Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicentre, open-label, randomised controlled trial

*DiPALS Writing Committee, on behalf of the DiPALS Study Group Collaborators**

Summary

Background Non-invasive ventilation is part of the standard of care for treatment of respiratory failure in patients with amyotrophic lateral sclerosis (ALS). The NeuRx RA/4 Diaphragm Pacing System has received Humanitarian Device Exemption approval from the US Food and Drug Administration for treatment of respiratory failure in patients with ALS. We aimed to establish the safety and efficacy of diaphragm pacing with this system in patients with respiratory muscle weakness due to ALS.

Methods We undertook a multicentre, open-label, randomised controlled trial at seven specialist ALS and respiratory centres in the UK. Eligible participants were aged 18 years or older with laboratory supported probable, clinically probable, or clinically definite ALS; stable riluzole treatment for at least 30 days; and respiratory insufficiency. We randomly assigned participants (1:1), via a centralised web-based randomisation system with minimisation that balanced patients for age, sex, forced vital capacity, and bulbar function, to receive either non-invasive ventilation plus pacing with the NeuRx RA/4 Diaphragm Pacing System or non-invasive ventilation alone. 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. Analysis was by intention to treat. This trial is registered, ISRCTN number 53817913.

Findings Between Dec 5, 2011, and Dec 18, 2013, we randomly assigned 74 participants to receive either non-invasive ventilation alone (n=37) or non-invasive ventilation plus diaphragm pacing (n=37). On Dec 18, 2013, the Data Monitoring and Ethics Committee (DMEC) recommended suspension of recruitment on the basis of overall survival figures. Randomly assigned participants continued as per the study protocol until June 23, 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. Survival was shorter in the non-invasive ventilation plus pacing group than in the non-invasive ventilation alone group (median 11·0 months [95% CI 8·3–13·6] *vs* 22·5 months [13·6–not reached]; adjusted hazard ratio 2·27, 95% CI 1·22–4·25; p=0·009). 28 (76%) patients died in the pacing group and 19 (51%) patients died in the non-invasive ventilation alone group. We recorded 162 adverse events (5·9 events per person-year) in the pacing group, of which 46 events were serious, compared with 81 events (2·5 events per person-year) in the non-invasive ventilation alone group, of which 31 events were serious.

Interpretation Addition of diaphragm pacing to standard care with non-invasive ventilation was associated with decreased survival in patients with ALS. Our results suggest that diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure.

Funding The National Institute for Health Research Health Technology Assessment Programme; the Motor Neurone Disease Association of England, Wales, and Northern Ireland.

Lancet Neurol 2015

Published Online July 31, 2015 http://dx.doi.org/10.1016/S1474-4422(15)00152-0

See Online/Comment http://dx.doi.org/10.1016/S1474-4422(15)00185-4

See Online for podcast

*Collaborators listed at end of paper

Correspondence to: Dr Christopher J McDermott, Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield S10 2HQ, UK
c.j.mcdermott@sheffield.ac.uk

Introduction

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a neurodegenerative disorder in which death occurs on average 3 years after symptom onset, in most cases because of respiratory failure.[1] The only disease-modifying treatment is riluzole, a glutamate-release modulator, which improves survival by an average of 3 months.[2,3] Non-invasive ventilation is part of the standard of care for treatment of respiratory failure in patients with ALS, extending life by an average of 7 months.[4] However, non-invasive ventilation is not without problems, and claustrophobia, problems in the interface between device and patient, a physical barrier to communication, asynchrony between non-invasive ventilation and patients' natural breathing, a fairly poor uptake in patients with bulbar dysfunction, and concerns about increasing aspiration of secretions lead to adherence rates of roughly 72%.[5,6] Therefore, an

Research in context

Evidence before this study

We searched PubMed for reports published before April 1, 2015, with the terms "amyotrophic lateral sclerosis", "motor neuron disease", "ALS", "MND", and "diaphragm pacing". We included all prospective studies of diaphragm pacing in patients with amyotrophic lateral sclerosis (ALS). We did not identify any randomised controlled studies. We identified one cohort study that has been partially reported in various publications, including in a summary of safety and probable benefit (SSPB) published after Humanitarian Device Exemption approval for diaphragm pacing from the US Food and Drug Administration. In the SSPB, median overall survival for implanted patients was 56 months (4·7 years) from disease onset and 19 months (1·6 years) from implantation. A subgroup of patients were matched with historical controls and survival from diagnosis in the historical non-invasive-ventilation control group (n=43) was 21·4 months compared with 37·5 months for non-invasive ventilation plus pacing (p<0·001).

Added value of this study

This is the first randomised controlled trial of non-invasive ventilation alone versus non-invasive ventilation plus pacing. Patients receiving diaphragm pacing had decreased survival, unlike those in the previous cohort study of a selected ALS population, which showed a benefit of diaphragm pacing.

Implications of all the available evidence

Our findings suggest that diaphragm pacing should not be used as a treatment for patients with ALS at the point of respiratory failure. The disparity between our results and those of the previous uncontrolled cohort study demonstrates the importance of undertaking randomised controlled trials to identify benefits and exclude harm of interventions, whether they are drugs or medical devices.

alternative or complementary means of maintaining or supporting respiratory function is highly appealing.

Diaphragm pacing or, more accurately, phrenic nerve stimulation leading to contraction of the diaphragm, has historically largely been used in patients with spinal cord injury. Challenges with this approach have been the significant risk of iatrogenic phrenic nerve injury and, until recently, the need to undertake a thoracotomy.[7] The NeuRx RA/4 Diaphragm Pacing System (Synapse Biomedical, Oberlin, OH, USA) has an advantage compared with the earlier approach in that the phrenic nerves are stimulated near the motor endpoints within the diaphragm muscle.[8] Therefore, a minimally invasive laparoscopic abdominal procedure can be used to insert the electrodes into the undersurface of the diaphragm.

