 patients, within 1 hour, 6-12 h, 24h, and 72 h post-resuscitation. Most studies had a sensitivity greater than 82% at all assessment time points with the exception of Lin 2020 (50%) and Anton-Martin 2020 (40%) and corresponding FPR ranged from 3.2% to 67%. Within 12 hours of ROC the FPR was less than 33% in 3 out of 4 studies reporting this time period [Anton-Martin 2020 607, Brooks 2018 324, Lin 2020 534]. FPR increased (38-68%) at 24-72 hours and corresponding sensitivity for predicting good neurological outcome was 100% at 48-72 hrs following ROC [Abend 2012 32, Fink 2014	

	664]. No studies evaluated automated pupillometer monitoring devices.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on pupillary reactivity may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes pupil reactivity (e.g. medication).	

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 from pupil light reflect is very low because of the risk of bias, especially self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest.	

	A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a falsely optimistic prediction (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the high sensitivity of pupillary light reflex and lower false positive rate in the first 12 hours, the balance of effects favours use of pupillary light reflex as a predictor of good neurological outcome in the early time period after ROC.	

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 for the assessment of pupillary reflex are negligible. However, no study assessing savings from prognostication based on pupillary reflex has been included in our review.	

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 any studies assessing cost of pupillary light reflex.	

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 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	Considering the negligible costs of pupillary light reflex, a problem of inequity is unlikely.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of pupillary light reflex does not require special skills. The key requirement is a light source. The examiner needs to be familiar with the basics of clinical neurological examination.	

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 using pupillary light reflex within 12 hours after return of circulation for predicting good neurological outcome in children after cardiac arrest (weak recommendation, very low certainty of evidence).

Justification

For pupillary light reflex, limited evidence suggests that the specificity for prediction of good neurological outcome is similar across all assessment time points (<1 hour to 72hours or later) after cardiac arrest, although the FPR ranges from 3.2-67%.

This may be partly due to confounding from the effect of sedatives used for delivery of neuroprotective interventions (e.g., targeted temperature management) or to facilitate ventilation.

No studies reported any assessment of counfounding influence of medication. No studies included blinding of test results from treating clinician and only one study had blinded outcome assessment.

Only part of the included studies specifically excluded the presence of residual sedation at the time PLR was assessed. Lack of blinding is a major limitation of PLR, even if WLST based on PLR only has not been documented in any of the studies included in our review.

Despite its limitations, given the ease of assessment and the minimal equipment required, the balance between the costs and benefits favours benefits.

Subgroup considerations

None

Implementation considerations

Pupillary light reflect is an easy clinical assessment; however, the examiner requires knowledge of basic neurological examination.

Monitoring and evaluation

None

Research priorities

The examination of the impact of residual medication on pupillary light reflex assessment in infants and children is needed. No studies evaluated automated pupillometer monitoring devices, research is needed to assess cost and benefits of the use of pupillometry compared to pupillary light reflex assessment.

QUESTION

Should coma score be assessed vs. none for predicting good neurological outcomes in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	coma score assessed within 10 days after cardiac arrest.
COMPARISON:	none
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioral scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	The relationship between coma assessment using the Glasgow Coma Score (GCS) motor score alone, or total GCS and good neurological outcome at intensive care unit or hospital discharge and 6 months, were evaluated in 3 studies [Nishisaki 2007 10, Lin 2013 285, Lin 2020 534] in 296 patients. In one study, GCS motor score ≥4 within 1 hour and at 4-6 hours post ROC, for predicting good neurological outcome at 6 months, had a sensitivity of 17 and 50% with a corresponding FPR of 6 and 7%, respectively [Lin 2020 534]. Using total GCS measured at resuscitation or within 1 hour, a score of ≥5 predicted good neurological outcome with a low sensitivity of 30% and a FPR of 14% [Lin 2013 285]. Whereas, using a total GCS score ≥8 had a slightly higher sensitivity of 31% with a low FPR of 6% [Nishisaki 2007 10]. However, only one study was available to assess each test	High risk of confounding with sedation and medication. Not blinded. Not always clear on inclusion and denominator values (eg could they be fully assessed, or under sedation, neuromuscular blockade, etc).

	using total GCS or GCS motor score cut off, or at each testing time point.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on comas score may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from medication, sedation and neuro-muscular blocking drugs, impairing coma assessment.	

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 from coma score is very low because of the risk of bias, especially risk of confounding from concurrent medication (sedative drug) use and risk for self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in	

	prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the sensitivity of coma score prediction, relatively low false positive rate at all time points, but limited studies examining each predictive testing threshold, timepoint and score, the balance of effects neither favors for or against the use of coma scores as a predictive test for good neurological outcome.	

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 for the assessment of coma are negligible. However, no study assessed savings from prognostication based on coma score have been included in our review.	

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 any studies assessing cost assessing coma score.	

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 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	Considering the negligible costs of coma score, a problem of inequity is unlikely.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of coma score requires basic training of clinical neurological examination. No additional equipment is required and is therefore feasible in resource limited 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 cannot make a recommendation for or against using total GCS, GCS motor score or motor response after ROC for predicting good neurological outcome in children after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

For coma score, limited evidence suggests that the specificity for prediction of good neurological outcome is similar across all assessment time points (<1 hour to 4-6hours) after cardiac arrest, although the FPR ranges from 6-14%.

Inconsistency in specificity across timepoints raises concern about the heterogeneity of studies, patient inclusion and accuracy of this prognostic test. This may be partly due to confounding from the effect of sedatives used for delivery of neuroprotective interventions (e.g. targeted temperature management) or to facilitate ventilation.

No studies reported any assessment of the confounding influence of medication on coma score. No studies included blinding of test results from treating clinicians and no study had blinded outcome assessment.

None of the included studies specifically excluded the presence of residual sedation at the time coma score was assessed. Lack of blinding is a major limitation of coma score, even if WLST based on coma score only has not been documented in any of the studies included in our review.

Despite its limitations, given the ease of assessment and no requirement for additional equipment required, (the balance between the costs and benefits may favours benefits).

Subgroup considerations

None.

Implementation considerations

Coma score is an easy clinical assessment; however, the examiner requires knowledge of basic neurological examination.

Research priorities

Use of coma score, including GCS motor score and other reported scores (eg FOUR score), require assessment in the paediatric population.

QUESTION

Should presence of motor response vs. absence of motor response be used for predicting good neurological outcomes in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Presence of motor response
COMPARISON:	Absence of motor response
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioral scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The presence of a motor response to any stimulus was evaluated in 1 study [Abend 2012 32] at <1h, 48, and 72 hours post return of circulation with up to 27 patients. Sensitivity and FPR improved for time since return of circulation, where if performed at <1h post ROSC the sensitivity was 38% and FPR was 30%, whereas at 72h the sensitivity was 100% and the FPR was 23%.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on motor response may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes.	

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 from motor response is very low because of the risk of bias, especially risk of confounding from concurrent medication (sedative drug) use and risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force	

	to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the high sensitivity, low FPR at 72h but only one small study evaluation the test, the balance of effects neither favors for or against the use of this test for predicting good neurological outcome.	

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 for the assessment of motor response are negligible. However, no study assessed savings from prognostication based on motor response have been included in our review.	

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 any studies assessing cost of motor response assessment.	

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 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	The cost of assessing motor response is related to training the provider, and is standard practice, but actually performing the test is free, thus no impact on equity is anticipated.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of motor response does not require special skills. The examiner needs to be familiar with the basics of clinical neurological examination.	

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 cannot make a recommendation for or against using total GCS, GCS motor score or motor response after ROC for predicting good neurological outcome in children after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

If performed at 72h the sensitivity of present motor response was 100% and the FPR was 23% for good neurological outcome. There is a high risk of bias with important confounders but this is an easy quick test that can be performed by any provider.

Implementation considerations

This test cannot be used if confounded by sedatives and paralytics.

QUESTION

Should the presence of brain stem reflexes vs. none be used for predicting good neurological outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	brain stem reflexes present within 10 days after cardiac arrest
COMPARISON:	none
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioral scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The presence of brain stem reflexes to predict good neurological outcome at intensive care unit or hospital discharge were evaluated in 2 studies [Brooks 2018 324, Topjian 2021 282] which including 118 patients. Evoked response to pain, gag reflex, and cough reflex were assessed at 6-12 hours, and 24h. Predictive sensitivity of presence of pain response at 6-12hours was 100% with a FPR of 67%. A present gag and cough reflex at 24h both predicted a good neurological outcome with a sensitivity of 40% and FPR of 32- 35%, respectively.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on presence of brain stem reflex may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from medication, sedation and neuro-muscular blocking drugs, impairing brain stem assessment.	

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 from brain stem reflexes is very low for predicting good neurological outcome because of the risk of bias, especially risk of confounding from concurrent medication (sedative drug) use and risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false	

	pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the moderate sensitivity of brain stem reflex prediction, relatively low false positive rate at all time points but only one study evaluating the test, the balance of effects neither favors for or against the use of the test for predicting good neurological outcome	

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 for the assessment of brain stem reflexes are negligible. However, no study assessed savings from prognostication based on brain stem reflexes have been included in our review.	

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 any studies assessing cost assessing of brain stem reflex test.	

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 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	Considering the negligible costs of brain stem reflex testing, a problem of inequity is unlikely.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of brain stem reflex test requires basic training of clinical	

○ Varies ○ Don't know	neurological examination. No additional equipment is required and is therefore feasible in resource limited 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 cannot make a recommendation for or against the use of brainstem tests after ROSC for predicting good neurological outcome in children after cardiac arrest.

Justification

The FPR was moderate to high in 2 studies (n=118) for predicting good neurological outcome using presence of brainstem reflexes. The predictive sensitivity of presence of pain response at 6-12h was 100% with a FPR of 67%. A present gag and cough reflex at 24h both predicted a good neurological outcome with a sensitivity of 40% and FPR of 32- 35%, respectively.

Inconsistency in specificity across timepoints raises concern about the heterogenity of studies, patient inclusion and accuracy of this prognostic test. This may be partly due to confounding from the effect of sedatives used for delivery of neuroprotective interventions (e.g. targeted temperature management) or to facilitate ventilation.

No studies reported any assessment of the confounding influence of medication on brain stem reflex test. No studies included blinding of test results from treating clinicians and no study had blinded outcome assessment.

None of the included studies specifically excluded the presence of residual sedation at the time coma score was assessed. Lack of blinding is a major limitation of brain stem reflex test, even if WLST based on coma score only has not been documented in any of the studies included in our review.

Implementation considerations

Brain stem reflex tests are easy clinical assessments; however, the examiner requires knowledge of basic neurological examination.

Research priorities

Use of brain stem reflex testing, with blinding of test results and outcome from clinicians making prognostic decisions requires assessment in the pediatric population.

QUESTION

Should blood lactate measurement be used for predicting good neurological outcomes in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Blood Lactate measurement
COMPARISON:	none
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is common and has a very high mortality, with neurologic injury as the most common cause of death. The majority of these deaths occur as a result of withdrawal of life-sustaining treatment (WLST) based on prediction of poor neurological outcome. Prediction of good neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Lactate was evaluated in 5 studies [De La Llana 2020 , Lopez-Herce 2014 607, Meert 2019 1441, Moler 2017 318, Moler 2015 1898]. Three studies documented <7% FPR for lactate <2mmol/L at <1h and 6-12 hours [Lopez-Herce 2014 607, Moler 2017 318, Moler 2015 1898] although sensitivity in these studies was low (16 - 28%). Lactate with cut off value <2mmol/L, at 24 to 48 hours was sensitive (69-86%) for good neurological outcome. However, this cut-off at 24 and 48h also had high FPR of 61 and 68%. FPR ranged 2 to 72%. Lactate <5mmol at <1h had moderate sensitivity (66%) and FPR (62%) and at 24h high sensitivity (89%) and low FPR (17%),	

	making the latter a useful test for prediction. Lactate clearance over 48h to <2mmol had high sensitivity (100%) and high FPR (77%).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on lactate levels below the cut off level may lead to inappropriate treatment in a patient with poor neurological outcome. This is likely to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from non-neurological causes of a raised lactate.	

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 from lactate is very low because of the risk of bias, especially self-fulfilling prophecy and non-specific nature of lactate metabolism.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a falsely optimistic prediction (test predicted a good outcome,	

	but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Even though lactate is non-specific, the balance of effect probably favours using the test for prediction of good neurological outcome at up to 12 hours due to high sensitivity and low FPR.	

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	Lactate is measured on blood gas analysers and is easily accessible. However, no study evaluated cost in our study.	

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 any studies specifically assessing costs of lactate for prognostication after cardiac arrest.	

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 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	A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Lactate is measured on blood gas analysers and is easily accessible. Although may not be available in resource limited 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 suggest using normal lactate (<2mmols) up to 12 hours following ROC for predicting good neurological outcome of children after cardiac arrest (weak recommendation, very-low-certainty evidence).

We cannot make a recommendation for or against using time to lactate clearance within 48 hours for predicting good neurological outcome in children after cardiac arrest.

Justification

Lactate is a common blood test in critically unwell children and associated with ischemia and hypoxic insult.

In one study, lactate <5mmol at 24h had near-optimal test characteristics, i.e., a high sensitivity (89%) and low FPR (17%). Lactate metabolism is complex and consideration of confounders and other predictors is critical.

Implementation considerations

Lactate levels and lactate clearance is widely used to guide therapy, thus only relevant implementation considerations are for settings without access to this biomarker and interpreting in context of whole patient because of the many potential confounders.

QUESTION

Should measuring blood neurobiomarkers vs. none be used for predicting good neurological outcomes in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	blood neurobiomarker
COMPARISON:	none
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Prediction of favourable or unfavorable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Only one study reported NSE, S100b and MBP values among 43 children [Fink 2014 664]. Cut off values were calculated and reported to classify either high sensitivity or low FPR for good neurological outcome. At 24 hours s100b level of 0.128 ng/ml predicted a good neurodevelopmental outcome with a sensitivity of 100% although an associated moderately high FPR of 62%. High (100%) sensitivity for predicting good outcome using NSE at 24hrs was identified at a cut off level of 53.1 ng/ml and 76.7 ng/ml at 48 hours (with a corresponding FPR 81 and 77% respectively). MBP level of 5.83 ng/ml at 24 hours and 5.43 ng/ml at 48 hours also had a high predictive sensitivity of 100% but high FPR of 96 and 88% respectively. Lower cut off values of s100B (0.001 ng/ml at 24 hours), NSE (0.48 ng/ml at 48 hours), or MBP (0.05 ng/ml at 48 hours)	

	reported a predicted sensitivity of 6 to 29% with corresponding very low FPR of <6% for good neurological outcome.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on blood neurobiomarkers may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity.	

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 from blood neurobiomarkers is low because of the 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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a falsely optimistic prediction (test predicted a good outcome,	

	but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering only one study evaluated neurobiomarkers, although at specific cut points the FPR was very low, the balance of effects neither favours for or against the use of the tests for predicting good neurological outcome.	

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 for the assessment of blood neurobiomarkers is variable. However, no study assessing savings from prognostication based on blood neurobiomarkers has been included in our review.	

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 any studies assessing cost of blood neurobiomarkers.	

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 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	Considering the variable cost of blood neurobiomarkers and their limited use in current clinical practice, it is likely that there would be inequity in access to this test.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely as it is simple to obtain blood and there is no patient harm in obtaining the blood.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of blood neurobiomarkers requires specialized laboratory equipment to perform- which is becoming more widely available.	

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 cannot make a recommendation for or against the use of blood neuro-biomarkers (eg, S100B NSE) after return of circulation for predicting good neurological outcome in children after cardiac arrest.

Justification

Only one study (Fink, 2014) has identified cut-offs for 2 blood neurobiomarkers (S100b and NSE) that are associated with favorable neurological survival with a low FPR, although sensitivity if also low. Furthermore, these tests require specialized laboratory equipment and are not widely available, even though they only require the patient's blood.

Subgroup considerations

No specific subgroup considerations.

Implementation considerations

Until neurobiomarkers become more widely used (i.e., more indications with higher certainty of evidence), this test will likely be used for research purposes primarily. The field is growing quickly and equipment is becoming more accessible so that the clinician may adopt this test in the future.

Monitoring and evaluation

None

Research priorities

This is a relatively new field of research and holds a lot of promise. There are other potential candidate biomarkers that should be explored and subgroups may exist where FPR is much lower. Higher number of participants need to be included in future studies.

QUESTION

Should blood pH be used vs. none for predicting good neurological outcomes in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	blood pH measurement
COMPARISON:	none
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioral scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	pH was evaluated in 4 studies [De La Llana 2020 , Lopez-Herce 2014 607, Moler 2017 318, Moler 2015 1898]. pH thresholds were >7.0, >7.3, and <7.5, and in intervals of 0.15 [Kane 2010 S241] at resuscitation and within 1 hour, 6-12 hours and 24 hours of return of circulation. The blood pH measured post resuscitation or < 1 hour from ROSC had a sensitivity of 27 to 95% for predicting good neurological outcome. A pH >7.0 was reported in 3 studies and had a sensitivity to predict survival (68-98%) and good neurological outcome (71-97%). FPR was above 80% for all except for pH cut off >7.0 at <1 hour post ROSC (45%), and >7.3 at < 1hour post return	

	of circulation (38%) for good neurodevelopmental outcome.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on pH may lead to inappropriate treatment in a patient with a poor neurological outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity and the potential for confounding from other causes of pH derangements (e.g., respiratory, toxic ingestions).	

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 from pH is low because of the risk of bias, especially self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a falsely optimistic prediction (test predicted a good outcome, but patient went on to have a bad outcome).	

	The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the high sensitivity of pH but high false positive rate at the corresponding time points, the balance of effects favours against the use of the tests for predicting good neurological outcome.	

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 for the assessment of pH are low. However, no study assessing savings from prognostication based on pH has been included in our review.	

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 any studies assessing cost of pH.	

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 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 study assessed the impact on health equity. A problem of inequity is possible, since assessment of biomarkers implies resources that cannot be universally available	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any study assessing acceptability, but acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Although feasibility was not specifically addressed in any of the studies included in this review, the assessment of pH is a common test and used to guide therapy in a critically ill patient. The requirement is a blood testing kit which is widely available.	

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 using pH after return of circulation for predicting good neurological outcomes in children after cardiac arrest (weak recommendation, very-low-certainty evidence).

Justification

pH values >7.0 and <7.5 6-24h hours after ROSC have high sensitivities for good neurological outcome following cardiac arrest, however they also have high FPRs. A pH>7.0 or 7.3 within 1 hour of ROSC has lower sensitivities (71 and 49%, respectively) but also lower FPRs (45 and 38%, respectively). All studies had a high risk of bias.

pH is widely but not universally available.

Subgroup considerations

pH can be confounded by underlying metabolic conditions, medications, and even cardiac arrest triggers- these must be taken into consideration when using pH as a predictor.

Implementation considerations

Post cardiac arrest care uses pH to guide ventilation- thus this is already routinely recommended.

QUESTION

Should presence vs. absence of N20 waves on somatosensory evoked potential recordings be used for predicting favorable neurodevelopmental outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Presence of N20 waves on somatosensory evoked potential recordings
COMPARISON:	Absence of N20 waves on somatosensory evoked potential recordings
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favorable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Somatosensory evoked potential (SSEPs), evaluating presence or absence of N20 wave, were reported in only one study, with a small sample size (n=9) reporting good neurological outcome (PCPC 1 to 3) at 3 timepoints (24, 48 and 72 hours) [McDevitt 2019]. Clinicians were blinded to test results and the SSEP assessor was blinded to outcome. The predicted sensitivity was 100% at 24 and 48	

	hours and 83% at 72 hours, with a very low FPR 0% at all time points.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	The false positive rate was very low (0%) making the presence of N20 wave highly specific (100%) for prediction of good neurodevelopmental outcomes in comatose children after cardiac arrest.	

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	Given the small sample size of the single included study, certainty of evidence would be considered low. The precision of the results was low with wide confidence intervals: Sensitivity 1.00 [0.48, 1.00] at 24 and 48 hours with sensitivity 0.83 [0.36, 1.00] at 72 hours; False positive rate 0.00 [0.00, 0.71] at 24 and 72 hours with FPR 0.00 [0.00, 0.60] at 48 hours. The findings were strengthened by the fact that clinicians were blinded to test results and SSEP assessor to outcome.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a	

	good outcome will have a falsely optimistic prediction (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a falsely pessimistic prediction (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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 presence of the N20 wave on somatosensory evoked potentials at 24 and 48 hours post cardiac arrest was 100% sensitive and 100% specific for prediction of good neurological outcomes in children post-cardiac arrest. However, this is from a single study and therefore the balance of effects neither favors for or against the use of presence of N20 waves for prediction of good neurological outcomes 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	We did not include any specific studies assessing costs of performing somatosensory evoked potentials in critically ill children for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in many 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	We did not identify any studies specifically assessing costs of performing somatosensory evoked potentials and/or screening for the presence of N20 wave.	

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 addressing cost-effectiveness of identifying N20 waves or performing somatosensory evoked potential recordings in children after cardiac arrest.	

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 specific equipment and skills needed to obtain somatosensory evoked potential recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of presence of N20 waves as a predictor of outcomes or that of somatosensory evoked potentials. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Evaluating for the presence of N20 waves on somatosensory evoked potential recordings for prognostication purposes requires specific equipment and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 cannot make a recommendation for or against the use of presence or absence of N20 response SSEPs for predicting good neurological outcome .

Justification

Overall justification

One study evaluated the utility of 'presence of N20 wave' in somatosensory evoked potentials as a predictor of good neurodevelopmental outcomes in comatose critically ill children after cardiac arrest [McDevitt 2019 30]. This study reported a 100% sensitivity at 24 and 48 hours with a 0% false positive rate. At the 72-hour time point, this study reported a 83% sensitivity with 0% false positive rate.

Detailed justification

Desirable Effects

100% sensitivity at 24- and 48-hour time points83% sensitivity at 72-hour time point

Undesirable Effects

100% specificity at all 3-time points0% false positive rate at all 3 time points

Certainty of evidence

Single study with a small number of subjects and low precision - Low certainty of evidence

Resources required

Specialized equipment and expertise are required for the conduct and interpretation of somatosensory evoked potentials in critically ill children

Equity

Resources required for SSEP recording and interpretation may not be available in many centers, especially in resource-limited settings.

Implementation considerations

Performance and interpretation of SSEPs in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Research priorities

Large multicenter studies are required to evaluate the sensitivity and false positive rate of positive N20 wave on SSEPs during the first 72 hours post cardiac arrest in critically ill children with higher precision.

QUESTION

Should presence or absence of sleep spindles or of sleep architecture on EEG be used for prediction of good neurological outcome in children with cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause,
INTERVENTION:	Presence of sleep spindles or sleep architecture on EEG
COMPARISON:	Absence of sleep spindles or sleep architecture on EEG
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The presence of sleep II architecture or sleep spindles were reported in two studies including 123 patients at 6-12- and 24-hours post-ROC after cardiac arrest. The presence of these features had a predicted sensitivity of 57-80% and low FPR (8.3-16%) [Ducharme-Crevier 2017 452, Topjian 2021 282].	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive result (presence of sleep spindles or architecture) may suggest that good neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a good outcome and continued treatment based on absence of reactivity on EEG may lead to inappropriate treatment in a patient with an poor neurological outcome. This is possible to occur given the low specificity and high false positive rates.	

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 about reactivity was low due to the limited number of studies, very low precision of studies and the risk of self-fulfilling prophecy. There was lack of definition of sleep spindles and sleep architecture.	

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	Neurological outcome is a critical outcome after cardiac arrest (Topjian 2020 e246). Tools and definitions used to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. However, change from baseline neurodevelopmental status may be more important than eventual neurodevelopmental level, especially in infants and children with pre-existing neurodevelopmental impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good	

	outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the false positive rate less than 20% for testing within 24hours, the presence of sleep spindles and sleep architecture on EEG as a predictive test within 24 hours favours using this as a test for good neurological outcome prediction.	

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	We did not include any specific studies assessing costs of assessing EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in 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	We did not identify any studies specifically assessing costs.	

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 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	The specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We have not identified any research that assessed acceptability of sleep spindles or sleep architecture as a predictor.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of sleep spindles on EEG requires specific equipment for recording EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 using the following EEG features after return of circulation for predicting good neurological outcome: presence of sleep spindle and sleep II architecture at 12 to 24 hours, or continuous or normal background EEG between 1 and 72 hours, or EEG reactivity between 6 to 24 hours (weak recommendation, very low–certainty evidence).

Justification

Two studies [Ducharme-Crevier 2017 452, Topjian 2021 282] ireported the presence of sleep II architecture or sleep spindles including 123 patients at 6-12- and 24-hours post-ROC after cardiac arrest. The presence of these features had a predicted sensitivity of 57-80% and low FPR (8.3-16%). The low FPR justified inclusion for use in good prognostication.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of EEG or continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should absence vs. presence of myoclonic seizures be used for predicting favorable neurodevelopmental outcomes in children after cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of myoclonic seizures
COMPARISON:	Presence of myoclonic seizures
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Based on two studies, absence of myoclonic seizures predicted good neurological outcomes with a sensitivity of 100% and a FPR of 79-83% at	

	PICU/hospital discharge [Brooks 2018 324, Ostendorf 2016 667].	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive result (absence of myoclonic seizures) may suggest that favorable neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a favourable outcome and continued treatment based on absence of myoclonic seizures on EEG may lead to inappropriate treatment in a patient with an unfavourable neurodevelopmental outcome. This is possible to occur given the low specificity and high false positive rates.	

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 about myoclonic seizures was very low due to presence of only two studies with low precision and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for	

	imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Due to the high FPR, the balance of effects favors against using the test for predicting good neurological outcome in children post-cardiac arrest.	

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	We did not include any specific studies assessing costs of ruling out myoclonic seizures on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings. Myoclonic seizures can be suspected clinically but need EEG for confirmation.	

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 any studies specifically assessing costs of performing continuous electroencephalography and/or ruling out myoclonic epilepsy.	

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 addressing cost-effectiveness of myoclonic seizure diagnosis using continuous electroencephalography after cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of absence of myoclonic seizures as a predictor of outcomes. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Evaluating myoclonic seizures on continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 using the following EEG features after ROC to predict good neurological outcome: absence of clinical or electrographic seizures; absence of status epilepticus; absence of myoclonic epilepsy; absence of burst suppression, burst attenuation, or GPEDs; or absence of attenuated, isoelectric, or flat EEG (weak recommendation, very low–certainty evidence).

Justification

Overall justification

Two studies [Brooks 2018 324, Ostendorf 2016 667] evaluated the utility of absence of myoclonic seizures for prediction of good neurodevelopmental outcomes in critically ill children post cardiac arrest. The two studies demonstrated excellent sensitivity (100%) but very low specificity (17-21%) and very high false positive rate (79-83%).

Detailed justification

Undesirable Effects

Very high false positive rate reported by this study played a major role in the inability to recommend the use of absence of myoclonic seizures for neuroprognostication.

Certainty of evidence

The only study that could be included did not adjust for effect of sedation or targeted temperature management on the absence of myoclonic seizures.

Resources required

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity

Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Myoclonic seizures represent a subtype of seizures. Evaluation of association between overall seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed.

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should presence or absence of reactivity on EEG be used for prediction of good neurological outcome in children with cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Presence of reactivity on EEG
COMPARISON:	Absence of reactivity on EEG
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic	

	expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The presence of reactivity within an EEG trace was reported in 3 studies with a moderate predictive sensitivity for good neurological outcome of 53-80% between 6 to 72 hours. [Ostendorf 2016 667, Topjian 2016 547, Yang 2019 223] FPR ranged 7 to 27% up to 24 hours post ROC in 2 studies [Ostendorf 2016 667, Topjian 2016]. However increased to 50% at 48 hours post-ROC in one study.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive result (absence of reactivity) may suggest that good neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a good outcome and continued treatment based on absence of reactivity on EEG may lead to inappropriate treatment in a patient with an poor neurological outcome. This is possible to occur given the low specificity and high false positive rates.	

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 about reactivity was low due to the limited number of studies, very low precision of studies and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (Topjian 2020 e246). Tools and definitions used to measure good neurological outcome in	

○ No important uncertainty or variability	our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. However, change from baseline neurodevelopmental status may be more important than eventual neurodevelopmental level, especially in infants and children with pre-existing neurodevelopmental impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the false positive rate less than 30% for testing within 24hours, the presence of reactivity on EEG as a predictive test within 24 hours favours using EEG reactivity as a test for good neurological outcome prediction.	The task force recognises the poor definition of reactivity and need for specialist neurophysiology input into accurate interpretation.

