National Institute for Health and Care Excellence

IP1115 Therapeutic hypothermia for acute ischaemic stroke

IPAC date: 14 February 2019

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Bard Limited	General	'Therapeutic hypothermia' to be replaced with 'Targeted Temperature Management' throughout the document. Reference: The Implementation of Targeted Temperature Management: An Evidence -Based Guideline from the Neurocritical Care Society: Lori Kennedy Madden et al - Neurocrit Care - October 2017 - TTM encompasses therapeutic hypothermia, controlled normothermia and treatment of fever.	Thank you for your comment. Evidence was only included on therapeutic hypothermia, not Targeted Temperature Management. The overview states that evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included. As such it would be misleading to change the terminology to include controlled normothermia.
2	Consultee 1 Company Bard Limited	**Page 1**	Replace the sentence - 'In this procedure, a cooling device is used .....immediately afer a stroke' with 'In this procedure a cooling device is used to reduce the body's temperature by 2 deg C to 4 deg C or to maintain the body in a normothermic state avoiding fever for several days after a stroke'.	Thank you for your comment. Evidence was only included on therapeutic hypothermia, not Targeted Temperature Management. The overview states that evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included.
3	Consultee 1 Company Bard Limited	**Page 1**	Replace the statement ;When the brain is cooler it needs less oxygen from the blood' with 'When core temperature is reduced, cerebral metabolism is lowered and the brain consumes less oxygen'.	Thank you for your comment and agree that it is absolutely right. However, this section of the draft guidance is a ‘lay description’ of the procedure and the suggested text is too technical for the lay section.

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4	Consultee 1 Company Bard Limited	**Page 1**	Replace the statement ' The aim is to limit the damage to brain cells caused by the stroke' with 'The aim is to limit the secondary brain injury to occur after the major insult from the stroke has occured'.	Thank you for your comment and agree that it is absolutely right. However, this section of the draft guidance is a 'lay description' of the procedure and easier to interpret. See response to comment 3.
5	Consultee 1 Company Bard Limited	**1.1**	Replace the statements 'Current evidence on the safety of therapeutic hypothermia for acute ischaemic stroke shows that there are serious complications. Evidence on efficacy does not show any meaningful improvement in outcomes.' with the following: Fever is common in critically ill patients with neurological conditions. In those with acute ischaemic stroke, fever can contribute to secondary brain injury and is associated with poorer functional outcomes and higher morbidity and mortality. Reference: Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018. Targeted Temperature is often used in neurocritical care to minimise secondary neurologic injury and improve outcomes. Reference: The Implementation of Targeted Temperature Management: An Evidence -Based Guideline from the Neurocritical Care Society: Lori Kennedy Madden et al - Neurocrit Care - October 2017	Thank you for your comment. The Committee decided not to change the recommendation in section 1.1 of the guidance. Evidence was only included on therapeutic hypothermia, not Targeted Temperature Management. The overview states that evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included.

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6	Consultee 1 Company Bard Limited	**1.1**	Replace the statement ' Therefore, the procedure should not be used' with the statement 'Therefore, the procedure should be used as 2nd or 3rd line therapy'.	Thank you for your comment. The Committee decided not to change the recommendation in section 1.1 of the guidance.
7	Consultee 1 Company Bard Limited	**2.3**	Replace the statement' The optimum timing and duration of therpeutic hypothermia has not yet been determined' with 'The optimum timing and duration of TTM has not yet been determined although it is widely acknowledged that temperature control should last as long as there is risk of fever'.	Thank you for your comment. Evidence was only included on therapeutic hypothermia, not targeted temperature management. The overview states that evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included.

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8	Consultee 1 Company Bard Limited	**2.3**	Replace the statement' Cooling may be continued for at least 12 to 24 hours, and temperature maintained at 33 to 35 deg C' with ' TTM should be maintained for as long as there is potential for secondary brain damage and the exact target temperature should be titrated against the level of ICP within a range of 34 - 36 deg C. References: Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018. Neurostatus - consensus recommendations on Targeted Temperature Management (TTM) in the neurologically injured patient - Rainer Kollmar et al - in publication in JAMA 2019	Thank you for your comment. Evidence was only included on therapeutic hypothermia, not targeted temperature management. The overview states that evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included. Section 2.3 of the guidance has been amended as follows: *Cooling may be continued for at least 12 to 24 hours, and body temperature maintained at 33°C to 36°C.*

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9	Consultee 1 Company Bard Limited	**2.4**	Replace the statement ' Before the procedure, the patient's temperature is measured usually with an infrared tympanic thermometer' with Core temperature measurement is important to enable effective identification, treatment and monitoring of fever. Reference: Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018.	Thank you for your comment. Evidence was only included on therapeutic hypothermia. The overview states that evidence on reducing the temperature to normal in patients with fever after ischaemic stroke has not been included. Core temperature measurement is part of the management of these patients. The text referred to in section 2.4 of the guidance has been amended as follows: *Before the procedure, the patient's temperature is measured with a thermometer and further temperature monitoring is done continuously with an internal (intravesical, rectal or oesophageal) probe connected to the cooling device.*

