NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease

Some patients with motor neurone disease (also called amyotrophic lateral sclerosis or ALS) need a mechanical ventilator to help them breathe. Intramuscular diaphragm stimulation involves keyhole abdominal surgery (laparoscopy) to implant electrodes into the diaphragm. Wires from the electrodes run under the skin to a battery-operated electrical stimulation system, which causes the diaphragm to contract as in normal breathing. The aim of the procedure is to strengthen the diaphragm, allowing patients to breathe without a ventilator and to improve their quality of life.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared in March 2017.

Procedure name

- Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease

Specialist societies

- Association of British Neurologists (ABN)
- Society of British Neurological Surgeons (SBNS)

- British Association of Spinal Cord Injury Specialists (BASCIS)
- Intensive Care Society (ICS)
- Faculty of Intensive Care Medicine.

Description

Indications and current treatment

Motor neurone disease is a neurodegenerative condition affecting the brain and spinal cord. The most common type of the disease is amyotrophic lateral sclerosis. Motor neurone disease is characterised by the degeneration of primarily motor neurones, leading to muscle weakness, limb weakness, problems with speech, swallowing and breathing, which ultimately leads to respiratory failure and death.

Current standard care for managing chronic respiratory failure in patients with motor neurone disease includes non-invasive forms of ventilation support (such as Bi-level positive airway pressure-[BiPAP]). In advanced stages of respiratory failure mechanical ventilation is done through a permanent tracheostomy.

What the procedure involves

The aim of intramuscular diaphragm stimulation is to make the diaphragm contract, strengthening it and allowing full or partial weaning from mechanical ventilation. This procedure needs intact phrenic nerve function, and avoids the need to access the phrenic nerve through the neck or thorax, as well as reducing the risk of phrenic nerve damage.

The procedure is done laparoscopically with the patient under general anaesthesia. A special probe is used to identify areas of the diaphragm where minimal electrical stimulation causes maximal diaphragm contraction (known as the 'motor points'). Two intramuscular electrodes are implanted on the abdominal surface of each hemi-diaphragm at the motor points. The electrode leads are tunnelled subcutaneously to an exit site in the chest where they are connected to an external battery-powered pulse generator. A reference electrode (anode) is also implanted and the leads tunnelled with the other electrodes. Intraoperative stimulation and voltage calibration tests are carried out to confirm adequate contraction of the diaphragm. After implantation, the patient has a diaphragm conditioning programme, which involves progressive use of the system for increasing periods of time with gradual weaning from the ventilator.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease. The following databases were searched, covering the period from their start to 08-08-2016: 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). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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 caused by motor neurone disease or amyotrophic lateral sclerosis.
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.

List of studies included in the IP overview

This IP overview is based on 247 patients with ventilator-dependent chronic respiratory failure caused by motor neurone disease or amyotrophic lateral sclerosis from 2 randomised controlled trials and 4 case series. Other studies that were considered to be relevant to the procedure and indications but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease/amyotrophic lateral sclerosis

Study 1 McDermott CJ (2015)

Details

Study type	Randomised controlled trial [DiPALS study]
Country	UK
Recruitment period	2011-13
Study population and number	n=**74 amyotrophic lateral sclerosis [ALS] patients with respiratory insufficiency (37 non-invasive ventilation [NIV] plus diaphragm pacing [DP] versus 37 NIV alone)** ALS type: NIV plus pacing: sporadic [n=34], familial [n=3]; NIV alone: sporadic [n=35], familial [n=2] Site of ALS onset: NIV plus DP: limb [n=26], bulbar [n=10], respiratory [n=1]; NIV alone: limb [n=28], bulbar [n=6], respiratory [n=1]. Time from symptom onset: NIV plus DP: <12 months [n=12], 12-24 [n=14], >24 [n=11]; NIV alone <12 months [n=14], 12-24 [n=12], >24 [n=11]
Age and sex	NIV plus DP: mean 60 years; 78% (29/37) male NIV alone: mean 54 years; 78% (29/37) male
Patient selection criteria	Eligible participants were aged 18 years or older with laboratory supported probable, clinically probable, or clinically definite ALS according to the World Federation of Neurology revised El Escorial criteria; with stable riluzole treatment for at least 30 days; and respiratory insufficiency determined by one or more measurements and with clinically acceptable bilateral phrenic nerve function. Exclusion criteria: previous use of non-invasive ventilation; pre-existing implanted electrical device; underlying cardiac disease, pulmonary disease, or other disorders that would affect pulmonary tests, or increase the risk of general anaesthesia or adversely affect survival; pregnancy or breastfeeding; significant decision-making incapacity preventing informed consent; obesity, or significant scoliosis or chest-wall deformity; involvement in any respiratory trial that could affect this study; pre-existing diaphragm abnormality; and a forced vital capacity [FVC] of less than 50% predicted or a sniff nasal inspiratory pressure of less than 30 cm H_2O in patients unable to undergo FVC because of potential anaesthetic risk.
Technique	After preoperative assessment, an intramuscular diaphragmatic stimulator (NeuRx RA/4 Diaphragm Pacing System) was implanted laparoscopically (in 32 patients). Pacing sessions were 5 times per day with each session lasting for 30 minutes in the first month, and gradually lengthened in the second month. Pacing was switched from during the day to overnight if used for 6-7 hours per day. Usage data were recorded at follow-up visits in a patient dairy. Non-invasive ventilation was initiated in both groups after screening. A minimum 4 hours of use was set for patients during daytime and as long as possible overnight. Usage data were downloaded from machines.
Follow-up	**3 years**
Conflict of interest/source of funding	Funding: The National Institute for Health Research Health Technology Assessment Programme; the Motor Neurone Disease Association [MNDA] of England, Wales, and Northern Ireland. Seven authors declared conflicts of interest (3 received grants from the funding bodies and non-financial support from the manufacturer, 2 reported honoraria and travel subsistence or fees, 1 reported membership of a steering committee of a trial and 1 membership of MNDA.

Analysis

Follow-up issues: Scheduled follow-up visits were at 2, 3, 6, 9, and 12 months. In December 2013, the Data Monitoring and Ethics Committee (DMEC) recommended to suspend recruitment on the basis of a concern in the overall survival figures. Randomly assigned participants continued as per the study protocol until June 2014, when the DMEC advised discontinuation of pacing in all patients. Follow-up assessments continued until the planned end of the study in December, 2014.

Study design issues: A multicentre, randomised controlled trial at 7 specialist ALS and respiratory centres. Patients were randomly assigned via a centralised web-based randomisation system with minimisation that balanced patients for age, sex, forced vital capacity, and bulbar function. Patients, carers, and outcome assessors were not masked to treatment allocation. The primary outcome was overall survival, defined as the time from randomisation to death from any cause. Patient quality of life (QOL) was assessed with the SF-36 and the Sleep Apnoea QOL questionnaire, carer QOL assessed with the Caregiver Burden Inventory. Adverse events were also reported. A post-hoc analysis of tracheostomy-free survival (the time from randomisation to the insertion of tracheostomy or death) was done to aid comparability with other studies of ALS. Analysis was by intention to treat.

Study population issues: patients in the pacing group were older than those in the non-invasive ventilation alone group but otherwise baseline characteristics were similar between groups. Some patients across the groups received additional respiratory interventions.

Other issues: cost-utility analysis and health-care resource use data were not extracted as it is outside the remit of the IP programme.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **74 (37 versus 37)**

Survival and Quality of life

Outcomes	NIV+DP (n=37)	NIV alone (n=37)	HR or MD (95% CI)	P value
Primary outcome (Kaplan-Meier survival analyses)				
Overall survival (months, 95% CI)	11.0 (8.3 to 13.6)	22.5 (13.6 to NR)	2.28 (1.27 to 4.10)	0.006
Adjusted for minimisation covariates	-	-	2.27 (1.22 to 4.25)	0.009
Stratified by site	-	-	2.02 (1.21 to 3.84)	0.012
Secondary outcome				
Post-hoc analyses of overall survival by NIV use				
No use of NIV (<1 hour)	7.7 (3.4 to11.6)	NR	4.67 (1.50 to 14.5)	0.008
Low use of NIV (1-3.9 hours)	10.9 (6.3 to NR)	13.6 (11.3 to NR)	1.28 (0.34 to 4.8)	0.719
High use of NIV (>4hours)	13.6 (5.3 to 19.1)	17.1 (10.8 to 30.1)	1.67 0.70 to 3.97)	0.246
Tracheostomy-free survival	11.0 (8.3 to 13.6)	22.5 (13.6 to NR)	2.42 (1.28 to 4.59)	0.007
Survival from symptom onset (median months, 95% CI)	28 (22 to 45)	45 (32 to not reached)		
Quality of life				
SF-36 (% complete)	72 (110/154)	76 (133/174)	-	-
Aggregate PHS	23.8 (12.2)	21.3 (12.0)	0.3 (-2.0 to 2.7)	0.780
Aggregate MHS	42.7 (16.5)	47.7 (17.8)	-3.5 (-7.9 to 0.8)	0.112
SAQLI (% complete)	72 (110/154)	76 (132/174)	-	-
Score	3.9 (1.6)	4.6 (1.5)	-0.3 (-0.7 to 0.1)	0.117
Carer Burden Inventory (% complete)	60 (93/154)	70 (121/174)	-	-
Score	28.0 (9.0)	29.6 (11.9)	1.2 (-2.7 to 5.0)	0.558