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	We did not include any specific studies assessing costs of assessing EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in 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	We did not identify any studies specifically assessing costs of performing continuous electroencephalography and/or ruling out seizures.	

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 addressing cost-effectiveness of seizure detection using continuous electroencephalography after cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We have not identified any research that assessed acceptability of EEG reactivity as a predictor.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of reactivity on EEG requires specific equipment for recording EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 using the following EEG features after return of circulation for predicting good neurological outcome: presence of sleep spindle and sleep II architecture at 12 to 24 hours, or continuous or normal background EEG between 1 and 72 hours, or EEG reactivity between 6 to 24 hours (weak recommendation, very low–certainty evidence).

Justification

Three studies reported the presence of reactivity within an EEG trace with a moderate predictive sensitivity for good neurological outcome of 53-80% between 6 to 72 hours. [Ostendorf 2016 667, Topjian 2016 547, Yang 2019 223], the low FPR (7 to 27% up to 24 hours post ROC) in 2 studies [Ostendorf 2016 667, Topjian 2016] justified inclusion.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of EEG or continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should absence vs. presence of seizures be used for predicting good neurological outcomes in children following a cardiac arrest?	
POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of seizures
COMPARISON:	presence of seizures
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Twelve studies reported the relationship between absence or presence of seizures in children post-cardiac arrest and good neurological outcomes at PICU/hospital discharge, 6 months, and 12 months [Brooks 2018 324, Ducharme-Crevier 2017 452, Fung	

	2019 349, Kirschen 2021 e719, Lin 2019 534, Meert 2019 393, Moler 2017 318, Moler 2015 1898, Ostendorf 2016 667, Topjian 2016 547, Yang 2019 223]. These studies included 1165 children, of which 4/12 studies reported using the ACNS criteria [Ducharme-Crevier 2017 452, Fung 2019 349, Ostendorf 2016 667, Yang 2019 223]. Absence of seizures up to 24 hours post-ROC had a sensitivity of 50-100% with a FPR of 63-98% for predicting good neurological outcome at various time points. Absence of seizure after 24 hours had a sensitivity of 50-100% with a FPR of 42-100% for predicting good neurological outcome.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive result of EEG may suggest that favorable neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a favourable outcome and continued treatment based on absence of seizures on EEG may lead to inappropriate treatment in a patient with an unfavourable neurodevelopmental outcome. This is possible to occur given the variability of cut offs for sensitivity and specificity.	

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 about seizures was low due to the limited number of studies, very low precision of most studies and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline	

	neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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 absence of clinical or electrographic seizure (as defined by American Clinical Neurophysiology Society) was 50-100% sensitive and FPR of >40% for prediction of good neurological outcomes in children post-cardiac arrest. The balance of effects therefore favors against the use of this as a predictive test for good neurological outcome.	

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	We did not include any specific studies assessing costs of assessing seizures on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in 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	We did not identify any studies specifically assessing costs of performing continuous electroencephalography and/or ruling out seizures.	

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 addressing cost-effectiveness of seizure detection using continuous electroencephalography after cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of clinical or electroencephalographic seizures as a predictor, or that of the American Clinical Neurophysiology Society's definition of electrographic seizures. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of seizures on continuous EEG requires specific equipment for recording EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 suggest against using the following EEG features after ROC to predict good neurological outcome: absence of clinical or electrographic seizures; absence of status epilepticus; absence of myoclonic epilepsy; absence of burst suppression, burst attenuation, or GPEDs; or absence of attenuated, isoelectric, or flat EEG (weak recommendation, very low–certainty evidence).

Justification

Overall justification

For clinical or electrographic seizures, 12 studies suggest that their absence up to 24 hours or beyond 24 hrs post cardiac arrest had a reasonable sensitivity but high FPR for predicting good neurological outcomes.

Detailed justification

Certainty of evidence

None of the studies adjusted for the confounding effect of sedation or targeted temperature management on the absence of seizures

Resources required

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity

Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurological outcomes is needed.

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should absence vs. presence of burst suppression or burst attenuation be used for prediction of good neurological outcome in children with cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	absence of burst suppression or burst attenuation

COMPARISON:	presence of burst suppression or burst attenuation
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Absence of burst suppression, burst attenuation or GPEDS were reported in 6 unblinded studies including 395 patients [Brooks 2018 324, Fung 2019 349, Ostendorf 2016 667, Topjian 2016 547, Topjian 2021 282, Yang 2019 223] . Sensitivity increased from 81-100% within 6-12 hours, to a highly sensitive test (100% with high precision (95%CI 100-100) at 24, 48 and 72 hours. However, the FPR was high at all time periods (67-100%) for a predicting a good neurodevelopmental outcome.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive result (absence of burst suppression, burst attenuation or GPEDS) may suggest that good neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a good outcome and continued treatment based this EEG feature may lead to inappropriate treatment in a patient with an poor neurological outcome. This is likely to occur given the low specificity and high false positive rates at all time points.	

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 about reactivity was low due to the limited number of studies, very low precision of studies and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (Topjian 2020 e246). Tools and definitions used to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. However, change from baseline neurodevelopmental status may be more important than eventual neurodevelopmental level, especially in infants and children with pre-existing neurodevelopmental impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (eg <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false	

	pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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 high false positive rate balances in favour of not using absence of burst suppression, burst attenuation or GPEDS as a predictor for good neurological outcome.	The high sensitivity rate may be a useful feature for using this test as a predictor for poor neurological outcome and requires further evaluation.

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	We did not include any specific studies assessing costs of identifying absence of burst suppression, burst attenuation or GPEDS on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in 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	We did not identify any studies specifically assessing costs of performing EEG post cardiac arrest.	

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 addressing cost-effectiveness of using EEG post cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We have not identified any research that assessed acceptability for absence of burst suppression, burst attenuation or GPEDS on EEG as a predictor.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes	Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of background patterns on EEG requires specific equipment for recording EEG	

○ Varies ● Don't know	and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 using the following EEG features after ROC to predict good neurological outcome: absence of clinical or electrographic seizures; absence of status epilepticus; absence of myoclonic epilepsy; absence of burst suppression, burst attenuation, or GPEDs; or absence of attenuated, isoelectric, or flat EEG (weak recommendation, very low–certainty evidence).

Justification

Overall justification

Absence of burst suppression, burst attenuation or GPEDS were reported in 6 unblinded studies including 395 patients [Brooks 2018 324, Fung 2019 349, Ostendorf 2016 667, Topjian 2016 547, Topjian 2021 282, Yang 2019 223] . Sensitivity increased from 81-100% within 6-12 hours, to a highly sensitive test (100% with high precision (95%CI 100-100) at 24, 48 and 72 hours. However, the FPR was high at all time periods (67-100%) for a predicting a good neurodevelopmental outcome. Therefore the task force judged that the recommendation should be against using for predicting good neurological outcome.

Resources required
Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity
Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Absence of burst suppression, burst attenuation or GPEDS have a high sensitivity and precision which may indicate that this is a useful test for predicting poor neurological outcome. Further evaluation is therefore required.

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should presence or absence of continuous or normal background on EEG be used for predicting good neurological outcome?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.

INTERVENTION:	presence of continuous or normal background on EEG
COMPARISON:	absence of continuous or normal background on EEG
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The presence of a normal EEG background (defined as normal, continuous, and reactive, continuous, and unreactive, and nearly continuous by ACNS definitions) were reported in 10 studies with 18 different testing timings and included 563 patients. [Brooks 2018 324, Ducharme-Crevier 2017 452, Fink 2014 664, Fung 2019 349, Kessler 2011 37, Kirschen 2021 e719, Ostendorf 2016 667, Topjian 2016 547, Topjian 2021 282, Yang 2019 223]. Studies using normal or continuous EEG reported a low to moderate sensitivity 10/18 time points were less than 50%. However, FPR was also low with all tests less than 50% and 11/18 < 30%. In the largest study by Topjian 2016, the sensitivity of continuous EEG at 6-12 hours was 7.3% with a FPR of 0%. FPR was higher in studies assessing prognostic accuracy at and beyond 48 hours post-ROC.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive result may suggest that good neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a good outcome and continued treatment based on presence of continuous or normal background on EEG may lead to inappropriate treatment in a patient with an poor neurological outcome. This is possible to occur given the low specificity and moderate to high false positive rates especially at 48 hours and beyond.	

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 about reactivity was low due to the limited number of studies, very low precision of studies and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (Topjian 2020 e246). Tools and definitions used to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. However, change from baseline neurodevelopmental status may be more important than eventual neurodevelopmental level, especially in infants and children with pre-existing neurodevelopmental impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more	

	desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the majority of studies reporting a false positive rate less than 30% for testing within 24hours, the presence of a continuous or normal background on EEG as a predictive test within 24 hours favours using this as a test for good neurological outcome prediction.	

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	We did not include any specific studies assessing costs of assessing EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in resource-limited settings.	There is no data to recommend the duration of EEG monitoring.

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 any studies specifically assessing costs of performing EEG post cardiac arrest.	

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 addressing cost-effectiveness of seizure detection using EEG post cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We have not identified any research that assessed acceptability for continuous or normal background EEG as a predictor.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of background patterns on EEG requires specific equipment for recording EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 using the following EEG features after return of circulation for predicting good neurological outcome: presence of sleep spindle and sleep II architecture at 12 to 24 hours, or continuous or normal background EEG between 1 and 72 hours, or EEG reactivity between 6 to 24 hours (weak recommendation, very low–certainty evidence).

Justification

The presence of a normal EEG background (defined as normal, continuous, and reactive, continuous, and unreactive, and nearly continuous by ACNS definitions) were reported in 10 studies in 18 timepoints. 11/18 test reported a FPR <30% and justified inclusion as a test for prediction of good neurological outcome.

Continuous EEG background requires expert assessment and equipment. ACNS definitions and variation in interpretation existed across studies. Further research is needed to understand implementation and definitions.

Should not be used in isolation as a single test.

Further evidence on the type of EEG, and duration of monitoring.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of EEG or continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should absence vs. presence of attenuated isoelectric or flat EEG be used for prediction of good neurological outcome in children with cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of attenuated, isoelectric or flat EEG
COMPARISON:	Presence of attenuated, isoelectric or flat EEG
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The absence of an attenuated, isoelectric, or flat EEG was reported in 10 studies including up to 526 patients (although there is a risk of overlapping patient populations) [Brooks 2018 324, Ducharme-Crevier 2017 452, Fink 2014 664, Fung 2019 349, Kessler 2011 37, Kirschen 2021 e719, Ostendorf 2016 667, Topjian 2016 547, Topjian 2021 282, Yang 2019 223]. The sensitivity to predict a good neurological outcome was very high in 8 studies (91-100%); however there was a wide range of FPR of 0-83% with the majority of studies reporting >40% FPR.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive result (absence of an attenuated, isoelectric, or flat EEG) may suggest that good neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a good outcome and continued treatment based this EEG feature may lead to inappropriate treatment in a patient with an poor neurological outcome. This is likely to occur given the low specificity and high false positive rates at all time points.	

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 about reactivity was low due to the limited number of studies, very low precision of studies and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (Topjian 2020 e246). Tools and definitions used to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. However, change from baseline neurodevelopmental status may be more important than eventual neurodevelopmental level, especially in	

	infants and children with pre-existing neurodevelopmental impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (eg <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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 high false positive rate balances in favour of a suggestion against using absence of an attenuated, isoelectric, or flat EEG as a predictor for good neurological outcome.	The high sensitivity rate in most studies may be a useful feature for using this test as a predictor for poor neurological outcome and requires further evaluation.

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	We did not include any specific studies assessing costs of identifying absence of an attenuated, isoelectric, or flat EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in 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	We did not identify any studies specifically assessing costs of performing EEG post cardiac arrest.	

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 addressing cost-effectiveness of using EEG post cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability for absence of an attenuated, isoelectric, or flat EEG as a predictor.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Diagnosis of background patterns on EEG requires specific equipment for recording EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day. However, in centres with access to EEG monitoring bedside clinical staff can identify these features.	

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

We suggest against using the following EEG features after ROC to predict good neurological outcome: absence of clinical or electrographic seizures; absence of status epilepticus; absence of myoclonic epilepsy; absence of burst suppression, burst attenuation, or GPEDs; or absence of attenuated, isoelectric, or flat EEG (weak recommendation, very low–certainty evidence).

Justification

Overall justification

The absence of an attenuated, isoelectric, or flat EEG was reported in 10 studies including up to 526 patients (although there is a risk of overlapping patient populations) [Brooks 2018 324, Ducharme-Crevier 2017 452, Fink 2014 664, Fung 2019 349, Kessler 2011 37, Kirschen 2021 e719, Ostendorf 2016 667, Topjian 2016 547, Topjian 2021 282, Yang 2019 223]. The sensitivity to predict a good neurological outcome was very high in 8 studies (91-100%); however there was a wide range of FPR of 0-83% with the majority of studies reporting >40% FPR. The high FPR led to the decision to suggest against the recommendation.

Resources required
Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity
Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Absence of an attenuated, isoelectric, or flat EEG have a high sensitivity and precision which may indicate that this is a useful test for predicting poor neurological outcome. Further evaluation is therefore required.

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should absence vs. presence of status epilepticus be used for predicting good neurological outcomes in children after a cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of status epilepticus up to 10 days post ROC.
COMPARISON:	Presence of status epilepticus up to 10 days post ROC.
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, has a low rate of survival and high chance of neurological injury. Most of these deaths occur because of withdrawal of life-sustaining treatment (WLST) based on prediction of unfavorable neurological outcome. Prognostication is of utmost importance because inappropriate WLST can be avoided in those likely to survive with good neurological outcomes. Prediction of favourable neurodevelopmental outcome is a key skill for clinicians to guide appropriate	

	treatment and realistic expectation with parents and/or legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Absence of status epilepticus was reported in three studies [Fung 2019 349, Topjian 2016 547, Yang 2019 223]. Two of these studies used ACNS criteria to define status epilepticus. Good neurological outcome at PIC/hospital discharge were predicted with a high sensitivity of >90%, although FPR remained high 81-91%.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A false positive result (absence of status epilepticus) may suggest that good neurological outcome is likely in patients with an eventually poor neurological outcome. A false positive prediction of a favourable outcome and continued treatment based on absence of status epilepticus on EEG may lead to inappropriate treatment in a patient with an unfavourable neurological outcome. This is possible to occur given the low specificity and high false positive rates.	

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 about status epilepticus was low due to the limited number of studies, very low precision of studies and the risk of self-fulfilling prophecy.	

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	Neurological outcome is a critical outcome after cardiac arrest (Topjian 2020 e246). Tools	

○ Probably no important uncertainty or variability ○ No important uncertainty or variability	and definitions used to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. However, change from baseline neurodevelopmental status may be more important than eventual neurodevelopmental level, especially in infants and children with pre-existing neurodevelopmental impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic prediction* (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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 high false positive rate balances in favour of suggesting against using the absence of status epilepticus (as defined by American Clinical Neurophysiology Society). for predicting good neurological outcome.	The high sensitivity rate may be a useful feature for using this test as a predictor for poor neurological outcome and requires further evaluation.

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	We did not include any specific studies assessing costs of ruling out status epilepticus on EEG for neuroprognostication. However, specific equipment and skills are required for performing continuous EEG monitoring in critically ill children and these may not be available in 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	We did not identify any studies specifically assessing costs of performing continuous electroencephalography and/or ruling out status epilepticus.	

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 addressing cost-effectiveness of status epilepticus diagnosis using continuous electroencephalography after cardiac arrest.	

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 specific equipment and skills needed to obtain EEG recordings in critically ill children post cardiac arrest may not be available everywhere and every time. This can create a problem in terms of equity.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	We have not identified any research that assessed acceptability of absence of status epilepticus as a predictor of outcomes or that of the American Clinical Neurophysiology Society's definition of status epilepticus. However, acceptability is likely.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility was not specifically addressed in any of the studies included in this review. Evaluating status epilepticus on a continuous critical care EEG recording for prognostication purposes requires specific equipment for recording continuous EEG and the expertise to interpret the tracing. This may not be feasible everywhere or during all times of the day.	

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 using the following EEG features after ROC to predict good neurological outcome: absence of clinical or electrographic seizures; absence of status epilepticus; absence of myoclonic epilepsy; absence of burst suppression, burst attenuation, or GPEDs; or absence of attenuated, isoelectric, or flat EEG (weak recommendation, very low–certainty evidence).

Justification

Overall justification

Three studies evaluated 'absence of status epilepticus' [Fung 2019 349, Topjian 2016 547, Yang 2019 223], and found that good neurological outcome at discharge were predicted with a high sensitivity of >90%, but specificity of 9-19% and FPR of 81-91%. The high FPR led to the recommendation against using this test for predicting good neurological outcome by the Task Force.

Detailed justification

Certainty of evidence

None of the studies adjusted for the confounding effect of sedation or targeted temperature management on the absence of seizures

Resources required

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources.

Equity

Resources required for continuous EEG monitoring and interpretation may not be available in resource-limited settings.

Subgroup considerations

None

Implementation considerations

Performance and interpretation of continuous EEG in the pediatric critical care environment requires resources and these may not be uniformly available even in resource-rich settings.

Monitoring and evaluation

None

Research priorities

Status epilepticus represents increased seizure burden in comparison to individual seizures. Evaluation of association between seizure burden during the first 72 hours post cardiac arrest and neurodevelopmental outcomes is needed. Absence of status epilepticus has a high sensitivity and should be evaluated as a predictor or poor neurological outcome in future research.

Future studies should also more carefully adjust for the confounding effect of medications, targeted temperature management and other critical care interventions.

QUESTION

Should absence vs. presence of abnormality on cranial CT be used for predicting good neurological outcome in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of abnormality on cranial CT
COMPARISON:	Presence of abnormality on cranial CT
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate	

○ Varies ○ Don't know	treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Head CT was evaluated in three studies and reported the relationship to good neurological outcome (PCPC 1 to 3) in 173 patients [Fink 2014 664, Starling 2015 542, Yang 2019 223]. The majority of CT imaging was acquired at 24 h or 48 h after the cardiac arrest. Neurological outcome was assessed on discharge from the intensive care unit or hospital in two studies and six months in one. Reported factors from CT included presence and absence of intracranial haemorrhage, cerebral oedema or ischemia measured by the 'reversal sign', grey white matter (GWM) differentiation and sulcal or basal cistern effacement. Two studies described methods of estimating GWM differentiation [Starling 2015 542, Yang 2019 223] and two reported radiologists qualitative reports [Fink 2014 664, Starling 2015 542]. The presence of GWM differentiation on CT at 24 hours, had a sensitivity of 64-100%, and FPR 35-70%. Absence of CT lesions, oedema, or intracranial haemorrhage predicted good neurological outcome with a sensitivity ranging 72-100%; however, a wide range of FPR (14% to 90%) was reported. Absence of effacement of sulci or basal cisterns predicted good neurological outcome with a high sensitivity (93-100%) with a FPR 32-73%. Clinicians were not blinded to the CT results in any study.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on CT imaging may lead to inappropriate treatment in a patient with a poor neurological outcome. This is termed false optimism. This is possible to occur given the variability of cut offs for sensitivity and specificity (FPR). It remains unclear when CT imaging should exactly be timed after cardiac arrest to increase its sensitivity and specificity. A CT scan involves exposure to radiation which can increase lifetime exposure risk of radiation induced injury.	

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 from CT imaging is very low because of the risk of bias, lacking of blinding, especially self-fulfilling prophecy. In addition only selected patients received CT scan as a diagnostic tool and there is a high risk of selection bias.	Differently from other predictors, like those based on clinical examination, imaging is not affected by sedation or paralysis, and it can be potentially assessed blindly.

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. A low false positive rate means that a low proportion of patients, predicted to have a good outcome will have a *falsely optimistic*	The task force identified that the current use of a dichotomised neurological outcome cut off is a limitation for families and patients in considering the range and acceptability of outcomes for individual children after cardiac arrest in children.

	prediction (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accuracy of predicting a good outcome - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. This will involve increased resources and treatment; however, may also allow more time for further prognostic evaluation. Also, reasons for not achieving a very low false positive rate may be non-neurological causes of poor outcome or death, not attributable to the index test assessment. A high sensitivity means the majority of patients, who have a good outcome, tested positive and therefore a corresponding low proportion will have a *falsely pessimistic prediction* (test predicted a poor outcome, but patient went on to have a good outcome). When considering the accuracy of predicting a poor outcome (compared to predicting a good outcome), then a low rate of falsely pessimistic predictions is very important. Our cut off threshold for considering precise sensitivity was therefore higher (>95%), as the consequences of inaccurate poor outcome prediction (e.g. false pessimism) may lead to a decision to limit or withdraw life sustaining therapies in a patient who could have a good neurological 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	Considering the high false positive rate of using absence of abnormality on CT imaging as a predictive test at all time points studied, the balance favours not using CT imaging as a test for good neurological outcome prediction.	A CT scan may be performed for other diagnostic indications (e.g. identify the cause of cardiac arrest) and the information may be combined with other prognostic tests. The moderate to high sensitivity at 24-48 hours indicates that CT imaging may have a role in predicting poor outcome (with a low to moderate level of false pessimism). But due to the low precision and wide range of sensitivity the data does not favour either performing or not performing the test for poor outcome prediction.

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	Specialist equipment and training in interpretation to perform cranial CT is required. Costs and access to cranial CT imaging may be variable depending on the health care setting. CT requires exposure to radiation. No study assessing cost of CT imaging has been included in our review; compared to other brain imaging modality such as magnetic resonance imaging, CT requires less acquisition time and less costly.	

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 any studies specifically assessing costs of performing CT imaging after cardiac arrest in children. However, the use of specialist personnel, training and equipment may require significant local resources to perform.	

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 addressing cost-effectiveness of CT imaging after cardiac arrest.	

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 study assessed the impact on health equity. However, due to the high cost of CT imaging, there may be health inequity in receiving this investigation and prognostic test.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We have not identified any study assessing acceptability.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Although feasibility was not specifically addressed in any of the studies included in this review. However, requires significant resources, personnel and training and this may limit the feasibility in all health care settings. Imaging studies used for neuroprognostication after cardiac arrest cannot be performed at the bedside, and most often require transportation to a Radiology Department, with additional clinical and safety risks.	

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 using normal CT at 24-48 hours from return of circulation for predicting good neurological outcome (weak recommendation, very-low-certainty evidence).

Justification

The high false positive rate (low specificity) for predicting good neurological outcome may lead to a high rate of false optimism if a normal CT (absence of intracranial haemorrhage, cerebral oedema or ischemia measured by the 'reversal sign', grey white matter (GWM) differentiation and sulcal or basal cistern effacement) predicts a good neurological outcome, but the patient proceeds to have a poor neurological outcome. We therefore suggest against using a normal CT as a prognostic test for good outcome.

A head CT may be indicated for diagnostic purposes in infants and children following a cardiac arrest to identify causes of cardiac arrest, coma, or intracranial pathology requiring treatment.

The sensitivity of a normal CT to predict a good neurological outcome is moderate to high, but up to 30% of may be falsely categorised and a falsely pessimistic prediction made. Therefore, with the low number of studies and patients, high risk of bias in studies, lack of blinding and risk of self-fulfilling prophecy, and risk of confounding by selection, we cannot make a recommendation for or against the use of abnormal CT for predicting poor neurological outcome.

Subgroup considerations

none

Implementation considerations

CT required infrastructure, resource and skilled radiologists to perform and interpret imaging. Access to this may be limited or not available in some health care setting.

Monitoring and evaluation

none

Research priorities

A consistent regional GWR threshold for predicting poor neurological outcome after cardiac arrest should be identified.

A standardisation of the methods for GWR calculation is urgently needed.

The optimal timing for prognostication using brain CT after cardiac arrest is still unknown. Studies assessing serial brain CT after cardiac arrest are desirable.

QUESTION

Should absence vs. presence of abnormality on cranial MRI be used for predicting good outcome in children after cardiac arrest?

POPULATION:	Children (<18 years) who achieve a return of spontaneous or mechanical circulation (ROC) after resuscitation from in-hospital cardiac arrest (IHCA) and out-of-hospital (OHCA), from any cause.
INTERVENTION:	Absence of abnormality on cranial MRI
COMPARISON:	presence of abnormality on cranial MRI
MAIN OUTCOMES:	Prediction of survival with good neurological outcome: defined as a Pediatric Cerebral Performance Category (PCPC) score of 1, 2 or 3, or Vineland Adaptive Behavioural scale-II ≥ 70. PCPC score ranges 1 (normal), 2 (mild disability), 3 (moderate disability), 4 (severe disability), 5 (coma), and 6 (brain death). We will also separately report studies defining good neurological outcomes with other assessment tools, or as a PCPC score 1 or 2, or change in PCPC score from baseline ≤2.
STUDY DESIGN	Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols*) and animal studies were excluded. We selected studies where the sensitivity and false-positive rate (FPR) of the prognostic (index) test are reported and a 2s2 contingency table could be created.
TIMEFRAME	All years and all languages were included as long as there was an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Literature search updated to Feb 17th, 2022.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cardiac arrest is uncommon in children; however, it has a low rate of survival and high chance of neurological injury. Prediction of good or poor neurological outcome is a key skill for clinicians to guide appropriate treatment and realistic expectation with parents and legal guardians.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	MRI imaging was reported in four studies to predict good neurological outcome. Two studies reported presence or absence of abnormalities in multiple regions of the brain in 3 sequences (Diffusion weighted imaging (DWI), T1 and T2) [Fink 2013 31, Fink 2020 185]. Another study presented a composite of presence or absence of 1 (or more) region of abnormality [Kirschen 2021 e719]. Apparent diffusion coefficient (ADC) thresholds cut off values and overall qualitative MRI reporting of evidence of hypoxic ischaemic injury was assessed by one study [Yacoub 2019 103]. In three studies, MRIs were performed between 4 to 6 days and one at two weeks. Three	

	studies ensured the neuroradiologists MRI assessment was blinded to patient clinical status. However, the MRI findings were known by the treating clinicians and neurological outcome assessment was not blinded. [Fink 2013 31, Fink 2020 185, Kirschen 2021 e719]. Absence of any region of abnormality on restricted diffusion predicted good neurological outcome with a sensitivity of 88% and corresponding very low FPR 2% [Kirschen 2021 e719]. ADC threshold above >600 x10 power -6 mm2/s in >93% and >650 x10 power -6mm2/s in >89% of brain volume predicted good neurological outcome with a sensitivity of 100% and low FPR (20%) [Yacoub 2019 103]. In the same study, a normal MRI by qualitative reporting of absence of hypoxic ischaemic injury, predicted a good neurological outcome at 6 months with a sensitivity of 81% and FPR of 10% [Yacoub 2019 103]. For individual regions of the brain, at 4-6 days post cardiac arrest, DWI MRI sequence had a sensitivity for predicting good neurological outcome ranging 67-100% although associated FPR rates with moderate to high. Absence of lesion in the Lentiform regions on T2 weighted imaging had a sensitivity of 67% and the lowest FPR (7.7%) for any single region of the brain.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	A false positive prediction of a good outcome and continued treatment based on MRI may lead to treatment in a patient with the outlook of a poor neurological outcome. This is termed false optimism. The low false positive rates for assessment of global injury on MRI (ADC, qualitative reporting of evidence of hypoxic ischaemic injury, or absence of multiple regions of injury) provide a lower risk of false optimism compared to CT imaging.	

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 from MRI is low. The high sensitivity and low FPR combined with consistency in results across the two studies of global injury provided some certainty. The risk of bias was very high due to risk of selection bias, as only a small subset of patients alive at 4-6 days after cardiac arrest were imaged. Although MRIs were reported by radiologists blinded to patients' condition and outcome, the initial MRI was used by treating clinicians to decide on treatment management and therefore there is a risk of self-fulfilling prophecy.	Although the certainty of evidence from MRI was low, the task force identified that the evidence for MRI was more certain that clinical examination, biomarkers, or other imaging modalities.