Case series of the spinal cord injury and ALS populations have emphasised the apparent simplicity and operative safety of the NeuRx RA/4 Diaphragm Pacing System.[9,10] Data from an uncontrolled multicentre cohort study led to Humanitarian Device Exemption approval of the Diaphragm Pacing System from the US Food and Drug Administration (FDA).[11] Since this approval on humanitarian grounds, insertion of the NeuRx RA/4 Diaphragm Pacing System as a treatment for respiratory failure in patients with ALS has become frequent practice worldwide. Although the evidence to date suggests that insertion of the NeuRx RA/4 Diaphragm Pacing System is a fairly straightforward procedure, and despite the encouraging provisional data for the benefits of diaphragm pacing, we and others[12] recognised the need to establish, by means of a randomised controlled trial, the long-term safety amd efficacy of diaphragm pacing with the NeuRx RA/4 Diaphragm Pacing System when used in addition to non-invasive ventilation, compared with the standard care of non-invasive ventilation alone.[12]

Methods

Study design and participants

We did this multicentre, open-label, randomised controlled trial at seven specialist ALS and respiratory centres in the UK. The full protocol is described elsewhere.[13] Participants aged 18 years or older were eligible for inclusion if they had laboratory supported probable, clinically probable, or clinically definite ALS, according to the World Federation of Neurology revised El Escorial criteria;[14] were stabilised on riluzole treatment for at least 30 days; had respiratory insufficiency as determined by one or more of forced vital capacity (FVC) less than 75% predicted, supine vital capacity less than 75% of sitting or standing vital capacity, sniff nasal inspiratory pressure less than 65 cm H_2O (men) or 55 cm H_2O (women) in the presence of symptoms, sniff nasal inspiratory pressure less than 40 cm H_2O, partial carbon dioxide pressure ($PaCO_2$) of more than 6 kPa (daytime) or 6·5 kPa (overnight), or significant overnight O_2 desaturation (>5% of night with oxygen saturation <90% during overnight oximetry); and had clinically acceptable bilateral phrenic nerve function, defined either by the absence of paradoxical abdominal wall movement during a supine sniff manoeuvre (sharp inhalation through the nose) and less than a 10% decline of FVC when moving from sitting to supine position, or by ultrasound evidence of at least 1 cm of downward diaphragm movement independent of thoracic or abdominal wall movement during a sniff manoeuvre.

Exclusion criteria were previous use of non-invasive ventilation; a pre-existing implanted electrical device; underlying cardiac disease, pulmonary disease, or other disorders that would affect pulmonary tests independently of ALS, or increase the risk of general anaesthesia or adversely affect survival over the course of the study; current pregnancy or breastfeeding; significant

decision-making incapacity preventing informed consent; obesity affecting surgical access to the diaphragm, or significant scoliosis or chest-wall deformity; involvement in any respiratory trial that could affect the safety or outcome measures of this study within 3 months of the planned implantation of the device or during the year of follow-up; pre-existing diaphragm abnormality, such as a hiatus hernia or paraoesophageal hernia, leading to ascent of abdominal contents into the thoracic cavity; and an 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 (eg, patients with bulbar muscular atrophy) because of potential anaesthetic risk. These criteria are consistent with the indications for use outlined in the FDA summary of safety and probable benefit (SSPB) report for the NeuRx RA/4 diaphragm pacing system.[11]

Patients provided written informed consent before screening or, for individuals unable to write, verbal consent was given and a witness signed to acknowledge the consent of the participant. The East of England Central Cambridge Research Ethics Committee provided ethics approval for the study (reference 11/EE/0226).

Randomisation and masking

We randomly assigned patients (1:1), via a central web-based randomisation system, to receive either non-invasive ventilation plus diaphragm pacing with the NeuRx RA/4 Diaphragm Pacing system or non-invasive ventilation alone (control group). The first ten participants were allocated with simple randomisation and thereafter patients were allocated by non-deterministic minimisation (with an allocation probability of 0·8), balancing for age, sex, FVC, and bulbar function. Patients, carers, and outcome assessors were not masked to treatment allocation.

Procedures

Scheduled follow-up visits were at months 2, 3, 6, 9, and 12 after randomisation. Sites were allowed to initiate non-invasive ventilation in both groups any time after commencing screening as per their standard practice. A minimum target of 4 h of overnight use of non-invasive ventilation was set for patients, who were encouraged to use non-invasive ventilation for as long as possible overnight and, if clinically required, during the daytime.

For patients allocated to diaphragm pacing, surgery was scheduled for as soon as was practicable after randomisation. Before surgery, a preoperative assessment was done to ensure the respiratory criteria for each patient remained within the safe range for anaesthesia (FVC ≥45%, sniff nasal inspiratory pressure ≥30 cm H_2O) and to ensure that they were otherwise safe to undergo the procedure. The procedure for insertion of the NeuRx RA/4 Diaphragm Pacing System was done as previously described and is detailed in the appendix.[9,10,13]

The initial target for pacing sessions was five times per day, with each session lasting at least 30 min. Patients were advised to build up to this target over the first month. In the second month, patients were asked to gradually lengthen the pacing sessions. When using the pacing system for 6–7 h a day, patients were advised to switch from pacing during the day to pacing overnight whilst asleep. At this stage patients were allowed to use the pacing device additionally during the day if they experienced benefit. Adherence to target use of diaphragm pacing and non-invasive ventilation was recorded by a study nurse at each follow-up in a patient diary and also at each follow-up visit, at which patients were asked how much they had paced or used non-invasive ventilation on a typical day that they identified within the previous week; use was categorised post hoc as high use (≥4·0 h per day), low use (1·0–3·9 h), or no use (<1 h). Usage data for non-invasive ventilation were downloaded from non-invasive ventilation machines when available. Means were calculated from the machine data and diary data available since the previous study visit.