Safety

Adverse events

	NIV+DP % (n=37)		NIV alone % (n=37)	
Mortality within 30 days	0		0	
Overall mortality	76 (28/37)		51 (19/37)	
Cause of death, n				
Respiratory failure	16		13	
Chest infection	5		2	
ALS	6		4	
Hypothermia	1		0	
Patients with adverse events	78 (29/37)	Total events 162	62 (23/37)	Total events 81
Patients with serious events	**73 (27/37)**	**46**	**51 (19/37)**	**31**
Respiratory	68 (25/37)	45	38 (14/37)	19
Chest infection	32 (12/37)	20	19 (7/37)	11
Decompensated respiratory failure	27 (10/37)	10	14 (5/37)	5
Breathlessness	11 (4/37)	5	5 (2/37)	3
Pneumothorax or capnothorax	14 (5/37)	5	0	0
Blocked airway	3 (1/37)	3	0	0
Pulmonary embolism	3 (1/37)	1	0	0
Cough	3 (1/37)	1	0	0
Pain	27 (10/37)	23	16 (6/37)	10
Gastrointestinal	27 (10/37)	17	24 (9/37)	12
Symptoms of MND	22 (8/37)	18	8 (3/37)	7

Post-hoc analyses of patient quality of life				
EQ-5D-3L health state (% complete)	74 (131/178)	77 (161/2090	-	-
Survivors	0.02 (0.37)	0.13 (0.44)	-0.12 (-0.24 to 0.00)	0.056
All patients (0 assigned from death onwards)	0.01 (0.19)	0.11 (0.29)	-0.14 (-0.24 to 0.04)	0.001
EQ-5D-3L thermometer scale (% complete)	74% (132/178)	77% (160/209)	-	-
Survivors	36.0 (25.2)	40.0 (25.7)	-5.6 (-14.5 to 3.2)	0.212
All patients (0 assigned from death onwards)	14.8 (22.9)	27.4 (28.7)	-12.0 (-20.8 to -3.1)	0.008
Post-hoc analyses of carer quality of life^				
EQ-5D-3L health state (% complete)	61 (109/178)	71 (148/209)	-	-
Score	0.78 (0.34)	0.82 (0.25)	-0.08 (-0.17 to 0.01)	0.077
EQ-5D-3L thermometer scale (% complete)	62 (110/178)	71 (149/209)	-	-
Score	81.3 (22.6)	71.0 (27.7)	-0.2 (-7.4 to 7.1)	0.966

Data are median (95% CI) for survival outcomes and mean (SD) for quality of life outcomes (SF-36, SAQLI, Caregiver-Burden Inventory, and EQ-5D-3L). MD from longitudinal analysis of quality-of-life measures. ^ Not all patients had carers.

Implantation and pacing outcomes and NIV usage

	NIV+DP (n=37)	**NIV alone (n=37)**
DP implantation success %	86 (32/37)	NA
Patients using DP %	84 (31/37)	NA
Not using DP* %	16 (6/37)	NA
Use of DP (mean time)	6.2 hours	NA
NIV usage (mean time)	5.2 hours	4.8 hours

*14% (5/37) patients did not undergo surgery because of decline in respiratory function below the safety threshold (in 1), patient choice (in 2) and DMEC intervention (in 2) and pacing withdrawal after technical problems (in 1).

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.'

Insertion of PEG or PIG	14 (5/37)	9	24 (9/37)	10
Genitourinary	8 (3/37)	7	8 (3/37)	8
Infection of PEG or PIG	8 (3/37)	10	3 (1/37)	2
Dermatological	8 (3/37)	6	11 (4/37)	4
Wire problems (failure)	14 (5/37)	8	0	0
Cardiovascular system	11 (4/37)	4	5 (2/37)	2
Psychiatric	11 (4/37)	5	0	0
NIV specific	8 (3/37)	3	5 (2/37)	2
Wire infection	8 (3/37)	4	0	0
Central nervous system	3 (1/37)	1	3 (1/37)	1
Other	5 (2/37)	2	8 (3/37)	4

Abbreviations used: ALS, amyotrophic lateral sclerosis; CI, confidence interval; DP, diaphragm pacing; EQ-5D-3L, EuroQol 5D questionnaire 3-level format; HR, hazard ratio; MD, mean difference; MHS, mental health score; MND, motor neurone disease; NA, not applicable; NIV, non-invasive ventilation; NR, not reached; PEG, percutaneous endoscopic gastrostomy; PHS, physical health score; PIG, pre-oral image-guided gastrostomy; SAQLI, Sleep Apnoea Quality of Life questionnaire; SD, standard deviation; SF-36, 36 item short form health survey.

Study 2 Gonzalez-Bermejo J (2016)

Details

Study type	Randomised controlled trial [RespiStimALS]
Country	France
Recruitment period	2012-15
Study population and number	n=**74 amyotrophic lateral sclerosis [ALS] patients who do not yet have chronic hypoventilation (**37 active diaphragm stimulation versus 37 sham stimulation) ALS type: mainly sporadic; Site of onset: active group; bulbar 5, spinal 32; control: bulbar 11, spinal 26 Interval between randomisation and surgery: mean 2 days
Age and sex	Active stimulation group: mean 60 years; 76% (28/37) male Sham stimulation group: mean 54 years; 49% (18/37) male
Patient selection criteria	Patients with probable or definite ALS, moderate respiratory involvement (forced vital capacity 60–80% predicted), older than 18 years and bilateral responses of the diaphragm to diagnostic phrenic stimulation. Exclusion criteria: an indication for non-invasive ventilation (presence of respiratory symptoms and 1 or more of the following: FVC <50% predicted partial pressure of carbon dioxide in arterial blood [PaCO2] >45 mmHg, maximal inspiratory pressure [MIP] <60% predicted, sniff nasal inspiratory pressure [SNIP] <60% predicted, or nocturnal oximetry showing more than 5% of the recorded time spent with a peripheral capillary oxygen saturation [SpO2] below 90% or more than 5 consecutive min with an SpO2 below 89% in the absence of obstructive sleep apnoea); underlying respiratory disease affecting pulmonary function; previous non-invasive ventilation or continuous positive airway pressure; comorbidities with risk of anaesthesia or reduced survival; obesity or chest deformity making electrode implantation difficult; diaphragmatic hernia; respiratory tract infection or acute event in previous 2 months; presence of a cardiac pacemaker or implanted cardiac defibrillator; breastfeeding and pregnancy; or participation in other trials.
Technique	After preoperative assessment an intramuscular diaphragmatic stimulator (NeuRx RA/4 Diaphragm Pacing System) was implanted laparoscopically. An active or non-active cable for stimulation was inserted. Stimulation settings were standardised (30 minutes sessions 5 times per day, and gradually lengthened to 1 session per day lasting more than 3 hours).
Follow-up	**3 years**
Conflict of interest/source of funding	Funding: Hospital Program for Clinical Research, French Ministry of Health; French Patients' Association for ALS Research (Association pour la Recherche sur la Sclérose Latérale Amyotrophique); and Thierry de Latran Foundation. 4 authors declared conflicts of interest; mainly receiving honoraria from the manufacturer for educational activities, grants, and personal fees.

Analysis

Follow-up issues: follow-up visits scheduled every 3 months.

Study design issues: A multicentre, randomised, parallel group, triple-blind controlled trial in 12 ALS centres within secondary or tertiary hospitals. Patients were randomly assigned to receive either active or sham stimulation with a central web-based randomisation system (computer-generated list). Investigators, patients, carers, and outcome assessors were not masked to treatment allocation. The primary outcome was non-invasive ventilation-free survival. Safety outcomes were reviewed by an independent safety committee. Analysis was by intention-to-treat. An unplanned masked interim survival analysis was done after another trial (DiPALS) showed excess mortality with diaphragm pacing in patients with hypoventilation. Allocation of non-invasive ventilation was by an independent allocation committee that was also masked to treatment allocation (triple-blind design).

Study population issues: patients in the pacing group were older and there were a higher proportion with a definite diagnosis than those in the non-invasive ventilation alone group but otherwise baseline characteristics were similar between groups.

Other issues: the study was terminated early in July 2015 after an interim masked survival analysis showed a significant relationship between group difference for overall mortality (p=0.026).