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	Neurological outcome is a critical outcome after cardiac arrest (P-COSCA: Topjian, et al Circulation 2020; 142). However, tools and definitions to measure good neurological outcome in our studies were the PCPC 1 to 2 and 1 to 3, or <1 change in PCPC and the VABS II >70. Change from baseline neurodevelopmental status may be more important than the neurodevelopmental level, especially in infants and children with pre-existing neurological impairment. We defined good neurological outcome prediction as imprecise when the false positive rate (FPR) was above 30%. However, there is no universal consensus on what the acceptable limits for imprecision should be in prediction for infants and children after cardiac arrest. **A low false positive rate** means that a low proportion of patients, predicted to have a good outcome will have a ***falsely optimistic prediction*** (test predicted a good outcome, but patient went on to have a bad outcome). The task force felt that when focused on accurate **good** outcome prediction - a low false positive rate (e.g. <30%) is more desirable to avoid falsely optimistic prediction than a high sensitivity. The cut off of 30% FPR (equivalent to 70% specificity) was chosen as the consequences of false optimism were felt by the task force to be less critical than false pessimism. False optimism may result in continued life sustaining therapy in a patient who will eventually have a poor outcome. Also some of the reasons for not achieving very low false positive rate may be non-	The task force identified that the current use of a dichotomised neurological outcome cut off is a limitation for families and patients in considering the range and acceptability of outcomes for individual children after cardiac arrest in children. Our definitions of precision are less precise than the equivalent adults' recommendations which used the 95% confidence interval margins as their threshold values. For comparison, in the 2021 COSTR, the ALS Task force recommendations for poor outcome prediction in adults comatose after cardiac arrest, the definition of imprecision for a poor test predicting a poor neurological outcome was when the upper limit of 95% confidence intervals (CIs) for false positive rate (FPR) was above 5%. This is equivalent to the sensitivity of a good test predicting a good neurological outcome having the lower 95% confidence interval above 95%.

	neurological causes of poor outcome or death, not attributable to the index test assessment. **A high sensitivity** means the majority of patients who have the good outcome tested positive and therefore a low proportion will have a ***falsely pessimistic prediction*** (test predicted a poor outcome, but patient went on to have a good outcome). When considering accurate **poor** outcome prediction, then a high sensitivity (with a corresponding low rate of falsely pessimistic prediction) is more desirable than a low false positive rate. Our cut off threshold for considering precise sensitivity was higher (>95%), as the consequences of false pessimism may be decision to withdrawal life sustaining therapy in a patient who will have a good neurological outcome and therefore greater precision in prognostic accuracy is required.	

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	Considering the moderate to high sensitivity and low false positive rate of using absence of abnormality on MRI as a predictive test 4-6 days or two weeks, the balance probably favours using MRI as a test for **good** neurological outcome prediction.	An MRI scan may be performed for other diagnostic indications (e.g. identify the cause of cardiac arrest) and the information may be combined with other prognostic tests. The high sensitivity also indicates that MRI may have a role in predicting poor outcome. However, risk of false pessimism in up to 31% of patients, and low sample size led to a lack of precision.

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	Specialist equipment and training in interpretation to perform MRI is required. Costs and access to MRI may be variable depending on the health care setting. In some settings MRI may not be available or costs prohibitive. However, no study assessing cost of MRI imaging has been included in our review	

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 any studies specifically assessing costs of performing MRI after cardiac arrest in children. However, the use of specialist personnel, training and equipment may require significant local resources to perform.	

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 addressing cost-effectiveness of MRI after cardiac arrest.	

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 study assessed the impact on health equity. However, due to the high cost of MRI, there may be health inequity in receiving this investigation and prognostic test.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We have not identified any study assessing acceptability.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Although feasibility was not specifically addressed in any of the studies included in this review. However, requires significant resources, personnel and training and this may limit the feasibility in all health care settings. Imaging studies used for	

	neuroprognostication after cardiac arrest cannot be performed at the bedside, and require transportation to a Radiology Department, with additional clinical and safety risks.	

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 using normal MRI between 72 hours and 2 weeks after return of circulation for predicting good neurological outcome (weak recommendation, low-certainty evidence).

Justification

Overall justification

The low false positive rate (high specificity) for normal MRI on global assessment for predicting good neurological outcome reduces the chance of false optimism if a normal MRI predicts a good neurological outcome.

The sensitivity of a normal MRI to predict a good neurological outcome is moderate to high, but up to 30% of may be falsely categorised and a falsely pessimistic prediction made. Therefore, with the low number of studies and patients, high risk of bias in studies, risk of self-fulfilling prophecy, and risk of confounding by selection, we cannot make a recommendation for or against the use of normal or abnormal MRI for predicting poor neurological outcome.

The definition of a presence DWI or cut off values for ADC level was inconsistent in the included studies. There is a risk of pseudo normalisation with later timing of MRI.

Detailed justification

Desirable Effects

The low false positive rate (high specificity) for predicting good neurological outcome reduces the chance of false optimism if a normal MRI predicts a good neurological outcome.

Subgroup considerations

none

Implementation considerations

MRI is an expensive test and requires specialist equipment, training, interpretation, and patient transport to obtain the information. This may be prohibitive in physiologically unstable patients, or some health care settings.

Monitoring and evaluation

none

Research priorities

The criteria for defining a positive DWI MRI after cardiac arrest need to be standardised.

The role of regional areas of brain for predicting outcome, or the use of Magnetic resonance spectroscopy requires further research.

QUESTION 2.

Should thermal mattress vs. thermal mattress be used for preterm neonates born at less than 34 weeks' gestation or equivalent birth weight, immediately after birth?	
POPULATION:	Preterm neonates born at less than 34 weeks' gestation or equivalent birth weight, immediately after birth
INTERVENTION:	Thermal mattress
COMPARISON:	No thermal mattress
MAIN OUTCOMES:	Primary outcomes • Survival to hospital discharge (critical) • Rate of normothermia on admission to neonatal unit or postnatal ward (important) Secondary outcomes: • Body temperature (and rates of moderate hypothermia, cold stress and hyperthermia) on admission to neonatal unit or before transfer to neonatal unit or postnatal ward, or at times ≤ 1 hour of age (as defined by authors). • Response to resuscitation, e.g., need for assisted ventilation, highest FiO_2 • Major morbidity: bronchopulmonary dysplasia (important), intraventricular hemorrhage all grades (important) and severe (critical), necrotising enterocolitis (important), respiratory distress syndrome (surfactant treatment for), late onset sepsis.
SETTING:	Birth environment, in or out of hospital
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Thermal mattresses have been recommended by ILCOR for maintaining normal body temperature in preterm infants after birth, in order to prevent adverse outcomes including death. {Perlman 2015 S204} The systematic review of evidence for this intervention was updated to include studies published since the previous systematic review. Thermal mattresses may provide an external source of heat to augment or replace a radiant warmer. Note that the term 'thermal mattress' is used to describe self-heating gel mattresses designed to prevent hypothermia in newborn infants and is used synonymously with 'exothermic mattress', a term used in many of the included studies.
CONFLICT OF INTERESTS:	Authors Trevisanuto and de Almeida wrote a recent review article on maintaining normothermia in newborn infants at birth. {Trevisanuto 2018 333} Author Ramaswamy is an author of a network meta-analysis of methods to maintain normal temperature in infants in the delivery room {Abiramalatha e210775}

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	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	

● Probably yes ○ Yes ○ Varies ○ Don't know	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} In preterm infants it is common to measure a lower-than-normal body temperature. A systematic review from data collected for the EPICE European collaboration project 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. In a large cohort of 5697 infants < 32 weeks' gestation Wilson et al. {Wilson 2016 61} showed that 53.4% of the cohort had a body temperature at admission less than 36.5°C, and 12.9% below 35.5°C. In their model adjusted for pregnancy complications, singleton or multiple pregnancy, antenatal corticosteroids, mode of delivery, gestational age, infant size and sex, and Apgar score <7 at 5 minutes, an admission temperature <35.5°C was associated with increased mortality at postnatal ages 1-6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7-28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age. {Wilson 2016 61} A recent network meta-analysis examining benefit and safety of interventions to reduce mortality and morbidity from hypothermia reported that various interventions aimed at improving thermoregulation can improve body temperature at admission and are associated with a lower risk of mortality and major brain injury. {Abiramalatha 2021 e210775}	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Two different types of studies were available for this comparison: Two randomized controlled trials (RCTs) compared a thermal mattress to no thermal mattress. Infants in both groups received the same cointerventions (such as radiant warmer, hat and plastic bag or wrap) in each arm of the study. {Chawla 2011 780, McCarthy 2013 e135} These two studies were considered to have no serious indirectness with respect to the comparison of thermal mattress to no thermal mattress and yielded low to moderate certainty evidence. Two RCTs compared a thermal mattress without a plastic barrier (bag or wrap) to a plastic barrier without a thermal mattress. {Mathew 2013 317, Simon 2011 33} These two studies were meta-analysed separately and were considered to have very serious indirectness with respect to the comparison of thermal mattress to no thermal mattress and yielded very low certainty evidence. Meta analysis of the two pairs of studies is shown separately. **<u>Primary outcomes:</u>** In the two studies that compared thermal mattress to no thermal mattress, for the important primary outcome **survival to hospital discharge, clinical benefit or harm cannot be excluded** (relative risk (RR) 1.02 95% confidence intervals (CI) 0.98 to 1.06, absolute risk difference (ARD) 19 more infants per 1000, 95% CI 19 fewer to 56 more per 1000) **low certainty evidence** downgraded for risk of bias and imprecision from two RCTs enrolling 174 participants. {Chawla 2011 780, McCarthy 2013 e135} There were similar findings in the two studies comparing thermal mattress to a plastic bag or wrap; **clinical benefit or harm cannot be excluded** (RR 0.96 95%CI 0.87 to 1.05, ARD 35 fewer per 1000,	We do not know the effect size in the presence of additional or fewer co-interventions. Infants in both the thermal mattress and no thermal mattress groups were equally exposed to additional thermoregulation measures, for example radiant warmer and plastic bag for infants < 28 weeks' gestation.

95% CI 114 fewer to 44 more per 1000) **very low certainty evidence,** downgraded for indirectness and imprecision from two RCTs enrolling 77 participants. {Mathew 2013 317, Simon 2011 33}

In a study that compared use of a thermal mattress to no thermal mattress, for the second primary outcome **normothermia on admission** there was **possible clinical harm** (RR 0.53, 95% CI 0.34 to 0.81, ARD 363 fewer infants per 1000 were normothermic on admission with use of a thermal mattress, 95% CI 147 fewer to 509 fewer per 1000) **moderate certainty evidence**, downgraded for imprecision from 1 RCT enrolling 72 participants. {McCarthy 2013 e135} This study compared thermal mattress with no thermal mattress.

Primary outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with thermal mattress	Risk difference with thermal mattress
Survival – control group no thermal mattress	174 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,b]	**RR 1.02** (0.98 to 1.06)	929 per 1,000	**19 more per 1,000** (19 fewer to 56 more)
Survival – control group plastic bag or wrap	77 (2 RCTs)[3,4]	⨁◯◯◯ Very low[a,c,d]	**RR 0.96** (0.87 to 1.05)	875 per 1,000	**35 fewer per 1,000** (114 fewer to 44 more)
Normothermia on admission (36.5-37.5ºC) – control group no thermal mattress	72 (1 RCT)[2]	⨁⨁⨁◯ Moderate[a,e]	**RR 0.53** (0.34 to 0.81)	771 per 1,000	**363 fewer per 1,000** (509 fewer to 147 fewer)

1. {Chawla 2011 780}
2. {McCarthy 2013 e135}
3. {Simon 2011 33}
4. {McCarthy 2013 e135}

a. Optimal information size (OIS) criterion not satisfied
b. One included study that contributed a large proportion of the participants was at high risk of bias
c. Study(ies) compared a thermal mattress with use of a plastic bag or wrap
d. Both studies were at low risk of bias
e. The only included study was at low risk of bias

	Secondary Outcomes For **mean body temperature on admission**, there was **possible clinical benefit.** The mean difference (MD) in temperature was 0.46°C higher in the thermal mattress group (95% CI 0.22 to 0.69°C) **low certainty evidence,** downgraded for risk of bias and imprecision from two RCTs enrolling 174 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780, McCarthy 2013 e135} However, the two studies that compared thermal mattress with a plastic bag or wrap found a minimal MD in temperature: The mean temperature was 0.09°C higher in the thermal mattress group 95% CI 0.59 lower to 0.77°C higher), **low certainty evidence** downgraded for indirectness and imprecision from two RCTs enrolling 77 participants. {Mathew 2013 317, Simon 2011 33} This lack of improvement in temperature in most infants, which may be because two measures to maintain normal temperature were being compared with each other, should be taken into account when considering other outcome data for these studies. For **hypothermia < 36.5°C on admission to the NICU, clinical benefit or harm cannot be excluded** RR 2.58 (95% CI 0.47 to 14.26), **moderate certainty evidence** downgraded for indirectness and imprecision from one RCT enrolling 49 participants. {McCarthy 2013 e135} For **IVH > Grade 2, clinical benefit or harm cannot be excluded** (RR 4.62, 95% CI 0.56 to 38.19, ARD 74 more per 1000 infants, 95% CI 9 fewer to 759 more), **very low certainty evidence** downgraded for risk of bias and imprecision from one RCT enrolling 102 participants that compared thermal mattress with no thermal mattress. {Chawla 2011 780} and (RR 0.94, 95% CI 0.24 to 3.57, ARD 118 fewer infants per 1000, 95% CI 219 fewer to 75 more infants per 1000), **very low certainty evidence** downgraded for indirectness and imprecision from two RCTs enrolling 77 participants that compared thermal mattress to plastic bag or wrap. {Mathew 2013 317, Simon 2011 33} For **NEC**, **clinical benefit or harm cannot be excluded** (RR0.642, 95% CI 0.33 to 1.23, ARD 118 fewer infants per 1000, 95% CI 219 fewer to 75 more infants per 1000), **very low certainty evidence** downgraded for risk of bias an imprecision from one RCT enrolling 102 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780} and (RR 1.83, 95% CI 0.58 to 5.76, ARD 83 more infants per 1000, 95% CI 42 fewer to 476 more per 1000), **very low certainty evidence** downgraded for indirectness and imprecision from two RCTs enrolling 77 participants that compared thermal mattress with plastic bag or wrap. {Mathew 2013 317, Simon 2011 33} and For **BPD, clinical benefit or harm cannot be excluded** RR 1.59 (95% CI 0.94 to 2.66, ARD 119 more infants per 1000, 95% CI 12 fewer to 336 more infants per 1000), **low certainty evidence** downgraded for risk of bias and imprecision from two RCTs enrolling 174 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780, McCarthy 2013 e135} and RR 0.75,(95% CI 0.40 to 1.3), very low certainty evidence downgraded for indirectness and imprecision from one RCT enrolling 36 participants that compared thermal mattress with plastic bag or wrap. {Simon 2011 33} For the outcome **late onset sepsis clinical benefit or harm cannot be excluded** (RR 0.90 95% CI 0.37 to 2.19, ARD 27 fewer infants per 1000, (95% CI 167 fewer to 316 more per 1000), **very low certainty evidence** downgraded for risk of bias and imprecision from one RCT enrolling 102 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780} For the other secondary outcomes intubation in the delivery room and serious haemorrhage (e.g., pulmonary, subgaleal) there were no data.	

Secondary outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with thermal mattress	Risk difference with thermal mattress
Mean body temperature – control group no thermal mattress	174 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,b]	Not applicable	The mean body temperature was **36.3**°C	MD **0.46°C higher** (0.22 higher to 0.69 higher)
Mean body temperature – control group plastic bag or wrap	77 (2 RCTs)[3,4]	⨁◯◯◯ Very low[b,c,d]	Not applicable	The mean body temperature was **36.1**°C	MD **0.09°C higher** (0.59 lower to 0.77 higher)
Admission temp <36.5ºC (control group no thermal mattress)	36 (1 RCT)[2]	⨁⨁⨁◯ Moderate[b,e]	**RR 2.58** (0.47 to 14.26)	684 per 1,000	**1,081 more per 1,000** (363 fewer to 9,073 more)
IVH > Grade 2 (control group no thermal mattress)	102 (1 RCT)[1]	⨁◯◯◯ Very low[b,f,g]	**RR 4.62** (0.56 to 38.19)	20 per 1,000	**74 more per 1,000** (9 fewer to 759 more)
IVH > Grade 2 (control group plastic bag or wrap)	77 (2 RCTs) [3,4]	⨁◯◯◯ Very low[b,c,d]	**RR 0.64** (0.33 to 1.23)	327 per 1,000	**118 fewer per 1,000** (219 fewer to 75 more)
NEC (control group no thermal mattress)	102 (1 RCT)[1]	⨁⨁◯◯ Low[a,b]	**RR 0.64** (0.33 to 1.23)	327 per 1,000	**118 fewer per 1,000** (219 fewer to 75 more)
NEC – studies comparing with plastic bag or wrap	77 (2 RCTs)[3,4]	⨁◯◯◯ Very low[b,d,f]	**RR 1.83** (0.58 to 5.76)	100 per 1,000	**83 more per 1,000** (42 fewer to 476 more)

BPD (author defined) – studies comparing with no thermal mattress	174 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,b]	**RR 1.59** (0.94 to 2.66)	202 per 1,000	**119 more per 1,000** (12 fewer to 336 more)
BPD (author defined) (control group plastic bag or wrap)	36 (1 RCT)[3]	⨁◯◯◯ Very low[b,d,f]	**RR 0.75** (0.40 to 1.37)	632 per 1,000	**158 fewer per 1,000** (379 fewer to 234 more)
Late onset sepsis (control group no thermal mattress)	102 (1 RCT)[1]	⨁◯◯◯ Very low[b,f,g]	**RR 0.90** (0.37 to 2.19)	265 per 1,000	**27 fewer per 1,000** (167 fewer to 316 more)

[1] {Chawla 2011 780}
[2] {McCarthy 2013 e135}
[3] {Simon 2011 33}
[4] {Mathew 2013 317}

a. One included study that contributed a large proportion of the participants was at high risk of bias
b. OIS criterion not satisfied
c. Both studies were at low risk of bias
d. Study(ies) compared a thermal mattress with use of a plastic bag or wrap
e. The only included study was at low risk of bias
f. Low event rate and wide CIs

For beneficial outcomes, the observational studies did not change the outcomes of the review, so they are not described further.

The rationale for considering the effect varies is that there was moderate certainty evidence for a small decreasein the number of normothermic participants with use of a thermal mattress compared to no thermal mattress, and yet very low certainty evidence for a small improvement in mean body temperature. From studies comparing thermal mattress to a plastic bag or wrap, there was minimal benefit for temperature.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	For the important adverse outcome **hyperthermia** (temp on admission >37.5°C) there was evidence of **possible harm** (RR 2.77 95% CI 1.24 to 6.17, ARD 126 more infants were hyperthermic per 1000, 95% CI 17 more to 369 more) **low certainty evidence**, downgraded for risk of bias and imprecision from two RCTs enrolling 174 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780, McCarthy 2013 e135}. In RCTs comparing a thermal mattress without a plastic barrier (bag or wrap) to a plastic barrier without a thermal mattress, one reported this outcome; (RR 12.29 95% CI 0.02 to 77700.79) **very low certainty evidence** downgraded for indirectness and imprecision from one RCT enrolling 36 participants. {Simon 2011 33} The systematic review also found 5 observational studies that examined use of a thermal mattress combined with use of a plastic bag or wrap compared to use of a plastic bag or wrap alone (no thermal mattress) in a total of 1027 infants. {Ibrahim 2010 795, Lewis 2011 160, McCarthy 2011 1534, Pinheiro 2011 357, Singh 2010 45} For the important adverse outcome of **hyperthermia** on admission the observational studies that reported this outcome also suggested **evidence of possible harm** (RR 3.44 95% CI 1.91 to 6.20, ARD 113 more infants were hyperthermic per 1,000, 95% CI from 42 more to 241 more infants per 1000), **moderate certainty evidence** downgraded for risk of bias from 4 observational studies including 703 infants. {Ibrahim 2010 795, McCarthy 2011 1534, Pinheiro 2011 357, Singh 2010 45}	Note that the McCarthy 2013 study stopped recruitment after enrolling 58 infants following a pre-planned review by an external data safety monitoring committee (DSMC). {McCarthy 2013 e135} The DSMC identified that a significant difference between groups for the primary outcome had been determined. It is not clear if the study was stopped early mainly for concerns about efficacy or concerns about safety. In both the McCarthy 2013 and Chawla 2011 studies, infants in both the thermal mattress and control groups were equally exposed to additional thermoregulation measures, for example radiant warmer. Some {Chawla 2011 780} or all {McCarthy 2013 e135} infants in each group were managed with a plastic bag. These additional measures may have affected body temperatures. The effect size (for benefit or harm) may be different in the presence of additional or fewer co-interventions, and caution is warranted to ensure that the target of normal temperature is being met. To underscore the importance for careful monitoring when a thermal mattress is used in conjunction with a radiant warmer the British Association of Perinatal Medicine (BAPM) has warned users to be aware of the risk of hyperthermia and skin burns. (Safety Issue - Transwarmer Mattresses | British Association of Perinatal Medicine (bapm.org) ww.bapm.org/articles/44-safety-issue-transwarmer-mattresses. Manufacturer's instructions also advise against the use of any other heat source while using the Transwarmer®mattress. https://www.coopersurgical.com/product-resources/ef950206-9f7e-4dcf-a3d7-cb79379ed189_TransWarmer-Infant-Transport-Matterss-Instructions-for-Use.pdf

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with thermal mattress	Risk difference with thermal mattress
Temperature > 37.5°C	174 (2 RCTs)[1,2]	⨁⨁◯◯ Low[a,b]	**RR 2.77** (1.24 to 6.17)	71 per 1,000	**126 more per 1,000** (17 more to 369 more)
Temperature >37.5°C Simon	36 (1 RCT)[3]	⨁◯◯◯ Very low[b,c,d]	**RR 12.29** (0.02 to 7700.79)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

[1] {Chawla 2011 780}
[2] {McCarthy 2013 e135}
[3] {Simon 2011 33}

a. One included study that contributed a large proportion of the participants was at high risk of bias
b. OIS criterion not satisfied
c. Study(ies) compared a thermal mattress with use of a plastic bag or wrap
d. Low event rate and wide CIs

	The rationale for considering the effect small was because the effect size was considered to be possibly clinically important. The outcome of temperature >38°C was considered more likely to cause harm, but it was not reported by most 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	The certainty of evidence for the two primary outcomes was very low to moderate and for secondary outcomes was very low to moderate.	

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}	Cold stress and hypothermia are common particularly among preterm infants and has been associated with increased mortality and morbidity {de Almeida 2014 271, Perlman 2015 S204}

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 possible clinical benefit for mean temperature on admission to the NICU, however there was an increased rate of hyperthermia.	Recent observational studies have confirmed an association between hyperthermia on admission and adverse outcomes. {Brophy 2022 1706, Wilson 2016 61} A thermal mattress might be useful to prevent hypothermia when other forms of thermal support (radiant warmer, plastic bag/wrap) are not available in out of hospital 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	Among included studies, estimates of cost were $46.50 (US) {McCarthy 2013 e135}; $14.52 (US) {Simon 2011 33} and $17(US) per unit. {Lewis 2011 160}	The cost of a thermal mattress differs between brands. Regardless, the cost may make the device unaffordable in middle or low resource settings. The devices are marketed as single 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	Two of the included RCTs and one observational study provided an estimate of cost of a thermal mattress. There may be variation between brands and locations.	

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 investigated cost-effectiveness.	Single use thermal mattresses are a relatively expensive intervention compared with some other interventions to maintain normal temperature in the delivery room, but they may be cost-effective where devices such as radiant warmers are unavailable (such as for out-of-hospital births). Accurate estimates of cost effectiveness would need to include studies large enough to estimate effects on survival and major neonatal morbidities. All included studies were well below the OIS for these outcomes.

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 providing a thermal mattress is likely to be unaffordable in low-income and some 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	There were no data available from studies in this review. However, using a thermal mattress to promote thermoregulation is already standard care in some high resource settings described in publications reporting quality improvement activities. {Aley-Raz 2020 476, Billimoria 2013 455, Croop 2020 530, Frazer 2018 520, Harer 2017 1242, Harriman 2018 462, Lee 2008 754, Manani 2013 8, Russo 2014 31055}	Many neonatal retrieval/transport services use thermal mattresses to maintain normal temperature during inter-hospital transport. {L'Herault 2001 210, LeBlanc 1984 593}

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Using a thermal mattress to promote thermoregulation is already standard care in some high resource settings described in publications describing quality improvement activities. {Aley-Raz 2020 476, Billimoria 2013 455, Croop 2020 530, Frazer 2018 520, Harer 2017 1242, Harriman 2018 462, Lee 2008 754, Manani 2013 8, Russo 2014 31055}	In one study using a thermal mattress was described as technically easy to use. {McCarthy 2013 e135} Where a radiant warmer is not available a thermal mattress might be a useful alternative.

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

In preterm infants, born at less than 34 weeks' gestation, where hypothermia on admission is identified as a problem, it is reasonable to consider addition of a thermal mattress, but there is a risk of hyperthermia. (Conditional recommendation, low certainty evidence).

Justification

The effect of a thermal mattress varied between studies. There was an increased risk of hyperthermia on admission. The combined studies did not meet the optimal information size to confirm other benefits or harms.

Subgroup considerations

Subgroups identified a priori for this review were gestational age (< 28 weeks' compared with ≥ 28 weeks' gestation, inborn compared with outborn births, high resource compared with low resource settings, and the effect of early or delayed cord clamping

- Outcomes for the subgroup gestational age < 28 weeks' compared with ≥28 weeks' gestation were reported in two studies.

Two studies reported data for infants <28 weeks' gestation and found conflicting results: Chawla et al found no difference in admission temperatures in infants <28 weeks' gestation exposed to a thermal mattress vs no thermal mattress, whereas McCarthy et al found larger increases in body temperature in infants <28 weeks' gestation and no difference for those ≥ 28 weeks' gestation. McCarthy et al found more hyperthermic infants in the lower gestational age group. {Chawla 2011 780, McCarthy 2013 e135}

One study reported data for 21 infants <750 g compared with infants ≥750 g. The mean (±SD) admission temperature was significantly lower in the group of infants <750 grams exposed to a thermal mattress compared with the no thermal mattress group 35 (±1.3)ºC and 36 (±0.4)ºC respectively. {Mathew 2013 317}

- For inborn compared with outborn births, there were no data.
- All studies reported outcomes from births in high resource settings.
- No studies reported the effect of umbilical cord clamping on outcomes.

Implementation considerations

Thermal mattresses are relatively simple to use and require only a few minutes of preparation time to reach effective temperatures. Care needs to be taken to use a barrier layer of towelling or sheeting between the mattress and the infant in order to prevent skin burns and hyperthermia, because they can reach temperatures of at least 42°C.{McCarthy 2013 e135} When using a thermal mattress frequent temperature monitoring is recommended (Good practice statement).

Monitoring and evaluation

Preterm neonates' temperatures on admission to neonatal intensive care units should continue to be monitored as important indicators of quality of care. {Perlman 2015 S204}

Research priorities

- Studies are needed comparing specific bundles of interventions to maintain normal temperature vs other specific bundles.
- What is the balance of risks and benefits when using a thermal mattress for preterm infants in the birthing room when other combinations of thermoregulation interventions (ambient temperature, plastic bag or wrap, thermal mattress, cap, servo-controlled radiant warmer) are applied?
- Cost effectiveness of thermal mattresses.
- Safety and effectiveness for various subgroups.
- Role of thermal mattresses during delayed cord clamping.
- Role of thermal mattresses in pre-hospital settings.

QUESTION 3.

