

National Institute for Health and Care Excellence

IP863/2 Temperature control to improve neurological outcomes after cardiac arrest

IPAC date: 9th November 2023

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response
1	Consultee 1 Becton Dickinson Company	Overview page 9	"Study 2 has since been updated as follows: ILCOR meta-analysis and the citation is Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW; International Liaison Committee on Resuscitation ILCOR Advanced Life Support Task Force. Temperature control after adult cardiac arrest: An updated systematic review and meta-analysis. Resuscitation. 2023 Aug 7;191:109928. doi: 10.1016/j.resuscitation.2023.109928. Epub ahead of print. PMID: 37558083."	Please respond to all comments Thank you for your comments. Study 2 in the overview has been updated.
2	Consultee 2 Resuscitation Council UK	1	"The Resuscitation Council UK (RCUK) is pleased to see the updated recommendations but wishes to make some further comments. 1.1. The RCUK welcomes this updated draft recommendation making fever prevention the standard of care. 1.3. This draft recommendation is unchanged – RCUK previously suggested that this be changed to SPECIAL arrangements given this remains part of standard practice in many settings globally, is used by some UK centres and remains part of European guidelines. In the final paragraph, we wish to highlight that the risk of harm is relatively small given the high risk scenario being treated, and that RCTs showed no harmful effect on overall outcomes. The main reasons for guidelines preferring and recommending fever prevention over hypothermia is	Thank you for your comments. IPAC chair considered your comments about unchanged draft recommendation in 1.3, the risk of harm and the reasons for guidelines recommending fever prevention over hypothermia. The chair noted that there is no evidence to support this intervention and states that there are safety issues associated with the procedure. "that it requires less intervention to achieve and fewer safety issues follow from this." count as safety issues associated with the procedure

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			that it requires less intervention to achieve and fewer safety issues follow from this."	
3	Consultee 2 Resuscitation Council UK	Overview page 9, 37, 41	<p>"1. In Table 2: The Granfeldt 2021 systematic review which is the International Liaison Committee on Resuscitation expert review has been updated – in the discussion there is an explanation as to why the outcomes in this SR are different to those in the Cochrane review based on interpretation and inclusion of studies: open access at https://www.resuscitationjournal.com/article/S0300-9572(22)00684-0/fulltext</p> <p>2. For International Liaison Committee on Resuscitation (ILCOR): International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations – for adult advanced life support (2022) the hyperlink is incorrect and opens the wrong webpage. The correct webpage to link to is https://www.resuscitationjournal.com/article/S0300-9572(22)00684-0/fulltext</p> <p>3. UK post resuscitation care guidelines should state Resuscitation Council UK post resuscitation care guidelines - these have now been aligned with the ERC-ESICM guidelines (there had been a delay in doing these), but all RCUK guidelines align with ERC guidelines. These now read:</p> <ul style="list-style-type: none"> • Continuously monitor core temperature in patients who remain comatose after ROSC. • Actively prevent fever (defined as a temperature > 37.7°C) for at least 72 h in post-cardiac arrest patients who remain comatose. <p>More recently the European Society of Cardiology - 2023 ESC Guidelines for the management of acute coronary syndromes. European Heart Journal (2023) 00, 1–107 https://doi.org/10.1093/eurheartj/ehad191 includes</p>	<p>Thank you for your comments.</p> <ol style="list-style-type: none"> 1. Study 2 in table 2 is updated in the overview. 2. The hyperlink for ILCOR is corrected and updated in the overview. 3. RCUK post resuscitation care guidelines is updated in the overview. 4. ESC guidelines for management of acute coronary syndromes is added to the overview.

