

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease

Some patients with spinal cord injuries cannot breathe on their own and require a mechanical ventilator to assist them. Intramuscular diaphragm stimulation involves keyhole abdominal surgery (laparoscopy) to implant electrodes into the breathing muscle (diaphragm) close to its main nerve supply. Wires are connected through the skin to a battery-operated electrical stimulation system which causes the diaphragm to contract as it does in normal breathing. The aim of the procedure is to allow patients to breathe without mechanical assistance and to improve their quality of life.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2008.

Procedure name

- Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease

Specialty societies

- Association of British Neurologists
- British Association of Spinal Surgeons
- Association of Anaesthetists of Great Britain and Ireland

- British Thoracic Society
- Royal College of Anaesthetists
- Association of Laparoscopic Surgeons.

Description

Indications and current treatment

Some patients with neurological disease or spinal cord injury develop respiratory failure and become dependent on mechanical ventilation via tracheostomy.

An alternative to mechanical ventilation for patients with neurological disease or spinal cord injury who have intact phrenic nerves (the nerves that contract the diaphragm) is phrenic nerve pacing. In this procedure, electrodes are implanted into suitable areas of each hemidiaphragm, which are stimulated by means of an external battery-powered pulse generator to provide respiratory movement and assist breathing.

What the procedure involves

The aim of intramuscular diaphragm stimulation is the same as that of phrenic nerve pacing, i.e. to enable ventilator-free respiration. This procedure differs from phrenic nerve pacing firstly in that the electrodes are implanted laparoscopically, and secondly in that they are directly implanted into the diaphragm at the point of entry of the phrenic nerve (motor point) rather than around the phrenic nerve. This procedure therefore avoids the need for cervical or thoracic access to the phrenic nerve, as well as the potential risks of phrenic nerve damage

Pre-operative patient selection and assessment may involve fluoroscopic assessment of phrenic nerve function and diaphragm contractility using phrenic nerve stimulation.

The procedure is done laparoscopically with the patient under general anaesthesia. Before electrode implantation, the diaphragm is mapped with a specialised probe to identify areas where stimulation causes maximal contraction (known as the motor points).

Two intramuscular electrodes are implanted into suitable areas of each hemidiaphragm. A fifth electrode is implanted in subcutaneous tissue in the upper chest for a return current pathway. Intraoperative stimulation and voltage calibration tests are carried out to confirm that adequate contraction of the diaphragm can be achieved. A lead from each electrode is tunneled to a percutaneous exit site in the chest and connected to an external battery-powered pulse generator.

The patient or caregiver can turn the system on and off. Initially, the patient may only be able to breathe using the system for several minutes. The patient undergoes diaphragm conditioning which involves progressive use of the system (for increasing periods of time). The aim is to gradually strengthen the diaphragm and wean the patient off mechanical ventilation.

List of studies included in the overview

This overview is based on around 80 patients with neurological disease or spinal cord injuries from 8 observational studies.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

In a case series of 26 patients with quadriplegia, intramuscular diaphragm stimulation systems were implanted successfully in all patients. Twenty five patients (96%) were able to achieve continuous use of the system. The median time until 4, 12 and 24 hours of continuous use of the system was 26, 59 and 142 days, respectively. One patient could not initiate the diaphragm conditioning phase because of severe muscle cramps. At the time of publication, 54% (14/26) of patients used the system full-time (24 hours a day), 23% (6/26) of patients used the system part-time (12–24 hours a day), and 20% (5/25) of patients were still in the diaphragm conditioning phase (duration of follow-up not stated)¹.

In a case series of 10 patients with tetraplegia who had an intramuscular diaphragm stimulation system implanted, the median time until 4 hours of continuous use was achieved was 1.9 weeks (range 0.1–5.9 weeks). At the time of publication, 4 patients used the system full-time (24 hours per day), 2 patients used the system part-time (daytime only) and 4 patients were still in the diaphragm conditioning phase (duration of follow-up not stated). All patients stated that they preferred breathing with this system than with a ventilator and would recommend it to others. They commented that it simplified mobility and transport, and they had fewer secretions and less suctioning².

