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**National Institute for
Health Research**

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Abstract

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease resulting in death, usually from respiratory failure, within 2–3 years of symptom onset. Non-invasive ventilation (NIV) is a treatment that when given to patients in respiratory failure leads to improved survival and quality of life. Diaphragm pacing (DP), using the NeuRx/4[®] diaphragm pacing system (DPS)[™] (Synapse Biomedical, Oberlin, OH, USA), is a new technique that may offer additional or alternative benefits to patients with ALS who are in respiratory failure.

Objective: The Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis (DiPALS) trial evaluated the effect of DP on survival over the study duration in patients with ALS with respiratory failure.

Design: The DiPALS trial was a multicentre, parallel-group, open-label, randomised controlled trial incorporating health economic analyses and a qualitative longitudinal substudy.

Participants: Eligible participants had a diagnosis of ALS (ALS laboratory-supported probable, clinically probable or clinically definite according to the World Federation of Neurology revised El Escorial criteria), had been stabilised on riluzole for 30 days, were aged ≥ 18 years and were in respiratory failure. We planned to recruit 108 patients from seven UK-based specialist ALS or respiratory centres. Allocation was performed using 1 : 1 non-deterministic minimisation.

Interventions: Participants were randomised to either standard care (NIV alone) or standard care (NIV) plus DP using the NeuRX/4 DPS.

Main outcome measures: 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 by European Quality of Life-5 Dimensions, three levels (EQ-5D-3L), Short Form questionnaire-36 items and Sleep Apnoea Quality of Life Index questionnaire]; carer quality of life (EQ-5D-3L and Caregiver Burden Inventory); cost–utility analysis and health-care resource use; tolerability and adverse events. Acceptability and attitudes to DP were assessed in a qualitative substudy.

Results: In total, 74 participants were randomised into the trial and analysed, 37 participants to NIV plus pacing and 37 to standard care, before the Data Monitoring and Ethics Committee advised initial suspension of recruitment (December 2013) and subsequent discontinuation of pacing (on safety grounds) in all patients (June 2014). Follow-up assessments continued until the planned end of the study in December 2014. The median survival (interquartile range) was 22.5 months (lower quartile 11.8 months; upper quartile not reached) in the NIV arm and 11.0 months (6.7 to 17.0 months) in the NIV plus pacing arm, with an adjusted hazard ratio of 2.27 (95% confidence interval 1.22 to 4.25; $p = 0.01$).

Conclusions: Diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure.

Future work: It may be that certain population subgroups benefit from DP. We are unable to explain the mechanism behind the excess mortality in the pacing arm, something the small trial size cannot help address. Future research should investigate the mechanism by which harm or benefit occurs further.

Trial registration: Current Controlled Trials ISRCTN53817913.

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Contents

List of tables	xiii
List of figures	xv
List of boxes	xvii
List of abbreviations	xix
Plain English summary	xxi
Scientific summary	xxiii
Chapter 1 Introduction	1
Management of amyotrophic lateral sclerosis	1
Evidence for diaphragm pacing in amyotrophic lateral sclerosis	1
Research objectives	2
Chapter 2 Methods	3
Trial design	3
Participants and eligibility criteria	3
<i>Inclusion criteria</i>	3
<i>Exclusion criteria</i>	4
Participant identification	4
Recruitment	4
Screening	5
Randomisation and blinding	5
Interventions	7
<i>Non-invasive ventilation</i>	7
<i>Diaphragm pacing system</i>	7
<i>Surgical implantation</i>	8
<i>Evaluation of electrodes and diaphragm pacing system training</i>	9
Outcomes	10
<i>Primary outcome</i>	10
<i>Secondary outcomes</i>	10
<i>Follow-up visits</i>	10
Data collection and management	10
<i>Data collection forms</i>	10
Database	10
Methods used for treatment allocation, sequence concealment and blinding	11
Sample size	11
Early stopping	12
Statistical methods	12
<i>Survival</i>	12
<i>Quality of life</i>	12
<i>Non-invasive ventilation and diaphragm pacing usage</i>	13
<i>Health resource use</i>	14
<i>Additional outcomes: Amyotrophic Lateral Sclerosis Functional Rating Scale and respiratory function</i>	14

Adverse events	14
General analysis considerations	14
Economic evaluation	15
Research governance	15
Sponsorship	15
Oversight committees	15
Research Ethics Committee	15
Medicines and Healthcare products Regulatory Agency	15
Serious adverse events	15
Protocol non-compliances	15
Monitoring and reporting	16
Important changes to methods after trial commencement	16
Patient and public involvement	18
Proposal development	18
During the trial	18
Study oversight	18
Study dissemination	18
Chapter 3 Early stopping	19
Recruitment suspension	19
Informing the Research Ethics Committee	20
Withdrawal of participants from diaphragm pacing system	20
Formal stopping of recruitment	21
Informing Research Ethics Committee, participants and investigators	21
Chapter 4 Trial results	23
Recruitment and participant flow	23
Baseline data	24
Primary outcome (overall survival)	25
Primary overall survival analyses	25
Overall survival at Data Monitoring and Ethics Committee intervention	26
Subgroup analyses of overall survival (preplanned)	26
Non-invasive ventilation and pacing usage	32
Non-invasive ventilation use	32
Pacing use	33
Overall survival by non-invasive ventilation and pacing	36
Non-invasive ventilation use and overall survival	36
Pacing use and overall survival	39
Non-invasive ventilation, pacing and overall survival	39
Secondary outcomes	41
Tracheostomy and tracheostomy-free survival	41
Participant quality of life	41
Carer quality of life	44
Relationship between quality of life, pacing and baseline symptoms	46
Resource use	47
Safety	48
Adverse events	48
Serious adverse events	49
Adverse events related to surgery or pacing	50
Cause of death	50
Physiological measurements	52

Chapter 5 Qualitative substudy	65
Outcomes	65
Qualitative substudy methods	65
<i>Sampling</i>	65
<i>Data collection</i>	65
Data analysis methods	66
Participant characteristics	66
<i>Usage of the diaphragm pacing system</i>	66
Results	66
<i>Patient and carer experiences</i>	66
<i>The surgery</i>	67
<i>Operating the equipment</i>	68
<i>Impact on life</i>	70
<i>Perceived outcomes</i>	73
Chapter 6 Discussion	75
Main findings	75
Survival in relation to non-invasive ventilation and diaphragm pacing use and compliance	76
Qualitative study	76
Understanding the results	77
The results of the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial in context	78
The Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial population compared with other studies of diaphragm pacing	78
Delivery of diaphragm pacing in the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial compared with other studies	79
Other confounders	79
Limitations	79
Developments since the completion of the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial	80
Chapter 7 Conclusions	81
Meaning of the study and implications for clinicians or policy-makers	81
Recommendations for future research	81
Acknowledgements	83
References	87
Appendix 1 Changes to protocol	91
Appendix 2 Trial summary	95
Appendix 3 Participant flow in each trial arm	97
Appendix 4 Screening and randomisation	99
Appendix 5 Patient information sheet: patient	101
Appendix 6 Patient information sheet: carer	107
Appendix 7 Patient information sheet: patient qualitative	111

Appendix 8 Patient information sheet: carer qualitative	115
Appendix 9 Consent form: patient	119
Appendix 10 Consent form: carer	121
Appendix 11 Consent form: patient qualitative	123
Appendix 12 Consent form: carer qualitative	125
Appendix 13 Statistical analysis plan	127
Appendix 14 Stop pacing patient letter (diaphragm pacing arm)	171
Appendix 15 Stop pacing patient letter (non-invasive ventilation arm)	175
Appendix 16 Stop pacing general practitioner cover letter (diaphragm pacing arm)	177
Appendix 17 Pacing discontinuation standard operating procedure	179
Appendix 18 Qualitative interview topic guide	183

List of tables

TABLE 1 Overview of components of DPS	8
TABLE 2 Baseline data	24
TABLE 3 Sensitivity analyses	27
TABLE 4 Statistical significance of the overall survival difference during data collection	27
TABLE 5 Average daily NIV usage after initiation	33
TABLE 6 NIV settings at initiation and at final visit	34
TABLE 7 NeuRX RA/4 DPS settings	35
TABLE 8 Pacing usage	36
TABLE 9 Overall survival by bulbar function and by NIV use	38
TABLE 10 Quality of life	42
TABLE 11 Resource use	47
TABLE 12 Adverse events	48
TABLE 13 Serious adverse events	49
TABLE 14 Adverse events related to pacing	51
TABLE 15 Cause of death	52
TABLE 16 Changes to protocol	91

List of figures

FIGURE 1 Participant flow diagram	6
FIGURE 2 Trial profile (CONSORT diagram)	23
FIGURE 3 Overall survival	26
FIGURE 4 Survival at 10 December 2013	28
FIGURE 5 Survival at 10 June 2014	28
FIGURE 6 Overall survival by bulbar function	29
FIGURE 7 Overall survival by NIV use	31
FIGURE 8 Average daily NIV usage after initiation	33
FIGURE 9 Survival by NIV use: NIV use in hours	37
FIGURE 10 Survival by NIV use: NIV use category	38
FIGURE 11 Survival by pacing use	39
FIGURE 12 Relationship between NIV and pacing use	40
FIGURE 13 Overall survival by pacing and NIV use	40
FIGURE 14 The EQ-5D-3L health utility among surviving participants over time: EQ-5D-3L health tariff	41
FIGURE 15 The EQ-5D-3L health utility among surviving participants over time: patient EQ-5D-3L health tariff, deaths imputed as zero	42
FIGURE 16 The SF-36 aggregate physical health component	44
FIGURE 17 The SF-36 aggregate mental health component	44
FIGURE 18 Sleep Apnoea Quality of Life Index	45
FIGURE 19 Carer EQ-5D-3L health tariff	45
FIGURE 20 Caregiver Burden Inventory	45
FIGURE 21 Change (12 months – baseline) in SAQLI score in relation to baseline SAQLI score (Q12–Q14)	46
FIGURE 22 Change (12 months – baseline) in SAQLI score in relation to baseline ALSRFS-r sum (Q11–Q12)	46
FIGURE 23 Forced vital capacity against time for implanted participants	53

FIGURE 24	Forced vital capacity against time for non-implanted participants	55
FIGURE 25	The $PaCO_2$ against time for implanted participants	57
FIGURE 26	The $PaCO_2$ against time for non-implanted participants	58
FIGURE 27	The ALSRFS-R score against time for implanted participants	60
FIGURE 28	The ALSRFS-R score against time for non-implanted participants	62
FIGURE 29	The patient journey trialling DP	67

List of boxes

BOX 1 Adverse events related to surgery or pacing

50

List of abbreviations

AE	adverse event	HUD	humanitarian-use device
ALS	amyotrophic lateral sclerosis	IQR	interquartile range
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised	NIV	non-invasive ventilation
CBI	Caregiver Burden Inventory	$PaCO_2$	partial pressure of carbon dioxide
CI	confidence interval	PI	principal investigator
CONSORT	Consolidated Standards of Reporting Trials	PPI	patient and public involvement
CTRU	Clinical Trials Research Unit	QoL	quality of life
DiPALS	Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial	RCT	randomised controlled trial
DMEC	Data Monitoring and Ethics Committee	REC	Research Ethics Committee
DP	diaphragm pacing	SAE	serious adverse event
DPS	diaphragm pacing system	SAQLI	Sleep Apnoea Quality of Life Index questionnaire
EPG	external pulse generator	SF-36	Short Form questionnaire-36 items
EQ-5D-3L	European Quality of Life-5 Dimensions, three levels	SMNDRAG	Sheffield Motor Neurone Disease Research Advisory Group
FDA	Food and Drug Administration	SNIP	Sniff Nasal Inspiratory Pressure
FVC	forced vital capacity	SOP	standard operating procedure
GP	general practitioner	SSPB	summary of safety and probable benefit document
HDE	humanitarian device exemption	TFS	tracheostomy-free survival
HR	hazard ratio	TMG	Trial Management Group
		TSC	Trial Steering Committee

Plain English summary

The research study aimed to compare two different treatments [non-invasive ventilation alone or non-invasive ventilation given alongside diaphragm pacing (DP)] for patients experiencing breathing difficulties due to amyotrophic lateral sclerosis (ALS). ALS is another name for motor neurone disease. Non-invasive ventilation is the treatment patients usually get where they wear a face mask and air is pushed into the lungs to help breathing. DP is a possible alternative treatment in which wires are inserted into the main breathing muscle to stimulate it directly to help patients breathe. The main outcomes of the study were to see if the addition of DP improved patient survival (how long patients lived) and improved quality of life.