Key efficacy and safety findings

Efficacy

Outcomes	Active stimulation (n=37)	Sham stimulation (n=37)	HR or MD (95% CI)	P value
Overall survival since randomisation (median months)*	15.6 (9 to 27)	NR (>33)	-	0.007
Overall survival since symptom onset (months)*	51 (39-74.1)	NR (>133)	-	0.03
Overall tracheostomy-free survival (adjusted)	-	-	3.14 (95% CI 1.31-7.53)	-
NIV-free survival since randomisation (months)^^	6.0 (3.6-8.7)	8.8 (4.2-NR)	1.96 (95% CI 1.08-3.56)	0.02
NIV-free survival since symptom onset (months)	38 (27.6-40.3)	35 (26.4-NR)	-	0.19
Number of patients receiving NIV at the end of study follow-up (%, N)^	30% (11/37)	35% (13/37)	-	0.62
Cumulative incidence of NIV since randomisation*	6 (5.1-12)	8.8 (4.7-NR)	-	0.42
Cumulative incidence of NIV since symptom onset**	40 (33.6-61.7)	34.1 (26.4-NR)	-	0.81

Safety

	Active stimulation % (n=37)	Sham stimulation % (n=37)
Overall mortality	49 (18/37)	19 (7/37)
Causes of death^		
Chest infection	44 (8/14)	29 (2/7)
Other cause of respiratory failure	28 (5/14)	14 (1/7)
Terminal respiratory insufficiency and received palliative care	28 (5/14)	57 (4/7)
At least 1 serious non-fatal adverse event	65 (24/37)	59 (22/37)
Serious adverse events		
Organ lesion during surgery (within 7 days)	0	8 (3/37)
Capnothorax or pneumothorax	5(2/37)	5 (2/37)
Acute respiratory failure (2 in each group within 7 days)	19 (7/37)	19 (7/37)
Venous thromboembolism	5 (2/37)	3 (1/37)
Gastrostomy	19 (7/37)	24 (9/37)
Other serious adverse events*	19 (7/37)	16 (6/37)
Pain	92 (34/37)	89 (33/37)
Pain needing reduction in intensity of pacing on day 2	54 (20/37)	0
Infection (needing antibiotics in 3 and 5 patients in each group)	22 (8/37) at stimulation cable entry point	19 (7/37)
Cumulative number of adverse events of any severity	229 (16.3 per person per year)	226 (13.6 per person per year)

Number of patients analysed: **74 (37 versus 37)**

Median survival and median time to initiation of NIV

Data are median (95% CI) or % (n)

*overall survival motivated to terminate the study

^^the primary outcome of the study; the time elapsed between the onset of symptoms and randomisation was longer in the active stimulation group than in the control group.

^19 patients in the active stimulation group and 30 patients in the sham stimulation group were alive at the end of study follow-up.

**death was considered to be a competing event.

Implantation and pacing outcomes and NIV usage

	Active stimulation (n=37)	**Sham stimulation (n=37)**
DP implantation success %	100 (37/37)	97 (36/37)*
Patients using DP %	97 (36/37)	NA
Not using DP^ %	3(1/37)	NA

*1 not implanted because of intra-abdominal adhesions. ^1 patient did not use the stimulator after implantation as the study was terminated immediately.

Post-hoc analyses n=40

The survival difference from symptom onset persisted after adjustment for age, ALS status, and rate of decline of the ALSFRS-R score (-0.73 points per month in the active group versus -0.65 in the control group) adjusted HR was 2.6 (95% CI 1.07-6.30, p=0.035).

Quality of life and sleep data did not differ significantly between the groups at inclusion or at follow-up.

Adverse events

^No treatment-related death was reported. Six patients died before NIV in the active stimulation group because of acute respiratory failure in 5 and sudden cardiac death in 1.

* Other serious adverse events reported include dyspnoea (in 3), loss of walking ability (in 3), oesophagitis (in1), admission to hospital for any cause (in 3), accidental removal of gastrostomy tube (in1), and reopening of the laparoscopy insertion orifice needing repair (in1).

Abbreviations used: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale-revised; CI, confidence interval; DP, diaphragm pacing; HR, hazard ratio; MD, mean difference; MND, motor neurone disease; NA, not applicable; NIV, non-invasive ventilation; NR, not reached.

Study 3 Onders RP (2009)

Details

Study type	Case series (prospective)
Country	USA
Recruitment period	2000-7
Study population and number	n=88 (**38** amyotrophic lateral sclerosis [ALS] patients with respiratory insufficiency and 50 SCI patients)
Age and sex	Not reported for ALS patients
Patient selection criteria	Patients with evidence of stimulatable diaphragm by contraction or phrenic nerve conduction studies (intact phrenic nerves).
Technique	Intramuscular diaphragmatic stimulation systems (NeuRx RA/4 Diaphragm Pacing System, Synapse Biomedical) were implanted laparoscopically under general anaesthesia and subsequently conditioned.
Follow-up	**Not stated for ALS patients.**
Conflict of interest/source of funding	The primary author has intellectual property rights involved with the device and equity in the company.

Analysis

Study design issues: 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 a multicentre pivotal trial which will eventually have 100 patients (efficacy outcomes were not reported in this paper).

Other issues: final outcomes for these pilot patients are reported in the Onders 2014 study below. Details about the spinal cord injury patients (n=50) were not extracted here but presented under the relevant section in the systematic review (Garara 2016).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **38**

Procedural success: 100%

Use of system (initial pilot of 16 ALS patients)

Follow-up not stated.

- 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)

(Results for the remaining ALS patients were not reported because they are part of an ongoing multicentre pivotal trial)

Safety

Adverse events

	% (n)
Suture granuloma causing infection at superficial wire connection site, treated by externalising the electrodes	1
Capnothorax and pneumothorax (patients had air in the diaphragm on intraoperative chest x-ray, classified as secondary to air tracking above the diaphragm, treated with aspiration, observation or chest drain)	13% (5/38)
Electrode erosions or migrations	0

Abbreviations used: ALS, amyotrophic lateral sclerosis; DP, diaphragm pacing.

Study 4 Onders RP (2014)

Details

Study type	Case series (prospective)
Country	USA
Recruitment period	2003-7
Study population and number	n=**16** amyotrophic lateral sclerosis [ALS] patients with respiratory insufficiency or Lou Gehrig's disease median time at enrolment since diagnosis: 19.6 months median time from ALS onset of symptoms:37.3 months bulbar involvement at baseline or during study: 8 Median FVC: average 57% at implantation
Age and sex	Mean age 50 years; 78% (13/16) male
Patient selection criteria	Patients with evidence of stimulatable diaphragm by contraction or phrenic nerve conduction studies (intact phrenic nerves).
Technique	Intramuscular diaphragmatic stimulators (NeuRx RA/4 Diaphragm Pacing System, Synapse Biomedical) were implanted laparoscopically under general anaesthesia and subsequently conditioned. Shor- acting neuromuscular blocking agents are used. Stimulus/output characteristics of each electrode were determined and diaphragm conditioning initiated (average values 13mA and 135 μs). Diaphragms conditioned with 5 daily stimulation sessions of 30 minutes each and were allowed to increase the usage.
Follow-up	**452 implant –months (average 28.2 months per patient post implant)**
Conflict of interest/source of funding	The primary author has intellectual property rights involved with the device and equity in the company.

Analysis

Study design issues: pilot study in 1 centre performed under FDA investigational device exemption GO40142. Patients had extensive assessments including pulmonary function tests, fluoroscopic evaluation of diaphragm movement, ultrasound analysis of diaphragm thickness and quality-of-life tests at regular intervals. Assessors were blinded to treatment to avoid bias.

Other issues: This study assesses the final outcome of the initial pilot patients (included in the worldwide experience with diaphragm pacing in ALS (Onders 2009).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **16**

Survival (Kaplan-Meier survival analysis)

Median survival from DP implantation was19.7 months, 39.5 months from diagnosis, and 51.1 months from initial onset.

Diaphragm thickness measurements using ultrasound

Test location (hemi-diaphragm /position)	Pre-implant thickness	Post-implant thickness	P value
Left inspiration	3.9±0.7	4.5±1.1	0.02
Left expiration	3.9±0.7	4.8±1.2	0.02
Right inspiration	3.9±1.0	4.3±0.7	0.13
Right expiration	3.8±0.9	4.7±1.1	0.01

Respiratory function (assessed with pulmonary function tests compared the rate of FVC pre and post implantation; n=13)

The slope of decline for the pre-implant treatment was -2.38±2.84% per month while it was -1.34±1.49% per month post-implant treatment. The paired FVC rate of decline (treatment-lead in) improved with DP 1.04±2.35% per month (p=0.14) showing a decrease in decline.

In all patients fluoroscopically measured diaphragm excursion was greater with diaphragm pacing than with maximal voluntary effort.

Impact of DP on quality of life (assessed using ALS-revised functional rating scale with 3 respiratory status questions and SF-36):

There was no statistically significant adverse effect of DP on the quality of life.

