

National Institute for Health and Care Excellence
IP1994 Phrenic nerve pacing for congenital central hypoventilation syndrome

IPAC date: 13th June 2024

Com . no.	Consultee name and organisation	Sec. no.	Comments [sic]	Response
Agreement on the recommendations				
1.	Consultees 2 to 12 Clinicians (n=11)	General	No comments but I agree with the recommendations	Thank you for your comments.
2.	Consultees 13 to 16 Patient Organisations (n=4)	General	No comments but I agree with the recommendations	Thank you for your comments.
3.	Consultees 17 to 56 Patients (n=40)	General	No comments but I agree with the recommendations	Thank you for your comments.
4.	Consultees 57 to 76 Public (n=20)	General	No comments but I agree with the recommendations	Thank you for your comments.
Indication and current treatments				
5.	Consultee 77 Avery Biomedical	Section 2.1	While in most CCHS patients the ventilatory drive is lost while asleep, causing the carbon dioxide in the blood to rise, some patients require 24-hour ventilation. In our tracking questionnaire, 120 patients responded, 13 answered they paced 24/7, and 45 left blank.	Thank you for your comment. The condition section is intended to be a summary of the condition. Section 3.11 has been added to the guidance, noting that pacing can be used 24 hours a day if needed.
6.	Consultee 78 Clinician	Indication	The indications for PNP in central hypoventilation are not restricted to CCHS, but even rarer forms of central hypoventilation disorders, including: ROHHAD - Rapid Onset Obesity, Hypothalamic Disorder, Hypoventilation and Autonomic Disorder	Thank you for your comment. Section 3.10 has been added to the guidance, noting that phrenic nerve

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			Brainstem disorders (congenital) like Arnold Chiari malformation (where usual neurosurgical correction has already been tried) Brainstem disorders, acquired due to surgery, radiation or trauma High cervical spinal disorders from trauma, infection (myelitis) (already commissioned by NHSE)	pacing may be used in other forms of central hypoventilation.
7.	Consultee 77 Avery Biomedical	Section 2.2	A pulse oximeter with built-in alarm is recommended while the patient is asleep to guarantee oxygen levels are always above 90%.	Thank you for your comment. The 'current treatments' section is intended to list the common treatments and does not include the procedure being assessed.
Procedure description				
8.	Consultee 77 Avery Biomedical	Section 2.4	Although section 2.4 states “the procedure is usually done by a thoracic approach,” a good percentage of surgeries is done by a cervical approach. Only at the end of the section it states that “a cervical approach can also be used and is done under general or local anaesthesia, but is less common.” This statement is not completely accurate. Based on the ABD database, a total of 1522 patients had been identified, 490 patients were implanted cervically (32%) and 580 were initially implanted thoracically (38%). Furthermore, the surgical approach is mainly decided based on the expertise of the available surgeons in the hospital and the age of the patient: “The cervical approach for phrenic nerve stimulator implantation may be considered in patients with functioning phrenic nerves who are greater than 2 years of age and who have not had significant lower neck trauma that would place the phrenic nerve at risk during the dissection.” (2021 Headley D; Diaphragm pacing using the minimally invasive cervical approach.) As an additional note, the advantage of cervical approach is that “it allows for the use of local or monitored anesthesia, does not require entering any body cavities, and keeps incision size small.” (2021	Thank you for your comment. The statement of ‘the procedure is usually done by a thoracic approach’ is supported by the key papers included in the overview and by the committee’s discussion. Headley (2023) - Diaphragm pacing using the minimally invasive cervical approach - is included in the overview and covers people with different indications. The paper states that most people with CCHS were implanted using the thoracic approach and that thoracic placement of the electrodes was more common in paediatric cases.