See Online for appendix

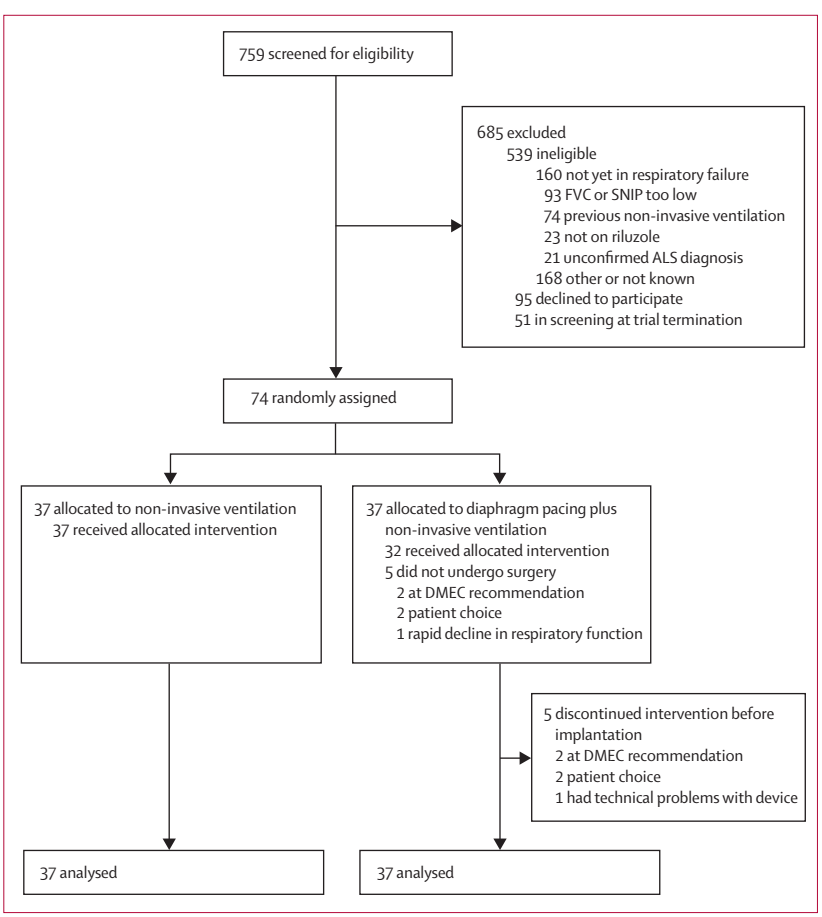

***Figure 1*: Trial profile**
FVC=forced vital capacity. SNIP=sniff nasal inspiratory pressure. DMEC=Data Monitoring and Ethics Committee. ALS=amyotrophic lateral sclerosis.

Outcomes

The primary outcome was overall survival, defined as the time from randomisation to death from any cause. Secondary outcomes were: patient quality of life (assessed with the 36-item Short Form Health Survey [SF-36] and the Sleep Apnoea Quality of Life [SAQLI] questionnaire); carer quality of life (Caregiver Burden Inventory); cost-utility analysis (the Euroqol 5D questionnaire 3-level format [EQ-5D-3L][15]) and health-care resource use; and tolerability and adverse events. Categorisation of adverse events was done with no knowledge of treatment allocation. A post-hoc analysis of tracheostomy-free survival (ie, the time from randomisation to the insertion of tracheostomy or death) was done to aid comparability with other studies of ALS.

	Non-invasive ventilation plus diaphragm pacing group (n=37)	Non-invasive ventilation alone group (n=37)
Centre		
Leeds	2 (5%)	5 (14%)
London	1 (3%)	1 (3%)
Manchester	6 (16%)	4 (11%)
Newcastle	6 (16%)	2 (5%)
Oxford	11 (30%)	13 (35%)
Plymouth	3 (8%)	3 (8%)
Sheffield	8 (22%)	9 (24%)
Age*	60 (10)	54 (12)
Sex*		
Male	29 (78%)	29 (78%)
Female	8 (22%)	8 (22%)
FVC (%)*†	66·1 (12·3)	64·6 (12·1)
ALS type		
Sporadic	34 (92%)	35 (95%)
Familial	3 (8%)	2 (5%)
ALS diagnosis		
Clinically definite	26 (70%)	22 (59%)
Clinically probable	7 (19%)	9 (24%)
Clinically probable, laboratory supported	4 (11%)	6 (16%)
Site of ALS onset		
Limb	26 (70%)	28 (76%)
Bulbar	10 (27%)	6 (16%)
Respiratory	1 (3%)	1 (3%)
Mixed	0	2 (5%)
Bulbar score*		
Mild (9–12)	26 (70%)	29 (78%)
Moderate (5–8)	8 (22%)	6 (16%)
Severe (0–4)	3 (8%)	2 (6%)
Time from symptom onset (months)	22 (18)	22 (15)
<12	12 (32%)	14 (38%)
12–24	14 (28%)	12 (32%)
>24	11 (30%)	11 (30%)
Rate of decline per month‡	0·99 (0·68)	0·94 (0·71)

Data are n (%) or mean (SD), unless otherwise indicated. ALS=amyotrophic lateral sclerosis. FVC=forced vital capacity (reported as the percentage of prediced FVC). *Minimisation factors. †Two participants had no FVC data recorded; their sniff nasal inspiratory pressure results were 53 cm H_2O (pacing) and 34 cm H_2O (control). ‡Calculated as (48–baseline ALS Functional Rating Scale-Revised)/(months since onset). 48 is the maximum possible score on the ALS Functional Rating Scale-Revised. If the patient is assumed to have the maximum score at onset, the result of the calculation represents the mean change per month.

***Table 1*: Baseline demographic and clinical characteristics**

Statistical analysis

The trial was powered to detect a 12 month survival improvement from 45% to 70%, corresponding to a hazard ratio (HR) of 0·45. With a schedule of 18 months' recruitment, 12 months' follow-up, and control group survival of 20% at 24 months and 10% at 30 months, 108 patients (54 per group) were needed to record the 64 events required by the log-rank test, with 85% power, a two-sided type I error of 5%, and 10% additional dropout.[16] We analysed overall survival and tracheostomy-free survival with Cox regression, with minimisation factors as covariates. We did a sensitivity analysis with the log-rank test stratified by centre. We analysed quality of life with a longitudinal model (generalised least squares) with baseline quality of life and minimisation factors as covariates. Missing data were imputed for survivors, first by interpolation if possible, and otherwise by multiple imputation. For further analysis of EQ-5D-3L, we used an imputed score of zero for timepoints following participant death. Analyses were by intention to treat, with pre-planned secondary analyses of overall survival based on protocol adherence and usage of non-invasive ventilation. Additional unplanned analyses of survival in relation to non-invasive ventilation and pacing usage were added thereafter. There was no planned interim analysis. The trial was overseen by an independent Trial Steering Committee and an independent Data Monitoring and Ethics Committee (DMEC). The DMEC monitored the results provided by the trial statistician with reference to safety. During this monitoring, a potential safety signal was identified and an unplanned interim survival analysis was done. Additional post-hoc (exploratory) analyses were subsequently added to investigate whether this signal could be explained by other factors, in particular, by use of non-invasive ventilation. We did analyses with Stata (version 12.1) and primary analyses were verified with SAS (version 9.4).[17] This study is registered, ISRCTN number 53817913.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between Dec 5, 2011, and Dec 18, 2013, we randomly assigned 74 participants to receive either non-invasive ventilation alone (n=37) or non-invasive ventilation plus diaphragm pacing (n=37; figure 1). On Dec 18, 2013, the DMEC recommended that recruitment be suspended on the basis of a concerning