Safety

Adverse events

	n
Perioperative or device-related adverse events	0
Pain, discomfort	0
Significant increases in creatinine kinase and calcium levels	0
Internal electrode failures	0
External electrode repairs (repaired the external connector holder)	7
Superficial wound infection (treated with antibiotics)	1
Respiratory infections (needing antibiotics)	5
Simultaneous PEG insertion	7
Deaths*	16
Cause of death: respiratory failure 5, traumatic fall 1, aspiration 3, cervical spinal fixation surgery 1, urosepsis 1, colon cancer 1, terminal hospice care 4	

*only 1 patient died in the first year and most lived up to 12 to 36 months post implant.

Abbreviations used: ALS, amyotrophic lateral sclerosis; DP, diaphragm pacing; FVC, forced vital capacity; PEG, percutaneous endoscopic gastrostomy; SF-36, 36 item short form health survey.

Study 5 Sengun IS (2013)

Details

Study type	Case series (prospective)
Country	Turkey
Recruitment period	2012
Study population and number	n=**11** amyotrophic lateral sclerosis [ALS] patients with respiratory insufficiency mean duration of illness: 2.73±1.43 years Site of ALS onset: bulbar 3, lower extremity 2, upper extremity 6 4 had tracheostomy, 4 had PEG, 3 had hypoxemia (partial arterial oxygen pressure [PaO_2] values <65%)
Age and sex	Mean age 57 years; 73% (8/11) male
Patient selection criteria	Patients with evidence of stimulatable diaphragm by contraction or phrenic nerve conduction studies (intact phrenic nerves).
Technique	Intramuscular diaphragmatic stimulators (NeuRx RA/4 Diaphragm Pacing System, Synapse Biomedical) were implanted laparoscopically under general anaesthesia and subsequently conditioned. All procedures were done at 60-70% maximal heart rate and minimum 90% SpO_2. Respiratory exercises and routine physiotherapy were applied to develop breathing control.
Follow-up	**Not stated**
Conflict of interest/source of funding	None

Analysis

Study design issues: small study in a single centre. SpO_2 values, clinical and functional outcomes were assessed.

Population issues: all patients had dyspnoea, sputum and fatigue.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **11**

Mean operative time: 169.09±29.73 minutes (range 130-215 minutes)

Mean duration of ICU stay: 8.36±5.84 days

Mean duration of hospital stay: 15.64±7.09 days

Clinical parameters

Peripheral oxygen saturation (SpO_2)	**Mean %**
Preoperative value	93.91±2.88%
Early postoperative value	95.82±1.89%
Late postoperative value	96.00±1.79%
Respiratory support (frequency)	**n**
Preoperative support	full time MV (FVC <45%) in 5
Postoperative support	1 weaned from MV and MV support decreased in 3, full time DP in 7

Functional status:

Preoperative mean ALSFRS score was 15.61/40 (range 1.40 to 34/40) (4 fully dependent, 3 fully independent, 4 moderately dependent at sitting level).

Postoperatively, sitting times and walking distances of patients improved, exertion-related fatigue tolerances developed.

Quality of life outcomes

	n
Better sleep quality	6
Increased appetite and weight gain	6
Improved swallowing function and speech quality	7
Improved morale and status on wellness	7 4 travelled long distances, 1 visited friends, 1 did short trips

Safety

Adverse events

	n
Deaths (1 as a result of pulmonary infection and 1 as a result of sudden cardiac death)	2
Urinary infection (admitted in hospital)	1
Severe pulmonary infection	1
Mild pneumonia (treated at home)	2

Abbreviations used: ALS, amyotrophic lateral sclerosis; ALSFRS, amyotrophic lateral sclerosis functioning rating scale; DP, diaphragm pacing; FVC, forced vital capacity; ICU, intensive care unit; MV, mechanical ventilation; PEG, percutaneous endoscopic gastrostomy; SpO2, peripheral oxygen saturation.

Study 6 Sanli A (2016)

Details

Study type	Case series (retrospective)
Country	Turkey
Recruitment period	2012-14
Study population and number	n=**34** amyotrophic lateral sclerosis [ALS] patients with respiratory insufficiency 8 had tracheostomy, 9 had gastrostomy insertion, and 7 had mechanical ventilator support.
Age and sex	Mean age 56 years; 65% (22/34) male
Patient selection criteria	Patients with evidence of stimulatable diaphragm by contraction or phrenic nerve conduction studies (intact phrenic nerves).
Technique	Intramuscular diaphragmatic stimulators (NeuRx RA/4 Diaphragm Pacing System, Synapse Biomedical) were implanted laparoscopically under general anaesthesia and subsequently conditioned.
Follow-up	**Mean 13 months (range 2-24 months)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 33% (6/18) patients with right diaphragm thickness of below 4.73 mm (mean) and 33% (6/18) patients with left diaphragm thickness of below 4.13 mm (mean) were lost to follow-up.

Study design issues: small study in a single centre. Study evaluated the effect of diaphragm thickness, which was measured by preoperative thorax computerised tomography on preoperative respiratory function tests, arterial blood gas analysis, postoperative 3 and 6 month oxygen saturations and mortality. Patients were evaluated before implantation of DPS by a multidisciplinary team. All implantations were performed by the same physician.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **34**

Diaphragm thickness (measured with CT) (median, IQR)

The right diaphragm thickness was 4.60 (2.95-6.00) mm and the left diaphragm thickness was 4.10 (2.77-6.00) mm.

	Right diaphragm (mean)		**Left diaphragm (mean)**	
PEG				
yes	4.05 mm	P=0.040	3.66 mm	P=0.069
No	4.98 mm		4.30 mm	
Tracheostomy				
yes	4.55 mm	P=0.555	4.20 mm	P=0.699
No	4.79 mm		4.11 mm	
Comorbid disease				
yes	4.92 mm	P=0.555	4.20 mm	P=0.760
No	4.67 mm		4.11 mm	
Preoperative respiratory support				
Yes	4.02 mm	P=0.048	3.61 mm	P=0.063
No	4.91 mm		4.27 mm	
Postoperative respiratory support				
Yes	4.73 mm	P=0.976	3.76 mm	P=0.543
No	4.73 mm		4.17 mm	
Mortality				
Dead	3.05 mm	P<0.001	2.90 mm	P<0.001
Alive	4.90 mm		4.45 mm	

When the cut-off values for diaphragm thickness were accepted as 3.5 mm, statistically significant higher mortality was observed among patients (6 with right diaphragm thickness and 6/8 with left diaphragm thickness below 3.5 mm, p<0.001)

No significant correlation was observed between the diaphragm thickness and preoperative PFT parameters, ABG parameters and postoperative 3 and 6 month peripheral oxygen saturations of patients (p>0.05).

Safety

Adverse events

	n
Deaths	6

Abbreviations used: ALS, amyotrophic lateral sclerosis; ABG, arterial blood gas; DP, diaphragm pacing; PEG, percutaneous endoscopic gastrostomy; PFT, pulmonary function test.

Efficacy

Survival

In a multicentre randomised controlled trial (RCT) of 74 patients with respiratory failure caused by amyotrophic lateral sclerosis (ALS), non-invasive ventilation (NIV) plus diaphragm pacing (n=37) was compared with NIV alone (n=37). Overall survival (defined as the time from randomisation to death from any cause) was statistically significantly shorter in the NIV plus pacing group than in the NIV-alone group (median 11.0 months; 95% confidence interval [CI] 8.3 to 13.6, compared with 22.5 months; 95% CI 13.6 to not reached, adjusted hazard ratio 2.27; 95% CI 1.22 to 4.25; p=0.009).Tracheostomy-free survival (defined as the time to death or tracheostomy) was also statistically significantly shorter in the NIV plus pacing group than in the NIV-alone group (median 11.0 months; 95% CI 8.3 to 13.6, compared with 22.5 months; 95% CI 13.6 to not reached, adjusted hazard ratio 2.42; 95% CI 1.28 to 4.59, p=0.007). Median survival from symptom onset was 28 months (95% CI 22 to 45) for NIV plus diaphragm pacing patients and 45 months (95% CI 32 to not reached) for those having NIV alone[1].

In another multicentre triple-blind RCT in 74 patients with probable or definite ALS, active stimulation (n=37) was compared with sham stimulation (n=37).The NIV-free survival in the intention-to-treat population was statistically significantly shorter in the active stimulation group than in the sham stimulation group (median 6.0 months; 95% CI 3.6 to 8.7, compared with 8.8 months; 95% CI 4.2 to not reached, adjusted hazard ratio 1.96; 95% CI 1.08 to 3.56, p=0.02)[4]. The cumulative incidence of NIV did not differ between the 2 groups (since randomisation: median 6; 95% CI 5.1 to 12, compared with 8.8; 95% CI 4.7 to not reached, p=0.42; since symptom onset: median 40; 95% CI 33.6 to 61.7, compared with 34.1; 95% CI 26.4 to not reached, p=0.81). A statistically significant difference in overall tracheostomy-free survival in favour of the sham survival group was seen in the final analysis (49% [18/37] of patients died in the active stimulation group compared with 19% [7/37]) in the sham stimulation group; adjusted hazard ratio 3.14; 95% CI 1.31 to 7.53). Overall survival from randomisation was statistically significantly shorter in the active stimulation group than in the sham stimulation group (median 15.6 months; 95% CI 9 to 27, compared with not reached [more than 33], p=0.007). This was also true for overall survival from symptom onset (median 51 months; 95% CI 39 to 74.1, compared with not reached [more than 133], p=0.03)[2].