We conducted our research in seven UK hospitals and enrolled 74 patients to the study (37 patients in each treatment group). Patients were enrolled between December 2011 and December 2013. The study stopped early based on recommendations from the committee charged with guarding patient safety. The committee felt that DP might be causing harm to patients. Patients in the group given DP alongside standard treatment had worse average survival (11.0 months) than those in the standard treatment only (non-invasive ventilation) group (22.5 months).

Based on study results, DP should not be used as routine treatment in ALS patients with breathing problems.

Scientific summary

Background

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease resulting in death, usually from respiratory failure, within 2–3 years of symptom onset. Affected individuals experience increasing weakness affecting the limbs, speech and swallowing, and breathing. Management is largely aimed at easing symptoms and supporting patients to maximise their function through a multidisciplinary approach. One treatment, riluzole, can marginally slow down disease progression, prolonging survival, usually by around 3 months.

Non-invasive ventilation (NIV) is a treatment that, when given to patients in respiratory failure, leads to improved survival and quality of life (QoL). A randomised controlled trial (RCT) demonstrated an improvement in QoL and a median survival benefit of approximately 7 months ($p = 0.006$) in ALS patients using NIV who had good bulbar function. However, some individuals are unable to tolerate using the mask and there comes a point in the course of the disease when NIV is no longer effective.

The NeuRX® RA/4 diaphragm pacing system (DPS)[™] (Synapse Biomedical, Oberlin, OH, USA) is a four-channel percutaneous neuromuscular stimulation system that may offer additional or alternative benefits to patients with ALS in respiratory failure. Stimulating electrodes are inserted into the undersurface of the diaphragm, using a minimally invasive laparoscopic technique. The leads (including an additional anode) are then tunnelled to an exit site on the abdomen and an external stimulator delivers the stimulus pulses.

Initial experience with the NeuRX RA/4 DPS in the spinal cord injury population suggested diaphragm pacing (DP) could reduce time spent on mechanical ventilation. The NeuRX RA/4 DPS is now licensed for use in spinal cord injury across many countries, including the USA, and within the European Union.

To date, the evidence base for DPS in the ALS population is limited to a case series and one uncontrolled, multicentre cohort study for which the full data have not been published. Their findings are consistent with those from the spinal cord patient population, and highlighted the apparent simplicity and operative safety of the NeuRX RA/4 DPS. The US Food and Drug Administration approved the NeuRX RA/4 DPS as a humanitarian-use device in ALS following the submission of a humanitarian device exemption application. Following the humanitarian-use device approval of the NeuRX RA/4 DPS for ALS there has been increasing use of this therapeutic option worldwide. The promising survival data, lack of apparent harm and absence of alternatives have made this an appealing option, especially among patients who are unable to tolerate NIV, who may account for up to 50% of patients with ALS. Moreover, pacing is expensive and it is not known if DPS would meet the National Institute for Health and Care Excellence threshold for cost-effective interventions for end-of-life care. Therefore, although the preliminary data are promising, DPS is unlikely to be widely introduced without robust, randomised evidence together with formal analysis of cost-effectiveness. This was our motivation for undertaking the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis (DiPALS) trial.

Objectives

The aim of this study was to perform a definitive RCT of the efficacy and long-term safety of the NeuRX RA/4 DPS when used in addition to NIV, compared with standard care of NIV alone in patients with ALS.

We planned to test the following specific hypothesis:

- The use of DPS in addition to NIV will improve overall patient survival.

We also planned to evaluate the effect of DP in addition to NIV on:

- QoL of participants
- QoL of the main carer
- safety [adverse events (AEs)] and tolerability (withdrawal from treatment)
- quality-adjusted life-years
- views and perceptions of patients and family carers regarding acceptability and impact on life.

Methods

The DiPALS trial was a multicentre, parallel-group, open-label RCT incorporating health economic analyses and a qualitative longitudinal substudy. Patients aged 18 years or above with a confirmed diagnosis of ALS (familial or sporadic ALS diagnosed as laboratory-supported probable, probable, or definite according to the World Federation of Neurology El Escorial criteria) were identified from seven participating UK hospitals. Patients were confirmed as eligible for the trial if they had been stabilised on riluzole therapy and had respiratory insufficiency and clinically acceptable bilateral phrenic nerve function.

Respiratory insufficiency was determined by one or more of:

1. forced vital capacity (FVC) < 75% predicted
2. supine vital capacity < 75% of sitting or standing vital capacity
3. sniff nasal inspiratory pressure (SNIP) < 65 cmH₂O for men or 55 cmH₂O for women in the presence of symptoms
4. SNIP < 40 cmH₂O in the absence of symptoms
5. partial pressure of carbon dioxide ($PaCO_2$) > 6 kPa (daytime) or $PaCO_2$ > 6.5 kPa (overnight)
6. significant overnight O₂ desaturation (> 5% of night with peripheral capillary oxygen saturation < 90%).

Phrenic nerve function defined as clinically acceptable by:

1. absence of paradoxical abdominal wall movement during a sniff manoeuvre (sharp inhalation through the nose) and recording < 10% decline of FVC when moving from sitting to supine position, or
2. on ultrasound: evidence of at least 1 cm of downward diaphragm movement independent of thoracic or abdominal wall movement during the patient performing a sniff manoeuvre.

Patients were not recruited to the trial if they met any of the exclusion criteria:

1. prior NIV prescription
2. pre-existing implanted electrical device such as pacemaker or cardiac defibrillator
3. underlying cardiac or pulmonary diseases, or other disorders that would affect pulmonary tests independently of ALS (increased risk of general anaesthesia or adverse effect on survival over the course of the study)
4. women who were pregnant or breastfeeding at the time of screening

5. significant decision-making incapacity (patient suffered from major depression, schizophrenia, dementia or similar disorder) preventing informed consent by the patient
6. marked obesity affecting surgical access to diaphragm or significant scoliosis/chest wall deformity
7. the involvement in any respiratory trial that could have influenced the safety or outcome measures of the study within 3 months of the planned implantation of the device or during the year of follow-up
8. pre-existing diaphragm abnormality such as a hiatus hernia or paraoesophageal hernia of abdominal contents ascending into the thoracic cavity
9. FVC < 50% predicted or SNIP < 30 cmH₂O in patients unable to perform FVC (bulbar patients) (because of potential anaesthetic risk).

Recruited patients were randomly allocated to treatment group using a centralised randomisation system. Patients were allocated their treatment (NIV alone or NIV plus DPS) by method of minimisation, using baseline bulbar function, baseline FVC, age and sex as the minimisation factors.

The primary outcome was overall survival. Secondary outcomes were quality-adjusted life-years [European Quality of Life-5 Dimensions, three levels (EQ-5D-3L)], QoL of the patient (EQ-5D-3L, Short Form questionnaire-36 items and Sleep Apnoea Quality of Life Index questionnaire); QoL of the main carer (EQ-5D-3L and Caregiver Burden Inventory); safety and tolerability of the device; health economic objectives and resource use; and perceptions of patients and carers regarding acceptability and impact of the device.

Follow-up visits were conducted at clinic (1 week, and at 2 months, 3 months, 6 months, 9 months and 12 months). Trial data were collected on the study case report form and patient diary and were entered into a validated bespoke web-based database system (Prospect) managed by the Sheffield Clinical Trials Research Unit (CTRU). Sheffield CTRU has developed Prospect in collaboration with epiGenesys (a software development company wholly owned by the University of Sheffield). Prospect's validation status reflects our approach of continuous development, so is not identified by a formal version number or release date. The source code version control system records all changes and associates these with a specific revision number. Prospect is hosted on servers operated by the University of Sheffield Corporate Information and Computing Services (CiCS) department.

We planned to recruit 108 patients (54 per group) to ensure a power of 85% using a two-sided type I error of 5%. The sample size was estimated based on log-rank test, using Simpson's rule, and estimated on a conservative (but clinically important) 1-year difference in survival of 45% versus 70%, which produced the estimated hazard ratio (HR) of 0.45.

Statistical analyses were by intention to treat, with preplanned secondary analyses of overall survival based on protocol adherence and NIV use. A significance level of 5% was used for significance testing, and all confidence intervals (CIs) were two-sided 95% intervals.

The primary end point was overall survival, defined as the time from randomisation to death from any cause. Overall survival was compared between the groups using the log-rank test and modelled using Cox proportional hazards regression, with the minimisation factors as covariates. QoL was analysed both longitudinally (i.e. over the duration of the trial rather than individual time points) and at the end of the study follow-up (12 months).

Average NIV use was defined as the average number of hours used from the date of NIV initiation onwards, and DPS usage was defined as the average daily use from the date of procedure onwards. The relationship between NIV and DPS usage by time point was also assessed. NIV use by participants was categorised as non-adherence (typical usage below 1 hour per day), low adherence (typical usage 1 to < 4 hours per day) or good adherence (typically \geq 4 hours per day).

Adverse events and serious AEs were coded by the chief investigator blind to the participant's treatment group. AEs were summarised for each AE category and overall as the number and percentage of patients affected and the number of events in total (as the same AE may occur more than once in the same patient).

Sheffield Teaching Hospitals NHS Foundation Trust sponsored the trial (reference STH15625). Oversight committees were established to govern study conduct: a Trial Management Group, a Trial Steering Committee and a Data Monitoring and Ethics Committee (DMEC). The trial was conducted in accordance with CTRU standard operating procedures with committees convening at appropriate intervals as dictated by both study requirements and standard operating procedures.

Qualitative substudy

A qualitative longitudinal study formed a subelement of the trial design.

The aim of the qualitative component was to evaluate the acceptability and perceived impact of the intervention on patients with ALS and their family.

Methods

We purposively selected participants for the qualitative element of the study from those randomised to the pacing intervention arm of the trial. We intended that our sample would include diversity in terms of patient sex, age and ALS type and across the different ALS centres taking part in the trial.

Qualitative interviews with patients and carers were carried out at two time points: 1 month following initiation of the pacing intervention and, when possible, 6 months later.

Early stopping

The DMEC recommended early stopping of the trial on safety grounds following review of unblinded survival data. The DMEC advised initial suspension of recruitment (December 2013), and subsequent discontinuation of pacing in all patients (June 2014).

Results (research findings)

In total, 74 participants (37 per arm) were randomised between 5 December 2011 and 18 December 2013, when the DMEC recommended that recruitment cease. Study follow-up concluded in December 2014, by which time 47 patients had died; one patient was last followed up in August 2014, with the remaining 26 known to be alive in December 2014.

The median survival (interquartile range) was 22.5 months (lower quartile, 11.8 months; upper quartile not reached) months in the NIV arm and 11.0 months (6.7–17.0 months) in the NIV plus pacing arm, with an adjusted HR of 2.27 (95% CI 1.22 to 4.25; $p = 0.01$). Patient QoL during 12-month follow-up was lower in the NIV plus pacing arm when assessed by EQ-5D-3L, but was similar on other measures. Carer QoL was similar on all measures.

Non-invasive ventilation was initiated in 70 out of 74 patients. Overall, 57 patients were initiated within 2 weeks of randomisation, a further six within 1 month and the remaining seven between 3 and 11 months. NIV use was similar in the two groups; the median (interquartile range) in the NIV plus pacing arm was 3.2 hours (0.5–8.2 hours) and in the NIV arm was 4.6 hours (0.0–7.8 hours).

Five pacing group participants did not undergo surgery; the reasons were respiratory function below safety threshold ($n = 1$), patient choice ($n = 2$) and DMEC intervention ($n = 2$). A sixth patient stopped pacing within 1 month because of device technical issues.

Implantation was successful for all who underwent surgery. When used, the median daily usage was 4.6 hours (interquartile range 3.0–8.4 hours), with target pacing largely achieved by 15 days.

Fourteen patients took part in the qualitative substudy; nine were interviewed both immediately following initiation of DP and 6 months later. The device was described as being easy to operate, having little impact on life, and was often preferred to NIV. Tolerance of DP varied, with some patients experiencing significant levels of pain, whereas others reported only a noticeable but minor sensation. Patients described hope that the intervention would lead to benefits in the longer term; however, few perceived any direct gains.