Should a plastic bag or wrap vs. standard care be used for preterm infants < 34 weeks' gestation or equivalent birth weight, immediately after birth ?	
POPULATION:	Preterm infants < 34 weeks' gestation or equivalent birth weight, immediately after birth
INTERVENTION:	Plastic bag or wrap
COMPARISON:	Standard care
MAIN OUTCOMES:	Primary outcomes • Survival to hospital discharge (critical) • Rate of normothermia on admission to neonatal unit or postnatal ward (important) Secondary outcomes: • Body temperature (and rates of moderate hypothermia, cold stress and hyperthermia) on admission to neonatal unit or before transfer to neonatal unit or postnatal ward, or at times ≤ 1 hour of age (as defined by authors). • Response to resuscitation, e.g., need for assisted ventilation, highest FiO_2 • Major morbidity: bronchopulmonary dysplasia (important), intraventricular hemorrhage all grades (important) and severe (critical), necrotising enterocolitis (important), respiratory distress syndrome (surfactant treatment for), late onset sepsis.
SETTING:	Birth environment, in or out of hospital
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Plastic bags or wraps have been recommended by ILCOR for maintaining normal body temperature in preterm infants after birth, in order to prevent adverse outcomes including death. {Perlman 2015 S204} The systematic review of evidence for this intervention was updated to include studies published since the previous systematic review. Plastic bags or wraps may prevent heat loss by reducing evaporative or convective heat losses.
CONFLICT OF INTERESTS:	Authors Ramaswamy and Trevisanuto were co-authors of a previous network metaanalysis of delivery room interventions for hypothermia in neonates. {Abiramalatha 2021 e210775} Author Trevisanuto was author of a study included in the systematic review, but was excluded from decisions about inclusion or risk of bias assessment for this study. {Trevisanuto 2010 914}

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 "F*or 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"). In preterm infants it is common to measure body temperatures in the cold stress or hypothermic range. 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. In a large cohort of 5697 infants < 32 weeks' gestation, 53.4% of the cohort had a body temperature at admission less than 36.5°C, and 12.9% below 35.5°C. {Wilson 2016 61} After adjustment for pregnancy complications, singleton or multiple pregnancy, antenatal corticosteroids, mode of delivery, gestational age, infant size and sex, and Apgar score <7 at 5 minutes, an admission temperature <35.5°C was associated with increased mortality at postnatal ages 1-6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7-28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age.) A recent network meta-analysis examining benefit and safety of interventions to reduce mortality and morbidity from hypothermia reported that various interventions aimed at improving thermoregulation can improve body temperature at admission and are associated with a lower risk of mortality and major brain injury. {Abiramalatha 2021 e210775}	

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 a **plastic bag or wrap when compared to standard care** for preterm infants (<34 weeks' gestation): For the critical primary outcome of **survival to hospital discharge,** there was **probable clinical benefit** (relative risk (RR) 1.05 95% CI 1.00 to 1.10), **high certainty evidence** from 11 RCTs enrolling 1419 infants. {Ahmed 2013 169, Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Reilly 2015 262, Reilly 2019 37, Smith 2013 235, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750} For the important primary outcome of **normothermia on admission** to a neonatal unit, there was **possible clinical benefit** (RR 2.86 95% CI 1.66 to 4.91), **low certainty evidence** downgraded for risk of bias and imprecision from 5 RCTs enrolling 449 infants. {Chantaroj 2011 S32, Knobel 2005 304, Nimbalkar 2019 122, Rohana 2011 468, Trevisanuto 2010 914}	We do not know the effect size in the presence of additional co-interventions. Infants in these studies were generally stabilized in the delivery room under radiant warmers set to manual mode. A majority of studies reported axillary temperatures. A small number of studies only measured rectal temperatures. Axillary temperatures are reported as lower than rectal temperature. {Cho 2021 180, McCarthy 2021 509} This difference could be important when comparing results between studies.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard care	Risk difference with a plastic bag or wrap
Survival				Study population	

	1419 (11 RCTs)[1-11]	⊕⊕⊕⊕ High[a,b,c,d]	**RR 1.05** (1.00 to 1.10)	816 per 1,000	**41 more per 1,000** (0 fewer to 82 more)
Normothermia	449 (5 RCTs)[2,4,5,9,12]	⊕⊕◯◯ Low[a,d,e,f]	**RR 2.86** (1.66 to 4.91)	Study population	
				128 per 1,000	**238 more per 1,000** (85 more to 501 more)

1. {Ahmed 2013 169}
2. {Chantaroj 2011 S32}
3. {Farhadi 2012 19}
4. {Knobel 2005 304}
5. {Nimbalkar 2019 122}
6. {Reilly 2015 262}
7. {Reilly 2019 37}
8. {Smith 2013 235}
9. {Trevisanuto 2010 914}
10. {Vohra 1999 547}
11. {Vohra 2004 750}
12. {Rohana 2011 468}

a. The PICO was similar in the included trials
b. Narrow 95% confidence interval with optimal information size criterion (OIS) satisfied for sample size and event rates as calculated for relative risk reduction of 25%
c. For this outcome, most of the trials with higher weightage contributing to the meta-analysis had a low risk of bias or some concerns.
d. The test for heterogeneity was not significant
e. For this outcome, with a control group event rate of 12.8%, for a RRR of 25% an approximate sample size of 2500 is required. Hence the OIS criterion was not satisfied
f. For this outcome, most of the trials with higher weightage in the meta-analysis had a high overall risk of bias

Among important secondary outcomes

For **mean body temperature on admission** to a neonatal unit, **there was possible clinical benefit.** Mean temperature measured by axilla was 0.65°C higher (95% CI 0.44 to 0.86 °C), and measured by the rectum was 0.77 °C (95% CI 0.44 to 0.86 °C), **low certainty evidence** downgraded due to serious risk of bias and possible publication bias from 12 RCTs enrolling 821 infants. {Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Nimbalkar 2019 122, Reilly 2015 262, Reilly 2019 37, Rohana 2011 468, Smith 2013 235, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750}

For **any hypothermia < 36.5°C on admission** to a neonatal unit **there was probable clinical benefit** (RR 0.64, 95% CI 0.50 to 0.82), **moderate certainty evidence** downgraded for risk of bias from 6 RCTs

enrolling 489 infants. {Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Nimbalkar 2019 122, Rohana 2011 468, Trevisanuto 2010 914}

For **moderate hypothermia on admission** to a neonatal unit there was **possible clinical benefit** (RR 0.40 ,95% CI 0.19 to 0.81), **very low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 4 RCTs enrolling 1055 infants. {Ahmed 2013 169, Bhavsar 2015 23, Reilly 2015 262, Rohana 2011 468}

For **IVH >grade 2, clinical benefit or harm could not be excluded** (RR 0.99 95% CI 0.69 to 1.41), **moderate certainty evidence** downgraded for imprecision from 4 RCTs enrolling 972 infants. {Knobel 2005 304, Reilly 2015 262, Reilly 2019 37, Rohana 2011 468}

For **NEC, clinical benefit or harm could not be excluded** (RR 0.95, 95%CI 0.61 to 1.50), **low certainty evidence** downgraded for indirectness, and imprecision from 3 RCTs enrolling 935 infants. {Reilly 2015 262, Reilly 2019 37, Rohana 2011 468}

For **late onset sepsis**, **clinical benefit or harm could not be excluded** (RR 0.92, 95%CI 0.76 to 1.11), **low certainty evidence** downgraded for inconsistency and imprecision from 3 RCTs enrolling 853 infants. {Reilly 2015 262, Reilly 2019 37, Smith 2013 235}

For **intubation in the delivery room, benefit or harm could not be excluded** (RR 1.02, 95%CI 0.82 to 1.26), **low certainty evidence** downgraded for risk of bias and imprecision from 3 RCTs enrolling 174 infants. {Rohana 2011 468, Trevisanuto 2010 914}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard care	Risk difference with a plastic bag or wrap
Mean body temperature (Axillary)	755 (10 RCTs)[3,5,6,8,9,10,11,12,13]	⨁⨁◯◯ Low[a,b,c,d]	n/a	The mean body temperature (axillary) was **35.52** °C	MD **0.65 °C higher** (0.42 higher to 0.87 °C higher)
Mean body temperature (Rectal)	348 (67 RCTs)[3,10,12,14,15,16]	⨁⨁◯◯ Low[a,d]	n/a	The mean body temperature (Rectal) was **35.86** °C	MD **0.77 °C higher** (0.5 higher to 1.04 °C higher)

Hypothermia < 36.5 degree °C	489 (6 RCTs)[1,2,3,4,5,6]	⊕⊕⊕◯ Moderate[b,e,f,g]	**RR 0.64** (0.50 to 0.82)	870 per 1,000	**313 fewer per 1,000** (435 fewer to 157 fewer)
IVH any grade	836 (2 RCTs)[7,8]	⊕⊕⊕◯ Moderate[f,h,i,j]	**RR 0.91** (0.72 to 1.14)	372 per 1,000	**34 fewer per 1,000** (104 fewer to 52 more)
IVH > grade 2	972 (4 RCTs)[1,6,7,9]	⊕⊕⊕◯ Moderate[c,f,h,i]	**RR 0.99** (0.69 to 1.41)	113 per 1,000	**1 fewer per 1,000** (35 fewer to 46 more)
NEC	935 (3 RCTs)[6,7,9]	⊕⊕◯◯ Low[c,h,i,k]	**RR 0.95** (0.61 to 1.50)	77 per 1,000	**4 fewer per 1,000** (30 fewer to 38 more)
Late onset neonatal sepsis	853 (3 RCTs)[7,8,9]	⊕⊕◯◯ Low[f,h,i,j]	**RR 0.92** (0.76 to 1.11)	332 per 1,000	**27 fewer per 1,000** (80 fewer to 36 more)
Intubation in the delivery room	174 (2 RCTs)[2,6]	⊕⊕◯◯ Low[e,f,i,j]	**RR 1.02** (0.82 to 1.26)	511 per 1,000	**10 more per 1,000** (92 fewer to 133 more)

1. {Knobel 2005 304}
2. {Trevisanuto 2010 914}
3. {Chantaroj 2011 S32}
4. {Farhadi 2012 19}
5. {Nimbalkar 2019 122}
6. {Rohana 2011 468}
7. {Reilly 2015 262}
8. {Smith 2013 235}
9. {Reilly 2019 37}
10. {Ahmed 2013 169}
11. {Bhavsar 2015 23}
12. {Gathwala 2010 24}
13. {Talakoub 2015 322}
14. {Knobel 2005 304}
15. {Vohra 1999 547}

16. {Vohra 2004 750}

a. Overall, most of the trials had similar weightage in the meta-analysis. Amongst them there were a significant number of trials which either had some concerns or a high risk of overall bias
b. Though I2 was high, this was attributed to difference between small and large magnitude of effect estimate
c. The 95% confidence interval did not cross the line of no effect and OIS criterion satisfied
d. Egger's test showed a possibility of publication bias with a p-value of 0.002
e. For this outcome, most of the trials with higher weightage in the meta-analysis had a high risk of overall bias
f. The PICO was similar in the included trials
g. 95% CI did not cross the line of no effect; OIS criterion satisfied for a control group event rate of 87% for RRR of 25%
h. For this outcome, the trial with the highest weightage had low risk of overall bias
i. The test for heterogeneity was not significant
j. The 95% CI cross the line of no effect
k. Two studies did not specified the staging of NEC and hence indirectness related to the outcome was adjudged.

The reason to consider the **overall effect size as moderate** was because there was possible or probable benefit for both primary outcomes and three secondary outcomes.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	For **hyperthermia (> 38.0°C**) there was **probable harm** (RR 3.73 95%CI 1.81 to 7.69), **moderate certainty evidence** downgraded for risk of bias from 12 RCTs enrolling 1652 infants.) {Bhavsar 2015 23, Farhadi 2012 19, Gathwala 2010 24, Knobel 2005 304, Lyu 2015 e150277, Nimbalkar 2019 122, Reilly 2015 262, Rohana 2011 468, Smith 2013 235, Trevisanuto 2010 914, Vohra 2004 750}	Measures to prevent hypothermia may increase the risk for hyperthermia. Preterm neonates may have deficient thermoregulation and their capacity to maintain normothermia is limited.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard care	Risk difference with a plastic bag or wrap
Hyperthermia	817 (9 RCTs)[1,2,3,4,5,6,7,8,9]	⨁⨁⨁◯ Moderate[a,b,c,d]	**RR 3.67** (1.77 to 7.61)	11 per 1,000	**33more per 1,000** (9 more to 81 more)

1. {Bhavsar 2015 23}
2. {Farhadi 2012 19}
3. {Gathwala 2010 24}

The risk of hyperthermia was identified in the 2015 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 morbidiy in both term and preterm infants*". {Perlman 2015 S204}

Recent observational studies have also reported an association between high admission temperatures and adverse outcomes including death. {Brophy 2022 1706, Cavallin 2020 }

	4. {Nimbalkar 2019 122} 5. {Reilly 2015 262} 6. {Rohana 2011 468} 7. {Smith 2013 235} 8. {Trevisanuto 2010 914} 9. {Vohra 2004 750} a. There were two trials that had contributed significant weightage in the meta-analysis. While one had some concerns, the other had a high risk of overall bias. b. The test for heterogeneity was not significant c. The PICO was similar across trials d. Though the event rate is low, this is a scenario where the presence of large sample size may override the OIS criterion **The reason to consider the effect as moderate** is because hyperthermia has been associated with adverse outcomes.	

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 the primary outcome survival was high. For the second primary outcome; rate of normothermia, the certainty was low. Certainty for the secondary outcomes varied from very low (moderate hypothermia) or low certainty (mean body temperature measured by axilla or rectal route, NEC, late onset sepsis, intubation in the delivery room) to moderate certainty (hyperthermia, and hypothermia < 36.5°C).	

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) has 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 hypothermia have not been ranked. However, they are likely to be ranked as important because of their potential effect on mortality.

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 some outcomes (survival, temperatures on admission) with the use of a plastic bag or wrap. However, there was some evidence of harm from an increased risk of hyperthermia.	The risk of hyperthermia could be mitigated by regular temperature monitoring

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 provided sufficient detail about the costs of universal of plastic bags or wraps for all preterm infants <34 weeks' gestation.	Plastic bags or wraps are likely to be an inexpensive method to improve thermoregulation in very preterm infants. However, the costs depend on whether bags or wraps specifically marketed for newborn care are used, or widely available products such as those used for food storage. The Task Force also considered the environmental impacts of recommending widespread use of plastic caps. However, this must be weighed against benefits, and also compared with the widespread use of other disposables in clinical care.

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	Studies included in the review did not measure cost-effectiveness. However, studies did make recommendations regarding cost-effectiveness of the intervention. Two studies described the use of a plastic bag as inexpensive {Chantaroj 2011 S32, Knobel 2005 304}, low cost {Nimbalkar 2019 122} or a cost effective intervention {Bhavsar 2015 23}	

○ Varies ○ No included studies		

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	Plastic bags or wraps are likely to be an intervention that could be applied easily in low-resource setting or in high- resource settings. The included studies were undertaken in high-income countries (USA, Canada (4), Australia, Italy) and middle-income countries (India (3), Turkey, Thailand, Malaysia, Egypt, Iran). (Ref https://blogs.worldbank.org/opendata/new-world-bank-country-classifications-income-level-2022-2023)	

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 in this review included information about acceptability regarding use of plastic bag or wrap in the delivery room. Within quality improvement studies assessed for this systematic review there was almost universal use of the plastic bag or wrap, suggesting a high level of acceptability. {Aley-Raz 2020 476, Ashmeade 2016 73, Billimoria 2013 455, Caldas 2018 368, Choi 2018 239, Cleator 2022 75, Croop 2020 530, DeMauro 2013 e1018, Ferretti 2021 e240, Frazer 2018 520, Frazer 2022 99, Godfrey 2013 311, Harer 2017 1242, Harriman 2018 462, Keir 2021 375, Lee 2008 754, Manani 2013 8, Peleg 2019 387, Pinheiro 2014 e218, Reuter 2014 397, Russo 2014 31055, Sharma 2020 1851, Sivanandan 2016 39, Sprecher 2021 270, Vinci 2018 e125, Wlodaver 2016 182, Yip 2017 922, Young 2021 2745}	The plastic bag does not hinder auscultation of an infant's heart rate, application of electrocardiogram or pulse oximeter sensors. The use of a plastic bag or wrap is considered standard of care in many neonatal services.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Use of a plastic bag or wrap appeared feasible in the middle- and high-income countries in which the included studies were performed. Quality improvement studies assessed for this systematic review resulted in almost universal use of the plastic bag or wrap, suggesting a high level of feasibility	Barriers to implementing plastic bag or wrap in the birthing room could be related to the cost and availability of the intervention. It is important to ensure that the plastic bag or wrap is opened or lifted as infrequently as possible, until the baby is transferred to

		a prewarmed, humidified incubator. Otherwise, the benefits of the plastic bag or wrap are likely to be reduced.

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

In newborn preterm infants (<34 weeks' gestation) immediately after birth we recommend the use of plastic bag or wrap to maintain normal temperature. (Strong recommendation, moderate certainty of evidence).

The risk of hyperthermia should be carefully monitored and managed (Good practice statement).

Justification

Overall justification

Plastic bag or wrap to maintain normal temperature in the delivery room is feasible.

Detailed justification
Problem
Hypothermia is a common problem in preterm infants (<34 weeks' gestation) has been associated with increased mortality and morbidity.

Desirable Effects
Plastic bag or wrap compared with standard care reduced the risk of hypothermia and improved mean temperature on admission, and may improve survival

Undesirable Effects
There was an increased risk of hyperthermia in infants in the plastic bag or wrap group

Certainty of evidence
The evidence was variable from low to high certainty

Cost effectiveness
There were no studies on cost effectiveness

Subgroup considerations

- *For subgroup analysis by gestational age groups: (<28 weeks vs 28-33+6 weeks)* a plastic bag or wrap was more efficacious in preventing moderate hypothermia in the lower gestation subgroup (test for subgroup differences (random effects): $\chi 2 = 5.27$, df = 1 ($p = 0.02$)). For all other outcomes results of tests for subgroup differences were not statistically significant.
- *For subgroup analysis high income vs middle income country setting* a plastic bag or wrap was more efficacious in preventing moderate hypothermia in high income countries, (test for subgroup differences (random effects): $\chi 2 = 5.20$, df =1 ($p =0.02$)). For all other outcomes results of tests for subgroup differences were not statistically significant.
- *For subgroup analysis by setting high resource vs low resource setting* there were no data.
- *For subgroup analysis by site (inborn vs outborn)* the tests for subgroup differences were not statistically significant.

Implementation considerations

Plastic bag or wrap for thermoregulation in the delivery room has been shown to be feasible in any resource setting. Practice change would be required to implement the intervention.

Monitoring and evaluation

Preterm neonate's temperature on admission to neonatal intensive care units should continue to be monitored as an important indicator of the quality of care. {Perlman 2015 S204}

Research priorities

- What is the balance of risks and benefits when using a plastic bag or wrap for preterm infants in the birthing room when other combination of thermoregulation interventions (ambient temperature, heated and humidified gases, exothermic mattress, head covering, servo-controlled radiant warmer) are applied?
- What is the evidence for cost effectiveness when using a plastic bag or wrap for preterm infants in the birthing room?
- More information is needed about the gestation-specific effects of plastic bags or wraps, especially in the context of numerous other interventions to maintain normothermia.

QUESTION 4.

Should plastic cap vs. no plastic cap be used for in preterm neonates born at less than 34 weeks' gestation or equivalent birth weight immediately after birth?

POPULATION:	in preterm neonates born at less than 34 weeks' gestation or equivalent birth weight immediately after birth
INTERVENTION:	Plastic cap
COMPARISON:	No plastic cap
MAIN OUTCOMES:	Primary outcomes • Survival to hospital discharge (critical) • Rate of normothermia on admission to neonatal unit or postnatal ward (important) Secondary outcomes: • Body temperature (and rates of moderate hypothermia, cold stress and hyperthermia) on admission to neonatal unit or before transfer to neonatal unit or postnatal ward, or at times ≤ 1 hour of age (as defined by authors). • Response to resuscitation, e.g., need for assisted ventilation, highest FiO_2 • Major morbidity: bronchopulmonary dysplasia (important), intraventricular hemorrhage all grades (important) and severe (critical), necrotising enterocolitis (important), respiratory distress syndrome (surfactant treatment for), late onset sepsis.
SETTING:	Birth environment, in or out of hospital
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	A head covering (cap or bonnet) has been recommended by ILCOR for maintaining normal body temperature in preterm infants after birth, in order to prevent adverse outcomes including death. {Perlman 2015 S204} The systematic review of evidence for this intervention was updated to include studies published since the previous systematic review. The scalp is a large proportion of body surface area in a preterm infant and hence is considered likely make a large contribution to evaporative, radiant, conductive or convective heat loss. The review intended to consider head coverings made from a variety of materials, but the only study that provided evidence of sufficient certainty to contribute to development treatment recommendation examined use of a double-layered plastic cap.

CONFLICT OF INTERESTS:	Author Trevisanuto was lead author on the only study eligible for this comparison, and was excluded from assessment of the study for inclusion, risk of bias assessment and certainty of evidence assessment. {Trevisanuto 2010 914} Author de Almeida was lead author on an observational study which examined the effects of a bundle of interventions including a cloth cap, and was excluded from assessment of the study for inclusion, risk of bias assessment and certainty of evidence assessment. {de Almeida 2014 271} Authors Trevisanuto and de Almeida wrote a recent review article on maintaining normothermia in newborn infants at birth. {Trevisanuto 2018 333} Author Ramaswamy is an author of a network meta-analysis of methods to maintain normal temperature in infants in the delivery room {Abiramalatha 2021 e210775}

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". In preterm infants it is common to measure body temperatures in the cold stress or hypothermic range. 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. In a large cohort of 5697 infants < 32 weeks' gestation, 53.4% of the cohort had a body temperature at admission less than 36.5°C, and 12.9% below 35.5°C. {Wilson 2016 61} After adjustment for pregnancy complications, singleton or multiple pregnancy, antenatal corticosteroids, mode of delivery, gestational age, infant size and sex, and Apgar score <7 at 5 minutes, an admission temperature <35.5°C was associated with increased mortality at postnatal ages 1-6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7-28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age. {Wilson 2016 61} A recent network meta-analysis examining benefit and safety of interventions to reduce mortality and morbidity from hypothermia reported that various interventions aimed at improving thermoregulation can improve body temperature at admission and are associated with a lower risk of mortality and major brain injury. {Abiramalatha 2021 e210775}	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies	For the primary outcomes:	We do not know the effect size in the presence of additional or fewer co-interventions. Infants in both groups were equally exposed to additional thermoregulation measures, for example radiant warmer.

○ Don't know	For the critical primary outcome of **survival**, **clinical benefit or harm could not be excluded** for the use of a plastic cap compared to no plastic cap. (RR 0.97 95% CI 0.84 to 1.12), **moderate certainty evidence** from 1 RCT enrolling 64 participants. {Trevisanuto 2010 914} For the important primary outcome of **normothermia on admission** to a neonatal unit, there was **possible clinical benefit** with the use of a plastic cap compared to no plastic cap (RR 6.00 95% CI 1.96 to 18.38, ARD 469 more infants per 1000 were normothermic, 95% CI 90 more to 1000 infants more, NNTB 2 infants), **moderate certainty evidence** from 1 RCT enrolling 64 participants. {Trevisanuto 2010 914}	Additional measures may affect infant thermoregulation. We do not know the effect size in the presence of additional or fewer co-interventions. Other types of caps might also be effective. There is indirect evidence from the companion review in Late preterm and term infants: For the comparison woollen vs cotton cap, the review found one RCT enrolling 126 participants that examined two outcomes relevant to the review and found small differences in mean temperature and the rate of moderate hypothermia favouring the woollen cap group. {Lang 2004 843, Ramaswamy 2022 81}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no plastic cap	Risk difference with plastic cap
Survival	64 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	**RR 0.97** (0.84 to 1.12)	938 per 1,000	**28 fewer per 1,000** (150 fewer to 113 more)
Normothermia	64 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b]	**RR 6.00** (1.96 to 18.38)	94 per 1,000	**469 more per 1,000** (90 more to 1,629 more)

[1] {Trevisanuto 2010 914}

a. Single study, 95% CI crossing line of no effect
b. Single study, Optimal information size (OIS) not satisfied

For secondary outcomes:

For **mean body temperature** there was **probable clinical benefit** (MD 0.8°C higher (0.41 to 1.19°C higher with the use of a plastic cap compared to no plastic cap), **moderate certainty evidence** downgraded for imprecision from 1 RCT with 64 participants {Trevisanuto 2010 914}

For **hypothermia < 36.5 C** there was **probable clinical benefit** (RR 0.48 95%CI 0.32 to 0.73, ARD 471 fewer infants were hypothermic per 1,000 95% CI 616 fewer to 245 fewer per 1000 infants) **moderate certainty evidence** downgraded for imprecision from 1 RCT with 64 participants (RR 0.48 95%CI 0.32 to 0.73) {Trevisanuto 2010 914}

For the **outcome of delivery room intubation clinical benefit or harm cannot be excluded, (**RR 0.82 95% CI 0.49 to 1.37, ARD 96 fewer infants were intubated per 1000, 95% CI 271 fewer to 197

more per 1000), **moderate certainty evidence** downgraded for imprecision from 1 RCT with 64 participants. {Trevisanuto 2010 914}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no plastic cap	Risk difference with plastic cap
Mean body temperature	64 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	The mean mean body temperature was **35.30°C**	MD **0.8°C higher** (0.41 higher to 1.19 higher)
Hypothermia < 36.5 C	64 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	**RR 0.48** (0.32 to 0.73)	906 per 1,000	**471 fewer per 1,000** (616 fewer to 245 fewer)
Delivery room intubation	64 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b]	**RR 0.82** (0.49 to 1.37)	531 per 1,000	**96 fewer per 1,000** (271 fewer to 197 more)

[1] {Trevisanuto 2010 914}

a. Single study, OIS not satisfied
b. Single study, 95% CI crossing line of no effect

The rationale for considering the effect moderate was that although no difference was found in the primary outcomes, hypothermia was avoided more often with a large absolute benefit. For the important secondary outcomes of **mean body temperature and hypothermia** < **36.5°C** there was **probable clinical benefit.**

Cloth cap compared to no cap:

An observational study compared the use of various interventions that included use of a plastic bag or wrap; use of a linen or woolen cap; use of heated gases for ventilation; and use of a transport incubator. All infants were cared for under radiant heaters in the DR, and exothermic mattresses were not used. Using logistic regression, the effects of a **cloth cap** (used in in 894 infants vs no cap in 870 infants) were estimated, with adjustment for maternal and neonatal characteristics at birth and variables related to neonatal thermal care in the DR and variables related to thermal care during transport from the DR to the NICU. For consistency with presentation of other data from

	the review, we have calculated an adjusted relative risk and adjusted absolute risk difference from the odds ratios reported in the paper. These results suggest that use of a **cloth cap** was associated with **lower rates of moderate hypothermia** (RR 0.84 95% CI 0.79 to 0.90, ARD 123 fewer infants were moderately hypothermic on admission with use of a cloth cap, 95% CI 77 fewer to 162 fewer infants per 1000) **low certainty evidence** downgraded for very serious risk of bias from one observational study including 1764 infants for this comparison. {de Almeida 2014 271}	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	In this review the one RCT did not report any episodes of hyperthermia in either group. {Trevisanuto 2010 914}	The one RCT in this review was small and did not satisfy the OIS for uncommon outcomes.

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 the primary outcomes, survival and normothermia and for the important secondary outcome measures of body temperature, hypothermia < 36.5°C, and delivery room intubation was moderate. The certainty of evidence for moderate hypothermia was 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 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}	

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 probable clinical benefit for two important secondary outcomes (any hypothermia < 36.5°C, and mean body temperature on admission to the NICU with MD 0.8°C higher temperature with the intervention. There was no evidence of harm. However, the single RCT was of insufficient size to measure uncommon 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 study included in this review did not provide an estimate of costs to determine the certainty of evidence for required resources.	The Task Force also considered the environmental impacts of recommending widespread use of plastic caps. However, this must be weighed against benefits, and also compared with the widespread use of other disposables in clinical care.

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 study provided in this review did not provide 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 in the review examined cost effectiveness of the plastic cap.	The Task Force considered that the effects of use of a plastic cap in decreasing rates of hypothermia on admission to a neonatal unit may offset the minimal cost of the plastic caps 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 one RCT identified in this review took place in a high resource setting. In high resource settings it may be relatively easy to introduce plastic caps in the delivery room. In low and middle resource settings plastic caps may be unavailable or unaffordable.	Alternatives to plastic caps that might be more readily available include woven or knitted hats made of various fibres.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The study included in this review did not report did not report any concerns about acceptability of plastic caps in the delivery room.	The ILCOR NLS Task Force has recommended the use of a cap as one of several measures to maintain normal temperature for preterm infants in the delivery room since 2015, (1) and this recommendation is reflected in many regional and national guidelines.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Use of a plastic cap appeared feasible in the setting in the study identified in this review. In addition, quality improvement studies identified for this systematic review commonly used some type of head covering for maintaining normal temperature in preterm infants, suggesting feasibility and acceptability	Some of the plastic wraps purpose-designed for maintaining normal infant temperatures at birth now incorporate a head covering, obviating the need for a separate cap.

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

In preterm infants (<34 weeks' gestation) immediately after birth we suggest the use of a head covering to maintain normal temperature. (Strong recommendation, moderate certainty evidence).

In preterm infants (<34 weeks' gestation) we recommend any head covering is preferable to no head covering (Good practice point)

In preterm infants (<34 weeks' gestation) it is reasonable to consider the use of a plastic cap as a head covering. (Conditional recommendation, moderate certainty evidence).

There is currently little published evidence that head coverings of other materials are effective in preterm infants (< 34 weeks' gestation), but they may also help maintain normothermia based on an observational study and studies in infants ≥ 34 weeks' gestation.

Justification

Overall justification

Applying a plastic cap to prevent heat loss from the head of a newly born preterm infant is feasible and effective.

Detailed justification

Problem

Hypothermia is a common problem in preterm infants (< 34 weeks' gestation) and has been associated with increased mortality and morbidity.