In a case series of 6 patients with tetraplegia because of high cervical spine injuries, 5 patients had an intramuscular diaphragm stimulation system implanted successfully (one patient required two operations to achieve placement of a functioning system). One patient had a failed procedure due to a false-positive result in the initial phrenic nerve conduction test (and would not have been able to have stimulated tidal volume). At the time of publication, 3 patients used the system full-time (24 hours per day), 1 patient used the system part-time (20 hours per day) and 1 patient was still in the diaphragm conditioning phase and used the system for 3 hours at a time (duration of

follow-up not stated). One patient using the system full-time had at least 3 years follow-up³.

In a case series of 50 patients with spinal cord injury (at least 10 of whom are reported in the studies described previously), 98% (49/50) were able to produce tidal volume with DPS of 15% over their basal requirements after diaphragm conditioning (1 patient had a failed procedure, described previously). At the time of publication (mean follow-up 2 years), 88% (44/50) of patients actively use the stimulation system for at least 4 continuous hours (5 patients died from causes unrelated to the procedure, all of whom had achieved success criteria of tidal volumes greater than basal requirements and more than 4 hours of continuous use)⁷.

One paper with 88 patients included 38 with amyotrophic lateral sclerosis (a form of motor neuron disease with progressive upper and lower motor neuron loss leading to ventilator dependence and death). In this paper diaphragmatic pacing reduced the rate of decline in forced vital capacity from 2.4% per month to 0.9% per month suggesting the potential for delay until mechanical ventilation became necessary⁷.

Safety

In the case series of 10 patients, there were no perioperative complications and all patients were discharged the day after the procedure².

The case series of 6 patients reported the following complications in 1 patient each: asymptomatic pneumothorax (which was treated by chest tube drainage), delayed wound infection and suture granuloma formation at the superficial wire connection site, and right shoulder pain during maximum stimulation of a single electrode (which was alleviated by reduced stimulation current). In addition, one patient redeveloped hay fever symptoms (which were common before his injury but absent during mechanical ventilation) and one patient had intermittent aspiration of food during meals. This was thought to be related to the large negative airway pressure generated during contraction of the diaphragm and was eliminated with the use of a specialised one-way valve (designed for patients with a tracheostomy tube) during meals⁴.

In the case series of 50 patients with spinal cord injury, 1 patient had a superficial wound infection which resolved with oral antibiotics and shortening and retermination of the tunneled electrodes (the patient had a chronic gastro-cutaneous fistula closed at the same time as electrode implantation). Forty-two percent (21/50) of spinal cord injury patients had capnothorax secondary to air tracking above the diaphragm and were treated with simple aspiration or observation⁷.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to diaphragm stimulation for chronic neuromuscular respiratory failure (requiring artificial ventilation). Searches were conducted of the following databases, covering the period from their commencement to 27/11/2008 and updated on 01/04/2009: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with ventilator-dependent chronic respiratory failure.
Intervention/test	Intramuscular diaphragm stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Table 2 Summary of key efficacy and safety findings on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease