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10	Consultee 1 Company Bard Limited	**2.4**	Replace the statement' Further temperature monitoring is done continuously with an internal (intravesical, rectal or oesophageal) probe connected to the cooling device' with ' Use of an oesophageal temperature probe or bladder temperature probe is recommended during all phases of TTM. Clinicians should monitor temperature continuously during TTM'. Reference: The Implementation of Targeted Temperature Management: An Evidence -Based Guideline from the Neurocritical Care Society: Lori Kennedy Madden et al - Neurocrit Care - October 2017	Thank you for your comment. The draft guidance refers to therapeutic hypothermia rather than targeted temperature management. The existing text explains that continuous temperature monitoring is done.
11	Consultee 1 Company Bard Limited	**2.4**	Replace the statement' Cooling devices can be classified into surface (ice-cold saline, surface cooling, cooling helmets and nasal cooling) and endovascular methods' with Cooling devics can be classified into basic cooling methods (ice, cold saline, water blankets and nasal cooling) and advance feedback controlled devices (endovascular cooling and gel pads).	Thank you for your comment. The relevant section in 2.4 of the draft guidance has been amended as follows: *Cooling devices can be surface (ice-cold saline, surface cooling, cooling helmets and nasal cooling) or endovascular systems*.

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12	Consultee 1 Company Bard Limited	**2.4**	Replace the statement' at a rate of 0.3 to 0.5 deg C every hour' with' at a rate of 0.25 deg per hour' Reference: Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018 An active and controlled return to normal temperature is recommended for patients with severe disease and raised ICP treated with hypothermia. This helps reduce the risk of temperature overshoot and rebound increase of ICP. Reference: Neurostatus - consensus recommendations on Targeted Temperature Management (TTM) in the neurologically injured patient - Rainer Kollmar et al - in publication in JAMA 2019	Thank you for your comment. The draft guidance refers to therapeutic hypothermia rather than targeted temperature management. section 2.4 about the rate of temperature change has been amended as follows: *After cooling, the body is slowly rewarmed, at a rate of 0.25°C every hour*. The cited reference does not appear to be published yet.

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13	Consultee 1 Company Bard Limited	**2.4**	Replace the statement' Drugs such as buspirone or meperidine may be used to manage shivering' with 'Shivering should be managed in patients receiving TTM with an intervention tailored to the patient and disease severity. For awake AIS patients with mild disease, shivering should be managed using counterwarming first line, and antishivering medication such as buspirone dexmedetomidine or meperidine second line. Sedation could be considered third line and neuromuscular blockade avoided for as long as possible. Shivering in patients with severe disease should be managed using counterwarming first line, antishivering medication second line and neuromuscular blockade third line. Ref: Neurostatus-consensus recommendations on Targeted Temperature Management (TTM) in the neurologically injured patient. Rainer Kollmar et al - in publication in JAMA 2019	Thank you for your comment. The relevant section of 2.4 in the draft guidance has been amended as follows: 'During cooling, patients need close cardiovascular monitoring in an intensive care environment, and may also need intubation and sedation. Drugs including neuromuscular blockers may be used to manage shivering.'
14	Consultee 1 Company Bard Limited	**2.6**	Replace the statement' The aim of the procedure is to limit the damage to brain cells' with ' The aim of the procedure is to reduce the risk of secondary brain injury'. Reference: Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018	Thank you for your comment. Section 2.6 of the draft guidance has been amended as follows: *The aim of the procedure is to reduce the risk of secondary brain damage.*

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15	Consultee 1 Company Bard Limited	**3.1**	Two recent publications mentioned below have not been included in the literature review. The Implementation of Targeted Temperature Management: An Evidence -Based Guideline from the Neurocritical Care Society: Lori Kennedy Madden et al - Neurocrit Care - October 2017 Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018.	Thank you for your comment. Andrews et al. (2018) refers to targeted temperature management of patients with fever, which is not within the remit of this guidance. Madden et al. (2017) refers to implementation guidelines for targeted temperature management. It does not include any recommendations on the use of therapeutic hypothermia for acute ischaemic stroke.
16	Consultee 1 Company Bard Limited	**3.3**	Fever contributing to secondary brain injury thus resulting in poor functional outcomes and higher morbidity and mortality. References: The Implementation of Targeted Temperature Management: An Evidence -Based Guideline from the Neurocritical Care Society: Lori Kennedy Madden et al - Neurocrit Care - October 2017 Targeted Temperature Management in patients with ICH, SAH or AIS: consensus recommendations: PJD Andrews et al - British Journal of Anaesthesia October 2018. Bleeding - this is only applicable with endovascular cooling devices.	Thank you for your comment. Section 3.3 refers to key safety outcomes from the hypothermia procedure itself.

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17	Consultee 1 Company Bard Limited	**3.3**	Please add the following: In patients with stroke and other brain injuries, fever/higher body temperature is consistently associated with worse outcomes regardless of the outcome measure used. Reference: Impact of fever on outcome in patients with stroke and neurologic injury - Greer et al: Stroke 2008;39:3029-3035	Thank you for your comment. Section 3.3 describes the key safety outcome measures for the hypothermia procedure as agreed by the committee and specialist advisers.
18	Consultee 2 Specialist Society Association of British Neurologists	**General**	The ABN Stroke Advisory Group consider that there is evidence of potential hazard and no evidence for efficacy for therapeutic hypothermia. We agree that based on current evidence it should not be used in acute stroke. However, it would be helpful to see the final published evidence from the EUROHYP-1 randomised controlled trial.	Thank you for your comment. Consultee agrees with main recommendation. The results from the EUROHYP-1 trial are due to be published in May 2019. NICE will review further evidence and update the guidance if new data concerning safety and efficacy of the procedure are published.

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