Desirable Effects

A plastic cap compared to no plastic cap increased mean body temperature and the proportion of infants who were hypothermic on admission to the NICU.

Undesirable Effects

No undesirable effects were identified. The study was of insufficient size to measure uncommon adverse outcomes including hyperthermia.

Certainty of evidence

The evidence was moderate for most outcomes reported

Cost effectiveness

There were no data to determine cost effectiveness

Subgroup considerations

In the single study identified in this review there were no data on the pre-specified subgroups analyses; inborn vs. outborn, by resources of setting, by gestational age or by effect of delayed cord clamping.

Implementation considerations

Covering the head of preterm infants (<34 weeks' gestation) in the delivery room is common practice in high-income countries. In low resource settings practice change might be required to implement the intervention.

Monitoring and evaluation

Preterm neonate's temperatures on admission to neonatal intensive care units should continue to be monitored as important indicators of the quality of care. {Perlman 2015 S204}

Research priorities

- What is the balance of risks and benefits when using head covering composed of different materials?
- We do not know if caps made from other materials, might be more, or less effective in maintaining normal temperature.
- What is the balance of risks and benefits of a plastic head covering for preterm infants when receiving other combinations of interventions to promote thermoregulation (heating and humidifying gases for positive pressure ventilation in the birthing room; ambient temperature, plastic bag or wrap, exothermic mattress, servo-controlled radiant warmer) are applied?
- Can plastic caps be used in the setting of delayed cord clamping?
- We do not know the costs and environmental impact of plastic caps.

QUESTION 5.

Should heated and humidified gas vs. non-heated non-humidified gases be used for resuscitation in the delivery room for preterm neonates born at less than 34 weeks' gestation or equivalent birth weight immediately after birth?	
POPULATION:	Resuscitation in the delivery room for preterm neonates born at less than 34 weeks' gestation or equivalent birth weight immediately after birth
INTERVENTION:	Heated and humidified gas
COMPARISON:	Non-heated non-humidified gases
MAIN OUTCOMES:	Primary outcomes • Survival to hospital discharge (critical) • Rate of normothermia on admission to neonatal unit or postnatal ward (important) Secondary outcomes: • Body temperature (and rates of moderate hypothermia, cold stress and hyperthermia) on admission to neonatal unit or before transfer to neonatal unit or postnatal ward, or at times ≤ 1 hour of age (as defined by authors). • Response to resuscitation, e.g., need for assisted ventilation, highest FiO_2 Major morbidity: bronchopulmonary dysplasia (important), intraventricular hemorrhage all grades (important) and severe (critical), necrotising enterocolitis (important), respiratory distress syndrome (surfactant treatment for), late onset sepsis.
SETTING:	Birth environment, in hospital
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Use of warmed and humidified gases is regarded as routine in mechanically ventilated patients in intensive care units, to prevent damage to the lungs. {Sottiaux 2006 } Heating and humidification may also play a key role in maintaining normal body temperature, {Gillies 2017 Cd004711} particularly in preterm infants. However, clinical trials of the use of heated and humidified gases during initial resuscitation at birth have only been published recently.
; (; CONFLICT OF INTERESTS:	Lead author J Dawson was a co-author of one of the trials included for this comparison, {McGrory 2018 47} and was excluded from decisions about inclusion and risk of bias assessment for this article.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	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	

○ Probably yes ● Yes ○ Varies ○ Don't know	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} In preterm infants it is common to measure a lower-than-normal body temperature. A large cohort study of 5697 infants < 32 weeks' gestation in 19 regions in 11 European countries found that hypothermia was common in infants born in hospitals (prevalence range, 32% to 85%) and homes (prevalence range, 11% to 92%), even in warm climates. {Wilson 2016 61} In this cohort, 53.4% had a body temperature at admission below 36.5°C, and 12.9% below 35.5°C. After adjusting for pregnancy complications, singleton or multiple pregnancy, antenatal corticosteroids, mode of delivery, gestational age, infant size and sex, and Apgar score <7 at 5 minutes, an admission temperature <35.5°C was associated with increased mortality at postnatal ages 1-6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7-28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age. {Wilson 2016 61} A recent network meta-analysis examining benefit and safety of interventions to reduce mortality and morbidity from hypothermia reported that various interventions aimed at improving thermoregulation can improve body temperature at admission and are associated with a lower risk of mortality and major brain injury. {Abiramalatha 2021 e210775}	

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 the use of heated and humidified gases, when compared to non-heated and non-humidified gases for resuscitation in the delivery room for preterm infants: For **survival to hospital discharge**, the first primary outcome for the review **clinical benefit or harm cannot be excluded** (RR 1.00 95% CI 0.94 to 1.05), **very low certainty evidence** downgraded for risk of bias and imprecision, from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} This result was supported by an observational study enrolling 112 participants, which also produced evidence of very low certainty. {te Pas 2010 e1427} For **normothermia on admission** to a neonatal unit (the second primary outcome) **clinical benefit or harm cannot be excluded** (RR 1.23 95% CI 0.93 to 1.62), **very low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} However, an observational study of 112 infants found **possible clinical benefit** (RR 3.53, 95% CI 1.65 to 7.55) **low certainty evidence** downgraded for risk of bias and imprecision. {te Pas 2010 e1427}	We do not know the effect size in the presence of additional or fewer co-interventions. Infants in both the heated and humidified gas and the non-heated and humidified gas group were equally exposed to additional thermoregulation measures, for example radiant warmer. Additionally, the least mature infants were managed with a plastic bag or wrap. These additional measures may have affected infant thermoregulation. We do not know the effect size in the presence of additional or fewer co-interventions.

Primary Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with non-heated non-humidified gases	Risk difference with heated and humidified gas
Survival	476 (2 RCTs)[1,2]	⨁◯◯◯ Very low[a,b,c]	**RR 1.00** (0.94 to 1.05)	918 per 1,000	**0 fewer per 1,000** (55 fewer to 46 more)
Survival	112 (1 observational study)[3]	⨁◯◯◯ Very low[c,d]	**RR 1.01** (0.92 to 1.12)	931 per 1,000	**9 more per 1,000** (74 fewer to 112 more)
Normothermia	476 (2 RCTs)[1,2]	⨁◯◯◯ Very low[a,b,c,e]	**RR 1.23** (0.93 to 1.62)	471 per 1,000	**108 more per 1,000** (33 fewer to 292 more)
Normothermia	112 (1 observational study)[3]	⨁⨁◯◯ Low[d,f]	**RR 3.53** (1.65 to 7.55)	121 per 1,000	**305 more per 1,000** (78 more to 791 more)

a. {Meyer 2015 245}
b. {McGrory 2018 47}
c. {te Pas 2010 e1427}
d. Of the two trials, one had some concerns for risk of bias
e. In the trials, plastic bag or wrap was used <28 weeks, <30 weeks or for all infants, according to each hospital's protocol
f. Optimal information size (OIS) criterion not satisfied and 95% CI crosses line of no effect
g. The study had a moderate risk of bias
h. I^2=52%
i. OIS criterion not satisfied

For secondary outcomes:

	For **mean body temperature on admission**, there was **possible benefit, but the clinical significance is uncertain** (mean body temperature was 0.15°C higher 95% CI 0.03 to 0.26°C higher), **moderate certainty evidence** from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **any hypothermia <36.5 °C** there was **possible clinical benefit** (RR 0.67 95% CI 0.51 to 0.87), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **mild hypothermia clinical benefit or harm cannot be excluded** (RR 0.61 95% CI 0.35 to 1.05), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **moderate hypothermia** there was **possible clinical benefit** (RR 0.58 95% CI 0.36 to 0.94), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **RDS requiring surfactant clinical benefit or harm cannot be excluded** (RR 0.91 95%CI 0.76 to 1.09), **low certainty evidence** downgraded for risk of bias, and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **delivery room intubation clinical benefit or harm cannot be excluded** (RR 1.10 95%CI 0.88 to 1.39), **low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **BPD clinical benefit or harm cannot be excluded** (RR 0.89 95%CI 0.70 to 1.13), **very low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **IVH >Grade 2,** there was **probable clinical benefit** (RR 0.39 95% CI 0.17 to 0.91), **moderate certainty evidence** downgraded for imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} For **NEC clinical benefit or harm cannot be excluded** (RR1.55 CI 95% 0.45 to 5.31), **very low certainty evidence** downgraded for risk of bias, and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}	

Secondary Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with non-heated non-humidified gases	Risk difference with heated and humidified gas
Mean body temperature	476 (2 RCTs)[1,2]	⨁⨁⨁◯ Moderate[a,b]	-	The mean body temperature was **36.59°C**	MD **0.15°C higher** (0.03°C higher to 0.26°C higher)
Hypothermia < 36.5 C	476 (2 RCTs)[1,2]	⨁⨁◯◯ Low[b,c,d]	**RR 0.67** (0.51 to 0.87)	389 per 1,000	**128 fewer per 1,000** (191 fewer to 51 fewer)
Mild hypothermia	476 (2 RCTs)[1,2]	⨁⨁◯◯ Low[b,c,d,e]	**RR 0.61** (0.35 to 1.05)	234 per 1,000	**91 fewer per 1,000** (152 fewer to 12 more)
Moderate hypothermia	476 (2 RCTs)[1,2]	⨁⨁◯◯ Low[c,d]	**RR 0.58** (0.36 to 0.94)	172 per 1,000	**72 fewer per 1,000** (110 fewer to 10 fewer)
IVH > grade 2	476 (2 RCTs)[1,2]	⨁⨁⨁◯ Moderate[a,b,d]	**RR 0.39** (0.17 to 0.91)	82 per 1,000	**50 fewer per 1,000** (68 fewer to 7 fewer)
RDS requiring surfactant therapy	476 (2 RCTs)[1,2]	⨁◯◯◯ Very low[b,c,f]	**RR 0.91** (0.76 to 1.09)	500 per 1,000	**45 fewer per 1,000** (120 fewer to 45 more)

NEC	203 (1 RCT)[1]	⊕◯◯◯ Very low[b,c,f,g]	**RR 1.55** (0.45 to 5.31)	39 per 1,000	**21 more per 1,000** (21 fewer to 167 more)
Late onset neonatal sepsis	476 (2 RCTs)[1,2]	⊕◯◯◯ Very low[b,c,f]	**RR 1.07** (0.75 to 1.54)	213 per 1,000	**15 more per 1,000** (53 fewer to 115 more)
BPD	476 (2 RCTs)[1,2]	⊕◯◯◯ Very low[b,c,f]	**RR 0.89** (0.70 to 1.13)	377 per 1,000	**41 fewer per 1,000** (113 fewer to 49 more)
Delivery room intubation	476 (2 RCTs)[1,2]	⊕⊕◯◯ Low[a,b,f]	**RR 1.10** (0.88 to 1.39)	344 per 1,000	**34 more per 1,000** (41 fewer to 134 more)

[1] {Meyer 2015 245}
[2] {McGrory 2018 47}

a. The trial with greatest weightage had a low risk of overall bias
b. In the trials, plastic bag or wrap was used <28 weeks, <30 weeks or for all infants, according to each hospital's protocol
c. Of the two trials, one had some concerns for risk of bias
d. Optimal information size (OIS) criterion not satisfied
e. 95% CI crosses line of no effect
f. OIS criterion not satisfied and 95% CI crosses line of no effect
g. Very low event rates with wide 95% CI

We found one before and after study enrolling 112 infants. This observational study provided moderate certainty evidence for each of the secondary outcomes, but none of the findings were statistically significant except for a lower risk of moderate hypothermia (RR 0.58 95% CI 0.36 to 0.94). {te Pas 2010 e1427}

The rationale for considering the effect small was that little difference was found in the primary outcomes. However, for the important secondary outcome **IVH > Grade 2** there was probable clinical benefit, albeit in two RCTs for which the combined number of participants fell well below the optimal information size (OIS) for this (and most other outcomes). The result of reduced IVH>grade 2 could easily be a type I error and would need to be replicated in larger studies. For the important secondary outcome **moderate hypothermia** there was **possible clinical benefit.** For the secondary outcome, **mean temperature on admission** infants in the heated and humidified gas group achieved a higher temperature by 0.15°C (0.03°C higher to 0.26°C higher) a difference that may not be clinically significant, because this increase and its confidence intervals

did not cross a threshold of treatment effect. In the included studies, other measures to maintain normal temperature were used for both intervention and control arms, including plastic bags or wraps (either for all infants or for all infants <28 weeks' gestation) and a radiant warmer. It is possible that in the presence of fewer other measures, the effect size for heated and humidified gases may be larger, or in the presence of more measures (e.g., increased ambient room temperature or addition of a thermal mattress) the effect may be smaller.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

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

RESEARCH EVIDENCE

This systematic review found that when heated humidified gas compared to non-heated and humidified gas for resuscitation in the delivery room for preterm infants:

- For **hyperthermia (> 37.5°C) clinical benefit or harm could not be excluded** (RR 1.46 95% CI 0.60 to 3.52), **very low certainty evidence**, downgraded for risk of bias, inconsistency, and imprecision from 2 RCTs enrolling 476 infants. {McGrory 2018 47, Meyer 2015 245}
- The observational study provided low certainty evidence also supporting that clinical benefit or harm could not be excluded. {te Pas 2010 e1427}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with non-heated non-humidified gases	Risk difference with heated and humidified gas
Hyperthermia (> 37.5 C)	476 (2 RCTs)[1,2]	⨁◯◯◯ Very low[a,b,c,d]	**RR 1.46** (0.60 to 3.52)	90 per 1,000	**41 more per 1,000** (36 fewer to 227 more)
Hyperthermia	112 (1 observational study)[3]	⨁⨁◯◯ Low[e,f]	**RR 2.15** (0.20 to 23.02)	17 per 1,000	**20 more per 1,000** (14 fewer to 380 more)

1. {Meyer 2015 245}
2. {McGrory 2018 47}

ADDITIONAL CONSIDERATIONS

Infants in both the heated and humidified gas and the non-heated and humidified gas group were equally exposed to additional thermoregulation measures, for example radiant warmer. Additionally, the least mature infants were managed with a plastic bag or wrap. These additional measures may have affected infant thermoregulation.

In one study infants were exposed to delayed cord clamping for 40 seconds. The effect of delayed cord clamping on thermoregulation in very and extremely preterm infants is unclear.

We do not know the effect size in the presence of additional or fewer co-interventions.

	3. {te Pas 2010 e1427} a. Of the two trials, one had some concerns for risk of bias b. I^2=55% c. Amongst the extremely preterm subgroup of neonates included in both trials, plastic bag or wrap was used as a co-intervention in neonates <28 weeks' gestation in one trial and <30 weeks at one site in the other trial d. OIS criterion not satisfied and 95% CI crosses line of no effect e. The trial had a moderate risk of bias f. 95% CI crosses line of no effect The reason for concluding that the effect on hyperthermia is not known is that although the point estimates suggested a greater likelihood of clinical harm, the confidence intervals were wide and crossed the line of no effect. The evidence was of very low certainty. Furthermore, in the included studies, other measures to maintain normal temperature were used for both intervention and control arms. The number and type of other measures used could affect the risk of hyperthermia.	

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 the primary outcomes (survival and normothermia) was very low. For the important secondary outcomes relating to body temperature the certainty of evidence was low, except for mean temperature on admission and IVH > grade 2, for which the certainty of evidence was moderate. For the remaining secondary outcomes, the certainty of evidence was 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 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}	Cold stress and hypothermia are common particularly among preterm infants and are associated with increased mortality and morbidity. {de Almeida 2014 271}

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 possible clinical benefit for three outcomes (any hypothermia < 36.5°C, moderate hypothermia and IVH >Grade 2) with heated and humidified gases for resuscitation in the delivery room. None of the remaining outcomes suggested increased likelihood of harm.	The mean temperature of piped wall air has been measured as 23.4°C and mean relative humidity 5.4%. {Dawson 2014 24} Exposure to cold dry gas in preterm lambs has shown a trend to increased proinflammatory interleukin-1Beta messenger RNA when compared to heated and humidified gas. {Greenspan 1991 , Pillow 2009 } Although these results have not been confirmed in studies of human preterm infants, the effects are likely to be similar. The additional potential benefits of using heated and humidified gas for resuscitation in the delivery room on biomarkers of lung injury were not measured specifically in trials included in this review. Warmed, humidified gases are considered mandatory for all subsequent respiratory support in all age groups. {Sottiaux 2006 }

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 two studies included in the review took place in high resource settings. One of the studies estimated that the additional equipment required to provide heated humidified gas in the delivery room could cost US$50 for the single-use humidification circuit and chamber. {McGrory 2018 47} The true cost is likely to be higher as this estimate did not include the cost of the heater, temperature probes and sterile water required to provide the intervention.	It is possible that the circuit used in the delivery room to provide respiratory support could "travel" with the baby to the NICU when ongoing respiratory support is required. Nevertheless, there is likely to be considerable expense to purchase and maintain equipment to safely heat and humidify gases in all locations where preterm infants are born. The costs of the additional devices and disposable components may well be unaffordable where resources are limited.

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 in the review examined cost effectiveness for use of heated and humidified gas for resuscitation in the delivery room.	

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 impact on health equity. In high resource settings, the equipment for heated and humidified gases for resuscitation in the delivery room is likely to be accessible because of routine use during subsequent NICU care. In low and middle resource settings, and especially where resources for subsequent respiratory support are limited, it may be unavailable or unaffordable.	Where resources are limited, providing heated and humidified gases in the delivery room could divert resources away from the NICU. Any potential harmful effect of using non-heated and non-humidified gases for resuscitation in the delivery room may be limited if respiratory support is only required for a short time. However, it is not established whether there is a safe duration for ventilation using non-heated and non-humidified gases before admission to a NICU. It is very unlikely that heated and humidified gases would be available in an out-of-hospital setting.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The two studies included in this review did not include information about acceptability of heating and humidifying gases for resuscitation in the delivery room. In the NICU it is considered mandatory to heat and humidify gases used for ventilation and CPAP.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Use of heating and humidification appeared feasible in the included studies.	Barriers to implementing heated and humidify gases in the birthing room are likely to be related to the cost of the intervention, and training requirements.

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

In newborn preterm infants (<34 weeks' gestation) receiving ventilatory support immediately after birth, we suggest heated and humidified gases for respiratory support in the delivery room can be used where audit shows that admission hypothermia is a problem and resources allow. (Conditional recommendation, very low certainty evidence) .

Justification

Overall justification

The evidence from this systematic review indicated that heating and humidifying gases for respiratory support in the delivery room is safe, feasible and confers a small clinical benefit for several secondary outcomes.

Detailed justification

Problem

Hypothermia is a common problem in preterm infants (<34 weeks gestation) and has been associated with increased mortality and morbidity.

Desirable Effects

The systematic review found 2 RCTs and 1 observational study that found improvements in some secondary outcomes of the review. For the important secondary outcome IVH > Grade 2 there was probable clinical benefit, albeit in two RCTs for which the combined number of participants fell well below the optimal information size (OIS) for this (and most other outcomes). The result of reduced IVH>grade 2 could easily be a type I error and would need to be replicated in larger studies. Any potential harmful effect of using non-heated and non-humidified gases for resuscitation in the delivery room may be limited if respiratory support is only required for a short time before heating and humidification can be provided. However, the safe upper limit of duration for ventilation using non-heated and non-humidified gases before admission to a NICU is not established.

Undesirable Effects

No undesirable effects (including risk of hyperthermia) were confirmed (although the evidence was of low to very low certainty).

Certainty of evidence

The evidence for various outcomes ranged from very low to moderate certainty. It should be noted that in the combined studies, the optimal information size was not met for most outcomes.

Cost effectiveness and equity

There were no data to determine cost effectiveness or effects on equity. However, there will be expense to purchase and maintain equipment to safely heat and humidify gases in all locations where preterm infants are born. In low- and middle-income countries and other low resource settings, the costs are likely to be unaffordable, or providing heated and humidified gases in the delivery room could divert resources away from the NICU. To mitigate this, it is possible that the circuit used in the delivery room to provide respiratory support could "travel" with the baby to the NICU when ongoing respiratory support is required.

Subgroup considerations

Predefined subgroup analyses for this review were by gestation groups (or approximate birth weight equivalent), by location of birth and resources of setting and by early vs later cord clamping.

There were insufficient data to perform formal analysis of interaction.

One study reported outcomes for the **subgroup of infants < 26 weeks' gestation**, (but not other gestation subgroups).

Primary outcome:

- For **normothermia on admission to a neonatal unit** (the second primary outcome) **clinical benefit or harm** cannot be excluded (RR 0.80 95% CI 0.48 to 1.34) (low certainty evidence from 1 RCT enrolling 69 participants < 26 weeks gestation. {McGrory 2018 47}

For important secondary outcomes:

- For **mean body temperature on admission**, there was **possible clinical benefit** (MD 0.40°C higher with use of heated and humidified gases, 95% CI 0.02 to 0.82°C higher) (moderate certainty evidence from 1 RCT enrolling 69 participants in this gestation group)
- For **any hypothermia <36.5 °C clinical benefit or harm cannot be excluded** (RR 0.79 95% CI 0.40 to 1.56) (low certainty evidence downgraded for risk of bias and imprecision from 1 RCT enrolling 69 participants). {McGrory 2018 47}
- For **moderate hypothermia** there was possible clinical benefit (RR 0.37 95% CI 0.13 to 1.06) (low certainty evidence downgraded for risk of bias and imprecision from 1 RCT enrolling 69 participants). {McGrory 2018 47}
- For **hyperthermia (> 37.5°C) clinical benefit or harm could not be excluded** (RR 2.57 95% CI 0.89 to 7.42)(very low certainty evidence, downgraded for risk of bias, inconsistency, and imprecision) from 1 RCT enrolling 69). {McGrory 2018 47}

Thus, the findings were similar for the <26-week gestation infants as for the study as a whole. However, the study did not report a test for interaction.

One study specified that delayed cord clamping was routinely performed for all study infants. {Meyer 2015 245} All infants in included studies were born in hospital and the studies were conducted in high income countries. {McGrory 2018 47, Meyer 2015 245, te Pas 2010 e1427}

Implementation considerations

Heating and humidifying gases used for respiratory support is standard care in NICUs in high-income countries. Depending on location, purchase, supply and maintenance of equipment and practice changes would be required to implement the intervention.

Monitoring and evaluation

Preterm neonates' temperatures on admission to neonatal intensive care units should continue to be monitored as important indicators of the quality of care. {Perlman 2015 S204}

Research priorities

- What is the balance of risks and benefits when heating and humidifying gases for preterm infants receiving positive pressure ventilation in the birthing room when other combinations of thermoregulation interventions (ambient temperature, plastic bag or wrap, exothermic mattress, cap, servo-controlled radiant warmer) are applied?
- What is the evidence for cost effectiveness when using heated and humidified gases in the delivery room when providing respiratory support?
- Can heating and humidifying gases be used in the setting of delayed cord clamping?
- Does use of heated and humidified gases during resuscitation reduce lung injury?
- Does use of heated and humidified gases from birth reduce the risk of severe IVH in studies that meet the optimal information size for this outcome, and if so, what is the mechanism?

QUESTION 6.

Should servo controlled radiant warmer mode vs. manual mode radiant warmer be used for preterm neonates born at less than 34 weeks' gestation or equivalent birth weight, immediately after birth?	
POPULATION:	Preterm neonates born at less than 34 weeks' gestation or equivalent birth weight immediately after birth
INTERVENTION:	Servo controlled mode radiant warmer
COMPARISON:	Manual mode radiant warmer
MAIN OUTCOMES:	Primary outcomes • Survival to hospital discharge (critical) • Rate of normothermia on admission to neonatal unit or postnatal ward (important) Secondary outcomes: • Body temperature (and rates of moderate hypothermia, and hyperthermia) on admission to neonatal unit or before transfer to neonatal unit or postnatal ward, or at times ≤ 1 hour of age (as defined by authors). • Response to resuscitation, e.g., need for assisted ventilation, highest FiO_2 • Major morbidity: bronchopulmonary dysplasia (important), intraventricular hemorrhage all grades (important) and severe (critical), necrotising enterocolitis (important), respiratory distress syndrome (surfactant treatment for), late onset sepsis.
SETTING:	Birth environment, in hospital
PERSPECTIVE:	Individual patients, their families and providers caring for those patients.
BACKGROUND:	Infants in the neonatal intensive care unit are generally nursed under a radiant warmer or in an incubator. The temperature of the incubator or radiant warmer can be adjusted manually or by servo controlling heater output to achieve a set neonatal body temperature measured at the site of a skin sensor. The previous ILCOR systematic review of Warming Adjuncts (and a subsequent evidence update NLS 599: EvUp) made no comment regarding use of manual or servo mode to control warmers used in the delivery room. {Perlman 2015 S204}
CONFLICT OF INTERESTS:	Author Trevisanuto was an author of the study of use of servo-control mode during newborn resuscitation included in this review, {Cavallin 2021 572} 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	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} In preterm infants it is common to measure body temperatures in the cold stress or hypothermic range. 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. In a large cohort of 5697 infants < 32 weeks' gestation, 53.4% of the cohort had a body temperature at admission less than 36.5°C, and 12.9% below 35.5°C. {Wilson 2016 61} After adjustment for pregnancy complications, singleton or multiple pregnancy, antenatal corticosteroids, mode of delivery, gestational age, infant size and sex, and Apgar score <7 at 5 minutes, an admission temperature <35.5°C was associated with increased mortality at postnatal ages 1-6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7-28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age. {Wilson 2016 61} A recent network meta-analysis examining benefit and safety of interventions to reduce mortality and morbidity from hypothermia reported that various interventions aimed at improving thermoregulation can improve body temperature at admission and are associated with a lower risk of mortality and major brain injury. {Abiramalatha 2021 e210775}	

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 when a radiant warmer in servo-controlled mode was used compared to using a radiant warmer in manual mode for preterm infants in the delivery room: For the critical primary outcome of **survival to hospital discharge**, **clinical benefit or harm could not be excluded** (RR 1.05, 95% CI 0.99 to 1.11), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants. {Cavallin 2021 572} For the important primary outcome of **normothermia on admission to a neonatal unit**, **clinical benefit or harm could not be excluded** (RR 0.94, 95% CI 0.75 to 1.17), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants. {Cavallin 2021 572}	We do not know the effect size in the presence of additional or fewer co-interventions. Infants in both the servo controlled and the manual warmer group were equally exposed to additional thermoregulation measures. The servo control system was set at 37°C, we do not know the effect of different set temperatures on the outcomes of interest. Manual mode was set at maximum output for ten minutes before the birth of an infant. We do not know the effect of specific manual mode settings other than those used in the studies. Also, if there was less time for the heater to warm up in manual mode before the birth of a baby, this could alter the difference between servo and manual modes (effect size).

Primary Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with manual mode radiant warmer	Risk difference with servo controlled radiant warmer
Survival	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	**RR 1.05** (0.99 to 1.11)	884 per 1,000	**44 more per 1,000** (9 fewer to 97 more)
Normothermia	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	**RR 0.94** (0.75 to 1.17)	422 per 1,000	**25 fewer per 1,000** (106 fewer to 72 more)

1. {Cavallin 2021 572}
a. 95% CI crossing line of no effect

For secondary outcomes:

For **mean body temperature on admission, there was probable clinical harm** (temperature 0.2°C lower, 95% CI 0.33 to 0.07 lower), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants) {Cavallin 2021 572}

For **hypothermia < 36.5 there was probable clinical harm** (RR1.20 95% CI 1.01 to1.42), **moderate certainty evidence** downgraded for imprecision from 1 trial enrolling 450 infants. {Cavallin 2021 572}

For **mild hypothermia (36.0 to 36.4°C)** there was **probable clinical harm** (RR 1.48 (95% CI 1.09 to 2.01), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For **moderate to severe hypothermia < 36.0**°C **clinical benefit or harm cannot be excluded** (RR 0.97 95% CI 0.71 to 1.31), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For **IVH (>grade 2) clinical benefit or harm cannot be excluded** (RR 0.87 95% CI 0.42 to 1.78), moderate certainty evidence downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For l**ate onset sepsis clinical benefit or harm cannot be excluded** (RR 1.39 95% CI 0.89 to 2.18), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For b**ronchopulmonary dysplasia clinical benefit or harm cannot be excluded** (RR 0.98 95%CI 0.68 to 1.41), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For **delivery room intubation** there was **possible clinical benefit**(RR 0.67 95%CI 0.46 to 0.97), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For **delivery room nasal positive pressure ventilation, clinical benefit or harm cannot be excluded** (RR 1.06 95%CI 0.90 to 1.23), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}

For other secondary outcomes, (RDS requiring surfactant, NEC) outcome data were not reported.