Study details	Key efficacy findings	Key safety findings	Comments
<p>Alsheklee (2008) ¹ USA Study period: Jan 00 – Study population: patients with quadriplegia due to motor vehicle accident (n =13), sport injury (n = 12), meningitis (n =1). n = 26 Age: 32 years (mean) Sex: 85% male</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Ventilator-dependent chronic quadriplegia • At least 18 years of age • Clinically stable with adequate oxygenation on room air (> 90%) • No overwhelming medical comorbidities • Intact bilateral phrenic nerves <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Absent bilateral or unilateral movement of the diaphragm on fluoroscopy following phrenic nerve stimulation • No recordable diaphragm compound muscle action potential • Hospitalisation for an active infection or treated active infection within the last 3 months • Significant scoliosis or chest wall deformity, obesity • Presence of any pre-existing implanted electrical device such as cardiac pacemaker or defibrillator <p>Technique: laparoscopic implantation of diaphragm pacing system with intramuscular electrodes</p> <p>Follow-up: not stated Conflict of interest: none stated</p>	<p>Procedural success: 100%</p> <p>Conditioning phase</p> <ul style="list-style-type: none"> • 25 patients (96%) achieved diaphragm conditioning. • Median time to achieve 4 hours, 12 hours and 24 hours of continuous pacing: 26, 59 and 142 days, respectively. • 1 patient could not initiate the diaphragm conditioning phase because of severe muscle cramps (no further details about this patient were reported). <p>Use of system among the 25 patients able to achieve diaphragm conditioning</p> <p>At time of publication (duration of follow-up not stated)</p> <ul style="list-style-type: none"> • 56% (14/25) of patients use the system continuously full-time (24 hours per day) (total 54% [14/26]). • 24% (6/25) of patients use the system part-time (total 23% [6/26]). • 20% (5/25) of patients are still in the diaphragm conditioning phase (total 19% [5/26]). 	<p>No safety outcomes were reported.</p>	

Study details	Key efficacy findings	Key safety findings	Comments
<p>Onders (2007)² USA Study period: not stated Study population: patients with tetraplegia who were injured at 18 years of age or younger n = 10 Age: 18–34 years Sex: 80% male</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Ventilator-dependent tetraplegia Intact bilateral phrenic nerves <p>Technique: laparoscopic implantation of diaphragm pacing system with intramuscular electrodes</p> <p>Follow-up: not stated Conflict of interest: none stated</p>	<p>Procedural success: 100%</p> <p>Conditioning phase Time until 4 hours of continuous use was achieved:</p> <ul style="list-style-type: none"> Range: 0.1–5.9 weeks Median: 1.9 weeks <p>(of 8 patients who have achieved 4 hours of continuous use, 2 patients are still in conditioning phase)</p> <p>Use of system At time of publication (duration of follow-up not stated):</p> <ul style="list-style-type: none"> 4 patients use the system continuously full-time (24 hours per day). 2 patients use the system part-time (during the daytime only). 4 patients are still in the diaphragm conditioning phase. <p>Tidal volume</p> <ul style="list-style-type: none"> All patients who have completed the conditioning phase (n = 8) were able to obtain respiratory tidal volumes above their expected basal rate by a significant percentage. Percent above expected basal needs: range 5–62%, median 44%. <p>Patient satisfaction</p> <ul style="list-style-type: none"> All patients stated that they preferred breathing with this system than with a ventilator and would recommend it to others. They commented that it simplified mobility and transport, and they had fewer secretions and less suctioning. 	<p>There were no perioperative complications and all patients were discharged the day after the procedure.</p>	<p>It is likely that these patients are also reported in the above study by Alshekhlee (2008). However, neither study states this explicitly.</p>