signal in the overall survival figures. Patients in the study already receiving diaphragm pacing continued with this intervention as per the study protocol. However, after randomisation, two patients who had been allocated to diaphragm pacing and were awaiting implantation had their surgery cancelled. The DMEC made the recommendation to end active pacing in all participants on June 23, 2014, and to continue follow up until the planned end of the study. Study follow-up concluded on Dec 3, 2014, at which time 47 patients had died; one patient was last followed up on Aug 4, 2014, with the remaining 26 patients alive at study close.

Patients in the pacing group were on average older than those in the non-invasive ventilation alone group, but otherwise baseline characteristics were similar between groups (table 1). Survival from randomisation was shorter in the non-invasive ventilation plus pacing group versus the non-invasive ventilation alone group (table 2, figure 2). Results were relatively unchanged when analysis was adjusted for study site (table 2). The unadjusted HR and the HR stratified by centre were similar (table 2). Only one patient underwent a tracheostomy (non-invasive ventilation plus pacing group, 31 months after randomisation); therefore, tracheostomy-free survival was very similar to overall survival (table 2). Median survival from symptom onset was 28 months (95% CI 22–45) for patients receiving diaphragm pacing and 45 months (32–not reached) for those receiving non-invasive ventilation alone.

Non-invasive ventilation was initiated in 70 (95%) of 74 patients: 57 (81%) patients started treatment within 2 weeks of randomisation, a further six (9%) patients started within 1 month, and the remaining seven (10%) patients started between 3 months and 11 months

	Non-invasive ventilation plus diaphragm pacing group (n=37)	Non-invasive ventilation alone group (n=37)	Hazard ratio or mean difference* (95% CI)	p value
Primary outcome				
Overall survival (months)	11·0 (8·3 to 13·6)	22·5 (13·6 to not reached)	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 outcomes				
SF-36 (% complete†)	110/154 (72%)	133/174 (76%)	..	..
Aggregate physical health score	23·8 (12·2)	21·3 (12·0)	0·3 (–2·0 to 2·7)	0·780
Aggregate mental health score	42·7 (16·5)	47·7 (17·8)	–3·5 (–7·9 to 0·8)	0·112
SAQLI (% complete†)	110/154 (72%)	132/174 (76%)	..	..
Score	3·9 (1·6)	4·6 (1·5)	–0·3 (–0·7 to 0·1)	0·117
Caregiver Burden Inventory (% complete†)	93/154 (60%)	121/174 (70%)		
Score	28·0 (9·0)	29·6 (11·9)	1·2 (–2·7 to 5·0)	0·558
Post-hoc analyses of primary outcome				
Overall survival by use of non-invasive ventilation (unadjusted)				
No use (<1·0 h)	7·7 (3·4 to 11·6)	Not reached‡	4·67 (1·50 to 14·5)	0·008
Low use (1·0–3·9 h)	10·9 (6·3 to not reached)	13·6 (11·3 to not reached)	1·28 (0·34 to 4·8)	0·719
High use (≥4·0 h)	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 not reached)	2·42 (1·28 to 4·59)	0·007
Post-hoc analyses of patient quality of life				
EQ-5D-3L health state (% complete†)	131/178 (74%)	161/209 (77%)	..	..
Survivors	0·02 (0·37)	0·13 (0·44)	–0·12 (–0·24 to –0·00)	0·056
All patients (zero 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†)	132/178 (74%)	160/209 (77%)	..	..
Survivors	36·0 (25·2)	40·0 (25·7)	–5·6 (–14·5 to 3·2)	0·212
All patients (zero 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†)	109/178 (61%)	148/209 (71%)	..	..
Score	0·78 (0·34)	0·82 (0·25)	–0·08 (–0·17 to 0·01)	0·077
EQ-5D-3L thermometer scale (% complete†)	110/178 (62%)	149/209 (71%)	..	..
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 (SF-36, SAQLI, Caregiver-Burden Inventory, and EQ-5D-3L), unless otherwise indicated. EQ-5D-3L=EuroQol 5D questionnaire 3-level format. SF-36=36-item Short Form Health Survey. SAQLI=Sleep Apnoea Quality of Life questionnaire. *Mean differences from longitudinal analysis of quality-of-life measures. †Completeness is number of questionnaires obtained within time windows as a ratio of the number expected (ie, not including post-death). ‡Median survival not reached. §Not all participants had assigned carers.