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			Temperature control (i.e. continuous monitoring of core temperature and active prevention of fever [i.e. >37.7°C]) is recommended after either out-of-hospital or in-hospital cardiac arrest for adults who remain unresponsive after return of spontaneous circulation. Alas 1 Level B recommendation."	
4	Consultee 3 Lead author of Cochrane review	2.4	I am not sure if its accurate to say that the mechanisms by which cooling may protect against brain injury are unknown. Several Neuroprotective mechanisms of hypothermia in brain ischaemia could be identified (Yenari et al. Nat Rev Neurosci 2012 and many others).	Thank you for your comment. IPAC chair considered your comment and amended section 2.4 as follows ' <i>The aim is to reduce brain injury and improve neurological outcomes. The exact mechanism by which cooling may protect against brain injury is unclear. Possible mechanisms include reductions in metabolic demand, release of excitatory neurotransmitters and inflammation after ischaemia</i> '.
5	Consultee 3 Lead author of Cochrane review	3.6	I know that this recommendation has been there for a longer period of time but maybe it is the time to and I feel that it is once more important to comment on it. Temperature control in the prehospital setting with large volumes of intravenous saline has shown to lead to an increased number of signs of pulmonary edema the chest x-ray. These findings were not followed by any clinical side effect and resolved on the following chest x-rays. I am not sure if this constitutes a "serious side effect".	Thank you for your comment. IPAC chair considered your comment and amended section 3.6 as follows ' <i>Using large volumes of intravenous saline to induce therapeutic hypothermia before admission to hospital can cause side effects such as pulmonary odeoma</i> '.
6	Consultee 3 Lead author of Cochrane review	Overview	May I please inform the committee that there are at least two upcoming multicenter RCTs: The PRINCESS 2 trial (https://ki.se/en/kisos/princess-2) and the EARLY-33 trial (Early well-controlled hypothermia at 33°C for 48 hours vs temperature control with fever prevention after out-of-hospital cardiac arrest, a randomized controlled multicenter study; 13 sites recruited, Medical University of Vienna, PI Wilhelm Behringer).	Thank you for your comments. The ongoing RCTs are added to the overview.

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			The latter has not been listed in clinicaltrials.gov, yet so may only be known by experts in the field.	
7	Consultee 3 Lead author of Cochrane review	Table 2 study 8	I would like to point out that it is not correct that the Cochrane review only included 10 studies. This is important as with 12 included studies it is the most comprehensive of all systematic reviews.	Thank you for your comments. The updated Cochrane review with 12 studies was included in the overview of evidence.
8	Consultee 3 Lead author of Cochrane review	Table 2 study 8	The Cochrane review was an updated review covering all literatures searches from previous versions. In contrast to the main text of the consultation document, all studies from inception of the databases up to September 2022 were included.	Thank you for your comments. The updated Cochrane review with 12 studies was included in the overview of evidence.
9	Consultee 3 Lead author of Cochrane review	Table 2 Study 8	Table 2 states that age was not reported in the Cochrane review, which is not correct. The mean age of participants of all included studies can be found in the Characteristics of studies table.	Thank you for your comments. Mean age of the participants of all included studies in the Cochrane review is included in study 8 in the overview.
10	Consultee 3 Lead author of Cochrane review	Study 8 in overview	<p>It seems that some of the subgroups that were analysed in the Cochrane review are missing in the table (but were reported for the other reviews):</p> <ul style="list-style-type: none"> 3.1 Cause of cardiac arrest 3.2 Location of cardiac arrest 3.3 Primary cardiac rhythm 3.4 Witnesses cardiac arrest 3.5 Bystander cardiopulmonary resuscitation rate 3.6 No-flow time 3.7 Duration of hypothermia 3.8 Time interval from return of spontaneous circulation (ROSC) to intervention 	Thank you for your comments. Relevant subgroup analysis (such as 'duration of hypothermia') from the Cochrane review is added to the overview.