Quality-of-life outcomes

In the multicentre RCT of 74 patients respiratory failure caused by ALS, there were no statistically significant differences between the NIV plus diaphragm pacing group and the NIV-alone group in patient or carer preplanned quality of life measures. These included the health questionnaire SF-36 (physical health score p=0.78, mental health score p=0.11), Sleep Apnoea Quality of Life (SAQLI,

p=0.11) and Caregiver Burden Inventory (CBI, p=0.55). The patient health utility (measured using the EQ-5D-3L) was slightly lower in the NIV plus pacing group than in the NIV-alone group (p=0.056), and the differences were statistically significant when a score of 0 was assigned to the EQ-5D-3L following death. Differences between groups were modest at any individual time point (at 12 months the mean difference was −0.12; 95% CI −0.24 to −0.00, p=0.056), but longitudinal analysis demonstrated statistically and clinically significant differences on all patient EQ-5D-3L questionnaires (mean difference −0.14; 95% CI −0.24 to −0.04, p=0.001)[1].

Safety

Mortality

In a multicentre RCT of 74 patients with respiratory failure caused by ALS, NIV plus diaphragm pacing (n=37) was compared with NIV alone (n=37). In the NIV plus pacing group 76% (26/37) of patients died and in the NIV-alone group 51% (19/37) of patients died[1]. The causes of death were similar across the groups (mainly respiratory failure, chest infection, ALS and hypothermia).

In another multicentre triple-blind RCT in 74 patients with probable or definite ALS, active stimulation (n=37) was compared with sham stimulation (n=37). More patients died in the active stimulation group than in the sham stimulation group (49% [18/37] compared with 19% [7/37]), as a result of chest infection, acute respiratory failure and terminal respiratory insufficiency. Six patients died before NIV in the active stimulation group because of acute respiratory failure in 5 and sudden cardiac death in 1. No deaths were related to treatment[2].

Serious adverse events

There were more adverse events reported in the NIV plus pacing group than in the NIV-alone group (162 events [5.9 events per person-year] in 78% [29/37] of patients compared with 81 events [2.5 events per person-year] in 62% [23/37] of patients) in the RCT of 74 patients with respiratory failure caused by ALS. More patients had serious adverse events in the NIV plus pacing group than in the NIV-alone group (73% [27/37] compared with 51% [19/37]; 46 events compared with 31 events). Respiratory events were the most common in both groups (68% [25/37] compared with 38% [14/37]) followed by gastrointestinal events (27% [10/37] compared with 24% [9/37]), symptoms of motor neurone disease (22% [8/37] compared with 8% [3/37]), gastrostomy (percutaneous endoscopic or per-oral image-guided insertion; 14% [5/37] compared with 24% [9/37]), genitourinary events (8% [3/37] in each group), cardiovascular events (11% [4/37] compared with 5% [2/37]) and dermatological problems (8% [3/37] compared with 11% [4/37])[1].

Serious adverse events (mainly capnothorax or pneumothorax, acute respiratory failure needing mechanical ventilation, venous thromboembolism and gastrostomy tube placement) were reported in 65% [24/37] of the active stimulation group and in 59% [22/37] of the sham stimulation group in the triple-blind RCT of 74 patients. Some patients had more than 1 adverse event. Other serious adverse events reported include dyspnoea (3 patients), loss of walking ability (3 patients), oesophagitis (1 patient), admission to hospital for any cause (3 patient), accidental removal of gastrostomy tube (1 patient), and reopening of the laparoscopy insertion point needing repair (1 patient)[2].

Capnothorax was reported in 13% (5/38) of patients with ALS in a case series of 88 patients. Capnothorax was managed successfully by simple aspiration, drainage or observation[3].

Infection

Suture granuloma causing infection at the superficial wire connection site (treated by externalising the electrodes) was reported in 1 patient with ALS in the case series of 88 patients[3].

Infection at the stimulation cable entry point was noted in 22% (8/37) of patients in the active group (3 patients needed antibiotics) and 19% (7/37) of patients in the control group (5 patients needed antibiotics) in the triple-blind RCT of 74 patients[2].

Respiratory infections (needing antibiotics) were reported in 5 patients in the case series of 16 ALS patients with respiratory insufficiency treated by diaphragm pacing[4]. Superficial wound infection (treated with antibiotics) was reported in 1 patient in the same study[4]. Urinary infection (needing admission to hospital) and severe pulmonary infection were reported in 1 patient each in a case series of 11 patients[5].

Electrode problems

External electrode repairs were needed in 7 patients in the case series of 16 patients with ALS[4].

Wire failure was reported in 14% (5/37) of patients in the NIV plus diaphragm pacing group in the RCT of 74 patients with respiratory failure caused by ALS[1].

Pain

Pain (needing analgesics) was commonly reported in the active stimulation and sham stimulation groups (92% [34/37] compared with 89% [33/37]) in the triple-blind RCT of 74 patients. Pain needing a reduction in the intensity of diaphragm pacing was noted on day 2 in 54% (20/37) of patients in the active stimulation group and none in the sham stimulation group in the same study[2].

Validity and generalisability of the studies

- Phrenic nerve stimulation, which involves direct stimulation of the phrenic nerve, is out of the scope of this guidance. Only intramuscular diaphragm stimulation using an abdominal laparoscopic approach is considered in this guidance.
- Only 1 device is currently available for this procedure.
- There are no studies comparing phrenic nerve stimulation and intramuscular diaphragm stimulation.
- Two randomised controlled studies were reported in patients with ALS (1 study compared diaphragm pacing plus NIV with NIV alone and the other study compared active diaphragm pacing or stimulation with sham stimulation). However, the study designs and populations were very different.

Existing assessments of this procedure

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

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Extracorporeal carbon dioxide removal for acute respiratory failure. NICE interventional procedure guidance 564 (2016). Available from https://www.nice.org.uk/guidance/IPG564
- Extracorporeal membrane oxygenation for severe acute respiratory failure in adults. NICE interventional procedure guidance 391 (2011). Available from https://www.nice.org.uk/guidance/IPG391

NICE guidelines

- Motor neurone disease: assessment and management. NICE guideline 42 (2016). Available from https://www.nice.org.uk/guidance/ng42

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 is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE did not receive a submission.

Issues for consideration by IPAC

- Ongoing studies
  - NCT01938495: Diaphragm pacing system in participants with amyotrophic lateral sclerosis; randomised controlled trial; n=180; primary completion date January 2017; (study suspended participant recruitment).
  - NCT01605006: Humanitarian device exemption post-approval study of NeuRx diaphragm pacing system for amyotrophic lateral sclerosis; interventional single group assignment; n=97; study completion date September 2017; status: ongoing.
  - NCT02354651: Response to diaphragmatic pacing in subjects with Pompe disease; observational cohort study; n=12; completion date: February 2017; status: recruiting participants.

References

1. DiPALS Writing Committee; DiPALS Study Group Collaborators, McDermott CJ, Bradburn MJ, Maguire C, Cooper CL, Baird WO, Baxter SK et al (2015). Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicentre, open-label, randomised controlled trial. Lancet Neurol volume 14, no 9: 883-92. doi: 10.1016/S1474-4422(15)00152-0. Epub 2015 Jul 30.
2. Gonzalez-Bermejo J, MoRelot Panzini C et al (2016). Early diaphragm pacing in patients with amyotrophic lateral sclerosis (RespiStimALS): a randomised controlled triple-blind trial. The Lancet Neurology Volume 15, No. 12, p1217–1227.
3. 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].
4. Onders R P, Elmo M, Kaplan C, Katirji B, and Schilz R (2014). Final analysis of the pilot trial of diaphragm pacing in amyotrophic lateral sclerosis with long-term follow-up: diaphragm pacing positively affects diaphragm respiration. American Journal of Surgery 207(3), 393-7.
5. Sengun I S, Sanli A, Ozalevli S, Onen A, Itil BO, Tasdogen A, Karacam V, Arslan Savas, A , Agaoglu B, and Ozdemir N (2013). Results of diaphragm pacing application in amyotrophic lateral sclerosis patients. First Turkish experience. Journal of Neurological Sciences 30(2), 305-313.
6. Sanli A, Sengun IS, Tertemiz KC, Alpaydin AO, Karacam V, Sanli BA, Oz D, Ozalevli S, and Ozdemir N (2016). Importance of diaphragm thickness in amyotrophic lateral sclerosis patients with diaphragm pacing system implantation. Surgical Endoscopy and Other Interventional Techniques 30(1), 154-158.