Study details	Key efficacy findings	Key safety findings	Comments
<p>Onders (2004)⁵, Onders (2005)³, DiMarco (2005)⁴</p> <p>USA</p> <p>Study period: Mar 2000 – Jan 2004</p> <p>Study population: first consecutive patients with tetraplegia (high cervical injuries) who had a diaphragm pacing stimulation system implanted.</p> <p>n = 6</p> <p>Age: 36 years (mean)</p> <p>Sex: 100% male</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Ventilator-dependent tetraplegia • Intact bilateral phrenic nerves • Free from active lung, cardiovascular, or brain disease, chest wall deformity or obesity • Aged greater than 18 years <p>Technique: laparoscopic implantation of diaphragm pacing system with intramuscular electrodes</p> <p>Follow-up: not stated</p> <p>Conflict of interest: none stated</p>	<p>Procedural success: 83% (5/6)</p> <ul style="list-style-type: none"> • 1 patient had a failed procedure due to a false-positive phrenic nerve conduction study. The patient had the procedure but was never able to have stimulated tidal volume. At surgery both diaphragms visually appeared denervated and on retrospective review of his phrenic nerve study he was found to have a false-positive original test result. The authors comment that their protocol for assessing phrenic nerve conduction before the procedure has since changed. • 5 patients had successful procedures either as outpatient surgery or 24-hour observation. • 1 patient required two operations to achieve placement of a functioning system. <p>Use of system</p> <p>At time of publication (duration of follow-up for most patients not stated):</p> <ul style="list-style-type: none"> • 3 patients use the system continuously full-time (24 hours per day) (for at least 3 years in 1 patient) • 1 patient uses the system part-time (20 hours per day) • 1 patient is still in the diaphragm conditioning phase and uses the system for 3 hours at a time. <p>Tidal volume</p> <ul style="list-style-type: none"> • Initial bilateral stimulation resulted in inspired volumes between 430–1060 ml. • Inspired volumes after diaphragm conditioning increased to 110–1240 ml. 	<p>Complications</p> <ul style="list-style-type: none"> • 1 patient had a delayed asymptomatic small pneumothorax which was evacuated by chest tube drainage. It was probably a result of the pneumoperitoneum tracking along the needle insertion site during the operation (protocol has changed to reduce this risk). • 1 patient had a delayed wound infection at the superficial wire connection site from a suture granuloma. • 1 patient developed right shoulder pain during maximum stimulation of a single electrode which was alleviated by reduced stimulus current. • 1 patient had hay fever symptoms which were common before his injury but had not been present when he was receiving mechanical ventilation. • 1 patient had intermittent aspiration of food during meals which was most likely related to the large negative airway pressure generated during contraction of the diaphragm. This problem was eliminated with the use of a PassyMuir valve during meals. 	<p>These results come from 3 publications reporting on the same patients.</p> <p>Some complications may be in the same patient.</p>

Study details	Key efficacy findings	Key safety findings	Comments
<p>DiMarco (2006)⁶ USA Study period: not stated Study population: patient with tetraplegia (spinal cord injury at C3 from motor vehicle accident) who had a diaphragm pacing stimulation system implanted. n = 1 Age: 32 years Sex: Male</p> <p>Technique: laparoscopic implantation of diaphragm pacing system with intramuscular electrodes</p> <p>Follow-up: not stated Conflict of interest: none stated</p>	<p><i>Use of system</i> Five weeks after a successful procedure, the patient was able to use the system continuously for 8 hours and after 8 weeks, for 24 hours.</p> <p><i>Patient satisfaction</i> The patient described the system as effortless and similar to normal breathing and “like night and day when compared to mechanical ventilation”. Specific benefits of the system included ease of transport from bed to chair and travel out of the home to social events and medical office visits, improved speech, and overall improved sense of well being characterised by this patient as “feeling more normal”.</p>	<p>No safety outcomes were reported.</p>	<p>This patient is the also reported in the above 3 studies (Onders and Di Marco).</p>