Conclusions

Meaning of the study and implications for clinicians or policy-makers

Diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure. We cannot exclude that in subgroup of patients there is a benefit; however, this should not be assumed. Our findings demonstrate that insertion of the NeuRX RA/4 DPS is harmful when instigated at the point at which an individual with ALS develops respiratory failure. A study investigating whether or not implanting earlier in the ALS disease trajectory is of benefit has recently been suspended, and the full results from this study are awaited (NCT01583088). DPS has also been approved for use in the spinal cord injury population. Before widespread use of DPS in the spinal cord injury population, or indeed other populations, we suggest that the evidence base needs to be firmly established.

A poor prognosis and the absence of curative therapy understandably encourage a 'nothing to lose' approach among patients and some clinicians alike, with an attendant lowering of the standards of evidence required to adopt a new intervention. Our trial demonstrates the potential for harm that can arise from adopting this approach. We strongly recommend that all interventions be subjected to appropriate study, which will usually mean a RCT, before adoption into routine practice. This should apply to medical devices, particularly those that expected to have an impact on survival or necessitate invasive procedures.

Recommendations for future research

We cannot exclude that a subgroup of highly selected individuals might benefit from DP, for example those with predominantly upper motor neurone disease. Future work may focus on exploring such uncertainties. Any further studies should include measures to understand the mechanism by which harm or benefit occurs as a result of DP.

Trial registration

This trial is registered as ISRCTN53817913.

Funding

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Chapter 1 Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with an annual incidence of 2–3 in 100,000 and a prevalence of 5–8 per 100,000.^{1–3} Affected individuals experience increasing weakness affecting the limbs, speech and swallowing, and breathing. There is no cure for ALS and patients usually succumb to the illness within 2–3 years.

Management of amyotrophic lateral sclerosis

Management is largely aimed at easing symptoms and supporting patients to maximise their function through a multidisciplinary approach.⁴ One treatment, riluzole, can marginally slow down disease progression, prolonging survival, usually by around 3 months.^{5,6} The exact mechanism by which riluzole affects the disease course is unclear, although it is known to modulate glutamate release, among other effects. However, the greatest impact on the disease course comes from the use of non-invasive ventilation (NIV). A randomised controlled trial (RCT) demonstrated an improvement in quality of life (QoL) and a median survival benefit of approximately 7 months ($p = 0.006$), in ALS patients using NIV who had good bulbar function.⁷ NIV, however, is not without its problems, as some individuals are unable to tolerate it because of problems with claustrophobia and mask interface issues. Furthermore, there comes a point in the course of the disease when NIV is no longer effective.

Phrenic nerve stimulation, in which the diaphragm is stimulated into contracting, is a potential alternative or complementary method of providing respiratory support. The approach originated in patients with spinal cord injury, and historically it required direct phrenic nerve stimulation. The challenges with this approach have been the significant risk of iatrogenic phrenic nerve injury and, until recently, the need to undertake a thoracotomy.⁸ More recently, phrenic nerve stimulation has been achieved using less invasive techniques. The NeuRX® RA/4 diaphragm pacing system (DPS)TM (Synapse Biomedical, Oberlin, OH, USA) is a four-channel percutaneous neuromuscular stimulation system. DPS has an advantage over the earlier direct approach, in that the stimulating electrodes can be inserted into the under-surface of the diaphragm using a minimally invasive laparoscopic technique.⁹ The leads are then tunnelled to an exit site on the abdomen and an external stimulator delivers the stimulus pulses and provides respiratory timing. Initial experience with the NeuRX RA/4 DPS in the spinal cord injury population¹⁰ suggested diaphragm pacing (DP) could reduce time spent on mechanical ventilation.¹¹ The NeuRX RA/4 DPS is now licensed for use in spinal cord injury in many countries, including the USA, and within the European Union.

Evidence for diaphragm pacing in amyotrophic lateral sclerosis

To date, the evidence for DPS in the ALS population is limited to case series and one uncontrolled multicentre cohort study. Their findings are consistent with those from the spinal cord patient population, and highlighted the apparent simplicity and operative safety of the NeuRX RA/4 DPS.^{7,10} The US Food and Drug Administration (FDA) approved the NeuRX RA/4 DPS as a humanitarian-use device (HUD) in ALS following the submission of a humanitarian device exemption (HDE) application. The FDA summary of safety and probable benefit document (SSPB) summarises the evidence on which the HDE approval is based, which is largely on data from the aforementioned cohort study.¹¹ The main inclusion criteria for the study were patients with ALS with evidence of residual bilateral phrenic nerve function and a forced vital capacity (FVC) of less than 85% at screening and above 45% at DPS implantation. The full data from this study, including baseline characteristics, Consolidated Standards of Reporting Trials (CONSORT) diagram, survival, etc., on the 144 patients enrolled have not yet been published. Of the 144, 106 were implanted with the NeuRX RA/4 DPS and survival data on 84 are presented in the SSPB.¹¹

Median survival data are reported as 39 months from ALS diagnosis and 19 months post implantation in the SSPB on 84 implanted patients. As the data are from a cohort study there is no randomised control population to compare survival with. Instead, a subgroup of the HUD patients ($n = 43$) was compared with a historical control group of NIV users. The DP HUD group patients demonstrated survival of 37.5 months from diagnosis, compared with 21.4 months from diagnosis for the historical NIV control group ($p < 0.001$).

Safety data have been published in the SSPB for 86 implanted patients from the cohort study. In these patients, there were no reported deaths and none who needed a tracheostomy with permanent ventilation within the 30-day postoperative period. Four serious adverse events (SAEs) were reported relating to implantation [capnothorax ($n = 2$), respiratory failure due to complications of surgery ($n = 1$) and serious anaesthetic reaction ($n = 1$)]. Therefore, the implantation procedure itself appeared to be relatively safe. Important adverse events (AEs) over the 12-month protocol reported were capnothoraces in 16 patients (19%), percutaneous site infection in eight patients (9%) and pacing-related discomfort, which was described as mild in 20 patients (23%) and moderate in two patients (2%). In the 86 patients implanted, there were no SAEs involving malfunctioning device components. There were 18 reports of anode malfunction in 18 patients (21%) and 44 reports of electrode malfunction in 28 patients (33%). Although there was relatively frequent electrode breakage, there was no need to reimplant any electrodes, as all occurred external to the body at the connector holder.

Following the HUD approval of the NeuRX RA/4 DPS for ALS, there has been increasing use of this therapeutic option worldwide.¹² The promising survival data, lack of apparent harm and absence of alternatives have made this an appealing option, especially among patients who are unable to tolerate NIV, who may account for up to 50% of patients with ALS.^{2,3,13,14} The evidence base for the NeuRX RA/4 DPS for ALS is limited. Moreover, pacing is expensive and it is not known whether or not DPS would meet the National Institute for Health and Care Excellence's threshold for cost-effective interventions for end-of-life care. At the time of conducting the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis (DiPALS) trial, the cost of DPS and implantation procedures (the excess treatment costs) was approximately £16,500 per participant. Therefore, although the preliminary data are promising, DPS is unlikely to be widely introduced without robust, randomised evidence together with a formal analysis of cost-effectiveness. This was our motivation for undertaking the DiPALS trial.

Research objectives

The aim of this study was to perform a definitive RCT on the efficacy and safety of the NeuRX RA/4 DPS when used in addition to NIV, compared with standard care of NIV alone, in patients with ALS. Specifically, we wished to assess whether or not the use of DP in addition to NIV prolongs survival, and also to quantify its impact on:

- QoL of the participant
- QoL of the main carer
- safety (AEs) and tolerability (withdrawal from treatment)
- quality-adjusted life-years
- views and perceptions of patients and family carers regarding acceptability and impact on life.

Chapter 2 Methods

The original protocol for DiPALS was submitted to *BMC Neurology*¹⁵ and was published 8 months into the recruitment phase of the trial, prior to any analyses being performed. The methods described in this chapter are consistent with those as published and with the conduct of the trial in practice, but changes were made to the protocol over the course of the project. These are detailed at the end of this chapter, and tabulated in *Appendix 1*. None of the changes affected the conduct of the trial with respect to the intervention, the primary outcome measures or their statistical analyses.

This report has been prepared in accordance with the CONSORT statement (2010)¹⁶ and the Template for Intervention Description and Replication checklist and guide.¹⁷

Trial design

The DiPALS trial was a multicentre, parallel-group, open-label RCT incorporating health economic analyses and a qualitative longitudinal substudy. The primary objective was to assess survival over the study duration of patients with ALS with respiratory failure, allocated to either standard care (NIV alone) or standard care (NIV) plus DPS using the NeuRX/4 DPS. Participants from seven UK hospitals were allocated to treatment using minimisation methods (see *Appendices 2 and 3*).

The trial was non-commercial, with input from Synapse Biomedical for quality assurance purposes, specifically for the training of surgeons and trial staff on implantation and technical aspects of the NeuRX/4 DPS.

Recruitment took place over 24 months (from December 2011 to December 2013).

Participants and eligibility criteria

Patients aged ≥ 18 years with a confirmed diagnosis of ALS were identified and screened at participating sites or patient referral sites against the following eligibility criteria.

Inclusion criteria

1. Aged ≥ 18 years.
2. Familial or sporadic ALS diagnosed as laboratory-supported probable, probable, or definite according to the World Federation of Neurology El Escorial criteria.¹⁸
3. Stabilised on riluzole therapy for at least 30 days.
4. Respiratory insufficiency as determined by one or more of:
 - i. FVC $< 75\%$ predicted
 - ii. supine vital capacity $< 75\%$ of sitting or standing vital capacity
 - iii. sniff nasal inspiratory pressure (SNIP) < 65 cmH₂O for men or 55 cmH₂O for women in the presence of symptoms
 - iv. SNIP < 40 cmH₂O (see exclusion criterion 9).
 - v. partial pressure of carbon dioxide (PaCO₂) > 6 kPa (daytime) or PaCO₂ > 6.5 kPa (overnight)
 - vi. significant overnight O₂ desaturation ($> 5\%$ of night with SpO₂ $< 90\%$ during overnight oximetry).

5. Bilateral phrenic nerve function clinically acceptable as defined by either:
 - i. absence of paradoxical abdominal wall movement during a sniff manoeuvre (sharp inhalation through the nose) and recording $< 10\%$ decline of FVC when moving from sitting to supine position, or
 - ii. on ultrasound: evidence of at least 1 cm of downward diaphragm movement independent of thoracic or abdominal wall movement during the patient performing a sniff manoeuvre.

Exclusion criteria

1. Prior NIV prescription.
2. Pre-existing implanted electrical device such as pacemaker or cardiac defibrillator.
3. Underlying cardiac, pulmonary diseases or other disorders that would affect pulmonary tests independently of motor neurone disease/ALS (increased risk of general anaesthesia or adverse effect on survival over the course of the study).
4. Current pregnancy or breastfeeding.
5. Significant decision-making incapacity preventing informed consent by the subject because of a major mental disorder such as major depression, schizophrenia or dementia.
6. Marked obesity affecting surgical access to diaphragm or significant scoliosis/chest wall deformity.
7. The involvement in any respiratory trial that can influence 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.
8. Pre-existing diaphragm abnormality such as a hiatus hernia or paraoesophageal hernia of abdominal contents ascending into the thoracic cavity.
9. FVC $< 50\%$ predicted or SNIP < 30 cmH₂O in patients unable to perform FVC (bulbar patients) (because of potential anaesthetic risk).

Participant identification

Potentially eligible patients were identified from NHS hospital clinics at lead research sites or participant identification centres by neurology or respiratory clinicians or a study research nurse (see *Appendix 4*).

All patients aged ≥ 18 years with a confirmed diagnosis of ALS underwent a 'prescreen' whereby their last routine respiratory measure was checked to determine whether or not:

1. patients were ineligible because of poor respiratory criteria or other reason
2. patients were potentially eligible
3. patients may be eligible in the future as their respiratory measure was currently too good.

All those potentially eligible were approached at clinic to discuss the trial in detail. If they were identified from the clinic list prior to attendance the study information was sent to them by post.