Appendix A: Additional papers on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease

The following table outlines the studies that are considered potentially relevant to the IP 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
Amirjani N, Kiernan M C, McKenzie D K, Butler J E, and Gandevia S C (2012) Is there a case for diaphragm pacing for amyotrophic lateral sclerosis patients?. Amyotrophic Lateral Sclerosis 13(6), 521-527	General review Diaphragm pacing has been offered to ALS patients.	Evidence-based data to determine its benefits remain lacking. The limited literature indicates progression of respiratory dysfunction in ALS patients despite diaphragm pacing. The data from clinical trials are inadequate to substantiate its survival and sleep benefits. Its advantages over non-invasive mechanical ventilation have not been directly investigated. At present, clinical effectiveness and long-term safety concerns remain to be addressed.	Review.
Alegret Monroig N, Serra P et al (2016). Diaphragmatic pacing stimulation: Anesthetic management at institut guttmann. Journal of Neurosurgical Anesthesiology (28 (2)) S6-S7.	Retrospective case series N=16 patients (5 pediatric) with DP indication due to spinal cord injuries, 63%; amyotrophic lateral sclerosis, 25%; or other neurological diseases, 12%.	General anesthesia was required for abdominal laparoscopy; we used intravenous 87% versus inhalatory induction 13% and total intravenous anesthesia (TIVA) 50% versus balanced 50% for maintenance anesthesia. Succinylcholine was administered to 31% of the patients for orotracheal intubation. Anesthetic deepening was needed during the surgery for pneumoperitoneum tolerance in 50% of cases in the balanced anesthesia group and in 25% of the cases in the TIVA group. Registered complications were: 31% mechanical ventilation difficulty during laparoscopy, pneumotorax 12.5%, and autonomic dysreflexia 6%.	Anaesthetic management for different indications including ALS.

Ito H, Fukutake S et al (2016). Clinical results of diaphragm pacing in Japanese patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration (17) 282-283.	Case series n=5 amyotrophic lateral sclerosis patients with NeuRx Diaphragm Pacing System Follow-up: 2 years	Patient 1 died of pneumonia after 232 days. Patient 2 died of chronic respiratory failure after 338 days. Patient 3 withdrew the pacing due to aspiration pneumonia after 151 days. Both Patient 4 and Patient 5 continue DP as of 1 May 2016 (Patient 4: 674 days, Patient 5: 609 days). There were no serious adverse events.	Larger studies included in table 2.
Ito H, Kamei T et al (2016). An Autopsy Case of Amyotrophic Lateral Sclerosis with Diaphragm Pacing. Internal Medicine (55) 23 3511-3513.	Case report N=1 autopsied patient with sporadic amyotrophic lateral sclerosis (ALS) who underwent diaphragm pacing (DP).	The pathology showed several localized adhesions with a markedly atrophied diaphragm. A marked loss of motor neurons with Bunina bodies and phosphorylated TDP-43 positive inclusions was found in the spinal cord and primary motor cortex. Mild hyalinization and a few multinucleated giant cells were present around the electrode tracks in the diaphragm. However, no infiltration of inflammatory cells was detected. Our findings suggest that full-time DP might not cause severe damage to adjacent diaphragm tissue.	Larger studies with longer follow-up included in table 2
Kotan D, Kaymak K, and Gundogdu AA (2015). Diaphragm pacing system implanted in a patient with ALS. J Back Musculoskelet Rehabil, vol. 29, no. 3, pp. 611-612.	Case report N=1 patient with ALS DPS implanted Follow-up; 1 year	In the 1 year follow-up period the need for ventilator support disappeared.	Larger studies with longer follow-up included in table 2.

Le Pimpec-Barthes , F , Legras A, Arame A, Pricopi C, Boucherie J C, Badia A, and Panzini C M (2016) Diaphragm pacing: The state of the art. Journal of Thoracic Disease 8(pp S376-S386),	Literature review	Reviewing all available literature shows that DP is an effective method to wean selected patients' dependent on ventilator and improve their daily life. Other potential indications will have to be evaluated by randomised control trials.	Review.
Mahajan KR, Bach JR et al (2012). Diaphragm pacing and non-invasive respiratory management of amyotrophic lateral sclerosis/motor neuron disease. Muscle & Nerve. Volume 46, Issue 6, Pages 841–850.	Retrospective analysis 354 non-DP and 8 DP ALS/MND patients. NIV and DP users' vital capacities (VCs) over time and duration of NIV and continuous noninvasive ventilation (CNIV) dependence were analyzed.	Patients had a higher rate of monthly VC decline before NIV use (5.1 ± 7.6%) than during NIV use (2.5 ± 3.6%) (*P* < 0.01, 95% CI 0.84–4.5); the decline for 4 DP users was 3.7–20%. 55 ALS/MND patients used part-time NIV for 19.9 ± 27.6 months until tracheostomy/death, whereas 113 others used it for 10.9 ± 10.5 months until CNIV dependence for another 12.8 ± 16.2 months. After placement, 7 DP users were CNIV dependent in 8.0 ± 7.0 months, whereas 6 underwent tracheostomy/died in 18.2 ± 13.7 months. CNIV prolonged the survival of 113 of the 354 non-DP and 6 DP ALS/MND patients by 12.8 and 10.2 months, respectively. DP provided no benefit on VC or mechanical ventilation–free survival.	Larger and longer follow-up studies included in table 2.

Miller R, Ennist D et al (2016). Novel trial design in a clinical study of diaphragm pacing (DPS) for ALS. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration (17) 282.	Randomized controlled trial (PARADIGM study)	Objectives: To further examine the impact of DPS upon survival of PALS already stabilized on non-invasive ventilation (NIV). Survival of those who elect to receive DPS will be compared to that for concurrent controls, historical controls, and virtual controls. Methods: Enroll 106 PALS who are using NIV and meet FDA-approved DPS indications of chronic hypoventilation and stimulatable diaphragm. PALS who decline DPS will be monitored as concurrent controls. All PALS will be followed until death, tracheostomy or 2-year follow-up. Other measures of ALS progression and adverse events will also be monitored.	Protocol only.

Onders RP, Elmo M, Khansarinia S et al. (2009) 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. 23:1433-1440.	Case series N=88 patients with ventilator-dependent SCI (n = 50) and respiratory-compromised ALS (n =38). Technique: laparoscopic implantation of diaphragm pacing system with intramuscular electrodes Time from SCI to implantation ranged from 3 months to 27 years. Follow-up: 2 years (mean: SCI)	Procedural success: 99% (87/88). 1 SCI patient had a failed procedure as a result of a false-positive phrenic nerve conduction study. There was no perioperative mortality even in ALS patients with forced vital capacity (FVC) below 50% predicted. There was no cardiac involvement from diaphragm pacing even when analyzed in 10 patients who had pre-existing cardiac pacemakers. No infections occurred even with simultaneous gastrostomy tube placements for ALS patients. In the SCI patients 96% were able to use DPS to provide ventilation replacing their mechanical ventilators and in the ALS studies patients have been able to delay the need for mechanical ventilation up to 24 months.	Included in systematic review (Garara 2016) added to table 2. 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.
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 safety performed. American Journal of Surgery 197:386-389.	Case series n=51 ALS patients Diaphragm pacing stimulator (DPS) implanted at 2 sites. Forced vital capacity ranged from 20-87%, pco_2 was 60. Follow-up: 1 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. 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 patients have been reported in Onders 2008 (ALS patients =38) in Table 2. Dates overlap. Onders 2008 reports on patients recruited March 2000 - September 2007 and this paper reports from March 2005 - March 2008. Paper mainly focuses on general anaesthesia techniques and operative safety.

Onders RP, Elmo M, Kaplan C, Katirji B, and Schilz R (2015) Identification of unexpected respiratory abnormalities in patients with amyotrophic lateral sclerosis through electromyographic analysis using intramuscular electrodes implanted for therapeutic diaphragmatic pacing. American Journal of Surgery 209(3), 451-6.	Retrospective analysis N=53 patients with ALS DP electrodes implanted.	36 had bilateral dEMG assessments, 18 had overnight readings with pulse oximetry and 19 had serial analysis. Several findings revealed an alteration in the central respiratory drive including central apnoea, hypoventilation and hypercarbia. The electrode showed unilateral dysfunction and demonstrated noni-invasive ventilation suppression of the diaphragm activity.	Study provides an observational analyses of electromyography activity of the diaphragm using DP electrodes to increase understanding of respiratory control abnormalities in ALS.
Perez IA, Kun S et al (2016). PATIENT EDUCATION, INFORMATION SERIES. Diaphragm Pacing by Phrenic Nerve Stimulation. American journal of respiratory and critical care medicine (193) 8 P13-P14 15.			General article
Rezania K, Gottlieb O, Guralnick A, Prachand V, Sweitzer BJ, Vigneswaran W, White SR, and Roos RP (2014) Venous thromboembolism after diaphragm pacing in amyotrophic lateral sclerosis. Muscle & Nerve 50(5), 863-5.	Case report N=2 ALS patients with respiratory insufficiency Intra-diaphragmatic phrenic nerve stimulator placed laparoscopically Follow-up: 1-10 days.	2 patients with no symptoms of deep vein thrombosis (DVT) before the surgical procedure then developed perioperative venous thromboembolism. These patients highlight the need to consider preoperative screening for DVT and postoperative thromboprophylaxis in high-risk ALS patients who undergo DPS placement.	Larger studies included in table 2. Adverse event is already described in table 2.