Abbreviations used: SCI, spinal cord injury; ALS, amyotrophic lateral sclerosis,			
Study details	Key efficacy findings	Key safety findings	Comments
<p>Onders (2008) ¹</p> <p>Study type: prospective case series Country: USA Study period: March 00 – Sept 2007 Study population: patients with ventilator-dependent SCI (n = 50) and respiratory-compromised ALS (n =38). n = 88 Age: 36 years (mean: SCI) Sex: 74% male (SCI)</p> <p>Inclusion criteria (SCI patients):</p> <ul style="list-style-type: none"> Chronic ventilator-dependent high-level SCI Stimulatable diaphragm (intact phrenic nerves) <p>Technique: laparoscopic implantation of diaphragm pacing system with intramuscular electrodes</p> <p>Follow-up: 2 years (mean: SCI) Conflict of interest: none stated</p>	<p>Procedural success: 99% (87/88)</p> <ul style="list-style-type: none"> The second SCI patient had a failed procedure due to a false-positive phrenic nerve conduction study. The patient had the procedure but was never able to have stimulated tidal volume. At surgery both diaphragms visually appeared denervated and on retrospective review of his phrenic nerve study he was found to have a false-positive original test result. The authors comment that their protocol for assessing phrenic nerve conduction before the procedure has since changed. <p>Use of system (SCI patients) At time of publication (mean follow-up: 2 years)</p> <ul style="list-style-type: none"> 98% were able to produce tidal volume with DPS of 15% over their basal requirements. 1 patient could not use the system (failed procedure) 96% use the system for more than 4 continuous hours > 50% had used the system for more than 24 continuous hours 88% (44/50) actively use the system (5 patients died from causes unrelated to the procedure, all of whom had achieved success criteria of tidal volumes greater than basal requirements and more than 4 hours of continuous use, 1 patient was never able to pace). <p>Use of system (initial pilot of 16 ALS patients) Follow-up not stated.</p> <ul style="list-style-type: none"> After conditioning, the diaphragm was thicker when assessed with ultrasound (p = 0.02) After conditioning, preliminary results show an average rate of decline in forced vital volume capacity of 0.9% per month (compared to 2.4% per month before the procedure) <i>(Results for the remaining ALS patients were not reported because they are part of an ongoing multicentre pivotal trial)</i> 	<ul style="list-style-type: none"> One delayed suture granuloma causing an infection at the epigastric port site where the diaphragm electrodes were connected to separate electrodes that were subsequently tunneled through the skin. This was treated by externalizing the electrodes and the DPS system was still functional (only 1 set of electrodes is now used for the procedure rather than 2). <i>The paper does not state whether this was an SCI or LAS patient).</i> Superficial wound infection: 2 (1 patient in each group). Both infections occurred along the tunneled wires (both cases were contaminated by other procedure done at the same operation). Infections resolved with oral antibiotics and shortening and retermination of the tunneled electrodes. Capnothorax: 42% (21/50) of SCI patients and 13% (5/38) of ALS patients had air in the diaphragm on intraoperative chest x-ray (classified as capnothorax secondary to air tracking above the diaphragm) and treated with simple aspiration or observation. There were no electrode erosions or migrations at the time of publication. 	<p>Ten SCI patients were injured as children and were reported in Onders et al (2007). It is likely that at least 16 more SCI patients are also reported in the above studies. However, the paper does not state this explicitly.</p> <p>The first 16 ALS patients were part of a feasibility and safety trial. The second 2 ALS patients were implanted under compassionate use. The last 20 ALS patients were part of multicentre pivotal trial which will eventually have 100 patients (efficacy outcomes were not reported in this paper).</p>

Validity and generalisability of the studies

- Most studies seem to have only short-term follow-up of patients (one study reports a patient who has had the system for 3 years).
- There are a very limited number of patients.
- All studies reported on patients with high cervical quadriplegia or tetraplegia.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Nick Hart (British Thoracic Society), Alan McLean (British Society of Rehabilitation Medicine), John Watt (International Spinal Cord Society, Intensive Care Society; Association of Anaesthetists, Royal College of Anaesthetists).

- The three Specialist Advisers have never performed the procedure before.
- One Adviser stated that the comparator was phrenic nerve stimulation using neural electrodes. The other Adviser thought that the comparator was invasive ventilation via a tracheostomy or non-invasive ventilation via a nasal/full face mask.
- Both Advisers stated that there is controversy about the use of this procedure outside spinal cord injury patients, in particular, in patients with progressive neuromuscular disease. One Adviser thought that the procedure will have limited benefit in patients with progressive neuromuscular disease, such as motor neurone disease.
- Theoretical adverse events included: implant or pulmonary infection, technical failure, muscle contracture failure and fatigue if frequency and amplitude of stimulus too high, stimulus pain, inadvertent cardiac stimulation with arrhythmia. Interference with cardiac pacemaker, implant damage or heating in MRI scanner. Failure of long-term commercial support.
- One Adviser thought that an uncertainty over safety was related to the fact that there is risk of infection with the present device which is not totally implantable and has electrode wires exiting the skin. He also stated that intramuscular electrode placement may avoid potential damage to the phrenic nerve itself which could be of greater importance in cases of central hypoventilation syndrome where the patient can breathe normally awake, but would have major additional disability if the phrenic nerve were damaged.
- One Specialist Adviser stated that the procedure does seem to offer advantages over conventional phrenic nerve pacing in spinal cord injury. The procedure is less invasive (no thoracotomy or risk to phrenic nerves) and the implant itself is simpler and cheaper. Although infection is a theoretical risk the reported infection rate is very low, and device removal also appears easier.