Secondary Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with manual mode radiant warmer	Risk difference with servo controlled radiant warmer
Mean body temperature	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	-	The median mean body temperature was **36.5°C**	MD **0.2**°C **lower** (0.33°C lower to 0.07°C lower)
Hypothermia < 36.5 C	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	**RR 1.20** (1.01 to 1.42)	498 per 1,000	**100 more per 1,000** (5 more to 209 more)
Mild hypothermia 36.0-36.4	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	**RR 1.48** (1.09 to 2.01)	222 per 1,000	**107 more per 1,000** (20 more to 224 more)

Moderate hypothermia < 36.0C	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b]	**RR 0.97** (0.71 to 1.31)	276 per 1,000	**8 fewer per 1,000** (80 fewer to 85 more)
IVH > grade 2	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b,c]	**RR 0.87** (0.42 to 1.78)	67 per 1,000	**9 fewer per 1,000** (39 fewer to 52 more)
Late onset neonatal sepsis	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b,c]	**RR 1.39** (0.89 to 2.18)	124 per 1,000	**49 more per 1,000** (14 fewer to 147 more)
BPD	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b,c]	**RR 0.98** (0.68 to 1.41)	209 per 1,000	**4 fewer per 1,000** (67 fewer to 86 more)
Delivery room intubation	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[c]	**RR 0.67** (0.46 to 0.97)	240 per 1,000	**79 fewer per 1,000** (130 fewer to 7 fewer)
Delivery room nasal positive pressure ventilation	450 (1 RCT)[1]	⨁⨁⨁◯ Moderate[b,c]	**RR 1.06** (0.90 to 1.23)	564 per 1,000	**34 more per 1,000** (56 fewer to 130 more)

1 {Cavallin 2021 572}

a. Single study, though optimal information size (OIS) satisfied
b. 95% CI crossing line of no effect
c. OIS not satisfied

We considered **the effect of servo control mode uncertain** because there were no important differences in the rates of primary outcomes. Among secondary outcomes, the mean difference in temperature was only 0.2°C lower in the servo control group, although this difference did cross a line of treatment effect, in that the mean temperature in the servo control group was in the cold stress (mild hypothermia) range. The proportion of infants who

	were mildly hypothermic was higher in the group exposed to servo control, but the confidence interval was wide.	

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 that when a servo controlled radiant warmer was used in the delivery room compared to using a radiant warmer in manual mode for preterm infants: For **Hyperthermia (> 38.0°C), clinical benefit or harm cannot be excluded** (RR 0.02 95% CI 0.00 to 8.46), **low certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 infants. {Cavallin 2021 572}	The single study in this review also used a plastic bag or wrap plus a hat for a similar proportion of infants in each group. Additionally, delayed cord clamping, or thermal mattress or heated humidified gases were used in a proportion of infants in each group. We do not know the effect size in the presence of fewer or more co-interventions. Radiant warmers in servo control mode require a sensor to adhere to the infant's skin or a probe inserted into the neonate's rectum. Both methods have some potential to cause harm. Tape used to secure the temperature sensor could cause skin damage in preterm infants due to their fragile, underdeveloped skin. {Mishra 2021 1627} Damage to the rectum from rectal temperature probes is possible but rare. {Morley 1992 122}

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with manual mode radiant warmer	Risk difference with servo controlled radiant warmer
Hyperthermia	450 (1 RCT)[1]	⨁⨁◯◯ Low[a]	**RR 0.02** (0.00 to 8.46)	27 per 1,000	**26 fewer per 1,000** (27 fewer to 199 more)

1. {Cavallin 2021 572}
   a. Single study with low event rates, 95% CI crossing line of no 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	The certainty of evidence for all outcomes was moderate except, "hyperthermia" which was 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	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}	Cold stress and hypothermia are common, particularly among preterm infants and are associated with increased mortality and morbidity {de Almeida 2014 271}

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 from a single study that it was improbable that there was benefit or harm for the two primary outcomes. The review found possible evidence of harm for three secondary outcomes measuring temperature on admission to the neonatal unit (mean temperature on admission, hypothermia < 36.5°C, mild hypothermia (36.0°C to 36.4°C)) for infants exposed to a servo controlled radiant warmer. In this study, servo control did not cause hyperthermia.	The single study did not present data in a form that enabled analysis by birthweight categories. It is possible that the balance of benefits and harms varies by birthweight or gestation subgroups.

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 one study included in the review was conducted in a high resource setting. No estimates of costs or resources required were provided in this, or other studies considered for inclusion.	Additional equipment expenses include a radiant warmer capable of servo control, disposable or reusable sensors or probes.

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 review found no specific information about 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	The study included in the review did not provide information 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	In high resource settings, radiant warmers capable of being used in either servo or manual mode are likely to be available for resuscitation of preterm infants in the delivery room. In low and middle resource settings, radiant warmers may be unavailable or unaffordable or capable of use only in manual mode. However, since the intervention (servo control) did not appear to be beneficial, the net effects on equity are unknown.	Servo controlled radiant warmers are likely to be more expensive than manual mode radiant warmers. In addition to the cost of the device there is an additional cost for the sensors that need to be applied to an infant's skin. In a low resource setting the need for additional servo control may be unaffordable. Servo control is not possible for all models of radiant warmer used in delivery rooms, particularly in low- or 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	In the one study included in this review the study protocol was followed for all infants, suggesting that both servo control and manual mode were acceptable in the context of the study. After NICU admission, it is standard practice in countries where suitable equipment is available, to use servo control for thermoregulation.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Use of servo or manual control appeared feasible in the setting in the study.	Barriers to implementing servo-controlled heating in the delivery room are likely to be related to the cost of the intervention.

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

In preterm infants (<34 weeks' gestation) immediately after birth there is insufficient published human evidence to suggest for or against the use of a radiant warmer in servo-controlled mode compared to manual mode for maintaining normal temperature. (Weak recommendation, moderate certainty evidence).
In preterm infants (<34 weeks' gestation) immediately after birth a radiant warmer is recommend (Good practice statement)

Justification

Overall justification

Use of servo control mode for radiant warmers did not affect primary outcomes of the systematic review but did result in lower body temperatures and more infants with temperatures in the mildly hypothermic range.

Detailed justification
Problem
Hypothermia is a common problem after birth in preterm infants and is associated with increased morbidity and mortality.

Desirable Effects
The effects of servo control compared with manual control were small but favoured use of manual control.

Undesirable Effects
Use of servo control did not affect rates of hyperthermia (the undesirable outcome examined in this review).

Certainty of evidence
The evidence is low or moderate certainty.

Balance of effects and Cost effectiveness
No evidence was found.

Equity
The additional cost of servo controlled radiant warmers and associated consumables is likely to preclude use in low resource settings.

Subgroup considerations

There were insufficient data from the single included study to undertake meaningful sub group analyses by gestational age, location of birth or effect of deferred cord clamping.

Implementation considerations

Servo controlled radiant warmers are widely used in neonatal units for thermoregulation. Manual mode radiant warmers are cheaper, depending on location the additional cost for servo controlled radiant warmers might be an unacceptable expense.

Monitoring and evaluation

Neonate's temperatures on admission to neonatal units should continue to be monitored as an important indicator of care. {Perlman 2015 S204}

Research priorities

- The role of servo control in maintaining normal temperature in preterm infants requiring prolonged resuscitation
- The balance of risks and benefits of servo controlled radiant warmers in the setting of various levels of ambient temperature and humidity.
- The balance of risks and benefits of servo control when there is variation in the co-interventions to prevent hypothermia (e.g. plastic bag of wrap, skin-to-skin care, thermal mattress, warmed and humidified resuscitation gases) are used in conjunction with a radiant warmer.
- Are there servo-controlled devices that could be adapted for use during deferred cord clamping?
- Does position of the temperature sensor probe affect the outcomes?

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QUESTION

NLS 5200 - Heart rate assessment methods in delivery room- diagnostic characteristics	
POPULATION:	Newborn infants in the delivery room
INTERVENTION:	Use of auscultation, palpation, pulse oximetry, Doppler device, digital stethoscope, photoplethysmography, video plethysmography, dry electrode technology or any other newer modalities
COMPARISON:	ECG, or between intervention comparisons
MAIN OUTCOMES:	Time to first heart rate assessment from the device placement (important) Time to first heart rate assessment from birth Accuracy of heart rate assessment
SETTING:	Delivery Room
PERSPECTIVE:	Population perspective
BACKGROUND:	This question was last assessed in 2015, where it was found that ECG provided a faster and more accurate heart rate assessment when compared to auscultation with or without pulse oximetry {Wyckoff 2015 S546}. This systematic review identified newer methodologies for heart rate assessment for comparisons.
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	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 (HR) below 100 beats per minute (bpm) or gasping or apnea. Rising HR is the most important indicator of effective PPV in initially bradycardic newborns {Wyckoff }. HR is critical to decision-making in the delivery room (DR); 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 DR, there is limited evidence to date as to which is the best method for HR assessment in terms of rapidity and accuracy {Dawson 2013 957; Henry 2020 3; Iglesias 2018 F236; Kamlin 2008 758; van Vonderen 2015 51}.	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}. Recommendations for HR assessment vary among resuscitation councils.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ●Moderate ○ Large ○ Varies ○ Don't know	The certainty of evidence for all comparisons remains low. **Comparison 1: Pulse oximeter (PO) vs electrocardiogram (ECG)** PO is slower and more imprecise for newborn HR assessment in the DR compared to ECG {Abbey 2021 1; Bjorland 2020 1; Bobillo-Perez 2021 785; Bush 2021 F551; Dawson 2013 955; Henry 2021 72; Iglesias 2016 274; Iglesias 2018 F233; Kamlin 2008 756; Katheria 2012 e1180; Mizumoto 2012 205; Murphy 2019 F548; Murphy 2021 F438; van Vonderen 2015 49}.	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. Dry electrode technology may provide more accurate HR assessment during resuscitation when compared to ECG. Accuracy of HR assessment was examined by pooled Bland-Altman (B-A) analysis. The B-A plot is a method to quantify agreement between two quantitative measurements. {Bland 1995 1085, Bland 1999 135, Bland 1986 307, Giavarina 2015 141, Montenij 2016 750} This analysis was used to quantify agreement between ECG (reference technique) and other HR monitoring methods (experimental techniques). Bland–Altman (B-A) analysis determines the bias, or mean difference between the experimental and reference technique, as a measure of accuracy. B-A plot also includes limits of agreement (LoA), as a measure of precision. These statistical limits are calculated by using the mean difference (Bias) and the standard deviation(s) of the differences between two measurements. The LoA indicates the interval within which 95% of the differences between the two methods fall. If more than 1 study reported B-A plot analysis, we pooled that data together to create a summary estimate of accuracy and precision. The B-A plot method only defines the intervals of agreements, it does not say whether those limits are clinically acceptable or not. For this systematic review, agreement within +/- 10 bpm was considered acceptable. The B-A plot can also uncover whether the bias and differences are same or differ across various levels of HR

Outcome	Participants (studies)	Certainty of the evidence (GRADE)	Pooled median difference bias	95% CI
Time to first HR from device placement (RCTs)	136 (2 RCTs)[12,13]	⊕◯◯◯ Very low [a,b,c]	12 s slower	38 s faster to 13 s slower
Time to first HR from device placement (Observational studies)	323 (6 observational studies)[2,4,7,8,10,14]	⊕⊕◯◯ Low [a,c]	57 s slower	101 s slower to 13 s slower
Time for first HR from birth (RCTs)	87 (2 RCTs)[1,13]	⊕⊕◯◯ Low [a,c]	6 s slower	23 s faster to 10 s slower, p>0.05
Time for first HR from birth (Observational studies)	334 (6 observational studies)[2, 3, 5, 9, 11, 14]	⊕⊕◯◯ Low [a,c]	52 s slower	94 s slower to 9 s slower, p<0.05
Accuracy of HR assessment	216 infants (1 RCT, 4 observational studies 28,211 observations) [1, 5, 6, 9, 14]	⊕⊕⊕◯ Moderate[a]	**Mean bias**	**LoA* 95% CI**
			HR_{PO} – HR_{ECG}: -1.2 bpm	LoA: - 17.9 to 15.5 bpm(95% CI -32.8, 30.4)
Accuracy of HR assessment (sensitivity and specificity of PO for HR<100 bpm)	124 (3 studies)[1, 7, 9] 124 infants 8,342 observations	⊕◯◯◯ Very low [a,b,c]	Sensitivity 0.83 (5% CI 0.7 to 0.88) Specificity 0.97 (95% CI 0.93 to 0.94) No similar data for severe neonatal bradycardia (ECG HR <60 bpm)	

*Limit of agreement: LoA with lower and upper LoA

[1]{Abbey 2021 1}, [2]{Bjorland 2020 1}, [3]{Bobillo-Perez 2021 785}, [4]{Bush 2021 F551}, [5]{Dawson 2013 955}, [6]{Henry 2021 72}, [7]{Iglesias 2016 274}, [8]{Iglesias 2018 F233}, [9]{Kamlin 2008 756}, [10]{Katheria 2012 e1180}, [11]{Mizumoto 2012 205}, [12]{Murphy 2019 F548}, [13]{Murphy 2021 F438}, [14]{van Vonderen 2015 49}

a. Risk of bias
b. Inconsistency
c. Imprecision

CI, confidence interval; ECG, electrocardiography; HR, heart rate; HR_{ECG}, heart rate measured using ECG; HR_{PO}, heart rate measured using pulse oximetry; LoA, limits of agreement; PO pulse oximetry; RCT, randomized controlled trial; s, seconds.

Comparison 2: Auscultation compared to ECG

Auscultation may be faster than ECG for HR assessment at birth. Auscultation may be accurate but imprecise for HR estimation at birth {Bobillo-Perez 2021 785; Cavallin 2020 90; Kamlin 2006 320; Murphy 2018 F490-1; Treston 2019 F227}.

Outcome	Participants (studies)	Certainty of the evidence (GRADE)	Pooled median difference bias	95% CI
Time for first HR from device placement	105 (3 observational studies)[1,4,5]	⊕⊕⊕◯ Moderate[a]	4 s faster	10 s faster to 2 s slower p>0.05
Time for first HR from birth	70 (2 observational studies)[1,5]	⊕⊕◯◯ Low[a,b]	24 s faster	45 s faster to 2 s faster p<0.05
Accuracy of HR assessment	71 (2 observational studies)[3,4]	⊕⊕◯◯ Low[a,b]	**Mean bias**	**LoA* 95% CI**
			HR_{AUS} – HR_{ECG} - 9.9 bpm	LoA -32 to 12 bpm (95% CI to 217, 198)
Accuracy of HR assessment at 90 s	80 (2 observational studies)[1,2]	⊕⊕◯◯ Low[a,b]	-9.6 bpm	LoA -52 to 33 bpm (95% CI to 307, 203)
Accuracy of HR assessment at 120 s	80 (2 observational studies) [1,2]	⊕⊕⊕◯ Moderate[a]	-0.4 bpm	LoA -34 to 35 bpm (95% CI -594 to 189)

*Limit of agreement: LoA with lower and upper LoA

[1]{Bobillo-Perez 2021 785}, [2]{Cavallin 2020 90}, [3]{Kamlin 2006 320}, [4]{Murphy 2018 F490-1}, [5]{Treston 2019 F227}

a. Risk of bias
b. Imprecision

CI, confidence interval; ECG, electrocardiography; HR, heart rate; HR_{ECG}, heart rate measured using ECG; HR_{AUS}, heart rate measured using auscultation; LoA, limits of agreement; s, seconds.

Comparison 3: Palpation compared to ECG

Palpation is inaccurate and imprecise for HR estimation at birth {Cavallin 2020 90; Kamlin 2006 320}.

Outcome	Participants (studies)	Certainty of the evidence (GRADE)	Mean ± SD	Mean difference ± SEM
Accuracy of HR assessment	21 (1 observational study)[2]	⊕◯◯◯ Very low[a,b,c]	HR_{palp} 147 ± 19 bpm vs HR_{ECG} 168 ± 22 bpm p<0.001	-21 ± 21 bpm

Outcome	Number of observations	Certainty of the evidence (GRADE)	Mean Pooled difference	LoA
Accuracy of HR assessment at 60 s	60 (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	-20 bpm	-80 to 40 bpm
Accuracy of HR assessment at 90 s	60 (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	-25 bpm	-73 to 22 bpm
Accuracy of HR assessment at 120 s	60 (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	-23 bpm	-6 to 20 bpm
Accuracy of HR assessment at 300 s	60 (1 observational study)[1]	⊕◯◯◯ Very low[a,b]	-31 bpm	-96 to 34 bpm

*Limit of agreement: LoA with lower and upper LoA

[1]{Cavallin 2020 90}, [2]{Kamlin 2006 320}

a. risk of bias
b. applicability concerns
c. imprecision

CI, confidence interval; ECG, electrocardiography; HR, heart rate; HR_{ECG}, heart rate measured using ECG; HR_{palp}, heart rate measured using palpatiomn; LoA, limits of agreement; s, seconds.

Comparison 4: Palpation compared to auscultation

Auscultation provides more accurate HR over time than palpation {Cavallin 2020 90; Owen 2004 215}.

Outcome	Number of observations	Certainty of the evidence (GRADE)	Mean difference	95% CI
Accuracy of HR assessment	60 (1 RCT)[2]	⊕◯◯◯ Very low[a,b]	No pooled summary available	
Accuracy of HR assessment	60 (1 observational study)[1]	⊕◯◯◯ Very low[a,c]	-4 bpm (at each minute after birth)	-6 to -1 bpm* p=0.007

*Limit of agreement: LoA with lower and upper LoA

[1]{Cavallin 2020 90}, [2]{Owen 2004 215}

a. risk of bias
b. imprecision
c. applicability concerns

bpm, beats per minute; HR, heart rate

Comparison 5: Digital stethoscope (DS) compared to ECG

Digital stethoscope may be accurate but imprecise for HR estimation at birth {Gaetner 2017 F370}.

Outcome	Number of observations	Certainty of the evidence (GRADE)	Mean difference	95% CI
Accuracy of HR assessment (crying periods included)	23 (1 observational study)[1]	⊕◯◯◯ Very low[a,c]	$HR_{DS} - HR_{ECG}$: 0.2 bpm	−17.6 to 18 bpm*
Accuracy of HR assessment (crying periods excluded)	23 (1 observational study)[1]	⊕◯◯◯ Very low[a,c]	$HR_{DS} - HR_{ECG}$: 1 bpm	−10.5 to 12.6 bpm*

*Limit of agreement: LoA with lower and upper LoA

[1]{Gaetner 2017 F370}

a. risk of bias
b. imprecision
c. applicability concerns

bpm, beats per minute; HR, heart rate; HR_{ECG}, heart rate measured using ECG; HR_{DS}, heart rate measured using digital stethoscope; CI, confidence intervals

Comparison 6: Doppler ultrasound (DU) compared to ECG

Doppler US may be accurate and precise for HR assessment but certainty of evidence is very low {Agrawal 2019 2056; Shimabukuro 2017 1070}.

Outcome	Participants (studies)	Certainty of the evidence (GRADE)	Median Time (IQR)	
Time for first HR from birth	131 (1 Observational study)[1]	⊕◯◯◯ Very low[a,b]	HR_{DU}: 76 s (IQR 51 s to 91 s) vs HR_{ECG}: 96.5 s (IQR 74.2 s to 118 s) p<0.05	
Accuracy of HR assessment	164 (2 Observational studies)[1,2]	⊕⊕◯◯ Low[a,c]	**Summary Mean bias**	**LoA* 95% CI**
			$HR_{DU} – HR_{ECG}$ - 0.2 bpm	-5 to 6 (95% CI -222 to 223)

*Limit of agreement: LoA with lower and upper LoA

[1]{Agrawal 2019 2056}, [2]{Shimabukuro 2017 1070}

a. risk of bias
b. applicability concerns
c. imprecision

bpm; beats per minute; ECG, electrocardiography; HR, heart rate; HR_{ECG}, heart rate measured using ECG; HR_{DU}, heart rate measured using Doppler ultrasound; IQR, interquartile range.

Comparison 7: Dry electrodes incorporated in a belt (DEB) compared to (conventional 3 lead) ECG

Dry electrodes incorporated in a belt may be faster than conventional 3 lead ECG for HR estimation at birth. DEB may be accurate and precise for HR estimation at birth when compared to conventional 3 lead ECG {Bush 2021 F551; Rettedal 2021 5; van Twist 2022 1139}.

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Outcome	Number of observations	Certainty of the evidence (GRADE)	Median Time (IQR)
Time for first HR assessment from device placement (Observational study)	48 (1 Observational study)[2]	⊕◯◯◯ Very low[a,b]	HR_{DEB} at 22 s (IQR CI 13 s to 45s) vs HR_{ECG} 171 s (IQR 129 s to 239 s)

Time for first HR from birth (Observational study)	28 (1 Observational)[1]	⊕◯◯◯ Very low[a,b]	HR_{DEB} 13 s (IQR CI 10 s to 18 s) vs HR_{ECG} 42 s (IQR 31 s to 63 s)	
Accuracy of HR assessment	66 (2 Observational studies)[2,3]	⊕⊕◯◯ Low[a,c]	**Summary Mean bias**: $HR_{DEE} - HR_{ECG}$ – 1.4 bpm	**LoA* 95% CI**: -2.5 to 5.2 (95% CI -30 to33)

[1]{Bush 2021 F551}; [2]{Rettedal 2021 5}; [3]{van Twist 2022 1139}

a. risk of bias
b. imprecision
c. applicability concerns

bpm; beats per minute; ECG, electrocardiography; MD, mean difference; HR, heart rate; HR_{ECG}, heart rate measured using ECG; HR_{DEB}, heart rate measured using dry electrodes incorporated in a belt; IQR, interquartile range.

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 the use of ECG or other modalities to detect HR in the delivery room would cause clinical harm.	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 in resuscitation interventions. It remains unclear if this assessment is beneficial or harmful. There are 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	All evidence was of low certainty, downgraded for risk of bias and applicability concerns.	
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 time for first HR assessment from the device placement, time for first heart rate assessment from birth and accuracy of HR assessment as outcomes. We included outcomes that were previously judged to be 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.	Outcome ratings were adopted from the following publication: {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	The potential undesirable effects are unknown. One theoretical concern is the detection of pulseless electrical activity (PEA) with ECG monitoring, leading providers to inappropriately stop resuscitative efforts. The incidence of PEA within this population of newly born infants is not known, so the impact is unclear. If one assumes PEA is rare and newborns needing resuscitation is less rare, the balance of effects may favor the faster and more accurate HR assessment method of ECG.	

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; other 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 should be considered. As such, it is deemed a moderate cost.	It is possible that the routine use of ECG for HR assessment in infants receiving positive pressure ventilation immediately after birth may reduce the need for further neonatal resuscitation interventions and long-term undesirable outcomes. Currently, there is insufficient evidence to determine whether routine use of ECG improves resuscitation efforts and clinical outcomes.

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, potentially improving equity.

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 ECG monitoring in the DR. We speculate this is predominantly due to the lack of evidence of impact on clinical 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 the feasibility of using ECG in newly born infants in various settings {Perlman 2015 S207}.	

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

- Where accurate HR estimation is needed for a newborn infant immediately after birth and resources permit, we suggest that the use of ECG for HR assessment of a newly born infant in the DR is reasonable (Conditional recommendation, low certainty of evidence).
- PO and auscultation may be reasonable alternatives to ECG for HR assessment, but the limitations of these modalities should be kept in mind (Conditional recommendation, low certainty of evidence).
- There is insufficient evidence to make a treatment recommendation regarding use of any other device for HR assessment of a newborn infant immediately after birth.
- Auscultation with or without PO should be used to confirm the HR when ECG is unavailable, not functioning or when pulseless electrical activity is suspected (Good practice point).

Justification

- The available data suggest that ECG provides a more rapid and accurate assessment of HR in the DR when compared to pulse oximetry, and more accurate assessment than palpation or auscultation. but the but the certainty of evidence ranges from moderate to very low
- Most studies did not include the infants in whom rapid, accurate assessment of heart rate may be most important, e.g. those who were bradycardic, those requiring resuscitation as positive pressure ventilation, or extremely premature infants. The companion ILCOR systematic review which assessed clinical outcomes found that it is unclear if the rapidity, accuracy and precision of HR estimation at birth results in clinically relevant differences in resuscitation interventions, resuscitation team performance or clinical outcomes for newborn infants. [36]
- Auscultation or pulse oximetry or both have been routinely used for HR assessment in newborns at birth. Where resources are limited, addition of another device may be impractical or unaffordable.

Subgroup considerations

The available data did not support any subgroup analyses

Implementation considerations

Acquiring ECG monitors in the delivery room: many centers might be able to re-allocate monitors from existing resources; other 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

- More data on the characteristics of measurement of HR in the delivery room using devices such as digital stethoscope, Doppler ultrasound (audible or visible displays), reflectance-mode green light photoplethysmography or transcutaneous electromyography of the diaphragm. Such studies should include evaluation of time to first HR assessment from birth and from device placement.
- Cost effectiveness of different modalities for HR assessment in the delivery room.
- The impact of different HR assessment methods on resuscitation team performance, resuscitation interventions and neonatal clinical outcomes.
- Evidence as to whether different devices are better suited to different subgroups of infants (e.g., by gestation or by anticipated need for advanced resuscitation).

