National Institute for Health and Care Excellence

IP1784 Maintaining normothermia using temperature modulation devices to improve outcomes after stroke or subarachnoid haemorrhage

IPAC date: 13 May

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS professional British Association of Stroke Physicians	**2.1**	Definition of stroke used is historic and should be updated to that recommended by the AHA/ASA (Sacco R et al. Stroke. 2013;44:2064-2089)	Thank you for your comment. In line with NICE CG168, the definition of stroke has been changed to: "*stroke is an acute neurological event presumed to be vascular in origin and causing cerebral ischaemia, cerebral infarction or cerebral haemorrhage*."
2	Consultee 1 NHS professional British Association of Stroke Physicians	**2.2**	Uncertain what "interrupt blood flow around or inside the brain" means?	Thank you for your comment. Section 2.2 has been changed to: "*Both conditions can interrupt blood flow **to** the brain, damage brain cells and cause abnormalities of thermoregulation and an abnormal body temperature (a non-infectious fever)…"*
3	Consultee 1 NHS professional British Association of Stroke Physicians	**2**	The distinction between hyperthermia and fever should be made early on, as should the distinction between brain v core (body) temperature, before embarking upon the cooling devices. It would be useful to provide a rationale by citing literature suggesting that fever is associated with worse outcome in patients with acute stroke/ brain injury. Also what is normothermia defined as?	Thank you for your comment. Section 2.2 has been changed to: *"Both conditions can interrupt blood flow **in** the brain, damage brain cells and cause abnormalities of thermoregulation and an abnormall**y high** body temperature (**neurogenic** fever). The abnormall**y high** temperature may result in*

				*secondary neurological injury and is associated with **worse outcomes,** greater morbidity and mortality."* The temperature range for normothermia has been added to section 2.4: *"In this procedure, a temperature modulation device is used to maintain the patient's core temperature within normal limits **(37.0±0.5ºC)**…"*
4	Consultee 1 NHS professional British Association of Stroke Physicians	**Overview**	In the RCT of 102 patients undergoing endovascular cooling, what was the primary outcome measure and was there a sample size calculation? What was conventional fever management? What patients were included (just says "with cerebrovascular disease")	Thank you for your comment. The overview provides more details about individual studies (e.g. Broessner et al., 2009).
5	Consultee 1 NHS professional British Association of Stroke Physicians	**Overview**	For "Neurological outcomes", it is difficult to interpret the GOS (and the other outcomes which follow) without knowing more about the included patients e.g. type of stroke, severity, other interventions e.g. thrombectomy/neurosurgical interventions etc	Thank you for your comment. The overview provides more details about the included patients in individual studies.
6	Consultee 1 NHS professional British Association of Stroke Physicians	**Overview**	In the criteria for identifying relevant studies, how was "good quality" defined and evaluated?	Thank you for your comment. The interventional procedures programme manual (sections 9.2 and 9.3) describes how the relevant studies are selected and how the overview is approached.
7	Consultee 2 NHS Professional	**1.2**	With respect to recommendation 1.2 Patient selection should also include how source of fever is differentiated, e.g. how is fever as a result of infection excluded. Patient selection should also include time period from neurological insult that therapy is initiated. E.g. what time period is strict temperature management beneficial	Thank you for your comment. Section 1.2 has been changed to: *"Further research should preferably be randomised controlled trials. It should report details of patient selection (including **cause of fever,** severity of stroke and neurological injury),*