Table 2: **Survival and quality of life outcomes**

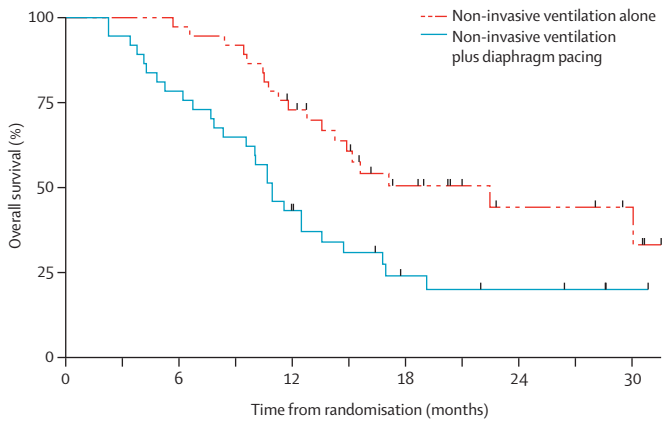

***Figure 2*: Overall survival**
Vertical lines indicate censored patients.

	Non-invasive ventilation plus diaphragm pacing group (n=37)	Non-invasive ventilation alone group (n=37)
Initiated non-invasive ventilation	35 (95%)	35 (95%)
Time of initiation		
During screening or on date of randomisation	13 (37%)	14 (40%)
1–14 days post-randomisation	16 (46%)	14 (40%)
15–28 days post-randomisation	2 (6%)	3 (9%)
>28 days post-randomisation	4 (11%)	4 (11%)
Use of non-invasive ventilation		
Mean time (h)	5·2 (5·1)	4·8 (4·6)
Median time (h)	3·2 (0·5–8·2)	4·6 (0·0–7·8)
No use (<1 h)	10/34 (29%)	10/34 (29%)
Low use (1–3·9 h)	8/34 (24%)	6/34 (18%)
High use (≥4 h)	16/34 (47%)	18/34 (53%)
Patients using diaphragm pacing	31 (84%)	0
Patients not using diaphragm pacing	6 (16%)	NA
Did not undergo surgery	5	NA
Withdrew with minimum usage after technical problems	1	NA
Time to surgery (days; n=32 implanted)		
Within 14	5 (16%)	NA
15–28	12 (38%)	NA
29–56	10 (31%)	NA
>56	5 (16%)	NA
Use of diaphragm pacing		
Mean time (h)	6·2 (4·6)	NA
Median time (h)	4·6 (3·0–8·4)	NA

Data are n (%), n/N (%), mean (SD), or median (IQR), unless otherwise indicated. NA=not applicable.

***Table 3*: Average daily use of non-invasive ventilation and diaphragm pacing after initiation**

(table 3). Non-invasive-ventilation usage was similar between groups (table 3). The appendix shows the association between adherence to non-invasive ventilation and overall survival. Although the difference between the non-invasive ventilation plus pacing and the non-invasive ventilation alone groups was greatest in the non-users subgroup, pacing was not more effective in any of the three subgroups of high, low, or no use (table 2). The association between overall survival and average non-invasive ventilation use was non-significant, with the HR for the linear association 0·97 per additional hour use (95% CI 0·92–1·04; p=0·52). No association was evident with pacing use (HR 1·00 per additional hour use, 95% CI 0·92–1·09; p=0·92).

Five (14%) participants in the pacing group did not undergo surgery because of a rapid decline in respiratory function to lower than the safety threshold for surgery (n=1), patient choice (n=2), and the DMEC intervention (n=2); a sixth patient had technical problems with the device and did not begin regular pacing (figure 1, table 3). Exclusion of these patients from the analysis did not change the findings, with the adjusted HR increasing when non-users were excluded (HR 2·71, 95% CI 1·39–5·27). All participants who underwent surgery had a successful implantation and a diaphragm that could be stimulated. When used, median daily usage was 4·6 h (IQR 3·0–8·4 h), with no association between daily use and survival (table 3). Most participants receiving diaphragm pacing were able to achieve the target pacing settings within 15 days of surgery and continued to titrate successfully over the course of the study as per the study protocol (table 3, appendix). Pacing was well tolerated, with only two (5%) patients choosing to discontinue pacing at months 6 and 12 after starting regular use.

The patient health utility (EQ-5D-3L) score was slightly lower with diaphragm pacing plus non-invasive ventilation than with non-invasive pacing alone, and the differences were significant when a score of zero was imputed to EQ-5D-3L after death (table 2, appendix). Other patient quality-of-life questionnaires were similar between the two groups, as were all carer quality-of-life measures (table 2, appendix). More adverse events were reported in the non-invasive ventilation plus pacing group than in the non-invasive ventilation alone group (162 events [5·9 events per person-year] *vs* 81 events [2·5 events per person-year]; table 4). More patients had serious adverse events in the pacing group than in the non-invasive ventilation alone group (table 4). No patients died within 30 days of procedure; table 4 shows causes of death.

A separate cost-utility analysis was planned; however, in view of the low efficacy of diaphragmatic pacing, this analysis did not proceed. We have included the quality-of-life component of the planned cost-utility analysis from the EQ-5D-3L to complement the SF-36 and SAQLI data. The appendix shows data for health-care resource use. Notably, the number of patients using aids (cough-assist devices, breath stacking, and suction machines) was similar between groups, but those who did use a mechanical cough-assist device or a suction machine tended to do so more in the non-invasive ventilation

	Non-invasive ventilation plus diaphragm pacing group (n=37)				Non-invasive ventilation alone group (n=37)			
	Number of AEs	Patients with an AE	Number of SAEs	Patients with an SAE	Number of AEs	Patients with an AE	Number of SAEs	Patients with an SAE
Any event	162	29 (78%)	46	27 (73%)	81	23 (62%)	31	19 (51%)
Respiratory	45	25 (68%)	29	21 (57%)	19	14 (38%)	13	11 (30%)
Chest infection	20	12 (32%)	10	9 (24%)	11	7 (19%)	6	5 (14%)
Decompensated respiratory failure	10	10 (27%)	10	10 (27%)	5	5 (14%)	5	5 (14%)
Breathless (unclassified)	5	4 (11%)	2	2 (5%)	3	2 (5%)	2	1 (3%)
Pneumothorax or capnothorax	5	5 (14%)	3	3 (8%)	0	0	0	0
Blocked airway	3	1 (3%)	3	1 (3%)	0	0	0	0
Pulmonary embolism	1	1 (3%)	1	1 (3%)	0	0	0	0
Cough	1	1 (3%)	0	0	0	0	0	0
Pain	23	10 (27%)	1	1 (3%)	10	6 (16%)	3	2 (5%)
Gastrointestinal	17	10 (27%)	3	3 (8%)	12	9 (24%)	2	2 (5%)
Symptoms of motor neuron disease	18	8 (22%)	1	1 (3%)	7	3 (8%)	0	0
Insertion or removal of PEG or PIG	9	5 (14%)	6	4 (11%)	10	9 (24%)	9	8 (22%)
Genitourinary	7	3 (8%)	0	0	8	3 (8%)	1	1 (3%)
Infection of PEG or PIG	10	3 (8%)	0	0	2	1 (3%)	0	0
Dermatological	6	3 (8%)	0	0	4	4 (11%)	1	1 (3%)
Wire problems	8	5 (14%)	2	2 (5%)	0	0	0	0
Cardiovascular system	4	4 (11%)	3	3 (8%)	2	2 (5%)	1	1 (3%)
Psychiatric	5	4 (11%)	0	0	0	0	0	0
Non-invasive-ventilation specific	3	3 (8%)	0	0	2	2 (5%)	0	0
Wire infection	4	3 (8%)	0	0	0	0	0	0
CNS	1	1 (3%)	0	0	1	1 (3%)	0	0
Other	2	2 (5%)	1	1 (3%)	4	3 (8%)	1	1 (3%)
Deaths								
Cause of death								
Respiratory failure	..	..	..	16/28	..	..	..	13/19
Chest infection	..	..	..	5/28	..	..	..	2/19
ALS	..	..	..	6/28	..	..	..	4/19
Hypothermia	..	..	..	1/28	..	..	..	0

Data are n (%) or n/N (%), unless otherwise indicated. AE=adverse event. SAE=serious adverse event. PEG=percutaneous endoscopic gastrostomy. PIG=per-oral image-guided gastrostomy. ALS= amyotrophic lateral sclerosis.