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QUESTION

NLS 5350 - Exhaled CO_2 to guide non-invasive ventilation at birth

POPULATION:	Newborn infants receiving intermittent positive pressure ventilation (IPPV) by any non-invasive interface at birth
INTERVENTION:	Use of exhaled CO_2 monitor in addition to clinical assessment, pulse oximetry and/or electrocardiogram (ECG)
COMPARISON:	Clinical assessment, pulse oximetry and/or ECG only
MAIN OUTCOMES:	The pre-specified primary outcome was endotracheal intubation in the delivery room (important). The secondary outcomes were divided as follows: 1) Resuscitation outcomes at birth: survival to neonatal intensive care unit (NICU) admission (critical); time to heart rate >100 bpm (important); duration of IPPV (important); use of IPPV corrective actions (important); and use of chest compressions (important); 2) Other major morbidity: survival to hospital discharge (critical); bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (all three important) in infants born at <34 weeks' gestation; and unexpected admission to special or intensive care unit (important) in infants born at ≥34 weeks' gestation.
SETTING:	Delivery room
PERSPECTIVE:	Individual patients, their families, health care providers and health service providers.
BACKGROUND:	Exhaled CO_2 application immediately after birth has been reviewed by ILCOR with the focus on the correct placement of an endotracheal tube {ILCOR 2006 e-978; Perlman 2010 S516; Perlman 2015 S204}. In 2010, ILCOR reviewed the use of colorimetric CO_2 detection to assess ventilation in non-intubated, bradycardic neonates and made the following treatment recommendation: there is insufficient evidence to recommend routine use of colorimetric exhaled CO_2 detectors during mask ventilation of newborns in the delivery room {Perlman 2010 S516}. However, quantitative, and qualitative analysis of exhaled CO_2 is being used in some centers to guide mask ventilation of preterm infants at birth {Blank 2014 1568; Blank 2018 1; Finer 2009 865; Hawkes 2017 74; Kakkilaya 2019 e20180201; Kong 2013 104}. The rationale for this use is that exhaled CO_2 may provide useful information related to potential airway obstruction {Finer 2009 865; Leone 2006 e202} or problems with lung aeration {Hooper 2013 e70895}, but there are concerns related to the dead space and increased resistance introduced into the ventilatory circuit {Brown 2016 1003}, and the reliability of colorimetric devices {Blank 2014 1568}. The impact on the resuscitation team, such as potential distraction when using an exhaled CO_2 monitor, is unknown. In this context, a search for evidence for utilizing exhaled CO_2 to guide non-invasive positive pressure ventilation immediately after birth 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	Over 140 million babies are born annually worldwide {United Nations - Population Division 2022}. It is estimated that up to 5% of newborns receive intermittent positive-pressure ventilation (IPPV) at birth {Wyckoff 2020 185}. The use of exhaled CO_2 may be relevant to infants receiving IPPV at birth.	Exhaled CO_2 may provide useful information on the effectiveness of mask ventilation. The absence of exhaled CO_2 may indicate airway obstruction, failure of lung aeration or cardiac compromise, and its presence may precede an increase in heart rate (HR) in bradycardic infants who are being adequately ventilated {Cereceda-Sanches 2019 358; Hawkes 2014 1315; Leone 2006 e202; Sankaran 2021 2580; Williams 2021 3148}. Quantitative and qualitative analysis of exhaled CO_2 is being used in some centers to guide mask ventilation of infants at birth {Blank 2014 1568; Blank 2018 1; Finer 2009 865; Kong 2013 104; Hawkes 2017 74; Kakkilaya 2019 e20180201}. However, there are

		concerns related to the dead space introduced into the ventilatory circuit {Brown 2016 1003}, the reliability of colorimetric devices {Blank 2014 1568}, and the distraction of the resuscitation team when using the exhaled CO_2 monitor in the delivery room.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Eligible studies were not found. Based on the narrative review, exhaled CO_2 monitoring during IPPV with facemask immediately after birth was available to providers in eight studies {Blank 2014 1568; Blank 2018 1; Finer 2009 865; Hawkes 2017 74; Kang 2014 e102729; Kong 2013 104; Mizumoto 2015 186; Ngan 2017 F525}, but no study had a comparator group of infants receiving IPPV without exhaled CO_2 monitoring. Six of these studies {Blank 2014 1568; Blank 2018 1; Finer 2009 865; Kang 2014 e102729; Mizumoto 2015 186; Ngan 2017 F525} reported some possible benefits: 1. Exhaled CO_2 and detection of airway obstruction: - Finer et al {Finer 2009 865} reviewed data from 18 infants with GA <32 weeks that received IPPV by facemask from a trial that randomly assigned patients to resuscitation with room air or 100% oxygen. Colorimetric CO_2 detectors were used to assist with IPPV in all patients. The interventions to correct the obstruction included repositioning of the head (n=10), checking the mask seal (n=5), a new operator (n=2), and increasing the pressure (n=1). The authors concluded that the use of a colorimetric detector provides the resuscitation team with a visible signal that can indicate airway patency. - Blank et al {Blank 2014 1568} reviewed the data of 41 preterm infants with bradycardia receiving PPV with T-piece and facemask at birth and were monitored with colorimetric CO_2 detectors. The interventions that were performed in response to colorimetric monitoring included increasing the inspiratory pressure (37%) and readjusting the position of the infant's airway or the position of the mask (24%). 2. Exhaled CO_2 to assess lung aeration: - Kang et al {Kang 2014 e102729} studied 51 infants <37 weeks' gestation and found that those on CPAP (n=31) had higher exhaled CO_2 values with lower tidal volumes compared to infants who received IPPV by T-piece and facemask (n=20). The authors concluded that exhaled CO_2 monitoring confirms that infants maintained on CPAP achieve better gas exchange (resulting from sufficient lung aeration) than infants requiring IPPV. - Ngan et al {Ngan 2017 F525} randomized infants <33 weeks' gestation to IPPV (n=86) or a 20-second sustained inflation (n=76) with facemask at birth. Exhaled CO_2 increased more rapidly after the sustained inflation. The authors concluded that sustained inflation resulted in better lung aeration compared with IPPV. - Blank {Blank 2018 1} used exhaled CO_2 to determine lung aeration prior to umbilical cord clamping in 44 infants $\geq$32 weeks' gestation. A T-piece with facemask was applied in infants needing respiratory support and the exhaled CO_2 was used as an indicator of pulmonary gas exchange. The authors concluded that it is feasible to	In a study by Linde et al {Linde 2018 1}, measured exhaled CO_2 data by a sidestream quantitative sensor were retrospectively assessed. Higher expired CO_2 (as % of expired air) was noted in infants receiving IPPV by facemask with self-inflating bag who survived vs. those who died (2.8 vs. 1.7%, respectively, p=0.001), possibly reflecting better CO_2 exchange in surviving newborns. Tidal volumes in both groups were within the recommended range. Because CO_2 data were retrospectively obtained after the resuscitation, the impact of real time CO_2 monitoring to the providers to guide ventilatory actions could not be assessed. Kakkilaya et al {Kakkilaya 2019 e20180201} implemented a resuscitation bundle, including the exhaled CO_2 detector, to optimize facemask IPPV in infants ≤29 weeks' gestation at birth. Comparing pre- (n=180) vs. post- (n=134) quality improvement cohorts, the latest had lower intubation rate in the delivery room, lower need for mechanical ventilation, lower rates of BPD and severe retinopathy of prematurity. It is not possible to know the effectiveness of the individual components of the bundle.

	provide resuscitation and monitor infants during delayed cord clamping using physiologic targets to indicate when the infant is ready for umbilical cord clamping. 3. Exhaled CO_2 as a predictor of increase in HR in initially bradycardic infants: - Blank et al {Blank 2014 1568} reviewed the data of 41 preterm infants with bradycardia receiving IPPV with T-piece and facemask at birth. All infants were monitored with colorimetric CO_2 detector. The authors observed that colorimetric CO_2 detection during mask IPPV at birth precedes a significant increase in HR. - Mizumoto et al {Mizumoto 2015 186} evaluated seven infants ventilated with flow-inflating bag and facemask. They found that an exhaled CO_2 >15mmHg preceded a HR increase to >100 bpm by 8-73 seconds. Among the eight studies with exhaled CO_2 monitoring during IPPV with facemask immediately after birth available to providers (none of them with a comparator group of infants receiving IPPV without exhaled CO_2 monitoring), two evaluated the effect of exhaled CO_2 monitoring at birth on the partial pressure of CO_2 (pCO_2) at NICU admission. Kong et al {Kong 2013 104} reported that guiding delivery room ventilation with exhaled CO_2 measurement did not result in more preterm infants having admission pCO_2 within the recommended range. Hawkes et al {Hawkes 2017 74} compared preterm infants receiving IPPV by T-piece and facemask monitored by quantitative or qualitative exhaled CO_2. Due to the lack of differences between study groups in primary or secondary outcomes, the authors concluded that the use of either form of exhaled CO_2 monitoring should be considered during newborn stabilization.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Based on the narrative review, there are some concerns with the use of exhaled CO_2 to guide IPPV by facemask at birth. As noted by van Vonderen {van Vonderen 2015 F514}, several factors can make interpreting exhaled CO_2 data at birth complicated. These factors include the following 1) Leak is frequent during mask ventilation and may decrease the CO_2 concentration in the sensor, underestimating the exhaled CO_2; 2) A poor correlation between the expired tidal volume and the exhaled CO_2 could be due to a closed glottis (while volume is measured due to pressurization of the upper respiratory tract, very little exhaled CO_2 will be measured); and 3) It is possible that dead-space ventilation of the mask, oropharynx and trachea causes insufficient renewal of the expired volume causing an overestimation of exhaled CO_2 levels. The exhaled CO_2 monitors may also be inadequate to detect periods of adequate ventilation during low pulmonary blood flow and/or low cardiac output after lung inflation {Blank 2014 1568}, i.e., CO_2 detection may not distinguish between resuscitations that are not going well because the lungs are not being aerated and those in which the lungs are not being perfused. Even in the absence of airway obstruction, exhaled CO_2 may be low in infants born at <29 weeks' gestation maybe due to insufficient inflation pressures to overcome the resistance of fluid filled small airways and the absence of fully vasodilated pulmonary circulation {Hunt 2019 17}. The reliability of colorimetric devices may be affected by contamination with gastric contents and medication {Blank 2014 1568; Muir 1990 41}.	Attention to the device may distract the resuscitators from paying attention to the newborn infant during resuscitation. The potential harms associated with any monitoring that may distract the resuscitation team have not been explored. Adverse effects of exhaled CO_2 monitoring may depend on the training and expertise of health care providers, but this issue has not been explored.

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 search found 2370 references. Full text review was conducted for 23 papers. No studies were identified which addressed the PICOST question.	

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 lack of appropriate studies to support the decision to use or not use exhaled CO_2 monitors to guide IPPV with non-invasive interfaces, such as facemasks, supraglottic airways, and nasal cannulae, immediately after birth.	

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 exhaled CO_2 monitoring to guide IPPV with non-invasive interfaces, such as facemasks, supraglottic airways and nasal cannulae, in newborns immediately after birth.	Given that about 5% of all newborns receive IPPV at birth {Wyckoff 2020 185}, the cost of using or not using exhaled CO_2 monitoring to guide IPPV with non-invasive interfaces is an important consideration. The use of exhaled CO_2 monitoring may add costs related to equipment, maintenance, supplies, and training of personnel. Qualitative CO_2 detectors are disposable and the use of capnography or capnometry requires specific monitors with related costs. Balancing this, Blank et al {Blank 2014 1568} speculated that colorimetric CO_2 monitoring may be helpful to indicate ineffective ventilation when other monitors, such as pulse oximeter and ECG, are unavailable. It should be noted that the colorimetric CO_2 detector requires no electricity.

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.	

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.	Although there are no published cost-effectiveness data, it could be speculated that monitoring of exhaled CO_2 may decrease costs if it is effective to guide IPPV with non-invasive interfaces, lowering endotracheal intubation rates and adverse effects associated with invasive ventilation at birth, especially in preterm infants.

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 cost of equipment and training resources may be significantly more limiting 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. Balancing this, Blank et al {Blank 2014 1568} speculated that colorimetric CO_2 monitoring may be helpful to indicate ineffective ventilation when other monitors, such as pulse oximeter and ECG, are unavailable. It should be noted that the colorimetric CO_2 detector requires no electricity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No data available.	The narrative review suggests that the intervention is accepted by providers in the delivery room of high resource settings: Hawkes et al {Hawkes 2017 74}, in UK, compared sidestream capnography with a colorimetric device and described that "exhaled CO_2 detection during facemask IPPV has been used regularly in our delivery room during the stabilization of preterm infants over the last 2 years." Kakkilaya et al {Kakkilaya 2019 e20180201}, in USA, implemented a resuscitation bundle, including a colorimetric exhaled CO_2 detector, to optimize facemask IPPV in 134 preterm infants at birth. The authors described that the use of the colorimetric CO_2 detector was easily incorporated by the team. Possibly, colorimetric exhaled CO_2 detectors would be more widely accepted by providers than quantitative devices, which need more resources and training to be implemented and used. Also, colorimetric exhaled CO_2 detectors are already recommended to verify endotracheal tube position during resuscitation at birth {Perlman 2015 S204}.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes	The eight studies with exhaled CO_2 monitoring during IPPV with facemask immediately after birth available to providers (none of them with a comparator group of infants receiving IPPV without exhaled CO_2 monitoring) show that exhaled CO_2 monitoring by quantitative or qualitative devices is feasible {Blank 2014 1568; Blank 2018 1; Finer 2009	Feasibility is likely to be device dependent. Colorimetric exhaled CO_2 devices are already used in several delivery rooms to verify endotracheal tube position. However, the use of quantitative devices to guide facemask IPPV has only been verified in small clinical trials {Hawkes 2017 74; Kang 2014 e102729; Kong 2013

● Varies ○ Don't know	865; Hawkes 2017 74; Kang 2014 e102729; Kong 2013 104; Mizumoto 2015 186; Ngan 2017 F525}. A review evaluated the feasibility of capnography use with facemask ventilation {Cereceda-Sanchez 2019 258} and concluded that, in newborn infants, exhaled CO_2 monitoring at birth is feasible.	104; Mizumoto 2015 186} and the feasibility outside the research settings is unknown.

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

There is insufficient evidence to suggest for or against the use of exhaled CO_2 to guide IPPV with non-invasive interfaces, such as facemasks, supraglottic airways, and nasal cannulae, in newborns immediately after birth.

Justification

In making this recommendation for newborns receiving non-invasive IPPV in the delivery room, the Task Force considered that there were no studies reporting outcomes comparing active CO_2 monitoring to guide IPPV with non-invasive interfaces to a group not using CO_2 monitoring. Therefore efficacy, effectiveness, and safety of exhaled CO_2 monitoring when being used via non-invasive devices could not be assessed.

The eight studies that reported data on infants receiving IPPV by facemask with exhaled CO_2 information available to the resuscitation team suggest that exhaled CO_2 monitoring may help recognize airway obstruction and inadequate tidal volume delivery/lung aeration during IPPV. The detection of exhaled CO_2 may precede an increase in HR in bradycardic neonates during IPPV with facemask {Blank 2014 1568; Blank 2018 1; Finer 2009 865; Hawkes 2017 74; Kang 2014 e102729; Kong 2013 104; Mizumoto 2015 186; Ngan 2017 F525}. Despite these findings, monitoring of exhaled CO_2 immediately after birth did not result in more infants having admission pCO_2 within the recommended range {Hawkes 2017 74; Kong 2013 104}. Survival was not assessed in any of these eight studies. In a study by Linde et al {Linde 2018 1}, measured exhaled CO_2 data by a sidestream quantitative sensor were retrospectively assessed. Higher expired CO_2 (as % of expired air) was noted in infants receiving IPPV by facemask with self-inflating bag who survived vs. those who died (2.8 vs. 1.7%, respectively, p=0.001), possibly reflecting better CO_2 exchange in surviving newborns. Tidal volumes in both groups were within the recommended range. Because CO_2 data were retrospectively obtained after the resuscitation, the impact of real time CO_2 monitoring to the providers to guide ventilatory actions could not be assessed.

In a quality improvement effort, Kakkilaya et al {Kakkilaya 2019 e20180201} implemented a resuscitation bundle, including an exhaled CO_2 detector to optimize facemask IPPV in infants ≤29 weeks' gestation at birth. Comparing pre- vs. post- (n=180 *vs*. n=134) quality improvement intervention cohorts, the latter had lower intubation rate in the delivery room (58 vs. 37%), lower administration of mechanical ventilation (85 vs 70%), lower rates of BPD (26 vs 13%), and severe retinopathy of prematurity (14 vs 5%). Despite these results, it is not possible to know the effectiveness of the isolated components of the bundle.

There are some potential concerns with the use of exhaled CO_2 to guide IPPV by facemask at birth. It is possible that dead-space ventilation of the mask, oropharynx, and trachea causes insufficient renewal of the expired volume, causing an overestimation of exhaled CO_2 levels {van Vonderen 2015 F514}. The exhaled CO_2 monitors may also be inadequate to detect periods of adequate ventilation during low pulmonary blood flow and/or low cardiac output {Blank 2014 1568}. Even in the absence of airway obstruction, exhaled CO_2 may be low in infants born at <29 weeks' gestation maybe due to insufficient inflation pressures to overcome the resistance of fluid filled small airways and the absence of fully vasodilated pulmonary circulation {Hunt 2019 665}.

The reliability of colorimetric devices may be affected by contamination with gastric contents and medications {Blank 2014 1568; Muir 1990 41}. The potential harms of exhaled CO_2 monitoring could include distraction from other important aspects of observing the infant and other monitoring devices, or anchoring bias (over-dependence on one observed value rather than consideration of all clinically important information). Furthermore, the implications for training and implementation of introducing CO_2 monitoring devices into routine practice have not been sufficiently explored.

In making the treatment recommendation, the Task Force noted the lack of studies to support the decision to use or not use exhaled CO_2 monitors to guide IPPV with non-invasive interfaces, such as facemasks, supraglottic airways and, nasal cannulae, immediately after birth.

Subgroup considerations

No data were found on the pre-specified subgroups: methods of exhaled CO_2 evaluation; types of non-invasive interface used in IPPV; indications of IPPV, and gestational age.

Implementation considerations

We anticipate that implementing exhaled CO_2 monitoring into routine clinical practice would require training and costs. In addition, there are human factor issues that need to be addressed should exhaled CO_2 monitoring become more widespread (see Research Priorities section below).

Monitoring and evaluation

If exhaled CO_2 monitoring during IPPV using non-invasive interfaces immediately after birth is implemented the following short and long term clinical outcomes should be carefully monitored: 1) Resuscitation outcomes at birth: endotracheal intubation in the delivery room, survival to NICU admission; time to HR >100 bpm; duration of IPPV; use of IPPV corrective actions; and use of chest compressions ; 2) Other major morbidity: survival to hospital discharge; BPD, severe IVH and PVL in infants <34 weeks' gestation; and unexpected admission to special or intensive care unit in infants ≥34 weeks' gestation. Also, possible harms associated with exhaled CO_2 monitoring as well as reliability issues of the different devices should be continuously evaluated.

Research priorities

In order to make evidence-based recommendations on the use of exhaled CO_2 to guide non-invasive positive pressure ventilation immediately after birth, it is important that research covers the following knowledge gaps:

- Efficacy and effectiveness of CO_2 monitoring to guide IPPV with non-invasive interfaces in newborns immediately after birth, considering the different methods of measurement and the different non-invasive interfaces
- Efficacy and effectiveness of CO_2 monitoring to guide IPPV with non-invasive interfaces in newborns immediately after birth with different indications of IPPV, such as apnea/irregular respirations or bradycardia/asystole, and different gestational ages, such as $<28^{0/7}$; $28^{0/7}$ -$33^{6/7}$; and $34^{0/7}$ or more weeks
- Optimal range of exhaled CO_2 in each minute after birth
- Potential risk due to undetected exhaled CO_2 in newborns with absent or insufficient circulation during effective IPPV
- Impact of cord management strategies on exhaled CO_2 detection
- Impact of the presence of gastric reflux, other secretions, blood, meconium, or medications on the reliability of colorimetric CO_2 detection
- Potential for CO_2 monitoring to distract or bias providers
- The cost-effectiveness and effects on equity of routine use of various HR assessment methods remain unclear

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QUESTION

Should there be an option for family presence vs. no family presence to be used in resuscitation after cardiac arrest?	
POPULATION:	Adults requiring resuscitation for cardiac arrest in any setting
INTERVENTION:	Family presence during resuscitation after cardiac arrest.
COMPARISON:	Family not present during resuscitation after cardiac arrest.
MAIN OUTCOMES:	• Patient outcomes (short and long term): return of spontaneous circulation, survival (to hospital admission, hospital discharge, 3 months, 6 months, 1 year), survival with good neurological outcomes (at same time points), depression and anxiety. • Family (or significant other) outcomes: (short and long term) PTSD, coping, perception of the resuscitation, depression and anxiety amongst family members, complicated grief syndrome. • Health care provider outcomes: perception of the resuscitation, performance, perceived futility in some circumstances, psychological stress including projection to provider's own family.
SETTING:	Any setting including public areas, homes and hospital settings.
BACKGROUND:	The low survival rates mean that cardiac arrest is a pivotal event during which family members may wish to be present during resuscitative efforts.[1] Advocates of family presence during resuscitation cite improved coping and grieving outcomes for the family, reduced litigation, and improved resuscitation team behaviours.[1-3] Conversely, concerns have been raised about the distress that family presence during resuscitation may cause families or healthcare providers, and the impact of family presence during resuscitation on team performance.[1,4] In 2021, an International Liaison Committee on Resuscitation (ILCOR) systematic review of family presence during neonatal and paediatric resuscitation showed: that parents/family members wanted the option to be present for their child's resuscitation; wide variation in health care provider attitudes towards family presence during paediatric or neonatal resuscitation; and insufficient evidence to demonstrate the effect of family presence during resuscitation on patient or family outcomes.[5]
CONFLICT OF INTERESTS:	None of the Task Force members declared any conflict of interest and this was acknowledged and managed by the Task Force Chairs and Conflict of Interest committee.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The low survival rates mean that cardiac arrest is a pivotal event during which family members may wish to be present during resuscitative efforts.[1] Systematic reviews related to family presence during adult resuscitation thus far have focused on RCTs, which may not provide a comprehensive assessment of the research evidence to date.	Cultural, religious, sociological factors may impact on practice related to family presence during resuscitation. COVID-19 may have impacted established practices around family presence during resuscitation in some settings.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Patient survival (short and long term)** Only four[6-9] (including one RCT[6]) of the 12 studies[6-17] reporting patient outcomes reported on the impact of family presence versus no family presence during adult resuscitation. Three found no significant difference in ROSC based on family presence or absence. One study favoured family absence during cardiac arrest for ROSC and survival to discharge. This study was potentially limited in the size of the 'family present' group. **Family outcomes** All participants (n=24) in one survey of family members[18] and 94% (n=44) in another[19] stated they would witness the resuscitation again. Two of three studies that questioned family members about regret found that none (of six family members),[17] and 3% (n=9)[6] regretted being present. Family members believed witnessing the resuscitation assisted them to cope with their grief (100%, n=24)[18] and adjust to their family members death (76%, n=36).[19] In an interview of 14 family members all believed witnessing the resuscitation was important and helpful.[12] Anxiety and anxiety symptoms at 90-days was found to be significantly lower than in those that witnessed a family member's resuscitation.[6,11,13] Finally, 64% (n=30) of family members believed their presence was meaningful to their dying family member and helped them to die peacefully (62%, n=29).[19] Themes that emerged in the qualitative studies centred around being able to choose whether to be present;[20,21] being physically (need for proximity) and emotionally present;[10,21-23] need for information and communication with providers;[10,21,22] and need for support (physical, emotional and spiritual).[10,22] Other studies reported notions of families knowing that 'everything was done'.[20,21] **Provider outcomes** Positive experiences of family presence during resuscitation were reported by 3.3%[24] to 22.4%[25] of providers.[24-27] Positive experiences were that the resuscitation team could provide reassurance to families,[28] and there was an opportunity for collaboration between providers and families in providing patient care, comfort and physical closeness.[28-30] Providers could alleviating family concerns, guide families through a traumatic experience and respond to families existential needs which they viewed to be a positive experience.[28,29,31] Around three-quarters of providers supported family presence during resuscitation,[12,19] and up to 68% believe their function during resuscitation was not impaired by family presence.[18,19] Providers believed that the patient benefited from family presence (50%),[32] family members benefited by being present (69%),[32] and family members were able to emotionally tolerate being present (58%).[32] Educational preparation and experience of providers was a key factor in managing the stressful situation of family presence during resuscitation, and managing family distress.[29,33,34]	None of the research considered the role of cultural, religious, sociological factors and reporting of any patient characteristics varied and was very limited. More clarity around the effect of family presence may be achieved when considered in the setting of these factors.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Patient survival (short and long term)** In one study, survival to hospital discharge was significantly lower when families were present in both unadjusted (p=0.04) and adjusted analyses (p=0.03),[35] but two other studies showed no difference in 28-day survival,[36] or 30-day survival[37] respectively. **Family outcomes** Depression screening was conducted in four studies,[6,11,13,38] three at 90-days[11,13,38] and one at 30-days.[6] One study found witnessing resuscitation was an independent predictor of depression at 90-days (95% CI: 1.27-35.34, p=0.03),[11] two found less depression/depression symptoms amongst those	**Family outcomes** Other factors contributing to depression or PTSD were not factored into the studies.

who witnessed resuscitation at 90-days (95% CI: 0.12-0.58;[13] 15% vs 26%, p=0.009[6]) and one found no significant difference between the groups at 30-days.[38]
Post-traumatic stress disorder (PTSD) symptoms were investigated in four studies.[6,13,38,39] One study reported that family members witnessing resuscitation had significantly higher PTSD symptom scores (14.47 vs.7.60, 95%CI: 0.57-13.17, p = 0.03),[39] and another reported higher likelihood of experiencing increased arousal at 60 days post event (40.9% vs 13.9%: 95%CI: 3.6-50.4%).[38] However, two other studies reported that family members present during resuscitation had less PTSD at 90-days (RR=0.05; 95%CI=0.01-0.15;[40] 27% vs 41%, p=0.001[36]).

Some studies reported that family members found being present during resuscitation a brutal and dehumanising experience[21] that was distressing,[20,21] and were worried about trying to remove thoughts about the resuscitation.[20] Family members reported being afraid of interfering or disrupting resuscitative efforts[20] or losing emotional control,[20] and others perceived that there was an excessive or unnecessarily heroic approach to resuscitation,[21] and that it was too long and possibly extended for their benefit.[19]

Provider Outcomes
Negative experiences included families preventing or interfering with resuscitation,[28] aggressive or disruptive family behaviours,[28,30] and provider concern about family trauma and heighted awareness of negative and visually distressing images for the family witnessing the resuscitation.[28-30]

A number of studies reported internal conflicts for providers who needed to balance compassionate care and technical competence,[29,30] reconcile unsettling emotions with their professional practice and responsibilities,[29] move from patient to family care, and resolve feelings of guilt and failure associated with termination of resuscitation or discomfort with performing futile resuscitation.[31]

A minority believed that family presence hindered care in terms of clinical performance (8.3%),[41] and interruptions (13.1%);[41] 12% agreed or strongly agreed that family members interfered in care,[32] and 12% agreed or strongly agreed that team communication was negatively affected by family presence.[32]

Three studies investigated provider anxiety[42] or stress.[6,43] Mean anxiety was 8/10 in providers who had family witnessing resuscitation compared to 3/10 for providers without family witnessing the resuscitation.[42] No difference was found in stress levels for either study reporting provider stress.[6,43]

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	See table below	There were 2 RCTs and 16 observational studies. The remaining studies were qualitative (12 studies) and mixed-methods (1 study). Certainty was downgraded to very low due to significant heterogeneity in study design, resuscitation setting, populations and assessment tools used. Sample sizes varied across the studies ranging from five[44] to 3,257[8].

Outcome	Certainty of evidence	
Patient outcomes	Very low	⊕
Family outcomes: depression, anxiety, PTSD	Very low	⊕
Family outcomes: experience of resuscitation	Very low	⊕
Provider outcomes: experience	Very low	⊕
Provider outcomes: anxiety, stress	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 important uncertainty or variability	Main outcome is survival, and neurologically intact survival. COSCA has confirmed importance of these outcomes.[45] Families and health care providers are likely to value the outcomes included in this systematic review.[46] Family and provider outcomes were decided and prioritised by the BLS and EIT Task Forces.	

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 is insufficient evidence to categorically state the effect on patient, family and provider outcomes. However, the evidence in this systematic review suggests little impact on patient outcomes, positive effects for family who are present during a loved-one's resuscitation and little negative psychological impact on providers. Furthermore, the outcomes of the systematic review suggest negative outcomes reported by providers can be addressed with the development of policies and procedures to assist healthcare providers to navigate family presence during resuscitation.	

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 reported on the costs associated with family presence. One study described an area had been set up to allow families to witness the resuscitation (i.e. a viewing window) but no costs were given.[42] It is possible that there may be costs associated with setting up viewing areas. The evidence is clear that providers would like family support personnel,[32,33,36,38,43,47,48] and policies or protocols for family presence during resuscitation,[18,25,26,48] and specific provider training manage family presence during resuscitation.[48,49] These initiatives would need to be funded.	

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 compared the cost-effectiveness of family presence versus no family presence.	

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 compared the cost-effectiveness of family presence versus no family presence. As stated, providers have identified the need for family support personnel,[32,33,36,38,43,47,48] and policies or protocols for family presence during resuscitation,[18,25,26,48] and specific provider training manage family presence during resuscitation.[48,49] All of these will require resourcing, and the cost effectiveness of this should be investigated.	

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 included studies addressed health equity in this setting.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	This will vary according to setting but overall the acceptability is 'probably yes'. Some of the apprehension apparent amongst some providers can be addressed with education and based policies or protocols around family presence.	The physical setting, cultural and social norms will impact upon this outcome for families and providers. Cultural and social norms will play a large part in the acceptability of this intervention.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Depending on the setting the feasibility varies. In the prehospital setting family presence is common and no action is needed. In the hospital setting the feasibility is dependent on resources and facilities.	Cultural and social norms influence the attitudes of both families and providers. In some settings, it may not be feasible for this intervention to be implemented based on these factors which may take time to change, if there is a desire to do so.

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 that family members be provided with the option to be present during in-hospital adult resuscitation from cardiac arrest. (weak recommendation; very low certainty of evidence)
- We suggest that family members be provided with the option to be present during out-of-hospital adult resuscitation from cardiac arrest acknowledging that providers are often not able to control this. (weak recommendation; very low certainty of evidence)
- Policies or protocols about family presence during resuscitation should be developed to guide and support healthcare professional decision-making. (Good Practice Statement)
- When implementing family presence procedures, healthcare providers should receive education about family presence during adult cardiac arrest resuscitation, including how to manage these stressful situations, family distress and their own responses to these situations. (good practice statement)

Justification

In making these recommendations, the Education, Implementation and Teams (EIT), the Basic Life Support (BLS), and the Advanced Life Support (ALS) Task Forces considered the following:

- Some of the participants in these studies may have cultural, religious or other sociological factors that can influence their attitudes and behaviors regarding family presence during adult resuscitation. The Task Forces considered the overall findings on patient, family and provider outcomes excluding these factors because none of the included studies investigated them.
- There will be a need for resuscitation councils to adapt the treatment recommendations to their local environments to meet the cultural, religious and sociological expectations of family presence during adult cardiac arrest resuscitation.
- The practice context (out-of-hospital versus in-hospital) can vary significantly in terms of attitudes and experiences of family presence during resuscitation, however establishing the overall impact on patient, family and provider outcomes was considered more important than isolating the findings to one setting.
- The nature of the cardiac arrest requiring resuscitation, or the characteristics of the patient (i.e. younger versus older adult, precipitating illness/ condition) were not reported in the included studies. Therefore, the Task Forces considered the overall findings on patient, family and provider outcomes in the absence of this information. . The age of family members viewing resuscitation may require further consideration especially when they are less than 18 years of age.
- There were only two RCTs comprising between 100-630 participants but these trials contained some methodological limitations.[6,42] Nonetheless, we acknowledge the difficulty in conducting an RCT in this setting where it would be unethical to stop a family member from being present or absent in these circumstances.
- In making the weak recommendations we considered the reported negative experiences of providers from a psychological and family management standpoint. However, we believe the implementation of provider education, and unit-based policies and protocols will address many of these issues.
- Provider education and unit-based policies or protocols were not directly examined in any of the studies, however two Good Practice Statements have been made based on the recommendations of the included studies and the absence of any evidence of harm.