Recruitment

Patients were approached by a member of the research team at sites when they attended routine clinic appointments. The study patient and carer information sheets formed a basis for a discussion with potential participants in clinics. Patients were given as long as they required to consider taking part in the trial, with further discussion by telephone or at another clinic offered. Informed consent was taken only if the researcher was satisfied that the patient fully understood the study procedures, was willing to undergo screening and participate in the trial, and was capable of giving full informed consent. Consent was obtained using participant and carer consent forms approved by the Research Ethics Committee (REC), as either full written consent, verbal consent given or consent given via the use of a communication aid

(for REC-approved patient information sheets see *Appendices 5–8* and for REC-approved consent forms see *Appendices 9–12*). When non-written consent was obtained an independent witness was asked to sign the consent form to verify that consent was taken.

If participants were willing to provide reasons for declining participation in the trial, these were entered onto the screening log. Anonymised basic details (age, sex and reason for exclusion) were collected on all eligible patients to allow completion of the CONSORT flow chart.

Participants were free to withdraw from the trial at any point without giving a reason, but data collected up to the point of study withdrawal were maintained and used in study analyses. Patients who asked to withdraw from treatment were encouraged to complete follow-up for QoL and safety to reduce attrition bias. All participants were followed up for survival until 12 months after the last participant was recruited, unless they specifically requested otherwise (*Figure 1*).

Screening

Once patient consent had been confirmed, a member of the site study team initiated the screening process. Patient eligibility was assessed against both non-clinical and clinical criteria, and baseline assessments. Eligibility for the study was based on all the inclusion and none of the exclusion criteria being met. To confirm eligibility, a combination of techniques was used. Researchers checked medical notes/data to assess past medical history, current prescriptions and any other known information relating to eligibility criteria. At the screening visit, participants were asked to perform a respiratory test to determine their FVC or other measure. An assessment was made of the participant's phrenic nerve function – a measure intended to ensure that, if the patient were randomised to DPS, it was likely that it would be possible to sufficiently stimulate the participant's diaphragm once the system was fitted. All criteria were checked and signed off by the recruiting clinician. Once eligibility was established, participants were asked to complete baseline assessments and could proceed to randomisation and study procedures (see *Figure 1*).

Randomisation and blinding

Once eligibility had been confirmed and consent acquired, the participants were randomly allocated to a treatment group. The recruiting clinician accessed a centralised web-based randomisation system provided by the Sheffield Clinical Trials Research Unit (CTRU) in partnership with a University of Sheffield wholly owned subsidiary software development company, epiGenesys. Sites were able to log on to the system using a site-specific username and password. Researchers were prompted to enter patient details (identification number, date of birth and the minimisation factors) and to confirm that consent and eligibility was complete. Following this, the randomisation system notified the user and the study manager of the treatment allocation. Patients were informed of their treatment allocation within 1 week of randomisation by telephone or letter.

The study was open label; it was not considered feasible to blind participants, carers or site staff as the study intervention involves a surgical procedure and ongoing use of an implanted medical device. A sham surgical procedure was considered but discounted as being an unnecessary burden to participants, given the objectivity of the primary outcome measure.

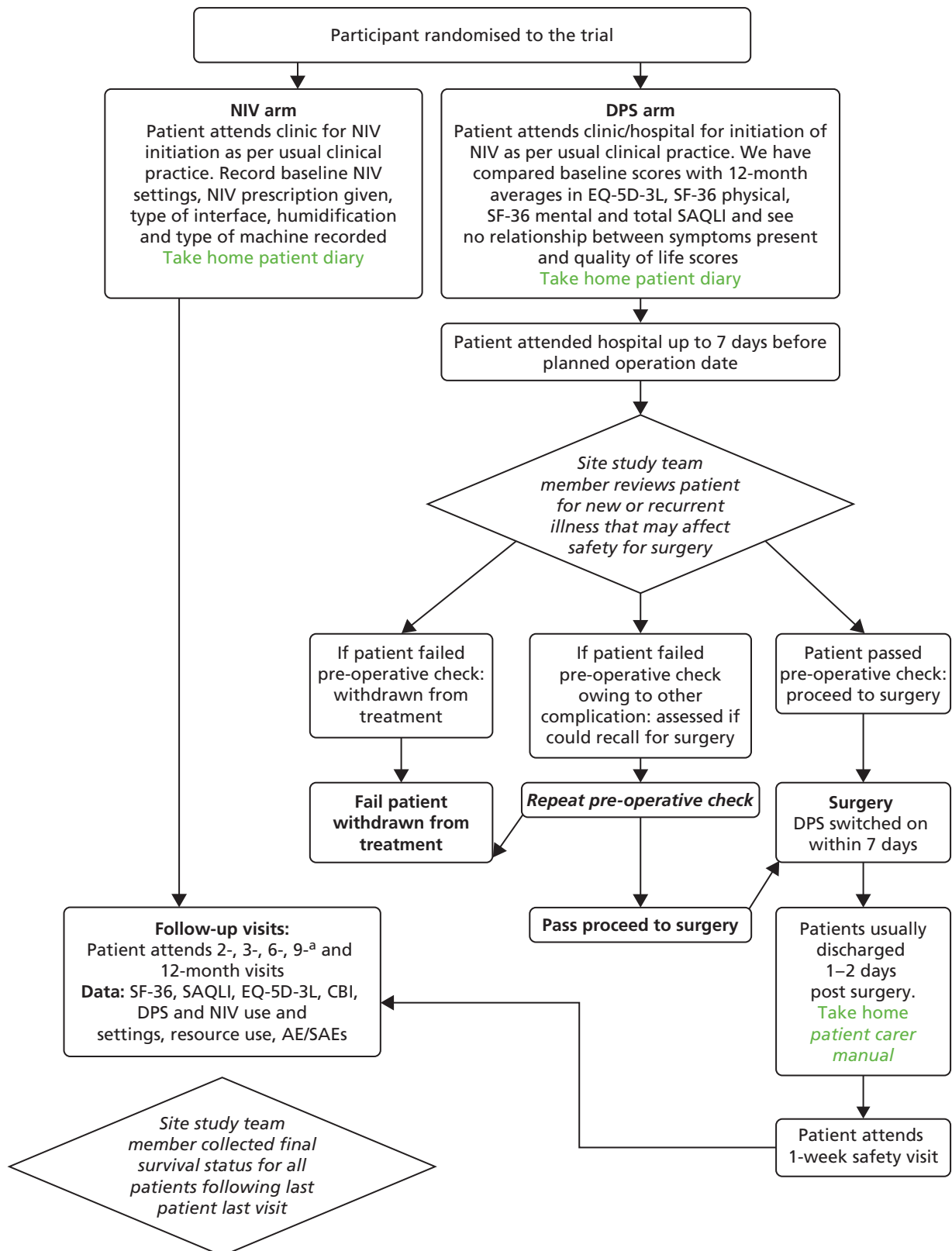


FIGURE 1 Participant flow diagram. a, At 9 months, only ED-5D-3L, DPS/NIV use, AEs and resource use collected. CBI, Caregiver Burden Inventory; EQ-5D-3L, European Quality of Life-5 Dimensions, three levels; SAQLI, Sleep Apnoea Quality of Life Index questionnaire; SF-36, Short Form questionnaire-36 items.

Patients were allocated their treatment (NIV alone or NIV plus DPS) by method of minimisation, using baseline bulbar function, baseline FVC, age and sex as the minimisation factors. Factors were categorised as follows: bulbar function (mild, moderate or severe); FVC (50–59%, 60–69% or $\geq 70\%$); age (≤ 39 years, 40–79 years or ≥ 80 years); and sex (male or female). The allocation incorporated a burn-in period of 10 participants (i.e. the first 10 participants were allocated using simple randomisation). Thereafter, allocation was performed using minimisation incorporating a random probability element of 80% into the allocation algorithm. That is each participant was allocated to the arm that reduced treatment imbalance with 80% probability and to the opposite arm with 20% probability.

The minimisation system was prepared by the study statistician; the study team did not have access to the allocation list in order to maintain allocation concealment. The study team and governance committees were blinded during the course of the study with the following exceptions: (1) the trial statistician and data management team had full access to unblinded outcome data; (2) the Data Monitoring and Ethics Committee (DMEC) had access to unblinded summaries of outcome data; (3) site staff were aware of the treatment allocation of their own participants; and (4) the chief investigator, study manager and site monitor were aware of individual participants' allocations and AEs but did not see unblinded comparative summaries. The trial unblinded statistician was responsible for providing the DMEC with the accumulating unblinded data summaries, but did not attend the closed meetings during which the DMEC reached its decisions.

The original analysis plan was signed off after recruitment start, by which point one participant had died. The updated analysis plan was written by the unblinded trial statistician and endorsed with minimal suggestions by the unblinded DMEC; all other reviewers and approvers did so blinded to outcome data.

Interventions

Participants were randomly allocated to receive either standard care (NIV) or standard care in addition to DPS using the NeuRX/4 DPS.

Non-invasive ventilation

Non-invasive ventilation was initiated as per usual clinical practice at the study site after randomisation.

Diaphragm pacing system

The NeuRX DPS is licensed for use in patients with ALS (Conformité Européenne certificate number 518356). The FDA approved the device under HDE for patients with ALS who had stimulatable diaphragms and were experiencing chronic hypoventilation but who had not progressed to a FVC of $< 45\%$ of their predicted capacity.

The system is a four-channel intramuscular, motor point stimulation system. Intramuscular diaphragm electrodes are implanted laparoscopically into the diaphragm, with leads tunnelled to an exit site on the abdomen. The external part of the electrodes are connected to an external pulse generator (EPG), which is a small, white, portable box. A clinical station is used to programme each of the parameters (pulse frequency, pulse duration, inspiration time, pulse amplitude, pulse ramp and respiratory rate) on the EPG, which controls the stimulation delivered to the diaphragm via the implanted wires electrodes. The EPG provides repetitive electrical stimulation to the implanted electrodes allowing the diaphragm to contract in a manner that mimics breathing.

The Motor Neurone Disease Association provided funding for the purchasing of the NeuRX DPSs from the manufacturers of the device, Synapse Biomedical, which supplied them at reduced cost. The DPS system consists of components to both allow implantation of the electrodes into the diaphragm and its subsequent stimulation (*Table 1*).

TABLE 1 Overview of components of DPS

Item	Description
Clinical station	Clinical station used to map the diaphragm during surgery (by surgeon) to find the point of maximal contraction. Enables programming of the EPG unit to adjust wire parameters at subsequent visits (by PI/research nurse)
Electrode delivery instrument	To enable surgical implantation of the device. Used during the laparoscopic procedure by surgeon
Clinical implantation kit	Electrodes and instruments required for implantation. Used in theatre by the surgeon
Patient kit	Includes EPG control unit and cables required for each patient. Used by PI/research nurse at sites

PI, principal investigator.

Members of the surgical team were responsible for clinical implantation of the system (see *Surgical implantation*). Theatre staff processed the electrode delivery instrument to allow its use in theatre including sterilisation and maintenance. Local procedures at each hospital for implanting the device were followed in order to complete documentation to allow sites to receive the system. Hospital medical equipment departments checked equipment prior to use following local hospital procedures.

Surgical implantation

On randomisation, the research nurse made arrangements for the participant to have DPS fitted. The time elapsed between randomisation and surgery varied according to availability, but the protocol encouraged investigators to fit the DPS within 8 weeks of randomisation. Participants were booked for a preoperative assessment up to 1 week prior to the operation to ensure their respiratory criteria remained within the safe range (FVC \geq 45% and SNIP \geq 30 cmH₂O) and to check they were otherwise able to undergo the procedure safely. The research nurse liaised with the trial manager, surgeons and anaesthetists and members of Synapse Biomedical to organise a theatre slot and medical equipment for the procedure. A member of Synapse Biomedical was present at each operation to provide verbal assistance to the surgeon including mapping the diaphragm and implantation of electrodes at the point of maximal stimulation, as per current standard practice. Synapse Biomedical technical staff received honorary contracts to attend each surgical procedure. Guidance was also provided by Synapse Biomedical in setting the DPS parameters postoperatively.