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			Headley D; Diaphragm pacing using the minimally invasive cervical approach.)	
9.	Consultee 77 Avery Biomedical	Overview – 'what the procedure involves'	Same comment as the previous one related to cervical approach. (Section 2.4)	Thank you for your comment. Please see response to comment 8.
10	Consultee 77 Avery Biomedical	Section 2.5	The diaphragm conditioning programme is required to spinal cord injury patients (SCI), because the period between the injury and the surgery is usually long (months if not years) and the diaphragm myofibers atrophy quickly. (VIDD - Ventilator-Induced Diaphragm Disuse) "The combination of 18 to 69 hours of complete diaphragmatic inactivity and mechanical ventilation results in marked atrophy of human diaphragm myofibers (Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans. Levine et al. NEJM, 2008, 358:1327-1335.) Although some centers implement this program (Ali, 2008), for CCHS patients, diaphragm conditioning is rarely required because the diaphragm is usually active part of the day.	Thank you for your comment. Section 2.5 has been removed.
11	Consultee 78 Clinician	Section 2.5	Patients with CCHS do not need to undergo a diaphragm conditioning programme (even though this is mentioned in Ali's paper – this is only needed for patients with high cervical spinal cord injury (SCI) where the phrenic nerve and diaphragm may not have been used for a prolonged period after SCI. Patients with CCHS can usually start phrenic nerve pacing within a few weeks of implantation, having allowed for surgical recovery. This is initiated by experienced specialists who will determine the correct thresholds and settings for pacing.	Thank you for your comment. Section 2.5 has been removed.
12	Consultee 78 Clinician	Overview – 'what the procedure involves'	Top of page 4 – a diaphragm conditioning programme is not needed for CCHS and is only mentioned in the paper by Ali; it is used in cases of high cervical spinal cord injury. Patients with CCHS can usually start phrenic nerve pacing within a few weeks of	Thank you for your comment. The wording relating to diaphragm conditioning has been removed.

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			implantation, having allowed for surgical recovery. This is initiated by experienced specialists who will determine the correct thresholds and settings for pacing.	
13	Consultee 77 Avery Biomedical	Overview - Procedure technique	<p>Thoracotomy is very rarely used nowadays since it is considerably more invasive, the surgery time and the post-operative course are longer, causes more complications, pleural drainage is reduced, and hospital stay is shorter, and with less morbidity.</p> <p>Using robotic surgery allows for more precise and flexible maneuvering of the instruments inside the chest cavity but the results are very similar to those of the VATS procedure.</p>	<p>Thank you for your comment.</p> <p>The 'procedure technique' section is intended to describe the common approach to the procedure technique based on the key papers included in the overview.</p> <p>The wording in section 2.4 has been amended.</p>
14	Consultee 77 Avery Biomedical	Overview - Procedure technique	<p>Although the response of the diaphragm can be monitored using fluoroscopy, a phrenic nerve conduction study can achieve better results since it mimics pacing, it stimulates the phrenic nerve in the neck, the right and left are performed separately and it records diaphragm Compound Muscle Action Potential (CMAP), and the generated test report shows data of the four main parameters: Latency, Duration, Amplitude, and Area. The other advantage is that the patient is not exposed to the radiation of the fluoroscopy machine.</p> <p>CCHS patients don't need a phrenic nerve conduction study because the diaphragm is active during wake hours.</p>	<p>Thank you for your comment.</p> <p>Please see response to comment 13.</p>
Committee comments				
15	Consultee 77 Avery Biomedical	Section 3.7	4 patients have been pacing for over 40 years, 45 patients for over 30 years, 53 patients for over 20 years, and 130 patients for over 10 years.	<p>Thank you for your comment.</p> <p>Section 3.7 has been changed to: "There are a small number of people who have had phrenic nerve pacing for over 40 years, although</p>