			I would like to see research which includes infection as an outcome. Research should also	*method and duration of cooling, time to initiate normothermic treatment after **neurological injury and** onset of fever, **procedure and** device-related complications, neurological outcomes assessed using validated measures, and patient-reported outcomes (including quality of life) in the long term"*
8	Consultee 3 Society of British Neurological Surgeons	**General**	Thank you for the request for comments. I have consulted the SBNS vascular expert [redacted]. The opinion is that this treatment is not part of current neurosurgical practice and there is no evidence to support its use.	Thank you for your comment.
9	Consultee 4 Private sector professional Bard Medical	**Title**	NICE interventional procedures consultation document, February 2021 **Title [Page 1]** • We would like to highlight that reference to "outcomes" in the title should be specific and state "neurological outcome" instead. • Also, the indication stated as "stroke or subarachnoid haemorrhage" should be extended to "stroke and subarachnoid haemorrhage".	Thank you for your comment. The committee has considered this comment but decided not to change the title. This procedure is not only to improve neurological outcome and there are other outcomes which can be achieved by this procedure. Using 'and' in the title might be interpreted as meaning the patient has to have both conditions but this procedure is for patients with stroke or SAH.
10	Consultee 4 Private sector professional Bard Medical	**Lay description**	**Summary [Page 1 – first text box]** • We would like to highlight that "brain cells **are** damaged" when blood flow in the brain is suddenly interrupted by a blockage (ischaemia) or bleeding (haemorrhage). • We observed that the normal temperature range has not been specified. It would be good to specify this range for clarity.	Thank you for your comment. The text has been changed to "*brain cells **are** damaged*". For the normal temperature range, please see comment 3.
11	Consultee 4 Private sector professional Bard Medical	**1.1**	**Draft recommendations 1.1 [Page 2]** • We acknowledge that there is limited specific evidence on maintaining normothermia using temperature modulation devices to improve outcomes after stroke and subarachnoid	Thank you for your comment. The committee has considered this comment but decided not to change the recommendation

			haemorrhage (SAH), however, there is evidence to suggest that fever has a negative impact on neurological outcomes. In addition, there are guidelines from the European Stroke Association, Neurocritical Care Society and a UK driven health outcomes consensus document providing a strong recommendation for TTM to prevent fever in these patients. There is also evidence from other specialities on the safety of TTM. The recently published largest TTM study, HYPERION showed no difference in complication between TTM and no TTM. The incidence of prespecified adverse events did not differ significantly between groups. **Supporting articles** Diringer et al. Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neruocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011; 15:211–240 Lascarrou J et al. Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm. The new England Journal of Medicine. 2019; 1-11 Saxena M., et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. Intensive Care Med. 2015;41:823–832 Steiner T et al. European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage. Cerebrovascular Diseases. 2013;35(2):93-112	- research. The committee makes decisions based on the assessment of the efficacy and safety of the procedure. Diringer et al. (2011) had been added to the existing assessment section. None of the following articles meet the inclusion criteria. Lascarrou et al. (2019): This is an open-label, randomised, controlled trial (HYPERION), including patients with coma after resuscitation from cardiac arrest with nonshockable rhythm. Saxena et al. (2015): This retrospective cohort study evaluated the relationship between peak temperature in the first 24 hours of intensive care unit admission and all-cause hospital mortality for acute neurological diseases. There was no information about the use of physical cooling. Steiner et al. (2013) recommended that 'increased temperature should be treated medically and physically (GCP)'. None of the referenced papers directly relates to this procedure.
12	Consultee 4 Private sector professional Bard Medical	**1.2**	**Draft recommendations 1.2 [Page 2]** • We would like to bring to your attention a randomised controlled trial being conducted by BD titled INTREPRID. The study is to assess the impact of advanced temperature control in preventing fever in brain injured patients. Here are the details of the study: **Study Design and Methodology**:	Thank you for your comment. The committee makes recommendations based on its assessment of the published evidence. Once the results from this randomised controlled trial have been published, NICE