The clinicians performing the procedure in the treatment arm were experienced surgeons who received training in the DPS implantation technique and were competent to perform the procedure. The training process was straightforward as the technique is a modification of a standard abdominal laparoscopic procedure, and mirrored that employed in the previous DP cohort study.¹¹ Training was provided by a surgeon from Synapse Biomedical. Given the simplicity of the implantation of electrodes for an experienced laparoscopic surgeon, all surgeons were judged competent by Synapse Biomedical after observation of one implantation procedure. Again this reflects the training of surgeons in the previous multicentre cohort study. A single surgeon undertook procedures in six of the centres; the seventh (London) referred participants in the intervention arm to undergo surgery at the Oxford site. At all surgeries, Synapse Biomedical technical staff were present to advise on implantation.

During the implantation procedure, incisions of 0.5–1 inch long were made in the abdomen. More than one incision was made to enable instruments to be passed through the abdominal wall as per standard laparoscopic procedure.

The surgeon identified the best location to place the electrodes within the diaphragm. A probe was used to temporarily place an electrode on the surface of the diaphragm and to stimulate the diaphragm muscle at several locations. Once the best locations were identified, the probe was removed and two electrodes were placed in each side of the diaphragm muscle. The lead wires from these electrodes travelled under the skin to the abdominal wall. The wires were trimmed so that the ends sticking out of the skin were only 2–6 inches in length. A radiograph was taken following the surgery to check the position of the wires and to make sure that no air had travelled above the diaphragm and into the chest. At the end of surgery the clinical station read out was printed for surgical quality control, which displayed the functioning stimulus connection for each electrode wire.

An assessment of phrenic nerve function formed part of the screening procedures, as described in this section. The purpose of this was to assess whether or not there was enough residual phrenic nerve function to enable meaningful stimulation of the diaphragm with the NeuRX DPS. However, it is only at the time of the operation when it is possible to know for certain if the diaphragm is stimlatable. If during the implantation procedure the diaphragm was not stimlatable (no contraction observed during mapping), then the operation was stopped and the device was not inserted.

Evaluation of electrodes and diaphragm pacing system training

Evaluation of the electrodes and DPS was performed prior to discharge from hospital. A system check of the wires was completed. Using the clinical station electrode evaluation was performed, by adjusting individual stimulus parameters (pulse amplitude, width and frequency) to achieve a comfortable level of stimulation for the diaphragm conditioning sessions. During the initial stimulation period, the participant's vital signs were monitored for any abnormalities. The patient was given a daily target for the number and length of DP sessions, which was recorded by the study team member in the patient diary for the patient to refer to at home.

Training of the participant and their caregiver took place prior to discharge. This included instruction in the care and use of the stimulator and data collection in the patient diary. Verbal and written instruction was provided in a patient/caregiver instruction manual.

Prior to discharge, the participant/or carer was required to show proficiency to the treating clinician in the following:

- cleaning and care of skin, wires and exit site
- care and use of the stimulator
- attachment and detachment of all components
- completion of patient diary.

It was accepted that initiation of pacing could be deferred until the 1-week postoperative appointment to allow patients to adjust to having the device fitted in the immediate postoperative period. This was to match practice at all sites, as it was recognised that this enables the patient to recover after their operation. Patients were able to turn the EPG control unit 'on' or 'off' after programming to provide an adequate stimulus. The initial target for pacing sessions for ALS patients was five times per day, with each session lasting at least 30 minutes. Patients were asked to build up to this target over the first month. In the second month, patients were required to gradually lengthen the training sessions. When pacing was being performed for 6–7 hours a day, patients were instructed to switch from pacing during the day to using the pacing device overnight while asleep. At this stage patients could additionally use the pacing device during the day if they felt it benefited them, but this was their decision. Patients were asked to continue to use their NIV as advised by their study doctor.

A patient diary was given to the participant (on NIV initiation) to take home to record the amount of time spent on DPS and/or NIV.

Outcomes

Primary outcome

The primary outcome was overall survival.

Secondary outcomes

- Quality-adjusted life-years, calculated from the European Quality of Life-5 Dimensions, three levels (EQ-5D-3L) health utility questionnaire.
- QoL, measured by the EQ-5D-3L, Short Form questionnaire-36 items (SF-36) and Sleep Apnoea Quality of Life Index questionnaire (SAQLI).
- QoL of the main carer, measured by the EQ-5D-3L and Caregiver Burden Inventory (CBI).
- Safety and tolerability of the device.
- Health economic objectives and resource use.
- Perceptions of patients and carers regarding acceptability and impact of the device.

Initially, all of these outcome measures were assessed as per the original protocol; however, as a consequence of the trial's early termination (see *Chapter 3, Recruitment suspension*), the above was amended. First, both the funder and sponsor agreed that given the substantial cost of the device and the apparent reduction in life-years in the pacing arm, the planned health economic analyses were now unnecessary. Second, the Trial Steering Committee (TSC) requested widening the scope of the statistical analyses to address usage of both NIV and DPS in relation to survival.

We also reported tracheostomy-free survival (TFS), defined as the time from randomisation to either death or the placement of tracheostomy, whichever occurred first. Although not preplanned, this outcome was added to aid comparability with other studies that have reported TFS.

Follow-up visits

Follow-up visits were conducted at clinic (at 1 week and at 2, 3, 6, 9 and 12 months). Some questionnaires were completed via post/e-mail when participants were unable to come into clinic.

Data collection and management

Data collection forms

Data for all participants were captured on the following key sources:

- screening log – prescreening details containing reasons for ineligibility or non-participation
- participant and carer consent forms – informed consent
- case report form – all other study forms including eligibility, baseline assessments, randomisation, surgery, follow-ups (at 1 week and at 2, 3, 6, 9 and 12 months) study completion (withdrawal), AEs/SAEs, concomitant medications and, unscheduled DPS visits
- patient diary – DPS and/or NIV usage.

Database

Trial data were entered into a validated bespoke web-based database system (Prospect) managed by the Sheffield CTRU in partnership with a University of Sheffield wholly owned subsidiary software development company, epiGenesys. Prospect stores all data in a PostgreSQL 9.1 (open-source software from The PostgreSQL Global Development Group) database on virtual servers hosted by Corporate Information and Computing Services at the University of Sheffield. Prospect uses industry standard techniques to provide security, including password authentication and encryption using Secure Sockets Layer/Transport Layer

Security. Access to Prospect was controlled by usernames and encrypted passwords, and a comprehensive privilege management feature was used to ensure that users had access to only the minimum number of data required to complete their tasks. An automated audit trail recorded when (and by which user) records were created, updated or deleted. Prospect provides validation and verification features which were used to monitor study data quality, in line with CTRU's standard operating procedures (SOPs).

Methods used for treatment allocation, sequence concealment and blinding

Patients were allocated their treatment (NIV alone or NIV plus DPS) by a method of minimisation, using baseline bulbar function, baseline FVC, age and sex as the minimisation factors. Factors were categorised as follows: bulbar function (mild, moderate or severe); FVC (50–59%, 60–69% or $\geq 70\%$); age (≤ 39 years, 40–79 years or ≥ 80 years); and sex (male or female). The minimisation was non-deterministic and incorporated a burn-in period of 10 participants and a random probability element of 80% into the allocation algorithm. In other words, the first 10 participants were allocated using simple randomisation; thereafter, each participant was allocated to the arm that reduced treatment imbalance with 80% probability and to the opposite with 20% probability. A centralised, web-based randomisation system hosted by the CTRU was used to allocate treatment allocations. Sites were able to log on to the system using a site-specific username and password. Researchers were prompted to enter patient details (identification number, date of birth and the minimisation factors) and to confirm consent and eligibility were complete. Following this, the randomisation system notified the user and the study manager of the treatment allocation.

The study was open label: it was not considered feasible to blind participants, carers or site staff.

Sample size

The sample size calculation was based on log-rank test, using Simpson's rule¹⁹ as implemented in Stata version 11.1 (StataCorp LP, College Station, TX, USA) to allow for the unequal length of follow-up. The study duration comprised an 18-month recruitment period and a 12-month follow-up period, giving a maximum follow-up of 30 months and a minimum of 12 months. Assuming control group survival proportions of 45%, 20% and 10% at the minimum, average and maximum follow-up times, respectively, a hazard ratio (HR) of 0.45 and an additional 10% loss to follow-up, a total of 108 patients (54 per group) were needed to ensure a power of 85% using a two-sided type I error of 5%. The control group figures were conservative estimates based on the sole RCT of NIV,¹ which is now considered standard care in the UK. We estimated the sample size on a conservative (but clinically important) 1-year difference in survival of 45% versus 70%, which produced the estimated HR of 0.45. It was expected that complete survival data would be available on all participants recruited, based on previous experience in ALS trials. We did, however, allow for a 10% loss to follow-up in the sample size calculation.

With regard to QoL data, we expected a low level of missing data due to loss to follow-up. We reviewed the patients who were initiated on NIV between July 2008 and June 2009 and had maintained contact with 100% of those patients surviving at 12 months. The appointment of a research nurse at each study site enabled home visits to collect the QoL data when necessary.

Early stopping

No interim analyses or early stopping was foreseen. However, in December 2013 the DMEC recommended that recruitment to DiPALS should cease on safety grounds (discrepancy in survival between the two treatment arms), and a final decision to stop the trial was made in June 2014. The recommendations and actions taken are reported fully in results (see *Chapter 3*).

Statistical methods

Survival

The primary end point was overall survival, defined as the time from randomisation to death of any cause. Participants were followed up after the last participant's last visit to determine their final status, and participants who remained alive were censored on the date last known to be alive. TFS was defined as the time from randomisation to either death or the placement of tracheostomy, whichever occurred first.

The Kaplan–Meier method was used to visualise survival data and to derive summary statistics of median survival, interquartile range (IQR) and 95% confidence interval (CI). The median survival was defined as the point the Kaplan–Meier curve first reached 0.5; if the survival curve did not drop this far, then the median survival is stated as 'not reached'. The IQR and the CI for the median are defined analogously. Overall survival and TFS were compared between the groups using the log-rank test and modelled using Cox proportional hazards regression using the Efron adjustment for tied survival times and with the minimisation factors as covariates. The primary analysis was the Cox regression (i.e. adjusted) analysis. Pretrial modelling found Cox proportional hazards to be the best fit to previous data, but the Cox proportional hazards assumption was checked by adding time-dependent covariates and graphing scaled Schoenfeld residuals against time.²⁰ If Cox proportional hazards were found not to fit the data adequately, an accelerated failure time alternative was fitted and the adequacy of its fit assessed using Q–Q plots.²¹ Finally, if this too did not fit, the non-parametric restricted mean survival analysis,²² derived from the area under the Kaplan–Meier survival curves, was used as the basis for summarising the treatment effect.

The overall survival was also reported as of the point at which the DMEC made the decision to (1) suspend the trial; and (2) terminate the trial with advice to stop pacing. In both of these additional analyses, participants who were randomised to pacing but did not receive it as a result of the DMEC decision (two patients) were excluded.

Quality of life

Quality of life was analysed both longitudinally (i.e. over the duration of the trial rather than at individual time points) and at the end of the study follow-up (12 months). Longitudinal analyses were performed using generalised least squares regression, with the baseline value and minimisation factors as covariates and the patient as a random intercept. End-of-study values were analysed using ordinary least squares regression, with the baseline value and minimisation factors as covariates. For each participant measure, a complete case analysis was followed by an analysis based on imputed data. First, in the case of participants for whom data for any visit were missing but data on either side were available (e.g. no month 2 data but baseline and month 3 data available), the value was imputed using the trapezoid rule. When absence of data persisted (e.g. because the participant withdrew from the study), the missing data were imputed using multiple imputation with chained estimation²³ using Rubin's rules and 50 imputations; the imputation model used the participant's age, sex, rate of prerandomisation Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) score decline, FVC, treatment group and any data at other time points for the instrument. Missing data arising because of participant death were not imputed other than for EQ-5D-3L, as the primary objective was to assess QoL among participants while they remained alive. No attempt was made to impute missing data for the carer QoL.

The following QoL instruments and measures were collected for participants:

- European Quality of Life-5 Dimensions, three levels: health utility/tariff score and health status ('thermometer scale'): the EQ-5D-3L questionnaire comprises six questions. Questions 1–5 are 3-point scales covering mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The responses to these questions map onto a health state in which 1 corresponds to perfect health and 0 to death. Negative values are possible; these are interpreted as a state worse than death. Question 6 is a standalone question that asks the participant to rate their overall state of health today on a continuous scale between 0 and 10.
- Short Form questionnaire-36 items (version 1): aggregate physical health and aggregate mental health: the SF-36 was used to derive overall physical and mental health among the participants. Both scores are scaled such that the general population has a mean score of 50 and a standard deviation of 10, with higher scores indicating a better QoL.
- Sleep Apnoea Quality of Life Index questionnaire: the SAQLI is a single-domain questionnaire comprising 14 questions, each scored from 1 to 7: the SAQLI score is the average. When the questionnaire is incomplete (i.e. < 14 questions are answered), the overall score was defined as the average, provided at least half of the questions (7 of the 14) had been answered. Higher scores indicate a better QoL.