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				replacement electrodes or receivers might be needed over time.”
16	Consultee 77 Avery Biomedical	Section 3.8	A pulse oximeter with built-in alarm is recommended while the patient is asleep to guarantee oxygen levels are always above 90%. Same comment as in section 2.2.	Thank you for your comment. For safety reasons (in case of device failure), section 3.8 was made by the committee after their deliberations.
Evidence				
17	Consultee 77 Avery Biomedical	Overview – table 3	<p>“Authors preferred to limit the period of pacing to 12 hours per day to minimize the risk of PN damage.”</p> <p>This misconception began in the 1970s and perpetuated for several decades. It had its origin from initial articles published by Dr. William Glenn and other researchers with experience in phrenic pacing programs in several hospitals.</p> <p>When the first studies were done in humans, they had noticed that tidal volume dropped due to the diaphragmatic contraction diminishing between 12 and 18 pacing hours per day. It was thought that the cause could be due to damage of phrenic nerve and diaphragm fibers. Later it was found that allowing the diaphragm to rest would regain its strength and gradual conditioning of the diaphragm would allow longer and longer periods of pacing without fatigue. Eventually, the diaphragm would gain the strength to be able to work 24/7. Furthermore, no phrenic nerve was found to be damaged due to continued stimulation for more than 50 years. This misconception was perpetuated by other authors in many published articles without any scientific proof.</p> <p>Additionally, the design of the Avery electrode is safe for continuous stimulation. Electrical stimulation of any nerve can cause tissue damage and electrode corrosion due to electrolysis. Calculating the charge density with the highest stimulus current and the largest pulse width – never actually used – the Avery electrode is several</p>	<p>Thank you for your comment.</p> <p>Table 3 contains the information and data extracted from the key papers included in the overview.</p> <p>Section 3.11 has been added to the guidance, noting that pacing can be continued for 24 hours if needed.</p>

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			times lower than the generally accepted safe limits of 100 $\mu\text{C}/\text{cm}^2$ for tissue damage and 300 $\mu\text{C}/\text{cm}^2$ for electrode corrosion. A good majority of the SCI patients implanted with the Avery pacemaker pace continuously, 24 hours per day. Many patients have been pacing for 20, 30 years and some for 40 years. Typically patients with CCHS don't experience diaphragm fatigue since their diaphragm is active by itself during wake hours.	
18	Consultee 77 Avery Biomedical	Overview - Efficacy	See comments above (Ali, 2008)	Thank you for your comment. This section describes the information based on the key studies included in the overview.
19	Consultee 77 Avery Biomedical	Validity and generality	The Avery pacemaker manual states: "If a cardiac pacemaker is implanted, the cardiac pacemaker leads should be bipolar and the breathing pacemaker receiver should be at least 10 cm from the cardiac pacemaker."	Thank you for your comment. This section states that "to avoid interference with a PN pacer, the use of bipolar cardiac pacing electrode was preferred (Weese-Mayer 2010; Trang 2020)." This section is intended to summarise the key points based on the key papers rather than detailing how the procedure should be done if a cardiac pacemaker is implanted.
20	Consultee 78 Clinician	Other references of interest	NICE should be aware of these other references of interest: Chen, Maida Lynn; Tablizo, Mary Anne; Kun, Sheila; Keens, Thomas G. Diaphragm pacers as a treatment for congenital central hypoventilation syndrome In: Expert Review of Medical Devices. Sep 01, 2005 2(5):577-585 https://browzine.com/articles/61092230 Ballard HA, Leavitt OS, Chin AC, et al.	Thank you for your comment. The 3 papers (Chen 2005; Ballard 2018; Morelot-Panzini 2013) identified by the consultee do not meet the inclusion criteria.

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			<p>Perioperative anesthetic management of children with congenital central hypoventilation syndrome and rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation undergoing thoracoscopic phrenic nerve-diaphragm pacemaker implantation. Pediatric Anesthesia 2018;28:963-973. https://doi.org/10.1111/pan.13475</p> <p>Morelot-Panzini C, Gonzalex-Bermejo J, Staus C, Similowski T. Reversal of pulmonary hypertension after diaphragm pacing in an adult patient with congenital central hypoventilation syndrome. International Journal of Artificial Organs 2013;36:434-438 DOI 10.5301/ijao.5000197</p>	
Existing assessment and professional society				
21	Consultee 77 Avery Biomedical	Existing assessment	Replace PH with PN (Phrenic Nerve)	Thank you for your comment. 'PH' has been changed to 'PN'.
22	Consultee 1 BSSFN	General	This is not within the remit of Neurosurgical practice in the UK	Thank you for your comment. Evidence shows that this procedure can be done by neurosurgeons.

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