Sanli A, Sengun I et al (2017). Preoperative parameters and their prognostic value in amyotrophic lateral sclerosis patients undergoing implantation of a diaphragm pacing stimulation system. Annals of Indian Academy of Neurology (20) 1 51-54.	Case series N=34 ALS patients implanted with DPS system. 2-year follow-up after the surgery	Twenty-eight of 34 patients with ALS survived after a 2-year follow-up. These patients were younger than those who died and had the disease for a longer time; however, differences were not significant. Both right and left hemidiaghragms were thicker in the survived patients ($P < 0.0001$ for each). Pulmonary function tests revealed no significant differences between the patients who survived. Arterial blood gas analysis demonstrated lower partial pressure of carbon dioxide in survived patients ($P = 0.025$).	Larger studies included in table 2.
Scherer K, and Bedlack RS (2012) Diaphragm pacing in amyotrophic lateral sclerosis: a literature review. Muscle & Nerve 46(1), 1-8.	Literature review on the currently available data on the diaphragm pacing system and its use in ALS.	Diaphragm pacing appears to be reasonably safe in carefully selected patients, but flaws in the reporting on it thus far preclude conclusions regarding efficacy. Further study is needed.	Review.
Schmiesing CA, Lee J, Morton JM, and Brock-Utne JG (2010) Laparoscopic diaphragmatic pacer placement--a potential new treatment for ALS patients: a brief description of the device and anesthetic issues. Journal of Clinical Anesthesia 22(7), 549-52.	Review on diaphragm pacing stimulator (DPS).	The FDA approved a trial using the DPS in patients with amyotrophic lateral sclerosis. Three patients with advanced ALS, who underwent laparoscopic diaphragmatic pacer placement, and their general anesthetic management, are presented.	Description of device and anaesthetic issues.

Wood H (2015) Motor neuron disease: Diaphragm pacing is associated with reduced survival in ALS patients with respiratory insufficiency. Nature Reviews Neurology 11(9).	Randomised controlled trial: DiPALS study 74 ALS patients with respiratory insufficiency randomised to non-invasive ventilation (NIV) alone or NIV plus diaphragm pacing.	The investigators conclude that diaphragm pacing cannot be recommended for routine use in patients with ALS at the onset of respiratory failure, and they warn against adopting a 'nothing to lose' approach in such patients. The possibility remains that the intervention might be beneficial in a carefully selected subset of patients at an earlier stage of the disease process.	Research highlights. Original article included in table 2.
Zeydan B, Benbir G, Akalin MA, and Karadeniz D (2016) Treatment of obstructive sleep apnea syndrome by diaphragm pacing stimulation in a patient with amyotrophic lateral sclerosis. Nobel Medicus 12(1), 94-96.	Case report N=1 patient with ALS and obstructive sleep apnoea syndrome treated with NIMV (BiPAP therapy) but later developed symptoms of respiratory dysfunction and DPS was implanted laparoscopically.	DPS was effective on obstructive sleep apnoea. For 4 months patient did not use BiPAP therapy and no symptoms of sleep apnoea.	Obstructive sleep apnoea in addition to ALS.

Appendix B: Related NICE guidance for intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease

Guidance	Recommendations
Interventional procedures	**Extracorporeal carbon dioxide removal for acute respiratory failure. NICE interventional procedure guidance 564 (2016)** 1 Recommendations 1.1 Current evidence on the safety of extracorporeal carbon dioxide removal ($ECCO_2R$) for acute respiratory failure shows several serious but well-recognised complications. Evidence on its efficacy is limited in quality and quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. 1.2 Clinicians wishing to do $ECCO_2R$ should: • Inform the clinical governance leads in their trusts. • Ensure that patients (if possible) and their families or carers understand the uncertainty about the procedure's efficacy and the risk of complications and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Audit and review clinical outcomes of all patients having $ECCO_2R$ (see section 1.4 and section 7.1). 1.3 Only patients with potentially reversible acute respiratory failure or those being considered for lung transplantation should be selected for this procedure. $ECCO_2R$ should only be used by specialist intensive care teams trained in its use. 1.4 NICE encourages clinicians to enter patients into ongoing trials such as the protective ventilation with veno-venous lung assist in respiratory failure (REST) trial, and to collaborate in data collection initiatives such as the Extracorporeal Life Support Organization register. Data collected should include information on patient selection criteria, thresholds for intervention, the type of $ECCO_2R$ technique being used and clinical outcomes. NICE may update the guidance on publication of further evidence.

	Extracorporeal membrane oxygenation for severe acute respiratory failure in adults. NICE interventional procedure guidance 391 (2011) 1 Guidance This document replaces previous guidance on extracorporeal membrane oxygenation in adults (interventional procedure guidance 39). 1.1 Evidence on the safety of extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults is adequate but shows that there is a risk of serious side effects. Evidence on its efficacy is inadequate to draw firm conclusions: data from the recent CESAR (Conventional ventilation or extracorporeal membrane oxygenation for severe adult respiratory failure) trial were difficult to interpret because different management strategies were applied among many different hospitals in the control group and a single centre was used for the ECMO treatment group. Therefore this procedure should only be used with special arrangements for clinical governance, consent and research. 1.2 Clinicians wishing to undertake ECMO for severe acute respiratory failure in adults should take the following actions. • Inform the clinical governance leads in their Trusts. • Whenever possible, ensure that patients and their carers understand the uncertainty about the procedure's efficacy and its risks and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG391/publicinfo). 1.3 Extracorporeal membrane oxygenation for severe acute respiratory failure in adults should only be carried out by clinical teams with specific training and expertise in the procedure. 1.4 Clinicians are encouraged to submit data on all adults undergoing ECMO for severe acute respiratory failure to the international Extracorporeal Life Support Organization register (www.elso.med.umich.edu). 1.5 NICE encourages further research into the use of innovative technologies for the management of severe acute respiratory failure, and may review this guidance on publication of further evidence.
NICE guidelines	Motor neurone disease: assessment and management (2016) NICE guideline NG42 **1.12 Respiratory function and respiratory symptoms** 1.12.1 Assess and monitor the person's respiratory function and symptoms. Treat people with MND and worsening respiratory impairment for reversible causes (for example, respiratory tract infections or secretion problems) before considering other treatments. **[new 2016]**

	1.12.2 Offer non-invasive ventilation as treatment for people with respiratory impairment (see section 1.14). Decisions to offer non-invasive ventilation should be made by the multidisciplinary team in conjunction with the respiratory ventilation service, and the person (see recommendations 1.5.1–1.5.5). **[new 2016]** 1.12.3 Consider urgent introduction of non-invasive ventilation for people with MND who develop worsening respiratory impairment and are not already using non-invasive ventilation. **[new 2016]** 1.12.4 Consider opioids[1] as an option to relieve symptoms of breathlessness. Take into account the route of administration and acquisition cost of medicines. **[new 2016]** 1.12.5 Consider benzodiazepines[1] to manage breathlessness that is exacerbated by anxiety. Take into account the route of administration and acquisition cost of medicines. **[new 2016]** **1.14 Non-invasive ventilation** **Information and support about non-invasive ventilation** 1.14.1 Offer to discuss the possible use of non-invasive ventilation with the person and (if the person agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times: • soon after MND is first diagnosed • when monitoring respiratory function • when respiratory function deteriorates • if the person asks for information. **[2010]** 1.14.2 Discussions about non-invasive ventilation should be appropriate to the stage of the person's illness, carried out in a sensitive manner and include information on: • the possible symptoms and signs of respiratory impairment (see box 1) • the purpose, nature and timing of respiratory function tests, and explanations of the test results • how non-invasive ventilation (as a treatment option) can improve symptoms associated with respiratory impairment and can be life prolonging, but does not stop progression of the underlying disease. **[2010, amended 2016]** 1.14.3 When discussing non-invasive ventilation, explain the different ways that people can manage their breathlessness symptoms. This should include: • non-invasive ventilation, and its advantages and disadvantages • using non-invasive ventilation at different points in the course of the person's lifetime • the possibility of the person becoming dependent on non-invasive ventilation • options for treating any infections