The following QoL instruments and measures were collected for carers:

- European Quality of Life-5 Dimensions, three levels: health utility/tariff score and health status ('thermometer scale'): the questionnaire was identical to that provided to participants.
- Caregiver Burden Inventory: the CBI is a one-domain questionnaire comprising 24 questions, each of which is scored from 0 to 4; the overall score is the total of these. Incomplete questionnaires are scaled up proportionate to the level of missing data unless 12 or fewer questions had been answered. Higher values indicate better QoL.

All questionnaires were completed at the screening visit and the at subsequent visits (2, 3, 6 and 12 months), the EQ-5D-3L (for participants and carer) was also completed at 9 months.

The analysis of EQ-5D-3L was conducted in two ways. First, an analysis of health status was conducted using data (possibly imputed) over the duration for which the participant was still alive. Second, the analysis was performed for all time points but with a score of 0 (which corresponding to a state of death) used following participant death. The two analyses answer different questions: the first is the health among survivors; and the second is the health of the population as a whole. The SF-36, SAQLI and CBI measures were analysed only for the duration in which the participant remained alive.

The EQ-5D-3L was further reported by subgroups (NIV tolerance and bulbar function). Testing for differential treatment effect between subgroups would necessitate a three-way interaction (treatment group × subgroup × time), which given the sample size would produce potentially unstable coefficients. Therefore, the focus here was on within-group summary statistics and graphical displays, separately by treatment group.

Non-invasive ventilation and diaphragm pacing usage

The original analyses of DPS and NIV usage were based primarily on diary data, augmented by participant recall at each visit when diary data were incomplete. Later on in the trial we were able to collect NIV usage data directly from the NIV machine itself, and this was the preferred source of average usage when available. Average NIV usage was defined as the average number of hours used from the date of NIV initiation onwards, and average DPS usage was defined as the average daily use from the date of procedure onwards.

The relationship between NIV and DPS usage by time point was also assessed. As the relationship between typical adherence (in hours) and survival was not expected to be linear, fractional polynomials were used to assess the fits of quadratic and other non-linear relationships.²⁴ Finally, usage was defined in categories. For NIV we followed the approach of Kleopa *et al.*,¹³ who characterised participants as non-adherent (typical usage < 1 hour per day), low-adherent (typical usage 1 to < 4 hours per day) and good adherence (typically ≥ 4 hours per day). Adherence to pacing was not categorised as (unlike NIV) normative data on optimal usage are not available, and also because of the small numbers within each category. Participants whose NIV or DPS adherence could not be determined based on the available data were excluded from these exploratory analyses.

Health resource use

Health resource use was summarised as the use of each of the following:

- health service use – hospital admission, emergency department attendance, minor injury clinic or walk-in centre or general practitioner (GP)
- respiratory device – cough assist machine, breath stacking, suction
- health and social care – physiotherapist, occupational therapist, other
- additional care/support – formal (e.g. home help) and informal (e.g. family/friends).

Additional outcomes: Amyotrophic Lateral Sclerosis Functional Rating Scale and respiratory function

In the light of the early stopping, the TSC requested additional respiratory function data be collected to augment that which was already collected at baseline (and for DPS, immediately pre surgery). Specifically, we wished to assess (1) whether or not the groups were comparable at baseline; (2) whether or not decline among the NIV plus DPS group appeared more pronounced in the postsurgery period than in the NIV group; and (3) the trajectory across time in general to see if it offered any other clues with which to explain the findings. We were able to obtain data at some, but not all, sites for FVC, arterial carbon dioxide and ALSFRS-R.

Adverse events

Adverse events were coded by the chief investigator blind to the participant's treatment group. AEs were summarised for each AE category and, overall, as the number and percentage of patients affected and as the number of events in total (as a patient may have more than one occurrence of the same AE). The summary was repeated for SAEs. All AEs that were adjudged related to pacing (either probably or definitely) are listed as recorded. Summaries are presented based on the randomised group (i.e. intention to treat), but any NIV plus DPS group AEs reported by non-implanted participants were highlighted.

General analysis considerations

All treatment comparisons use the NIV-only group as the reference (comparator); all statistical exploratory tests of main effects were two-tailed with $\alpha = 0.05$; and all CIs were two-sided, with 95% intervals. A permutation test was used to confirm the p -value from the primary end point.²⁵ As interaction tests have low statistical power, consideration was given to p -values below 0.1 when testing interactions (treatment \times centre and treatment \times subgroups).

Analyses were by intention to treat, with preplanned secondary analyses of overall survival based on protocol adherence and NIV usage. Analyses were undertaken using Stata version 12.1 and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Economic evaluation

Prior to the trial commencing, a modelling exercise was undertaken to assess the feasibility that pacing could be cost-effective at standard willingness-to-pay thresholds for end-of-life care. This modelling confirmed that pacing would be cost-effective if the trial were to demonstrate a treatment effect of similar magnitude as demonstrated by the SSPB cohort in comparison with historical data. A full cost-utility analysis was planned for this trial, but following the early termination of the trial the chief investigator and funder agreed that this was no longer necessary.

Research governance

Sponsorship

Sheffield Teaching Hospitals NHS Foundation Trust sponsored the trial (reference STH15625).

Oversight committees

Oversight committees were established to govern study conduct: Trial Management Group (TMG), TSC and DMEC. The trial was conducted in accordance with CTRU's SOPs, with committees convening at appropriate intervals as dictated by both study requirements and SOPs (see *Acknowledgements*).

The TMG consisted of the chief (chairperson) and principal investigators (PIs) and key staff within the CTRU, and this committee met monthly via teleconference during trial recruitment and follow-up. An independent consultant neurologist chaired the TSC, other external members comprising a respiratory clinical expert, an independent statistician and two lay representative/patient and public involvement (PPI) members. All TSC members were appointed by the Health Technology Assessment programme. The DMEC consisted of an independent statistician, clinical neurologist (chairperson) and consultant neurologist. The TSC received formal recommendations from the DMEC.

Research Ethics Committee

Cambridge Central National Research Ethics Service committee (reference 11/EE/0026) approved the trial and all subsequent amendments.

Medicines and Healthcare products Regulatory Agency

The intervention was used within its licence for intended use with appropriate Conformité Européenne mark documentation. Medicines and Healthcare products Regulatory Agency approval was not applicable.

Serious adverse events

Adverse events were reported in accordance with the CTRU's AEs and SAEs SOP (PM004) and supplementary study-specific guidance approved by the sponsor.

Expected disease progression was specified in the protocol as an expected AE that did not need to be reported. Other expected AEs were listed with the requirement to report: chest infection requiring the use of antibiotics, an infection at the site where DPS was fitted and revision of the DPS.

Protocol non-compliances

Protocol non-compliances were reported in accordance with CTRU's non-compliance SOP (PM011), but also additional study-specific guidance approved by the sponsor. Non-compliance categories were prespecified with the trial sponsor and are listed below. Major non-compliances were reported to the sponsor and immediate action taken; minor non-compliances were recorded by the CTRU and reported periodically to trial oversight committees and the sponsor.

Prespecified major non-compliances:

- Participants found to be ineligible following randomisation.
 - Action: participant withdrawn.
- Consent procedure or good clinical practice not followed correctly (e.g. patient not consented).
 - Action: participant reconsented.

Prespecified minor non-compliances:

- completion of any baseline data post randomisation
- minor errors on the consent form
- patient did not receive allocated treatment
- time-specific windows stated in the protocol missed (e.g. participant not randomised or informed of the arm allocated to within 7 days of screening).

Monitoring and reporting

The level and type of monitoring was informed by a risk assessment conducted during the set-up period of the study. A Data Monitoring and Management Plan and a Monitoring Plan were written and agreed with the sponsor prior to the start of trial recruitment. On-site and central data monitoring activities were completed to ensure participant safety, protocol compliance and data integrity.

Central monitoring

Data were centrally monitored based on parameters specified in the Data Monitoring and Management Plan. Checks included point of entry and post-entry validation checks and verification of data entry.

Site monitoring

The trial study manager completed a site initiation and training visit with research staff at sites prior to participant recruitment. Subsequent visits were conducted after sites had started recruitment to check the ongoing suitability of the site and to perform source data verification. Monitors checked data recorded on the case report form against medical records, discussed recruitment and issues with intervention delivery, SAEs/AEs, resolution of data queries and maintenance of the site file. A final closeout visit was performed at each site at the end of participant recruitment, scheduled once data collection was complete.

Monitoring issues were initially highlighted and discussed with sites, and remedial actions sent to the research nurse and PI. Any problem themes identified and specific issues with sites were discussed with the chief investigator and when required escalated to the sponsor, TSC and DMEC.

Reporting

The trial team were required to submit annual reports on trial progress, data completion rates, and safety and protocol compliance to the REC; and 6-monthly reports to the funding body.

Important changes to methods after trial commencement

Details of substantial amendments submitted to the REC, which were important changes to trial methodology, are listed below.

November 2012: amendment 5 (minor)

Protocol version 3 specified that participant be initiated onto NIV (in both arms) within 1 to 2 weeks of randomisation. The protocol was amended to allow sites to initiate NIV as per usual clinical practice after the participants enrol onto the trial and not necessarily before DPS implantation. This distinction was necessary as, although participants were experiencing respiratory insufficiency based on their clinical

assessments, clinicians wished to initiate NIV when participants were more symptomatic in line with their standard practice. The trial TSC were in agreement with this rationale. The protocol was also amended to allow DPS implantation to ideally occur within 8 weeks of randomisation based on the practical feasibility of getting participants into theatre.

June 2013: amendment 6 (substantial)

The protocol was clarified to state that blood gases were required only to assess PaCO₂ levels (inclusion criteria 4e); if alternative respiratory measures were used for eligibility assessment, blood gases were not required. A member of Synapse Biomedical (manufacturers of the device) was present at each operation as stated in the protocol; however, as sites (surgeons, research nurses and clinicians) gained experience and became competent in the use of the device, it was felt appropriate that the protocol be amended. This change was also reflective of standard practice for having DPS fitted worldwide. The wording in the protocol was amended to:

A member of Synapse will attend each procedure until sites become competent with use of the device to manage patients independently. The local site PI will be responsible, after liaising with local site staff, deciding when site staff are competent in performing the intervention without any input from Synapse. The Surgeon at the site will self-certify their competency to perform the operation independently at this stage.

Although this change was approved by the REC, none of the surgeries was performed independently and a member of Synapse Biomedical was present at each operation to provide verbal assistance during the procedure. The protocol was amended to allow patients not to start pacing until the 1-week postoperative appointment to allow patients to adjust to having the device fitted in the immediate postoperative period and to ensure standardisation of the process across sites. This amendment also added both postal or e-mail options to optimise data collection when it was difficult for patients/carers to attend in person.

October 2013: amendment 7 (substantial)

The protocol was amended to allow respiratory tests up to 2 weeks pre consent to be used for eligibility assessment. This was felt an appropriate cut-off point to not overburden participants with repeat tests while still ensuring that respiratory function would not have significantly changed. As part of this amendment, the instructions on the participant diaries were changed and a newsletter template was approved to both provide more clarity on how to collect the data but also to emphasise the importance of doing so.

November 2013: amendment 8 (minor)

The previous protocol allowed self-reported NIV data to be collected from participants. As the study progressed, it was apparent that more detail was required to build a more accurate picture of NIV use including NIV data collected directly from the NIV machines. The protocol was amended to allow NIV usage data from the machines to be collected.

January 2014: amendment 9 (substantial)

Following the DMEC's recommendation to the TSC, recruitment into the trial was halted and participants randomised to DPS but who had not undergone surgical implantation were not to do so. Otherwise, participant follow-up was to continue as planned for those already in the trial.