Table 4: **Adverse events**

alone group, and those who used breath stacking tended to do so more in the pacing group (appendix).

Discussion

Our findings show that addition of diaphragm pacing to the standard care of non-invasive ventilation was associated with decreased survival in patients with ALS. This result is in contradiction with the FDA SSPB, which reported a survival advantage for diaphragm pacing of 16·1 months from symptom onset and 9 months from the point of initiation of non-invasive ventilation, compared with non-invasive ventilation alone in a historical cohort.[11,18] Median survival from symptom onset in our study was 45 months in the non-invasive ventilation group and 28 months in the pacing group, compared with 56 months in the SSPB pacing study.

The complete dataset from the uncontrolled multicentre cohort study that led to FDA approval of the NeuRx RA/4 Diaphragm Pacing System on humanitarian grounds has to date not been published, although descriptions of safety and efficacy are available for the first 16 patients enrolled in the pilot phase of that study.[19] This partial reporting makes full understanding of the differences in the reported outcomes challenging. Some results are available within the FDA SSPB, in which 144 patients were reported to have been enrolled to the pilot and pivotal phases of that cohort study. The primary inclusion criteria were evidence of residual bilateral phrenic nerve function and an FVC of less than 85% at screening and more than 45% at implantation of the pacing system.[11] 106 (74%) of the 144 participants were implanted with the Pacing System. Details of the 38 (26%) patients who did not undergo implantation are not reported.

To establish whether the NeuRx RA/4 Diaphragm Pacing System met the Humanitarian Device Exemption criteria in ALS, analyses for the FDA SSPB were done in a subgroup of the 106 patients who were implanted. For survival analyses, this subgroup consisted of 84 patients

who met the criteria for Humanitarian Use Device Designation (designation number 10-0242)—ie, patients with ALS with a stimulatable diaphragm and who had chronic hypoventilation. The definition used for chronic hypoventilation was an FVC of less than 50%, a maximum inspiratory pressure less than 60 cm H_2O, a $PaCO_2$ greater than 45 mm Hg, or oxygen saturation less than 88% for 5 consecutive minutes or more overnight. Mean overall survival for implanted patients was 56 months (4·7 years) from disease onset and 19 months (1·6 years) from implantation. No separate control group was included and the study team compared their data with a previously published historical survival dataset for non-invasive ventilation.[18] For this comparison, the investigators selected patients (N=43) from the Humanitarian Use Designation group with an FVC between 45% and 65%. Survival from diagnosis in the historical non-invasive-ventilation dataset (N=43) was 21·4 months, compared with 37·5 months for the pacing and non-invasive ventilation group (p<0·001). Survival from initiation of non-invasive ventilation was 11·9 months for the historical group and 20·9 months for the pacing and non-invasive ventilation group.

The patient population in the present study is characteristic of the ALS population in terms of age, sex, site of onset, and proportion with a clear family history;[20] the population from which the subgroup data used in the FDA SSPB were obtained might be less generalisable to the wider ALS population.[11] The cohort study contained a lead-in phase of 3 months during which time patients were monitored, and not all went on to have implantation. Because of the progressive nature of ALS, some patients might have become ineligible, with their FVC decreasing to less than the study implantation safety threshold of 45% during the 3 months. This possibility might have enriched the implanted population with individuals who have a more slowly progressive disease course. However, whether such enrichment happened is not clear, and other criteria might have been used. Of the 106 patients who were implanted, data for only 84 patients contribute to the SSPB report, with two patients having been lost to follow-up and 20 patients not meeting the Humanitarian Use Device criteria. This cohort is therefore a selected group and might not be generalisable to the wider ALS population. By contrast, we used an intention-to-treat approach in which all consenting participants were analysed, including those who subsequently declined rapidly in either group.

The apparent harm recorded in the pacing group was not obviously due to immediate surgical complications, with no deaths within 30 days of procedure and only one within the first 3 postoperative months. However, a retrospective review of patients with ALS undergoing surgery for any cause showed an apparent acceleration of ALS disease progression post-surgery, suggesting a potential disease-modifying effect, albeit one that is not fully understood.[21] The survival differences in our study might partly be explained by such a process, which supports previous wider concerns regarding the undertaking of operative procedures in individuals with ALS. A further possibility is that the harm is due to a direct effect of the pacing, perhaps because stimulation of already damaged motor neurons is harmful. The physiological effects of pacing have not been studied in human beings. Findings from studies of canine and rodent models show that neuromuscular damage can be induced dependent on the parameters of pacing and that the effects recorded differ between healthy and disease models.[7,22] A simpler explanation could be that pacing causes excessive muscle fatigue, or that asynchrony between pacing-induced diaphragm contraction and breaths triggered by patients or non-invasive ventilation is an issue. We cannot exclude the possibility that a small subgroup of patients might benefit from diaphragm pacing. One particular group who might have most to gain from pacing would be low users of non-invasive ventilation—eg, patients with significant bulbar dysfunction. However, we noted the greatest difference in survival in low users of non-invasive ventilation; therefore, diaphragm pacing alone cannot be recommended as an alternative to non-invasive ventilation. Because of the small sample size, we are unable to make meaningful attempts to investigate possible subgroup effects further.