			Investigational Device Exemption (Approved) A randomized, controlled, multicentre, single-blind clinical investigation designed to assess fever burden and early, short- and long-term clinical outcomes of fever prevention (FP) using the Arctic Sun 5000 Temperature Management System (test device) compared to standard fever care (control device(s)) in the treatment of moderate-to-severe brain injured patients. **Treatment Arms**: Fever Prevention Group – Subjects randomized to the fever prevention group will be treated with the Arctic Sun® 5000 Temperature Management System in order to maintain normothermia (target temperature 37°C). Normothermia will be maintained through day 14 of the study or until the subject is discharged from the ICU, whichever comes first. **Standard Care Group** – In subjects randomized to the standard care group, fever may or may not develop. Should fever develop, it will be managed according to a standard, escalating treatment algorithm. Subjects will be treated according to the protocol through day 14 of the study or until the subject is discharged from the ICU, whichever comes first. **Study Population**: Adult subjects with a primary stroke diagnosis (acute ischemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage). **Primary Endpoint**: Daily average fever burden (°C-hour) between randomization and Day 14 (336 hours) or ICU exit, whichever comes first. **Key Secondary Endpoint:** Level of functional independence at 90 days post-injury (3-month) follow-up based on the modified Rankin Scale. **Other Secondary Endpoints**: Additional neurologic outcomes measured at varying time points, mortality, and ICU and hospital length of stay. Planned Number of Subjects: 1176 (1000 evaluable); 588 in each cohort.	would consider it when updating the guidance in the future.

			The study sample size is primarily driven by the key secondary endpoint, and the study is powered for both the primary endpoint and the key secondary endpoint. The interim results are expected to be available by August/September 2021. [Confidential] As this study would address most of the research details stated, we request that the committee takes this into consideration.	
13	Consultee 4 Private sector professional Bard Medical	**2.3**	**The condition, current treatments and procedure – Current treatments 2.3 [Page 3]** • We would like to highlight that antipyretic medications have been shown to be ineffective and a cause of further neurological injury in treating neurological fever. (Picetti et al. 2013 and Saxena et al. 2015)	Thank you for your comment. This section is for treatments that are currently in use but they have not necessarily been assessed by NICE. For Picetti et al. (2013) and Saxena et al. (2015), please see comment 15.
14	Consultee 4 Private sector professional Bard Medical	**2.4**	**The condition, current treatments and procedure – The procedure 2.4 [Page 3-4]** • We would like to clarify that the technique is to maintain temperature with close control to a set temperature. Precision is important, considering that temperature variability, as well as abnormal temperature may also cause secondary brain injury. (Abu-Arafeh et al. 2017).	Thank you for your comment. Section 2.5 has been changed to: "*This procedure aims to reduce brain injury and improve neurological outcomes after stroke or SAH by maintaining normothermia* ***with precise temperature control****."* For Aub-Arafed et al. (2017), please see comment 15.
15	Consultee 4 Private sector professional Bard Medical	**3.3**	**Committee considerations - The evidence 3.3 [Page 4]** • We observed that shivering was listed as a key safety outcome. Shivering is not a safety outcome, as it is a normal physiological response to a treatment that requires management, for example gag reflex when intubating requiring drugs. **Supporting articles**	Thank you for your comment. The committee has considered this comment but decided keeping shivering as a key safety outcome. None of the supporting articles meet the inclusion criteria: Abu-Arafeh et al. (2017): This is a randomised controlled trial, with the indication being TBI

			Abu-Arafeh A et al. Temperature Variability in a Modern Targeted Temperature Management. Trial. Critical Care Medicine. 2017; 46:223-228 Picetti et al. Intravenous paracetamol for fever control in acute brain-injured patients: cerebral and hemodynamic effects. Critical Care. 2013; 17(Suppl 2):P329 Saxena The Effect of Paracetamol on Core Body Temperature in Acute Traumatic Brain Injury: A Randomised, Controlled Clinical Trial. 2015. PLoS ONE 10(12): e0144740"	and interventions being therapeutic hypothermia and standard care compared with standard care. Picetti et al. (2013): conference abstract (intervention: intravenous paracetamol). Saxema et al. (2015): This is a randomised controlled trial, with the indication being severe TBI and intervention being intravenous paracetamol compared to placebo.

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