- Advisers thought that key efficacy outcomes were: ability to ventilate without need for a machine, hours of independence from mechanical ventilation; quality of life, ability to talk and smell, and long term survival.
- One Adviser stated that there was uncertainty about whether the intramuscular electrodes display increasing threshold over time and failure to stimulate.
- Advisers thought that clinicians should receive training in the use of the equipment from the manufacturer. The procedure requires laparoscopy theatre facilities, as well as neurophysiology department access and expertise.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme were unable to identify any trusts in the UK performing this procedure and so were unable to gain any patient commentary.

Issues for consideration by IPAC

- The 'scoped' title of the procedure implies direct stimulation of the diaphragm muscle. It is however apparent that the physiological principle of the technique relies on stimulation of the distal parts of the phrenic nerve. Consider re-titling of the procedure to "phrenic nerve pacing via intramuscular diaphragm electrodes for chronic neuromuscular respiratory failure (requiring artificial ventilation)".
- It is known that clinical research is being carried out about the use of the device in motor neuron disease (MND). However, all published evidence relates to spinal cord injury. The original scope and lay description of the procedure included MND. Is it appropriate to remove all reference to MND?

References

1. Alshekhlee A, Onders RP, Syed TU et al. (2008) Phrenic nerve conduction studies in spinal cord injury: Applications for diaphragmatic pacing. *Muscle & Nerve* 38: 1546-1552.
2. Onders RP, Elmo MJ, and Ignagni AR. (2007) Diaphragm pacing stimulation system for tetraplegia in individuals injured during childhood or adolescence. *Journal of Spinal Cord Medicine* 30: Suppl-9.
3. Onders RP, DiMarco AF, Ignagni AR et al. (2005) The learning curve for investigational surgery: lessons learned from laparoscopic diaphragm pacing for chronic ventilator dependence. *Surgical Endoscopy* 19: 633-637.
4. DiMarco AF, Onders RP, Ignagni A et al. (2005) Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. *Chest* 127: 671-678.
5. Onders RP, DiMarco AF, Ignagni AR et al. (2004) Mapping the phrenic nerve motor point: the key to a successful laparoscopic diaphragm pacing system in the first human series. *Surgery* 136: 819-826.
6. DiMarco AF, Onders RP, Ignagni A et al. (2006) Inspiratory muscle pacing in spinal cord injury: case report and clinical commentary. *Journal of Spinal Cord Medicine* 29: 95-108.
7. Onders RP, Elmo M, Khansarinia S et al. (2008) Complete worldwide operative experience in laparoscopic diaphragm pacing: results and difference in spinal cord injured patients and amyotrophic lateral sclerosis patients. *Journal of Surgical Endoscopy*. Published online Dec 6 [Epub ahead of print].