Our study has some limitations. Patients allocated to diaphragm pacing underwent surgical intervention and could not be masked to the intervention. The study assessors were also unmasked to the intervention. The trial statistician (MJB) was unmasked and gave survival data to the DMEC but withheld accumulating data from the study team. Because the primary outcome measure was objective (overall survival), the risk of bias is small, but some risk is unavoidable in the subjective patient-reported secondary outcome measures. We considered inserting the pacing devices in patients receiving non-invasive ventilation alone, but not connecting them (sham pacing), to reduce the risk of bias and be able to offer pacing to control patients at the end of the 12 month follow-up period, but concluded that this approach would be less rational in the event of an outcome showing no benefit of pacing. The effect of pacing on the ongoing use of non-invasive ventilation was a concern, and we asked whether patients stopped using the non-invasive ventilation system, which has established survival benefit, in favour of the pacing system. However, daily periods of non-invasive ventilation use were similar across both groups. Minor imbalances exist between the treatment groups in our study, with patients in the pacing group being slightly older than those in the non-invasive ventilation alone group. We have adjusted the hazard ratios for the covariate of age and propose that such a small age difference is unlikely to have had a large effect on ALS survival. Similar numbers of patients across each group were reported to receive additional respiratory interventions. However, we noted differences across the treatment groups in the

frequency of use of cough-assist devices, suction machines, and breath-stacking techniques among individuals given devices. The effects of these differences are unknown, but again, are unlikely to explain the poor survival in the non-invasive ventilation plus pacing group.

In conclusion, 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. Our findings suggest that insertion of the NeuRx RA/4 Diaphragm Pacing System at the point an individual with ALS develops respiratory insufficiency is harmful. Whether there is a point earlier in the disease trajectory when implantation and pacing might be of benefit is unknown and is currently being investigated (ClinicalTrials.gov, number NCT01583088). A poor prognosis and the absence of curative treatment understandably encourage a nothing to lose approach in patients and some clinicians alike, with an attendant lowering of the standards of evidence needed to adopt a new intervention.[23] Our findings show the potential for harm that can arise from adopting this approach.

Contributors

CJM was the chief investigator who oversaw all study conduct; helped develop all study materials including the trial protocol; assessed participant eligibility, and assisted with participant recruitment and data collection at the Sheffield site; participated in data analysis and interpretation of the results; and drafted and revised the manuscript. MJB was the trial statistician, providing advice and input to all statistical issues; compiled study reports; completed final data analysis and interpretation of results; and revised the manuscript. CM was the trial manager who coordinated all study activities, helped develop all study materials including the protocol and subsequent amendments, set up and provided training to sites, facilitated recruitment and collection of data from all sites, and revised the manuscript. CLC provided oversight to the trial design, helped develop study materials including the trial protocol, provided oversight to trial conduct, and revised the manuscript. WOB and SKB were the qualitative researchers providing advice and input into all the qualitative components, undertook qualitative interviews, completed qualitative data analysis and interpreted qualitative results, and revised the manuscript. SCB provided methodological input to the trial, completed data analysis and interpretation of results, and revised the manuscript. II, AB, JE, ME, COH, PH, RWO, PJS, KT, and TW were the principal investigators at research sites; assisted with development of the protocol and other study materials; referred or actively recruited participants at sites, assessed participant eligibility, delivered the trial interventions (including provision of non-invasive ventilation or switching on diaphragm pacing, and making setting changes), and assisted with data collection; interpreted results; and revised the manuscript. RA, RB, SG, DK, NM, and AKS were the surgeons at research sites, implanted the pacing system, and revised the manuscript. CY, AKS, LT, RL, and RD were external members of the trial steering committee, provided overall oversight to trial conduct, and revised the manuscript.

DiPALS Study Group Collaborators

University of Sheffield: Christopher J McDermott (chief investigator), Pamela J Shaw (principal investigator), Cindy L Cooper, Simon Dixon, Wendy O Baird, Mike J Bradburn, Patrick Fitzgerald, Chin Maguire; *Newcastle-upon-Tyne Hospitals NHS Foundation Trust:* Tim Williams (principal investigator), Simon V Baudouin, Dayalan Karat; *Oxford University Hospitals NHS Trust:* Kevin Talbot (principal investigator), John Stradling, Nick Maynard, Martin Turner; *Sheffield Teaching Hospitals NHS Foundation Trust*: Stephen Bianchi, Roger Ackroyd; *Northumbria Healthcare NHS Foundation Trust*: Stephen C Bourke; *Salford Royal Hospital NHS Foundation Trust:* John Ealing, Hisham Hamdalla; *University Hospital of South Manchester NHS Foundation Trust:* Andrew Bentley (principal investigator), Simon Galloway; *Royal Free London NHS Foundation Trust:* Richard W Orrell (principal investigator), Wisia Wedzicha; *Leeds Teaching Hospitals NHS Trust:* Mark Elliot; *Plymouth Hospitals NHS Trust:* Philip Hughes; *Plymouth University Peninsula Medical and Dental Schools:* C Oliver Hanemann.

DiPALS Writing Committee

University of Sheffield: Christopher J McDermott (chief investigator), Mike J Bradburn, Chin Maguire, Cindy L Cooper, Wendy O Baird, Susan K Baxter; *Northumbria Healthcare NHS Foundation Trust:* Stephen C Bourke; *South Devon Healthcare NHS Foundation Trust:* Ibrahim Imam; *University Hospital of South Manchester NHS Foundation Trust:* Andrew Bentley; *Salford Royal Hospitals NHS Foundation Trust:* John Ealing; *Leeds Teaching Hospitals NHS Trust:* Mark Elliott; Plymouth University Peninsula Medical and Dental Schools: C Oliver Hanemann; *Plymouth Hospitals NHS Trust:* Philip Hughes; *Royal Free London NHS Foundation Trust:* Richard W Orrell; *University of Sheffield:* Pamela J Shaw; *Oxford University Hospitals NHS Trust:* Kevin Talbot; *Newcastle-upon-Tyne Hospitals NHS Foundation Trust:* Tim Williams; *Sheffield Teaching Hospitals NHS Foundation Trust:* Roger Ackroyd; *Plymouth Hospitals NHS Trust:* Richard Berrisford; *University Hospital of South Manchester NHS Foundation Trust:* Simon Galloway; *Newcastle-upon-Tyne Hospitals NHS Foundation Trust:* Dayalan Karat; *Oxford University Hospitals NHS Trust:* Nick Maynard; *Leeds Teaching Hospitals NHS Trust:* Abeezar Sarela; *Walton Centre for Neurology & Neurosurgery NHS Foundation Trust:* Carolyn Young; *NIHR Respiratory Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust:* Anita K Simonds; *PAREXEL:* Lyn Taylor; *Motor Neurone Disease Association:* Roger Leek; *Independent PPI:* Roy Darlison.