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			They could provide important additional information on a possible dose response of the intervention and possible variations of the effect size in different subpopulations of cardiac arrest patients.	
11	Consultee 3 Lead author of Cochrane review		There is a systematic review and network meta-analysis specifically on the topic of methods of TTM which you might want to consider: Endovascular versus surface cooling methods - please consider this publication: Intravascular Versus Surface Cooling in Patients Resuscitated From Cardiac Arrest: A Systematic Review and Network Meta-Analysis With Focus on Temperature Feedback (Ramadanov et al. Crit Care Med. 2022 PMID: 35089906)	Thank you for your comments. This study has already been included in table 5 (additional relevant studies)
12	Consultee 3 Lead author of Cochrane review	Study 8 in overview	Please also consider the subgroup analysis 3.8. in the Cochrane review subgroup analyses of cardiac arrest conditions, Outcome 8: Time interval from return of spontaneous circulation (ROSC) to intervention. RCT that started temperature control within 2 hours of ROSC had a 57% higher chance for a good neurologic outcome (95% CI 1.27-1.94). All other RCTs (delays not reported and presumably longer) did not show an effect.	Thank you for your comments.
13	Consultee 4 Secretary European society for emergency medicine	1.1	"It is important to note that retrospective studies have consistently demonstrated significant benefits among a substantial subset of patients with presumed moderate brain damage who underwent hypothermia in the range of 32-34°C. Ref: Böttiger BW, Hellmich M, Wetsch WA: The effectiveness of targeted temperature management following cardiac arrest may depend on bystander cardiopulmonary resuscitation rates. Eur J Anaesthesiol 2022, 39(4):401-402. Testori C, Sterz F, Holzer M, Losert H, Arrich J, Herkner H, Krizanac D, Wallmuller C, Stratil P, Schober A et al: The beneficial effect of mild therapeutic	Thank you for your comments. Arrich 2023 is already included in table 2 in the overview. Evidence from retrospective studies was not considered in this rapid review of evidence. The assessment was based on systematic reviews and meta-analyses and RCTs.

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			<p>hypothermia depends on the time of complete circulatory standstill in patients with cardiac arrest. Resuscitation 2012, 83(5):596-601.</p> <p>Duan J, Zhai Q, Shi Y, Ge H, Zheng K, Du L, Duan B, Yu J, Ma Q: Optimal Time of Collapse to Return of Spontaneous Circulation to Apply Targeted Temperature Management for Cardiac Arrest: A Bayesian Network Meta-Analysis. Front Cardiovasc Med 2021, 8:784917.</p> <p>Okazaki T, Hifumi T, Kawakita K, Kuroda Y: Targeted temperature management guided by the severity of hyperlactatemia for out-of-hospital cardiac arrest patients: a post hoc analysis of a nationwide, multicenter prospective registry. Ann Intensive Care 2019, 9(1):127.</p> <p>Nishikimi M, Ogura T, Nishida K, Hayashida K, Emoto R, Matsui S, Matsuda N, Iwami T: Outcome Related to Level of Targeted Temperature Management in Postcardiac Arrest Syndrome of Low, Moderate, and High Severities: A Nationwide Multicenter Prospective Registry. Crit Care Med 2021, 49(8): e741-e750.</p> <p>Callaway CW, Coppler PJ, Faro J, Puyana JS, Solanki P, Dezafulian C, Doshi AA, Elmer J, Frisch A, Guyette FX et al: Association of Initial Illness Severity and Outcomes After Cardiac Arrest With Targeted Temperature Management at 36 °C or 33 °C. JAMA network open 2020, 3(7): e208215.</p> <p>Nutma S, Tjepkema-Cloostermans MC, Ruijter BJ, Tromp SC, van den Bergh WM, Foudraine NA, Kornips FHM, Drost G, Scholten E, Strang A et al: Effects of targeted temperature management at 33 °C vs. 36 °C on comatose patients after cardiac arrest stratified by the severity of encephalopathy. Resuscitation 2022, 173:147-153.</p>	

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			<p>Additionally, the most recent meta-analyses conducted by Cochrane, encompassing randomized clinical trials, have indicated that therapeutic hypothermia in the range of 32-34°C as compared to normothermia or no temperature control is associated with improved neurologic outcomes.</p> <p>Ref: Arrich J, Schütz N, Oppenauer J, Vendt J, Holzer M, Havel C, Herkner H: Hypothermia for neuroprotection in adults after cardiac arrest. Cochrane Database Syst Rev 2023, 5(5): Cd004128.</p> <p>Furthermore, it is noteworthy that no study has reported any detrimental effects of maintaining hypothermia on either neurological or overall outcomes. Therefore, the entirety of scientific evidence endorses the suggestion to promptly initiate hypothermia within the range of 32-34°C as soon as it is practically achievable and to sustain this temperature range for a minimum duration of 24 hours in all adult cardiac arrest patients who remain comatose."</p>	
14	Consultee 5 Department of Anaesthesiology and Intensive Care Medicine University of Cologne		No comments Agree with the recommendations.	Thank you.
15	Consultee 6 Company ZOLL Medical		No comments, agree with recommendations.	Thank you.

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