June 2014: amendment 10 (substantial)

Researchers clarified the protocol to allow sites to initiate NIV post consent rather than post randomisation. As the screening process could take a few weeks, it was accepted that NIV could be initiated based on clinical need for participants in this period between consent and randomisation. The collection of routine respiratory and ALSFRS-R data was added to the protocol during the 12 months of participants' involvement in the trial. This was to aid the analysis about the rate of participant deterioration over the course of the trial.

June 2014: amendment 11 (substantial)

Following unblinded data review on 23 June 2014, the DMEC recommended that participants in the pacing arm should be advised to discontinue using the DPS unless they specifically requested otherwise. All participants should remain under follow-up as scheduled. A specific SOP detailing discontinuation of DP at sites was written and submitted as part of the amendment, together with a GP letter and letters for participants still in the trial (one for each arm) to inform them of this decision and what to do next. Provision was made such that any participant wishing to continue using the DPS would be allowed to do so.

September 2014: amendment 12 (substantial)

A substantial amendment was submitted to allow central University of Sheffield researchers to interview site staff in relation to running the DiPALS trial locally. The interviews explored the experiences of the research staff recruiting participants, particularly with regard to the population (ALS participants at a later stage of disease); intervention (surgical intervention involving general anaesthesia, compliance with the intervention and standard care); and other barriers and facilitators to recruitment.

Patient and public involvement

Patient and public involvement was sought throughout the trial. The Sheffield Motor Neurone Disease Research Advisory Group (SMNDRAG), an independent research advisory group, was approached and agreed to be involved at an early stage. The SMNDRAG was established in 2008 following the principles of INVOLVE.²⁶ The group comprises members of the public, including several carers of ALS patients, patients and other lay individuals who responded to the call for members. Research training is provided to all members of the public that volunteer for the SMNDRAG as part of their induction and ongoing support. The SMNDRAG has been a valuable part of the DiPALS trial, collaborating as part of the research team at all stages of the research process.

Proposal development

The SMNDRAG was consulted about the concept, research question and design at the proposal application stage. SMNDRAG members collaborated in writing the proposal, with particular input to the lay summary. They also suggested modifications to the protocol; an example of this was the addition of methods to capture carer experience, using both CBI and qualitative interviews.

During the trial

Following the funding decision, the SMNDRAG was involved during the development of the trial protocol and associated essential documents. Members were asked periodically to comment on key changes to participant materials when required.

Study oversight

A PPI member from the SMNDRAG was invited to attend the monthly TMGs for day-to-day running of the trial. The trial TSC had two independent members (PPI and lay person) to assist in governing trial conduct and provide advice from the patient/lay perspective.

Study dissemination

At the end of the study, the SMNDRAG members assisted in dissemination of the trial results through networks that have been established regionally and nationally, and in reviewing the plain English summary.

Chapter 3 Early stopping

Trial recruitment was stopped earlier than planned on safety grounds. The recommendations from the DMEC were accepted in full, and the subsequent changes to trial conduct and recruitment are detailed in this chapter.

Recruitment suspension

The fourth DMEC meeting was held on 16 December 2013. The 'open' part of the meeting discussed trial progress with both internal and external DMEC members. This was followed by a 'closed' meeting when the external, independent members reviewed unblinded safety data.

Following the closed meeting, the chairperson of the DMEC contacted the chief investigator on 18 December to recommend that the trial suspend recruitment temporarily based on safety grounds, citing a discrepancy in survival between the two arms. In doing so, the DMEC acknowledged that the sample size was relatively small (74 randomised, 24 deaths at the point of this recommendation), and that their decision would be reviewed as additional data became available.

The DMEC provided the following response:

The DMEC has reviewed the unblinded data on survival in the DiPALS study and the members of the Committee are unanimous in recommending that recruitment should cease as soon as practicable for reasons of safety, that monitoring of safety and survival should continue, and that the DMEC should review the updated survival data at the end of February 2014, and periodically thereafter.

Suspension of recruitment did not constitute an 'urgent safety measure'.

In summary, the DMEC recommended that:

- recruitment be suspended with immediate effect
- implantation of new pacing devices be suspended
- other aspects of the trial remain unaltered; in particular, patients in the pacing arm should be encouraged to continue using their device.

The CTRU suspended the online randomisation system on the same day to ensure that no further patients were recruited to the trial. The TMG (PIs, co-investigators, research nurses and relevant members of the CTRU) were all notified of this decision immediately (18 December 2013). All planned surgeries for the DPS were cancelled. The PIs and chief investigator discussed the key message to give to any concerned trial participants while still remaining blinded to the data.

The TSC convened on 20 December 2013 to discuss the implications of this decision and their concerns that the data had not been thoroughly scrutinised. These included the consideration of centre effects; the effect of patient withdrawal and non-implantation with the device; chance; and non-compliance with either NIV or DPS. A second unblinded report was produced and circulated to only the external, independent DMEC members that incorporated analyses to ensure all these issues were considered.

A joint TSC and DMEC meeting was held on 13 January 2014 to allow all members to present any remaining concerns before responding to the DMEC. The TSC and study team remained blinded to trial results. The DMEC upheld its initial decision by providing the following response to the additional data analyses:

The DiPALS DMEC members, having reviewed the updated unblinded report and having considered the points raised during discussion with the TSC, remain unanimous in their advice that recruitment into the DiPALS trial should cease, but that follow-up should continue. This advice is based on analysis of the primary end point (patient survival during the course of the trial). The DMEC considers that secondary analyses are unlikely to alter the safety concerns raised by the primary intention-to-treat analysis. The DMEC will be happy to consider further reports and to provide advice as required.

The TSC jointly agreed and communicated its agreement with the DMEC to suspend recruitment to the trial team late on 15 January 2014. The TSC requested that the DMEC continue to review unblinded data every 3 months to capture any further changes that would warrant discontinuation of the use of the DPS for participants in follow-up.

Informing the Research Ethics Committee

The acting trial manager informed the REC on 6 January 2014 of the initial decision to suspend recruitment, with a further notification to the REC on 15 January 2015 after the final TSC decision. A formal substantial amendment was submitted to the REC on 5 February 2014. A full account (see *Recruitment suspension*) was provided to the REC as part of the amendment. The sponsors of the trial (Sheffield Teaching Hospitals) approved the amendment, and sought direct assurance from the chairperson of the DMEC that participants already in the trial would continue to be followed up as per protocol, that is would continue to receive the intervention as prescribed. The CTRU informed the REC that as the central study team (chief investigator, and study and data managers) and all site study staff (PIs and research nurses) remain blinded to the data disclosed in the closed part of DMEC they would be unable to provide any further detail than that provided. The REC was asked to contact the chairperson of the DMEC for any further assurance regarding the decisions made.

As trial participants remained in follow-up and continued to receive the DPS intervention, they were not informed of the decision to halt recruitment of new participants into the trial.

Withdrawal of participants from diaphragm pacing system

The DMEC continued to review unblinded data and the next meeting was convened on 24 March 2014. The DMEC reviewed further deaths in each group and other safety and tolerability data. The DMEC requested that the chief investigator consider a pathway for formal participant withdrawal from the intervention, which would need to be ethically approved should this be required. Following this meeting there was no change in the study status.

The subsequent DMEC meeting was held on the 23 June 2014. The following recommendations were made by the DMEC after the closed session:

- As the survival data suggest that DP poses an ongoing safety risk compared with standard care, in the interest of safety, DPS should be stopped in all participants using the approved process.
- Participants, however, subject to consent, should continue to be followed up and data acquisition should continue until the planned end of the trial (December 2014).

The DMEC also wished to review the statistical analysis plan (see *Appendix 13*) prior to database lock and advised that the trial team (chief investigator, PIs and other central study staff) remain blinded to the data prior to final database lock and analysis. The DMEC advised that the study group inform the REC and discuss the withdrawal procedure with PIs and then withdraw patients as soon as practicably possible.

Formal stopping of recruitment

The recommendation to formally stop recruitment was made by the DMEC in June 2014. This time, its recommendations went further:

- Participants in the pacing arm were to be informed of the concern and advised to cease use of their device forthwith (unless the patient and their clinician believed there were just grounds to do otherwise).
- Trial follow-up was to continue until all participants had either died or completed the 12-month follow-up.
- The TSC and trial team were to remain blind to the outcome data until this time.

Informing Research Ethics Committee, participants and investigators

The chief investigator and study manager drafted the following documentation to inform trial participants still in follow-up within the trial about the decision to stop pacing (see *Appendices 14–17*):

1. stop pacing participant letter – DPS arm
2. stop pacing participant letter – NIV arm
3. stop pacing GP letter – DPS arm
4. pacing discontinuation SOP.

A TMG meeting was held with study PIs the following day (24 June 2014) to review all drafted documents and agree the process. It is important to note that all the study team remained blinded to the data at this stage. Any modifications suggested to the process or documents were agreed at the meeting. Amended documents were submitted to the REC as part of a substantial amendment on 27 June 2014. Prior to this, the study manager sought confirmation about the nature of risk posed by the intervention; if there was an immediate risk, then urgent safety measures would be required. The DMEC confirmed that there was no evidence to suggest any immediate risk to participants in the DPS arm and, therefore, a more gradual approach was appropriate.

Research Ethics Committee approval was received on 4 July 2014. Individual research and development departments are required to approve a substantial amendment or raise no objections within 35 days of its valid receipt. Researchers did not wish to wait in order to implement this amendment and, therefore, the trial manager e-mailed, telephoned and spoke with each research and development department to approve the amendment to avert any delays in its implementation. The trial manager informed each PI and research nurse as soon as local approval was received. The chief investigator asked site PIs to use the approved documentation and process to directly inform participants of the study status and answer any questions that arose. The study manager asked to be notified of the status of each participant in the DPS arm after the conversation with the participant via the return of the participant discontinuation checklist.

The Motor Neurone Disease Association was informed of the advice to stop pacing. This was communicated to motor neurone disease patients via their website. The DiPALS trial website was updated to inform potential participants that the study was no longer in recruitment.

Chapter 4 Trial results

Recruitment and participant flow

In total, 74 participants (37 per arm) were randomised between 5 December 2011 and 18 December 2013, when the DMEC recommended that recruitment cease. Study follow-up concluded in December 2014, by which time 47 patients had died; one patient was last followed up in August 2014, with the remaining 26 known to be alive in December 2014 (Figure 2).