Data Monitoring and Ethics Committee

Brighton and Sussex Medical School: Nigel Leigh (independent chair); *University of London:* Michael Dewey (independent statistician); *Royal London Hospital:* Aleksandar Radunovic (independent clinician).

Declaration of interests

CJM reports grants from the National Institute for Health Research Health Technology Assessment Programme and the Motor Neuron Disease Association; and non-financial support from Synapse Biomedicalc, both during the conduct of the study and outside the submitted work. CM reports grants from the Motor Neuron Disease Association and non-financial support from Synapse Biomedical during the conduct of the study. AB reports honoraria and travel subsistence from Bio Marin to attend a Clinical Advisory Group in Berlin in April, 2015, on respiratory management of mucoploysaccharoidoses. AS reports membership of a steering committee of trial of adaptive servo ventilation in heart-failure patients with predominant obstructive sleep apnoea (Serve-HF). LT reports personal fees from PAREXEL International Corporation, outside the submitted work. RWO reports grants from the Motor Neurone Disease Association of England, Wales and Northern Ireland. RL is a member of the Motor Neurone Disease Association. All other authors declare no competing interests.

Acknowledgments

We thank the patients and carers who participated in this study and our funders for making this research possible. We gratefully acknowledge the hard work, support, and advice from Helen Wollff, Gail Mills, Alison Proctor, Theresa Walsh, and Muhammad K Rafiq (Sheffield Teaching Hospitals NHS Foundation Trust); Rachael Marsden and Hania Piotrowska (Oxford University Hospitals NHS Trust); Steven Dodds (The Newcastle-upon-Tyne Hospitals NHS Foundation Trust); Katie Lynch (University Hospital of South Manchester NHS Foundation Trust); Craig Armstrong and Clair Favager (Leeds Teaching Hospitals NHS Trust); Mark Baker and Concetta Brugaletta (Royal Free London NHS Foundation Trust) for participant screening, administering of the intervention, and data collection; and Hannah Cantrill (University of Sheffield) for data collection and study monitoring. CJM, PJS, and KT are supported by the EU Joint Programme—Neurodegenerative Disease Research (UK Medical Research Council and Economic and Social Research Council). PJS is supported as an National Institute for Health Research (NIHR) senior investigator. We acknowledge the support of the

NIHR Experimental Medicine Clinical Research Facility at Sheffield Teaching Hospitals. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS, or UK Department of Health. This study was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 09/55/33) and the Motor Neurone Disease Association of England, Wales, and Northern Ireland.

References

1 Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 2008; **79:** 6–11.

2 Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med* 1994; **330:** 585–91.

3 Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. *Lancet* 1996; **347:** 1425–31.

4 Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006; **5:** 140–47.

5 Gruis KL, Brown DL, Schoennemann A, Zebarah VA, Feldman EL. Predictors of noninvasive ventilation tolerance in patients with amyotrophic lateral sclerosis. *Muscle Nerve* 2005; **32:** 808–11.

6 O'Neill CL, Williams TL, Peel ET, et al. Non-invasive ventilation in motor neuron disease: an update of current UK practice. *J Neurol Neurosurg Psychiatry* 2012; **83:** 371–76.

7 Amirjani N, Kiernan MC, McKenzie DK, Butler JE, Gandevia SC. Is there a case for diaphragm pacing for amyotrophic lateral sclerosis patients? *Amyotroph Lateral Scler* 2012; **13:** 521–27.

8 Onders RP, DiMarco AF, Ignagni AR, Mortimer JT. The learning curve for investigational surgery: lessons learned from laparoscopic diaphragm pacing for chronic ventilator dependence. *Surg Endosc* 2005; **19:** 633–37.

9 Onders RP, Carlin AM, Elmo M, Sivashankaran S, Katirji B, Schilz R. Amyotrophic lateral sclerosis: the Midwestern surgical experience with the diaphragm pacing stimulation system shows that general anesthesia can be safely performed. *Am J Surg* 2009; **197:** 386–90.

10 Onders RP, Elmo M, Khansarinia S, et al. Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. *Surg Endosc* 2009; **23**: 1433–40.

11 US Food and Drug Administration. Summary of safety and probable benefit (SSPB). 2011. http://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006b.pdf (accessed April 11, 2015).

12 Scherer K, Bedlack RS. Diaphragm pacing in amyotrophic lateral sclerosis: a literature review. *Muscle Nerve* 2012; **46:** 1–8.

13 McDermott CJ, Maguire C, Cooper CL, et al. Protocol for diaphragm pacing in patients with respiratory muscle weakness due to motor neurone disease (DiPALS): a randomised controlled trial. *BMC Neurol* 2012; **12:** 74.

14 Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000; **1:** 293–99.

15 EuroQol G. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16:** 199–208.

16 Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983; **39:** 499–503.

17 StataCorp. Stata statistical software. College Station, TX: StataCorp, 2009.

18 Lechtzin N, Scott Y, Busse AM, Clawson LL, Kimball R, Wiener CM. Early use of non-invasive ventilation prolongs survival in subjects with ALS. *Amyotroph Lateral Scler* 2007; **8:** 185–88.

19 Onders RP, Elmo M, Kaplan C, Katirji B, Schilz R. Final analysis of the pilot trial of diaphragm pacing in amyotrophic lateral sclerosis with long-term follow-up: diaphragm pacing positively affects diaphragm respiration. *Am J Surg* 2014; **207:** 393–97.

20 Hoppitt T, Pall H, Calvert M, et al. A systematic review of the incidence and prevalence of long-term neurological conditions in the UK. *Neuroepidemiology* 2011; **36:** 19–28.

21 Pinto S, Swash M, de Carvalho M. Does surgery accelerate progression of amyotrophic lateral sclerosis? *J Neurol Neurosurg Psychiatry* 2014; **85:** 643–46.

22 Lepore AC, Tolmie C, O'Donnell J, et al. Peripheral hyperstimulation alters site of disease onset and course in SOD1 rats. *Neurobiol Dis* 2010; **39:** 252–64.

23 Sense about Science. I've got nothing to lose by trying it. 2013. http://www.senseaboutscience.org/resources.php/136/ive-got-nothing-to-lose-by-trying-it (accessed July 21, 2015).