National Institute for Health and Care Excellence

IP1566 – Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease
Consultation Comments table

IPAC date: July 2017

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Patient charity representative MND Association	**1 & General**	The MND Association has no objection to NICE's conclusion that the treatment should not be recommended for routine commissioning. We would like to clarify one small factual point: the consultation document incorrectly states that the DiPALS publication indicates that a sub group of MND may benefit from the treatment. This is incorrect - the paper states that we cannot exclude the possibility that a small subgroup may benefit, however there is no evidence that they do.	Thank you for your comment. Factual error (in study 1 on page 8 in the overview) will be amended as follows: *The authors conclude that 'diaphragmatic pacing should not be a routine treatment for patients with ALS in respiratory failure. A subgroup of patients might experience a benefit; however, this possibility should not be assumed.'*

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2	Consultee 2 The University of Sheffield Clinical Trials Research Unit	**4&5**	 DiPALS Lancet Paper Jul15.pdf The DiPALS Trial team conducted the first multicentre, open label randomised controlled trial to evaluate the efficacy and safety of diaphragm pacing in the UK. We used the NeuRx RA/4 Diaphragm Pacing System in patients with Motor Neurone Disease (MND) experiencing respiratory insufficiency. Participants were randomised to either receive standard treatment which is Non Invasive Ventilation (NIV) alone or NIV plus diaphragm pacing. The primary outcome was participant survival from randomisation till last patient last visit. The study results showed that survival was shorter in the non-invasive ventilation plus pacing group than in the non-invasive ventilation alone group (median 11·0 months [95% CI 8·3–13·6] vs 22·5 months [13·6–not reached]; adjusted hazard ratio 2·27, 95% CI 1·22–4·25; p=0·009). Our conclusions based on these data are addition of diaphragm pacing to standard care with non-invasive ventilation was associated with decreased survival in MND patients, and that diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure.	Thank you for your comment. This study has already been included in our draft guidance.

3	Consultee 3 Company Atrotech Ltd		*In the following text "electroventilation"[1] will be used for all methods providing artificial ventilation via electrically-induced contractions of the patients own muscles.* Pain and skin burns prevented transcutaneous electroventilation to be used except for emergencies[1 2 3]. About 10% of the first open heart surgery patients died from postoperative heart block. Pain and skin burns prevented transcutaneous pacing to become an acceptable mode of treatment. Results of open heart surgery improved, when a pacer wire was left in place for the critical first postoperative days (still done today). Fear of infection prevented chronic cardiac pacing via transcutaneous wire(s). Chronic cardiac pacing developed when long-lasting lithium batteries were developed for totally implanted cardiac pacers. – One electrical pulse is sufficient to cause a heart contraction. For a useful skeletal muscle contraction, a series of tens of electrical pulses is needed. Even in 2017 there are no batteries available to provide long-term the necessary current for a totally implantable electroventilator. Glenn's inductively-fed diaphragm pacer[4] was and still is the solution. It therefore astonishes to see offered a device for life-long use in patients with immunologic deficiency, i.e. C2 tetraplegics that depends on permanent transcutaneous wires (an infection port). In 1976 electroventilation using 20Hz resulted in full-time long-term (=24h life-long) use in 13 of 37 patients and in part-time use (<24h but >12h) in 10 patients; less than 12h was named "not satisfactorily[5]. Since 1976 it is known that the muscle fibre type depends on the stimulation frequency; slow-twitch fatigue resistant fibres develop at frequencies below 8 Hz [6]. WWL Glenn introduced this knowledge into clinical work in 1984 [7]. Since 1984 full-time long-term electroventilation is possible for all patients with intact phrenic nerves and without muscle diseases. Continuous diaphragm muscle stimulation with frequencies of 20 to 25 Hz will lead to muscle fatigue within a few hours[8]. Attempts to decrease acutely the stimulation frequency to below 20Hz results in a drop of tidal volume [9;10].	Thank you for your comments. NICE developed 2 pieces of draft guidance IP746/2 (high spinal cord injuries) and IP1566 (motor neurone disease) for this procedure. IPAC recommended that the procedure should only be used in the context of research for cervical spinal cord injuries and should not be used to treat motor neurone disease. In this procedure the electrodes are implanted in the diaphragm to provide direct muscle stimulation. The device (Atrostim PNS) referred by the consultee in paragraph 3 & 4 is a phrenic nerve stimulator and not relevant to intramuscular diaphragm pacing. Safety events referred by consultee related to intramuscular diaphragm pacing (pain and infection) have been included in the draft guidance.