Appendix A: Additional papers on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Cosendai G, De Balthasar C, Ignagni AR et al (2005) A preliminary feasibility study of different implantable pulse generators technologies for diaphragm pacing system. <i>Neuromodulation</i> 8 (3) 203–211.	n = 1 Follow-up: not stated	Both types of implantable pulse generators could achieve equivalent ventilatory requirements to the patient's current external stimulator.	Patient reported in another study in table 2. Study focuses on testing different types of implantable pulse generators (in the same patient).
DiMARco AF, Onders RP, Kowalski KE et al (2002) Phrenic nerve pacing in a tetraplegic patients via intramuscular diaphragm electrodes. <i>American Journal of Respiratory Critical Care Medicine</i> 166 1604–1606.	n = 1 Follow-up: not stated	Maximum inspired volumes in the left and right hemi-diaphragms increased significantly. Patient can comfortably tolerate full-time pacing.	Patient reported in another study in table 2.
Onders RP, Carlin AM, Elmo M et al. (2009) Amyotrophic lateral sclerosis: the Midwestern surgical experience with the diaphragm pacing stimulation system shows that general anesthesia can be safely performed. <i>American Journal of Surgery</i> 197:386-389.	n=51 Follow-up: one year	Diaphragm pacing stimulation (DPS) was synchronised with anaesthesiology ventilator and the change of respiratory compliance was measured before and after the use of DPS. Results showed 19% increase in respiratory compliance when DPS was used. No failures to extubate, 30 day mortalities or perioperative respiratory infections No outcomes reported about 'weaning off' or optimising the need for mechanical ventilation. 'Respiratory compliance' was not adequately defined in the paper.	Some of the pts have been reported in Onders 2008 (ALS pts =38) in Table 2. Dates overlap. Onders 2008 reports on pts recruited March 2000 - Sept 2007 and this paper reports from March 2005 - March 2008

Appendix B: Related NICE guidance for intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure due to neurological disease

Database	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	1/12/2008	Issue 4, 2008	2
Database of Abstracts of Reviews of Effects – DARE (CRD website)	28/11/2008	N/A	2
HTA database (CRD website)	28/11/2008	N/A	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	1/12/2008	Issue 4, 2008	11
MEDLINE (Ovid)	27/11/2008	1950 to November Week 3 2008	197
MEDLINE In-Process (Ovid)	27/11/2008	November 26, 2008	5
EMBASE (Ovid)	27/11/2008	1980 to 2008 Week 48	232
CINAHL (NLH Search 2.0)	28/11/2008	1981 to Present	72
BLIC (Dialog DataStar)	1/12/2008	N/A	0
National Research Register (NRR) Archive	1/12/2008	N/A	0
UK Clinical Research Network (UKCRN) Portfolio Database	1/12/2008	N/A	0
Current Controlled Trials <i>meta</i> Register of Controlled Trials - <i>m</i> RCT	1/12/2008	N/A	0
Clinicaltrials.gov	1/12/2008	N/A	Electrical Activation of The Diaphragm for Ventilatory Assist Motor-Point Stimulation for Conditioning the Diaphragm of Patients With

			Amyotrophic Lateral Sclerosis (ALS)
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The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	(diaphragmat* adj3 pac* adj3 stimulat*).tw.
2	(diaphragmat* adj3 stimulat*).tw.
3	(respirat* adj3 stimulat* adj3 system*).tw.
4	DPS.tw.
5	Electric Stimulation Therapy/
6	(electric* adj3 stimulat* adj3 therap*).tw.
7	5 or 6
8	Diaphragm/
9	diaphragm*.tw.
10	exp Respiration/
11	respir*.tw.
12	or/8-11
13	7 and 12
14	1 or 2 or 3 or 4 or 13
15	Respiratory Insufficiency/
16	(Respirat* adj3 Insufficienc*).tw.
17	Respiratory Paralysis/
18	(respirat* adj3 paralys*).tw.
19	(respirat* adj3 depress*).tw.
20	(ventilator* adj3 depress*).tw.
21	(respirat* adj3 fail*).tw.
22	exp Spinal Cord Injuries/
23	(spin* adj3 cord* adj3 injur*).tw.
24	Quadriplegia/
25	Quadriplegia*.tw.
26	tetraplegia*.tw.
27	Paraplegia/
28	Paraplegia*.tw.
29	Amyotrophic Lateral Sclerosis/

30	(Amyotrophic* adj3 Latera* adj3 Sclero*).tw.
31	ALS.tw.
32	(gehrig* adj3 diseas*).tw.
33	Motor Neuron Disease/
34	(motor* adj3 neuron* adj3 diseas*).tw.
35	exp Multiple Sclerosis/
36	MS.tw.
37	(multipl* adj3 scleros*).tw.
38	or/15-37
39	14 and 38
40	animals/
41	humans/
42	40 not (40 and 41)
43	39 not 42