- While none of the studies considered any other factors that may contribute to detrimental mental health outcomes following family witnessed resuscitation for family members or healthcare providers, there may be a need for education and/or structured follow-up regarding the possible long-term effects of witnessed resuscitation on these cohorts.

Subgroup considerations

As stated above, no consideration has been given to subgroups in arriving at the treatment recommendations, however future research should consider cultural, religious or other sociological factors as well as resourcing and setting factors.

Implementation considerations

- Cultural, religious or other sociological factors as well as practice context (out-of-hospital versus in-hospital) can influence attitudes and behaviors regarding family presence during adult resuscitation and these must be considered when implementing these Treatment Recommendations.
- The cost of policy or protocol development, education and resourcing (including staffing and infrastructure) must be considered when implementing the Treatment Recommendations.

Monitoring and evaluation

Following implementation of 'family presence during resuscitation' policies, ongoing monitoring of patient, family and healthcare provider outcomes should occur in order to ensure there is no detriment to any of these populations. This will allow for tailoring of provider educational opportunities and setting resourcing to ensure optimal outcomes.

Research priorities

Future research should focus on testing interventions such as provider training programs, use of family support persons and implementation of organisational guidelines and policies to reduce the individual decision burden, facilitate and operationalise care of families during adult resuscitation.

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QUESTION

Are alternative approaches to skills teaching superior to the 'Peyton 4 steps' approach?	
POPULATION:	Adults and children undertaking skills training related to resuscitation and First Aid in any educational setting.
INTERVENTION:	Approaches to skills teaching that are not the 'Peyton four-steps' approach. This includes: approaches without distinct stages: or modified 'Peyton four-steps' approaches with more or less than four steps; or with delivering one or more steps by alternative methods (e.g. video).
COMPARISON:	The 'Peyton four steps' approach for skills teaching.
MAIN OUTCOMES:	Improved educational outcomes: Skill performance after end of course; skill performance at end of course; participants' confidence to perform the skill on patients; participants' preference of teaching method. Patient outcomes: skills performed appropriately on real patient after the course Additional outcomes: Teachers' preference of teaching method; side effects of teaching
SETTING:	Any training of resuscitation skills
BACKGROUND:	The instructional approach for skills teaching is likely to impact later performance, and various methods have been described. Walker & Peyton proposed that a stepwise approach for skills teaching ('Peyton's 4 steps') would be more effective than other approaches (Walker 1998 171). Peyton's four-step approach is applied in the standard course formats of the ERC (Bullock 2000 139), the UK(RC), the Australian RC, and various National Resuscitation Councils in Europe. However, it is not clear in the literature whether a 4 step process is superior to modifications such as using less than 4 steps, or substituting single steps by e.g. video (Barelli 2010 1607), or to no sequencing (Gradl-Dietsch 2019 270). We decided to use 'Peyton's four steps' as the comparator since most studies regard 'Peyton's four steps' as the standard and compare alternative teaching approaches against it. Definitions: We use Walker & Peyton's definition of a 'stepwise approach' as a sequence of (a) 'demonstration' (of the skill, at normal pace, without commenting), (b) 'deconstruction' (of the skill, e.g., demonstration in slow motion, with detailed explanations for the learner with a special focus on critical steps), (c) 'comprehension' (by the learner, e.g., by explaining each step while talking the teacher through the skill), (d) 'performing and practicing' (of the skill by the learner, ideally until performance is sufficient).
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: Robert Greif and Andrew Lockey were excluded from data extraction and Risk of Bias assessment of one the studies as both were co-authors of this study [Greif 2010 1692]

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Evidence on how to conduct skills training for resuscitation is contradictory.	The teaching methodology of several Resuscitation Councils (e.g., the ERC and various NRCs) strongly focusses on the 'Peyton's four-step-approach' for skills training. However, it is known that many instructors do not adhere to the approach in practice. To bring this issue to a more evidence-based foundation, a systematic review of the literature appears important.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For the critical educational outcome of 'skill performance after 3 or more months' we found 5 studies (Risks of bias ranging from 'low' to 'serious', with very low certainty of evidence due to heterogeneity and imprecision). 4 studies showed no difference, and one found superior results of the group trained by a 4-step approach (in this study, 4 steps were one element of a bundle of 'best practice' strategies). For the important educational outcome of 'skill performance at end of course' (from end-of-course testing up to 2 months) we found 13 studies with differing Risks of Bias ranging from 'low' to 'serious' (certainty of evidence: very low). Overall, 11 studies did not show a difference between the groups and 2 studies found an advantage of 4-step approaches over 2-step approaches. For the important educational outcome of 'participants' confidence to perform the skill on patients' we found 5 studies. None of these studies showed differences between the groups.	While there is a solid justification in educational theory for 'Peyton's four-step-approach', literature suggests no (or very small) effects. A recent systematic review of the 'Peyton's four-step-approach' [Giacomino 2020 e10129] in respect to a wider range of skills in healthcare found a very small advantage of the four-step approach. However, some of the skills assessed had a significantly higher complexity than most of the skills related to resuscitation training. The main desirable effect of this review is to provide clear guidance for instructor courses in the field of resuscitation how to best teach skills (such as chest compressions, or airway control). In addition, it might be a possibility that skills training could be shortened since one study spent 20% less time for training when using a two-step approach (Bjornshave 2018 18).

	For the important educational outcome of 'participants' preference of teaching method' we found 3 studies. One study reported preferences for the 4-step approach as compared to 2 steps. For the critical clinical outcome of 'skills performed appropriately on real patient after the course' we did not find any study.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No negative effect reported	

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	<table><tr><th>Outcome</th><th>Certainty of evidence</th></tr><tr><td>Patient outcomes</td><td>-</td></tr><tr><td>Educational outcomes at ≥ 3 months</td><td>Very low</td></tr><tr><td>Educational out-comes end-of-course to 3 months</td><td>Very low</td></tr><tr><td>Confidence to per-form skill on pat.</td><td>Very low</td></tr></table>	Certainty of evidence is limited by many factors, mainly due to high heterogeneity of the studies and missing information for important confounders. Heterogeneity was significant • for the nature of skills studied (manual defib.:1, BLS/AED:2, BLS: 2; chest compressions (only): 3, naso-gastric tube: 2, iv-canulation: 1, NLS: 1, ATLS: 1, needle cricotomy: 1, laryngeal mask: 1, endotracheal intubation: 1), • skill complexity, and • populations (novice medical students, advanced medical students, nursing students, mixed HCP groups, and laypersons).

	Preference of teaching method: Very low	Regarding missing information on important confounders, none of the studies assessed the individual instructional quality of intervention and control (i.e., instructors' individual teaching performance). Therefore, instrumentation biases cannot be ruled out. Only 5 studies addressed a critical educational outcome. For all these studies, we noted relevant limitations. Finally, no studies addressing outcome at the patient level were found.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ mportant uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	none	More clarity for appropriate teaching strategies will be valued by instructors and by faculty of instructor courses.

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	undecided	Instructors and faculty of instructor courses might experience more freedom in tailoring their teaching strategies to the needs of course participants.

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	Brings opinion-driven discussions to a more scientifically based point. Teaching in instructor courses will be simplified. No specific resources required. As course material and instructor courses should be regularly revised and updated to the most recent evidence, results will be included within the natural updating process.

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	

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 direct influence on cost-effectiveness	Is likely to settle discussions on the specific type of teaching strategy. Thereby, discussion time in instructor courses could be saved, and teaching be focussed on more important content.

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	N/A	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	none	Will probably be well accepted. It appears important to emphasise that instructors should use (appropriate) stepwise approaches for skills teaching. If not, we see the risk of instructors paying too little attention to the way how skills are taught (laissez-faire). None of the studies included addressed the individual teaching quality of instructors. Developing this individual component of teaching quality might be much more important to the quality of courses and should be paid more attention to as an important moderator of teaching success.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	None	Easy 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
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

For resuscitation skills training there was no evidence that four-step approach as proposed by Walker & Peyton was superior to other approaches. Stepwise teaching of skills is well founded in educational theory and we suggest that this should remain a cornerstone of instruction (weak recommendation, very low certainty of evidence).

Justification

In making the recommendation, the EIT task force considered the following:

- We acknowledge a solid foundation of stepwise training approaches in educational theory.
- The optimal stepwise training approach (including the number and type of steps) may be dependent on the type of skills taught. A variation of the number and kinds of steps should be adapted to the nature of the skill taught.
- The two studies showing advantages of the Walker & Peyton's four-step approach compared it to 'two-steps' approaches. These 'two-steps' approaches appear to have little educational structure and should be regarded as non-stepwise approaches. We do not support the use of non-stepwise training approaches.
- Putting less emphasis on the need of 4-step training approach will prompt instructors and faculty of instructor courses to consider tailoring their teaching strategies to the needs of course participants. Therefore, the findings conclusion of this systematic review will be easy to implement into instructor courses with little to no costs.
- Most of the studies were conducted with health care students of various professions. It is possible that the results may not be translated to other learner populations (e.g., children)
- None of the studies identified controlled for the teaching quality of individual instructors although it is well established that individual teaching quality has most probable a stronger impact on learning as the method applied.
- We recognize the risk that instructors may move away from all types of stepwise training approaches. Instructor training should therefore continue to emphasize the importance of stepwise training approaches.
- Finally, we did not identify studies investigating effects on course participants' performance on real patients.

Subgroup considerations

We conducted no subgroup analysis

Implementation considerations

To be easily implemented into instructor courses. However, we anticipate the risk that instructor courses put less focus on the importance of stepwise skills teaching. Stepwise teaching of skills is well founded in educational theory and should therefore be a cornerstone of instruction.

Monitoring and evaluation

n.a.

Research priorities

Knowledge gaps identified in the published literature include

- The quality of the individual teacher performance should be controlled for in future studies,
- Unified reporting of educational outcomes should be established,
- Future studies should consider learning needs of different participants and how stepwise training approaches should be adapted (e.g., children, or elderly).
- While studies addressing effects on participants' performance on real patients appear unlikely to be feasible, those would however, be of specific importance. It would be desirable to at least find adequate surrogates at the patient level.

Supplemental Tables EIT

Table EIT-S1: Outcomes on patients, family, and health care providers, when family members are present during resuscitation of adult patients after cardiac arrest.

<table>
<tr><td colspan="5">1. Patient Outcomes (short and long term)</td></tr>
<tr><td>12 studies (including 6 - 1525 patients)[7-11,18,23,25,26,30,33,35]</td><td colspan="3">Impact of family presence versus no family presence during resuscitation:
4 of 12 studies reporting patient outcomes and found no significant difference to ROSC based on family presence.
• 1 study found significantly lower unadjusted (p=0.04) and adjusted (p=0.03) rates of survival to discharge when families were present.[8]
• 3 identified no significant difference in survival based on family presence[7,9,23]
• 2 studies investigating out-of-hospital[7] and in-hospital[23] resuscitation reported on survival to admission, 28-days and 30-days and found no significant difference between groups for survival.[7]</td><td>No consideration of family presence on overall survival:
8 of 12 studies reported only overall survival but did not account whether family were present or absent.[10,11,18,25,26,30,33,35]</td></tr>
<tr><td colspan="5">2. Family Outcomes (short and long term)</td></tr>
<tr><td>15 studies (including 5 - 570 family members)[6,7,10-14,22,24-27,30,33,35]</td><td>Depression:
Very conflicting results for depression in family members present during resuscitation:
• 1 study reports witnessing resuscitation of a family member as independent predictor of depression at 90-days,[10]
• 2 others reported fewer symptoms of depression at 30- and 90-days.[7,11]
• 1 study examining 30-day outcomes, found no significant difference in depression[12]</td><td>Anxiety: 3 studies
• 2 studies found witnessing a resuscitation was associated with less anxiety[10,11]
• 1 found fewer anxiety-related symptoms in those who witnessed resuscitation.[7]</td><td>Post-traumatic stress disorder (PTSD) symptoms:
• Two studies reported fewer PTSD symptoms at 90-days in family members who witnessed resuscitation.[7,11]
• Conversely, two other studies identified significantly higher PTSD symptom scores at 79-84 days[22] and increased arousal at 60 days in those who witnessed resuscitation of a family member.[12]
• In the latter study, no significant difference was seen in other PTSD symptoms such as re-experiencing or</td><td>Family member experience of witnessing resuscitation:
• The experience of family members present during resuscitation was investigated in nine studies.[13,14,24-27,30,33,35]
• Two quantitative studies reported that almost all respondents stated they would witness the resuscitation again,[13,14] that they believed it enabled them to better manage their grief[13], and adjust to their family member's death.[14]
• These findings were reflected in a mixed-methods interview study that found all witnesses of resuscitation of a family</td></tr>
</table>

			avoidance or depression symptoms.[12]	member thought it was important and helpful to be present.[33] • Two of three studies that questioned respondents about regret and found that very few[7,30] family members regretted being present, whereas one small study reported 3 of 5 family members interviewed regretted being present.[27] • One RCT reported that few of those who were not present during the resuscitation regretted being absent.[7] • 3 studies reported negative outcomes and found that family members who witness resuscitation found it brutal and dehumanizing,[24] distressing[24,26], and were concerned about having incomplete knowledge of the resuscitation.[26] • Two studies reported family members felt the resuscitation was too long[14] with an excessive or unnecessarily heroic approach to resuscitation.[24] • Family members who witnessed resuscitation reported being afraid of disrupting or interfering with the resuscitation process[26] or losing emotional control.[26]
3. Healthcare Provider Outcomes				

20 studies reported on provider outcomes (including 6 - 1710 providers)[6,7,13-21,23,28-34,36]	**Provider experience with family presence during resuscitation:** 7 quantitative studies[15,17-20,35] 6 qualitative studies[28,29,31,32,34,36] • Prevalence of provider experience with family presence during resuscitation ranged from 35% to 63%.[15-17] • Providers reported having little experience with inviting family members to be present[16,19,20] and this was more likely in critical areas than in general wards.[23] • Providers reported few positive or negative experiences with family presence during CPR in four quantitative studies.[16,17,19,20] • The qualitative studies reported positive experiences grounded in caring for the family.[29,32,34,36] • Negative experiences stemmed from aggressive or disruptive family members and provider concerns about psychological trauma for family members due to negative, visually distressing images of the resuscitation.[32,34]	**Factors influencing provider experience of family presence during resuscitation:** • Internal conflicts and emotional factors influencing provider experience of family presence during resuscitation included the need to balance compassionate care and technical competence,[34,36] professional practice and responsibilities,[34] and the shift from patient to family care and guilt associated with resuscitation termination.[29] • 1 study identified that experience alone was not sufficient for effective family support.[29] • 6 studies claimed the need for provider training for managing family presence, a support person for families and unit based policies or protocols for family presence during resuscitation.[15,18-20,29,31]	**Provider perceptions of family presence during resuscitation:** • Around three-quarters of providers supported family presence during resuscitation[14,33] • Up to 68% believe their function during resuscitation was not impaired by family presence.[13,14] • 2 qualitative studies identified negative provider perceptions of family presence during resuscitation, reporting that a minority felt family may hinder clinical performance and interrupt care[15] or interfere with care and negatively impact team communication[18] • 1 study investigated provider anxiety. Mean anxiety was higher in providers who had family witnessing resuscitation compared to providers who carried out resuscitation without family witnessing the process.[6] • 2 studies investigated stress. No difference was found in stress levels for either study reporting provider stress.[7,21]

Table. EIT S-2 Characteristics of included studies in the scoping review : Disparities in layperson resuscitation education

Reference (Country)	Methods	Study period	Participants	Enablers	Barriers	Key findings
Jensen 2022 (Denmark)[77]	Retrospective registry-based cohort study	2016 to 2019	All Danish BLS course participants during study period (N=704,640)	Male Healthy status Living in a rural area	Having small children in the household	1. Compared with the general population, BLS course participants were commonly younger (mean 31.3 years old vs. 51.3 years old, $p < 0.001$), and were less affected by chronic illness (male OR: 0.92, 95% CI: 0.89–0.94; female OR: 0.75, 95% CI: 0.73–0.76) 2. Participants in the BLS courses tended to live in rural areas with a

						lower degree of urbanization scores (DEGURBA). 3. Compared with those with no children, females with children aged 0–3 years were 0.83 times less likely to participate in a BLS course (OR: 0.83, 95% CI: 0.83–0.84), and the same effect was found in males (OR: 0.88, 95% CI: 0.88–0.89).
Andréll 2021 (Sweden)[65]	Cross-sectional web survey	08/07/2019 to 16/07/2019	Adult non-healthcare professionals respondents in Skåne County, Sweden (N=910)	Working age Female University education		1. Working age (18-65 years) and university education were associated with higher rate of CPR training during the last five years, with an OR of 4.91 (95% CI: 3.50-6.87) and 1.35 (95% CI: 1.01-1.81), respectively. 2. Male gender was associated with lower rate of prior CPR training during the last 5 years, with an OR of 0.73 (95% CI: 0.55-0.97).
Cartledge 2020 (Australia)[70]	Nationwide cross-sectional questionnaire survey	July 2017	Adult Australian respondents (N=1076)	Middle age (35-54 years) Born in Australia Higher levels of education		CPR training was associated with age (35 to 54 years) (compared with 18-34 years, OR 1.45, 95% CI: 1.06 to 2.0), being born in Australia (OR 1.59, 95% CI: 1.17 to 2.17) and higher levels of education (university, compared with high school or less. OR 1.86, 95% CI: 1.35 to 2.57), and older age group (>75 years) were least likely to be trained.
Teng 2020(China)[83]	Cross-sectional questionnaire survey	12/2018 to 12/2019	Healthy individuals in the city of Guangdong, who accompanied their relatives with heart disease to the outpatient department of cardiovascular disease (n=1644) and systemically healthy patients who came for regular ophthalmic examination and had no known relatives with heart	Higher education attainment	Lower income level	1. Higher education attainment was associated with a higher rate of CPR training, with an OR of 2.12 (95% CI: 1.45–3.23) for college or higher compared to high school education. 2. Lower income level was correlated with less CPR training experience, for less than $5,000/year compared with more than $50,000/year (OR 0.47, 95% CI 0.24 to 0.92; p=0.028).

			disease (n=813). (Total valid participants, N=2457)			
Alexander 2019 (US)[63]	Nationwide cross-sectional questionnaire survey	09/2015 to 11/2015	Nationally-representative adult respondents in the US (N=8345)	Younger Graduate from high school Laws requiring school-based training		1. Younger age (OR: 1.34, 95%CI: 1.20–1.50, p < 0.01), and graduation from high school (OR: 3.35 (95%CI: 2.08–5.39), p < 0.01) were associated with a higher likelihood of current CPR training. 2. Adults in states with required school-based training were 34% more likely to be currently trained than were individuals in states without required training (OR: 1.34, 95%CI: 1.20–1.50, p < 0.01) 3. Among respondents 18-24 years old, those in states with required school-based training for high school graduation were 81% more likely to be currently trained (OR: 1.81, 95%CI: 1.18–2,78, p = 0.01)
Hawkes 2019(UK)[75]	Online questionnaire survey	May 2017	Participants of online survey in the UK(N=2084)	Youth (18-34 years) Female, Married or living as married Employment Higher social grades, Full-time students Witnessed OHCA		1. Women, married or living as married, higher social grades, employed, full-time students, and witnessed OHCA were more likely to have trained in any type of resuscitation techniques (CPR (CO-CPR and/ or CPR) and/or Defibrillator Use) (OR: 1.25 (95%CI: 1.04–1.50), 1.37 (1.13–1.66), 1.25 (95%CI: 1.03–1.51), 1.57 (95%CI: 1.29–1.91)), 2.39 (95%CI:1.57–3.65), 2.60 (2.00–3.37). 2. Younger people were more likely to have trained than older people in the past 5 years (OR 1.63, 95%CI: 1.27–2.08).
Abdulhay 2019 (US)[62]	Cross-sectional cohort study	07/2016 to 04/2018	Survey respondents of adult laypersons in Philadelphia (USA) who participated in a community CPR training with The	Higher educational attainment Higher median household income (MHI)		1. Higher educational attainment was associated with a higher likelihood of prior CPR training (OR: 7.96 Master's or Doctoral compared to less than high school, 95%CI: 5.24–12.11, p < 0.001). 2. The average of the MHI was $4938 higher in subjects who previously received CPR training compared to those with no past training (p < 0.001).

			Mobile CPR Project. (N=1703)			
Owen 2018 (US)[81]	Nationwide cross-sectional questionnaire survey	09/2015 to 11/2015	Nationally-representative adult respondents in the US (N=9022)	Higher educational attainment	Hispanic/Latino Older	1. Whites and Blacks were more likely to have AED training compared to Latinos (OR: 1.90, 95%CI: 1.43–2.53 and OR: 1.73, 95% CI: 1.39–2.15, respectively) 2. Higher educational attainment was associated with an increased likelihood of training, with an OR of 4.36 (95% CI: 2.57–7.40) for graduate school compared to less than high school education. 3. Increased household income was not associated with an increase in AED training (p = .08). 4. Increased mean age was less likely to have AED training. (OR: 0.98, 95% CI: 0.97-0.98)
Dobbie 2018 (UK)[72]	Cross-sectional questionnaire survey	05/08/2015 to 10/08/2015	Survey respondents in Scotland (N=1027)	Younger Higher social grade		The likelihood of completed CPR training differed by age (p<0.001), and the younger population had higher prior training experience. Respondents with professional, managerial and non-manual occupations (ABC1) were more likely to have been trained than those in manual, unskilled occupations and the long-term unemployed (C2DE) (57% ABC1 vs. 48% C2DE, p<0.01).
Birkun 2018 (Russian Federation)[68]	Cross-sectional questionnaire survey	11/2017 to 01/2018	Adult respondents of the survey in the Crimean Peninsula (N=384)	Male University education Employment Student		Males (OR: 1.7, 95% CI: 1.1-2.6), those having had a university education (OR 2.4, 95% CI: 1.5-3.8), employed (OR: 2.7, 95% CI: 1.6-4.4) and students (OR: 6.9, 95% CI 2.5-19.2) were found to be associated with previous training in CPR.
Blewer 2017(US)[69]	Nationwide cross-sectional questionnaire survey	09/2015 to 11/2015	Nationally-representative adult respondents in the US (N=9022)		Older Lesser educational attainment Lower household income Hispanic/Latino	1. For each year of increased age, the likelihood of being currently CPR trained or ever trained decreased (currently trained: OR: 0.98, 95% CI: 0.97–0.99, p<0.01; ever trained: OR 0.99, 95% CI: 0.98–0.99, p=0.04). 2 Respondents who were graduate school educated or more had an OR of 3.36 (95% CI: 1.60–7.09) increased likelihood of being currently CPR trained (within two2 years) compared with those who had less than a high school education (p<0.01).

						3. Hispanic/Latinos, compared with whites, were less likely to be ever trained in CPR. (OR: 0.44, 95% CI: 0.37–0.52)
Bakke 2017 (Norway)[67]	Cross-sectional telephone survey	04/2014	Interviewees in Norwegian (N=1000)	Younger Male		Interviewees with first aid training were younger (mean 44 vs 56 years, p < 0.01), and men were more likely than women to be trained (91% vs 85%, p = 0.02).
Anderson 2014 (US)[64]	Retrospective registry-based study	07/01/2010 to 06/30/2011	People received CPR training in 3143 US counties. (N=13,123,113)		Living in a rural area Black Hispanic Lower income	1. For every 5 percentage point increase in the rural population composition, the odds of being in a lower tertile county with CPR training rates increased (OR: 1.12; 95% CI: 1.10-1.15) 2. For every 5 percentage point increase in the proportion of black race or Hispanic ethnicity residents, the adjusted OR of being in a lower tertile county with CPR training rates was 1.09 (95% CI: 1.06-1.13) and 1.06 (95% CI: 1.02-1.11), respectively. 3. For every $10,000 decrease in median household income, the adjusted OR of being in the lower tertile with CPR training rates was 1.18 (95% CI: 1.04-1.34).
Chair 2014 (China)[71]	Cross-sectional telephone survey		Respondents in Hong Kong aged from 15 to 64 years. (N=1013)	Full-time jobs Higher levels of education		Having full-time employment (OR=2.2, 95%CI: 1.6-3.1; p<0.001), middle level education—Form 4-7/technical institute (OR=2.3, 95%CI: 1.5-3.6; p<0.001), and a high level of education- college or higher (OR=2.7, 95%CI: 1.7-4.2; p<0.001), were significantly associated with having CPR training.
Meischke 2012 (US)[80]	Cross-sectional in-person interview survey	02/2010 to 07/2010	Cambodian participants in the city of Seattle (N=667)	Greater fluency in English	Fewer years of education Less proportion of life in the US	Participants with the most education, greatest fluency in English, and increased proportion of life in the US were more likely to have received CPR training than those with less education, limited English proficiency, and less proportion of life in the US. (p<0.01)
Sipsma 2011 (US)[82]	Cross-sectional	September 2008	Randomly selected residents in King County,		Older Male Less than a 2-	People who had never been trained in CPR were older(p<0.001), more likely to be men(p=0.001) and more likely to have less than a

	telephone survey		Washington (N=1,001)		year college degree	2-year college degree(p=0.001) than those who had ever been trained.
Jennings 2009 (Ireland)[76]	Cross-sectional questionnaire survey	2008	Survey respondents in Ireland (N=974)		Age over 65 years of age Lower social classes	Respondents over 65 years of age and those from lower social classes were significantly less likely to be trained (p < 0.0001) though no gender difference.
Kuramoto 2008 (Japan)[78]	Cross-sectional questionnaire survey	08/2006	Survey respondents in Japan (N=1132)	Younger Office or skilled workers Having a driver's license Experience with witnessing a collapsed person Aware of AED in public places		Younger age (<60 years of age) (OR: 1.6, 95% CI: 1.2-2.1), office worker or skilled worker (OR: 1.5, 95% CI: 1.1-2.0), having a driver's license (OR: 1.7, 95% CI: 1.2-2.4), having witnessed collapsed persons (OR: 1.5, 95% CI: 1.1-2.0), and awareness of AEDs often in public spaces (OR: 2.1, 95% CI: 1.4-3.1) were independently associated with having trained in CPR.
Hatzakis 2008 (Greece)[74]	Cross-sectional questionnaire survey		Adult respondents of the survey in the city of Heraklion, Greece. (N=390)	Younger Tertiary education		Younger age (OR: 0.96 for a unit increase in age, p < 0.01) and tertiary education (OR: 3.13, p = 0.01) were found to be significantly and independently associated with increased odds of participation in CPR training programs.
Axelsson 2006 (Sweden)[66]	Cross-sectional questionnaire survey	05/2000 to 08/2000	Survey respondents in Sweden (N=3167)	Younger Living in rural areas Born in Sweden Employees Students and		CPR training was associated with younger age (≤46 years(median)) (53.4% vs 5.8%, p<0.0001), living in a rural area (46.8% vs 40.7%, p<0.0001), being born in Sweden (46.6% vs 30.7%, p<0.0001) and in employees, students and military conscripts (<0.0001).

				military conscripts		
Flabouris 1996 (Australia)[73]	Retrospective analysis	1989-1991	CPR class attendances in Australia(N=15476)		Southern European-born (SEB) South East Asian born (SEAB) Poor proficiency in English (PENG)	Postcodes with a less than the community average of SEB, SEAB and PENG had an average proportion of CPR class attendees of 2.64% (95%CI: 2.43-2.85), 2.54% (95%CI: 2.35-2.73) and 2.65% (95%CI: 2.35-2.73) respectively, whilst those postcodes with a greater than community average had 2.03% (95%CI: 1.90-2.16), 2.07% (95%CI: 1.90-2.24) and 2.04% (95%CI: 1.90-2.18) proportion of CPR class attendees. (Significant difference in each category, $p<0.001$)
Lejeune 1987 (Belgium)[79]	Cross-sectional questionnaire survey	1980	Random sample of citizen who did not participate CPR training session. (N=600)		Older	The older the person, the less prone they are to participate in CPR training ($p < 0.05$).