	• support and information on how to recognise and cope with a distressing situation • the role of medication for breathing problems • psychological techniques and support. **[new 2016]** 1.14.4 Check that the person thinking about non-invasive ventilation: • understands what non-invasive ventilation is and what it can achieve • recognises the need for regular review • has enough information about non-invasive ventilation and other options for breathing problems to make decisions about how and when to use it. • understands possible problems with compatibility with other equipment, for example, eye gaze access systems. **[new 2016]** 1.14.5 Explain that non-invasive ventilation can be stopped at any time. Reassure people that they can ask for help and advice if they need it, especially if they are dependent on non-invasive ventilation for 24 hours a day, or become distressed when attempting to stop it. Inform people that medicines can be used to alleviate symptoms (see recommendation 1.14.29). **[new 2016]** 1.14.6 Ensure that families and carers: • have an initial assessment if the person they care for decides to use non-invasive ventilation, which should include: o their ability and willingness to assist in providing non-invasive ventilation o their training needs • have the opportunity to discuss any concerns they may have with members of the multidisciplinary team, the respiratory ventilation service and/or other healthcare professionals. **[2010]** **Non-invasive ventilation for treatment of respiratory impairment in people with MND** 1.14.17 Offer a trial of non-invasive ventilation if the person's symptoms and signs and the results of the respiratory function tests indicate that the person is likely to benefit from the treatment. **[2010, amended 2016]** 1.14.18 Consider a trial of non-invasive ventilation for a person who has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment only if they may benefit from an improvement in sleep-related symptoms or correction of hypoventilation. **[2010, amended 2016]** 1.14.19 Before starting non-invasive ventilation, the multidisciplinary team together with the respiratory ventilation service should carry out and coordinate a patient-centred risk assessment, after discussion with the person and their family and carers. This should consider:

	• the most appropriate type of non-invasive ventilator and interfaces, based on the person's needs and lifestyle factors and safety • the person's tolerance of the treatment • the risk, and possible consequences, of ventilator failure • the power supply required, including battery back-up • how easily the person can get to hospital • risks associated with travelling away from home (especially abroad) • whether a humidifier is required • issues relating to secretion management • the availability of carers. **[2010]** 1.14.20 Before starting non-invasive ventilation, the multidisciplinary team together with the respiratory ventilation service should prepare a comprehensive care plan, after discussion with the person and their family and carers (who should be offered a copy of the plan). This should cover: • long-term support provided by the multidisciplinary team • the initial frequency of respiratory function tests and monitoring of respiratory impairment • the frequency of clinical reviews of symptomatic and physiological changes • the provision of carers • arrangements for device maintenance and 24-hour emergency clinical and technical support • secretion management and respiratory physiotherapy assessment, including cough augmentation (if required) • training in and support for the use of non-invasive ventilation for the person and their family and carers • regular opportunities to discuss the person's wishes in relation to continuing or withdrawing non-invasive ventilation. **[2010, amended 2016]** 1.14.21 When starting non-invasive ventilation: • perform initial acclimatisation during the day when the person is awake • usually start regular treatment at night, before and during sleep • gradually build up the person's hours of use as necessary. **[2010]** 1.14.22 Continue non-invasive ventilation if the clinical reviews show: • symptomatic and/or physiological improvements for a person without severe bulbar impairment and without severe cognitive problems

	• an improvement in sleep-related symptoms for a person with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment. **[2010]** 1.14.23 Provide the person and their family and/or carers (as appropriate) with support and assistance to manage non-invasive ventilation. This should include: • training on using non-invasive ventilation and ventilator interfaces, for example: o emergency procedures o night-time assistance if the person is unable to use the equipment independently (for example, emergency removal or replacement of interfaces) o how to use the equipment with a wheelchair or other mobility aids if required o what to do if the equipment fails • assistance with secretion management • information on general palliative strategies • an offer of ongoing emotional and psychological support for the person and their family and carers. **[2010, amended 2016]** 1.14.24 Discuss all decisions to continue or withdraw non-invasive ventilation with the person and (if the person agrees) their family and carers. **[2010]** 1.14.25 Before a decision is made on the use of non-invasive ventilation for a person with a diagnosis of frontotemporal dementia, the multidisciplinary team together with the respiratory ventilation service should carry out an assessment that includes: • the person's capacity to make decisions and to give consent[2] • the severity of dementia and cognitive problems • whether the person is likely to accept treatment • whether the person is likely to achieve improvements in sleep-related symptoms and/or behavioural improvements • a discussion with the person's family and/or carers (with the person's consent if they have the capacity to give it). **[2010, amended 2016]** 1.14.26 Consider prescribing medicines to help ease breathlessness that people using non-invasive ventilation can take on an 'as-needed' basis at home, for example, opioids[1] or benzodiazepines[1]. **[new 2016]** 1.14.27 Inform services that may see the person in crisis situations, such as their GP and services that provide emergency or urgent care, that the person is using non-invasive ventilation. **[new 2016]** **Stopping non-invasive ventilation** 1.14.28 The healthcare professionals responsible for starting non-invasive ventilation treatment in people with MND should ensure that support is available for other healthcare professionals who may

	be involved if there is a plan to stop non-invasive ventilation, including the legal and ethical implications. **[new 2016]** 1.14.29 If a person on continuous non-invasive ventilation wishes to stop treatment, ensure that they have support from healthcare professionals with knowledge and expertise of: • stopping non-invasive ventilation • the ventilator machine • palliative medicines (see the NICE guideline on care of dying adults in the last days of life) • supporting the person, family members and/or carers (as appropriate) • supporting other healthcare professionals involved with the person's care • legal and ethical frameworks and responsibilities. **[new 2016]** 1.14.30 If a person on continuous non-invasive ventilation wishes to stop treatment, seek advice from healthcare professionals who have knowledge and experience of stopping non-invasive ventilation. **[new 2016]** 1.14.31 Healthcare professionals involved in stopping non-invasive ventilation should have up-to-date knowledge of the law regarding the Mental Capacity Act, DNACPR, ADRT orders, and Lasting Power of Attorney. **[new 2016]**

Appendix C: Literature search for intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	24/05/2017	Issue 5 of 12, May 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	24/05/2017	Issue 4 of 12, April 2017
HTA database (Cochrane Library)	24/05/2017	Issue 4 of 4, October 2016
MEDLINE (Ovid)	24/05/2017	1946 to May Week 2 2017
MEDLINE In-Process (Ovid)	24/05/2017	May 23, 2017
EMBASE (Ovid)	24/05/2017	1974 to 2017 Week 21
PubMed	24/05/2017	n/a
JournalTOCS	24/05/2017	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Database: Medline
Search Strategy: --- 1 (diaphragmat* adj4 pac* adj4 stimulat*).tw. (21) 2 (diaphragmat* adj4 stimulat*).tw. (149) 3 (respirat* adj4 stimulat* adj4 system*).tw. (56) 4 DPS.tw. (1302) 5 Electric Stimulation Therapy/ (18418) 6 (electric* adj4 stimulat* adj4 therap*).tw. (826) 7 5 or 6 (18809) 8 Diaphragm/ (19407) 9 diaphragm*.tw. (36470) 10 exp Respiration/ (107725) 11 respir*.tw. (371422) 12 or/8-11 (466766) 13 7 and 12 (497) 14 1 or 2 or 3 or 4 or 13 (1988) 15 Respiratory Insufficiency/ (28786) 16 (Respirat* adj4 Insufficienc*).tw. (7155) 17 Respiratory Paralysis/ (1791) 18 (respirat* adj4 paralys*).tw. (969)

19 (respirat* adj4 depress*).tw. (6370)
20 (ventilator* adj4 depress*).tw. (599)
21 (respirat* adj4 fail*).tw. (24285)
22 exp Spinal Cord Injuries/ (41716)
23 (spin* adj4 cord* adj4 injur*).tw. (28876)
24 Quadriplegia/ (7548)
25 Quadriplegia*.tw. (2278)
26 tetraplegia*.tw. (2326)
27 Paraplegia/ (12172)
28 Paraplegia*.tw. (9971)
29 Amyotrophic Lateral Sclerosis/ (14953)
30 (Amyotrophic* adj4 Latera* adj4 Sclero*).tw. (15415)
31 ALS.tw. (16153)
32 (gehrig* adj4 diseas*).tw. (93)
33 Motor Neuron Disease/ (3877)
34 (motor* adj4 neuron* adj4 diseas*).tw. (5214)
35 exp Multiple Sclerosis/ (48944)
36 MS.tw. (220519)
37 (multipl* adj4 scleros*).tw. (52772)
38 or/15-37 (398703)
39 14 and 38 (358)
40 animals/ not humans/ (4261687)
41 39 not 40 (318)
42 limit 41 to ed=20090401-20160808 (114)
(201608* or 201609* or 20161* or 2017*).ed.
41 and 42