			Full-time long-term electroventilation decreases significantly the frequency of respiratory infections and diminishes airway nursing costs in comparison to MV; the higher investment with Atrostim PNS compared to MV is payed off within average life time of C2 tetraplegic patients due to saved costs for treatment of respiratory infections and decreased costs for airway nursing and equipment [11]. It therefore astonishes to see a device using 20Hz stimulation frequency announced as progress; it does not provide full-time independence from MV. – 20 Hz is widely used in FES studies, obviously because the frequency recruits a large amount of fibres in every muscle for about 10 minutes (after which fatigue appears), enough time for demonstration of forceful contractions in experimental studies. The publications on the diaphragm muscle stimulator have been critically analysed and found to depict data unreliably[12]. They also contain a biased review of the literature: Diaphragm pacing and Atrostim-PNS are claimed to depend on a “dangerous” thoracotomy and to endanger the phrenic nerves. In fact, the nerves are best approached according to Glenn[13] parasternally through the second intercostal space; the skin incision is 8 to 10cm, the amount of traumatised tissue equals that of inguinal hernia repair. According to F Wells (Papworth Hospital, Cambridge) it is the easiest piece of thoracic surgery and takes about 20 minutes to perform. When writing about “high danger” for the nerves reference is to Glenn’s “Fundamental Considerations …” where he had collected multi centre data of 477 patients implanted with a DP; he calculated the frequency of nerve injuries, analysed the reasons for nerve injury and made suggestions how to avoid nerve injury[14]. The other reference for nerve danger is Glenn’s article on the results of his group until 1985[13]. Thanks to that work, today, surgical nerve injury is practically zero[15]. Glenn’s parasternal approach locates the electrodes to a place with almost no movement (in contrast to implantation in the neck).	

			The intramuscular hooked wires are implanted invasively into a moving muscle at its motor point. Moving wires break, moving foreign bodies cause scar formation. The device uses up to 25mA. Such an amount of current may cause inadvertent stimulation of adjacent structures[16]. Shoulder pain with intramuscular diaphragm stimulation has been published[17]. The low number of implanted devices in 2000, about 1600 devices world-wide, has been used as argument of bad performance[18]. The incidence of patients who might benefit from electroventilation (SCI and CHS) is between 0.16 (Finland, counted) and 0.55 (globally, calculated) 19 per million inhabitants per year. These are inhabitants of developed countries with well-performing social security, about 400 million people (about 100 million inhabitants of the USA without Obama Care). ALS is a neuro-muscular disease, thus muscular disease, a contraindication for electroventilation (see websites: Avery Co and Atrotech.com); obviously, here is a situation of alternative facts. The incidence of ALS is 1 to 3 per million inhabitants, thus two- to six-fold compared to that of C2-tetraplegia and CHS together. ALS patients die on average within 5 years after onset of first signs and within three months after onset of respiratory device dependency. Thus, most ALS patients will not develop a muscular implant infection within these three months. My specialty in medicine is anaesthesia (1971) and I worked in Tampere University Hospital from 1969 to 2002. I became involved in electroventilation in 1976 and participated in the development of the Atrostim PNS. TEKES, a Finnish foundation for funding of technical innovations, fortunately financed most of the development. [redacted]	

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			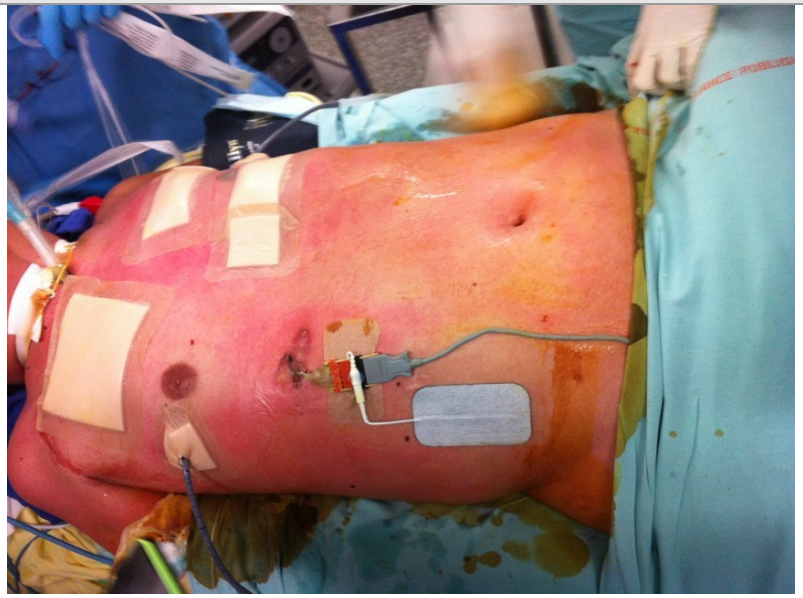	

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