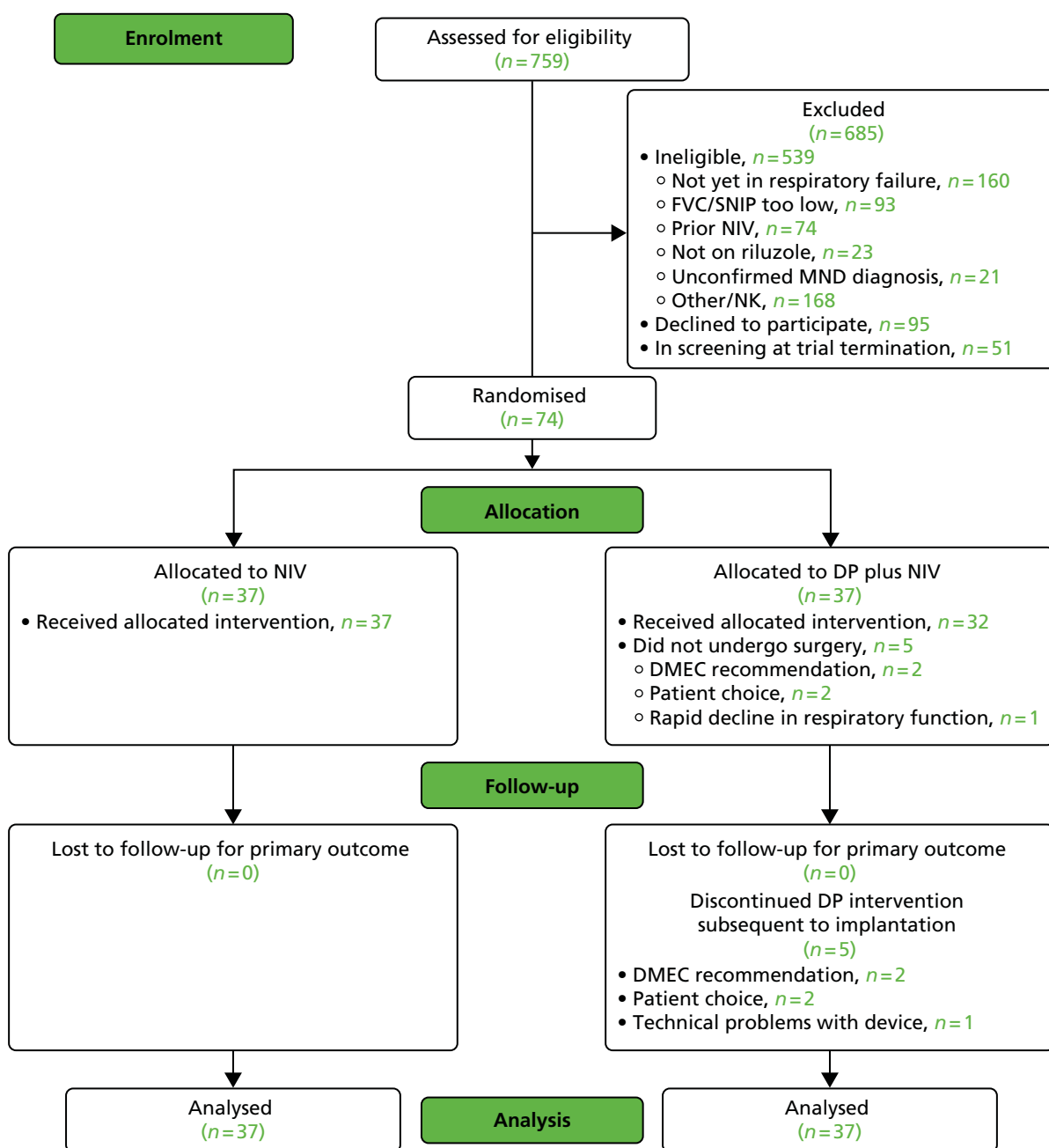


FIGURE 2 Trial profile (CONSORT diagram). MND, motor neurone disease; NK, not known.

Baseline data

A total of 74 participants were allocated (37 to each arm). The characteristics of the participants are presented in *Table 2*. Participants were predominantly male with sporadic (usually limb) onset and with mild bulbar impairment (74%). Despite age being included as a minimisation factor, the NIV plus DPS arm was slightly older (average 60 vs. 54 years), a consequence of most participants falling into the middle category of age 40–79 years; this imbalance was addressed in all comparisons, however, as all prespecified analyses included age as a covariate (continuous, rather than the categorisation used for the purpose of minimisation).

TABLE 2 Baseline data

Variable	Trial arm	
	NIV plus DPS (N = 37)	NIV (N = 37)
Centre, n (%)		
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 (years)^a		
Mean (SD)	60 (9.7)	54 (12.0)
Median (range)	61 (34–83)	53 (23–76)
Trial subgroup, n (%)		
< 40 years	1 (3)	3 (8)
40–79 years	35 (95)	34 (92)
≥ 80 years	1 (3)	0
Sex, n (%)^a		
Male	29 (78)	29 (78)
Female	8 (22)	8 (22)
Bulbar score (%)^a		
Mild (9–12)	26 (70)	29 (78)
Moderate (5–8)	8 (22)	6 (16)
Severe (0–4)	3 (8)	2 (6)
FVC (%)^a		
Mean (SD)	66.1 (12.3)	64.6 (12.1)
Median (range)	62.5 (51–105)	62.5 (42–97)
Trial subgroup, n (%)		
50–59%	13 (35)	16 (43)
60–69%	12 (32)	10 (27)
≥ 70%	11 (30)	10 (27)
Missing ^b	1 (3)	1 (3)

TABLE 2 Baseline data (continued)

Variable	Trial arm	
	NIV plus DPS (N = 37)	NIV (N = 37)
ALS onset type, n (%)		
Sporadic	34 (92)	35 (95)
Familial	3 (8)	2 (5)
ALS onset site, n (%)		
Limb	26 (70)	28 (76)
Bulbar	10 (27)	6 (16)
Respiratory	1 (3)	1 (3)
Mixed	0	2 (5)
ALS diagnosis, n (%)		
Clinically definite	26 (70)	22 (59)
Clinically probable	7 (19)	9 (24)
Clinically probable, laboratory supported	4 (11)	6 (16)
Time from symptom onset to randomisation (months)		
Mean (SD)	22 (18)	22 (15)
Median (range)	17 (4–89)	18 (3–66)
Trial subgroup, n (%)		
< 12 months	12 (32)	14 (38)
12–24 months	14 (38)	12 (32)
≥ 24 months	11 (30)	11 (30)
ALSFRS-R score		
Mean (SD)	32.9 (7.4)	33.7 (6.5)
Median (range)	33 (21–46)	35 (21–46)
Rate of ALSFRS-R score decline/month^c		
Mean (SD)	0.99 (0.68)	0.94 (0.71)
Median (range)	0.80 (0.02–2.92)	0.92 (0.20–3.72)

SD, standard deviation.

a Minimisation factors.

b Two participants in whom no FVC data were recorded; their SNIP results were 53 cmH₂O (pacing) and 34 cmH₂O (control).

c Defined as (48 – baseline ALSFRS-R score)/(number of months since onset). Forty-eight is the maximum possible ALSFRS-R score and is the assumed score at onset. The equation therefore represents the average change per month.

Primary outcome (overall survival)

Primary overall survival analyses

The Kaplan–Meier curve for overall survival is presented in *Figure 3*. The median survival was 11.0 months (95% CI 8.3 to 13.6 months) in the pacing arm and 22.5 months in the control arm. As the upper bound of the Kaplan–Meier survival curve never reached 50%, the upper limit of the 95% CI is unknown: the lower bound is 13.6 months. The HR (adjusting for minimisation covariates) was 2.27 (95% CI 1.22 to 4.25; $p = 0.01$), indicating the risk of death at any point in time was higher in the NIV plus pacing arm than in the control arm. A permutation test approach, as recommended by Scott *et al.*,²⁵ produced a p -value of 0.013 confirming the statistical significance of this difference.

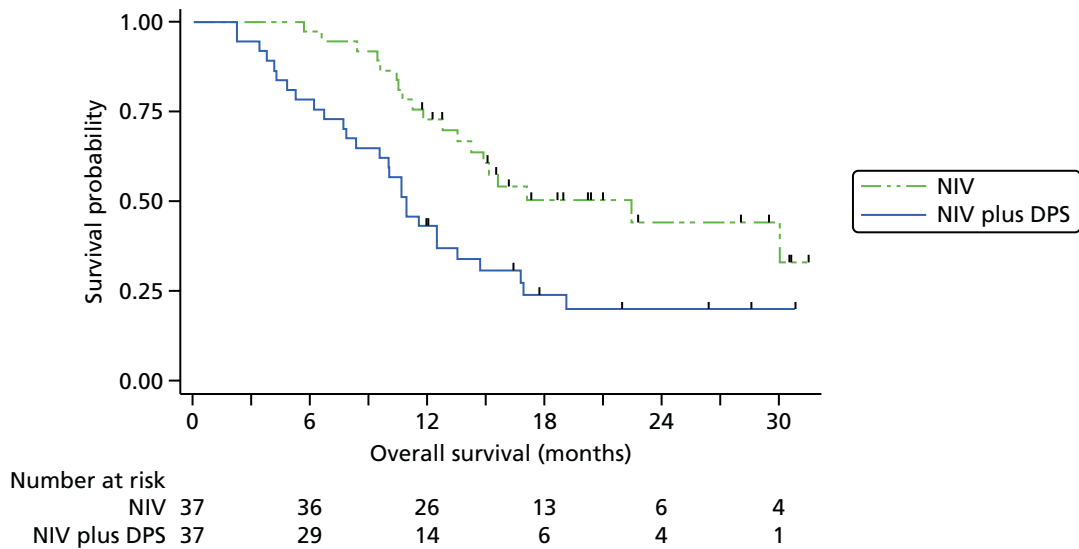


FIGURE 3 Overall survival.

Sensitivity analyses were undertaken to assess the consistency of findings to different covariates and to different models. First, we allowed for between-site differences via a stratified log-rank test in which the strata comprised the seven hospitals. The findings from doing this were not materially changed. There was, however, evidence of non-proportionality of the hazards of the two groups, as detected by the Grambsch–Therneau test²⁰ for the correlation between residuals and time ($\rho = -0.31$; $p = 0.03$). In other words, although overall NIV plus DPS was associated with a twofold increase in hazard, the impact was greater in early months and smaller among longer-term survivors. Two alternative modelling approaches were fitted: first, an accelerated failure time model (in which the time, rather than hazard, is modelled); and, second, a non-parametric restricted mean survival time, in which the difference in mean survival is estimated based on the area between the Kaplan–Meier curves.²² The findings from the sensitivity analyses analysis are presented in *Table 3*. Overall, the magnitude of the survival deficit in the NIV plus DPS group was remarkably consistent, with survivorship always significantly lower in the NIV plus DPS group.

Overall survival at Data Monitoring and Ethics Committee intervention

The DMEC did not prespecify rules for stopping because of safety, preferring to use clinical judgement about participant outcomes as a whole. Nevertheless, its recommendations were based primarily on overall survival, and for reference we present overall survival as of the following dates:

- 10 December 2013 (the date that data were seen by the DMEC, when it recommended suspension of recruitment and implantation)
- 10 June 2014 (the date that data were seen by the DMEC, when it recommended participants in the NIV plus DPS arm should cease pacing).

The statistical significance of the overall survival difference varied markedly during the data collection phase, both across time and also according to which of the aforementioned models were used to derive it. Nevertheless, as shown in *Table 4* and *Figures 4* and *5*, overall survival was significantly worse in the NIV plus DPS group at both time points.

Subgroup analyses of overall survival (preplanned)

We prespecified three subgroup analyses: (1) by NIV tolerance, based on estimated average NIV usage; (2) by bulbar function, as derived from the ALSFRS-R questionnaire; and (3) a per-protocol analysis excluding participants who were inappropriately randomised or who did not adhere to NIV and/or pacing (if that was their randomised allocation).

TABLE 3 Sensitivity analyses

Method of analysis	Trial arm		Comparison	p-value
	NIV plus DPS	NIV		
Cox proportional hazards regression	<i>Deaths per person-year follow-up</i>		<i>HR (95% CI)</i>	
Log-rank (univariate)	0.74	0.37	2.24 (1.30 to 4.19)	0.005
Log-rank (stratified by centre)	–	–	2.02 (1.21 to 3.84)	0.012
Cox regression (univariate)	–	–	2.28 (1.27 to 4.10)	0.006
Cox regression (including minimisation factors as covariates)	–	–	2.27 (1.22 to 4.25)	0.012
Accelerated failure time regression	<i>Median survival time (months)</i>		<i>Time ratio (95% CI)</i>	<i>p-value</i>
Gehan–Wilcoxon test (univariate)	11.0	22.8	–	0.002
Gehan–Wilcoxon test (stratified by centre)	–	–	–	0.029
Log-normal regression (univariate)	–	–	0.52 (0.36 to 0.77)	0.001
Log-normal regression (including minimisation factors as covariates)	–	–	0.52 (0.35 to 0.77)	0.001
Restricted mean failure time	<i>Mean survival time over first 30 months</i>		<i>Difference (95% CI)</i>	<i>p-value</i>
Univariate	13.7	20.6	–6.9 (–11.4 to –2.4)	0.003
Including minimisation factors as covariates	–	–	–6.8 (–11.5 to –2.2)	0.005

TABLE 4 Statistical significance of the overall survival difference during data collection

Data collection time point	Trial arm, number (%) of deaths			Intention-to-treat comparison (univariate)	
	NIV plus DPS		NIV	HR (95% CI) ^a	p-value
	All patients (n = 37)	Excluding non-implanted (n = 32)	All patients (n = 37)		
As of 10 December 2013	16 (44 ^b)	14 (44)	8 (22 ^b)	2.45 (1.05 to 5.74)	0.039
As of 10 June 2014	23 (62)	21 (66)	11 (30)	2.73 (1.33 to 5.60)	0.006
At end of study	28 (76)	26 (81)	19 (49)	2.28 (1.27 to 4.10)	0.006

a Univariate Cox regression.

b Thirty-six participants in each arm at this time. A further two participants were randomised between production of the database report and the DMEC meeting (18 December 2013). The number of participants implanted remained at 32.

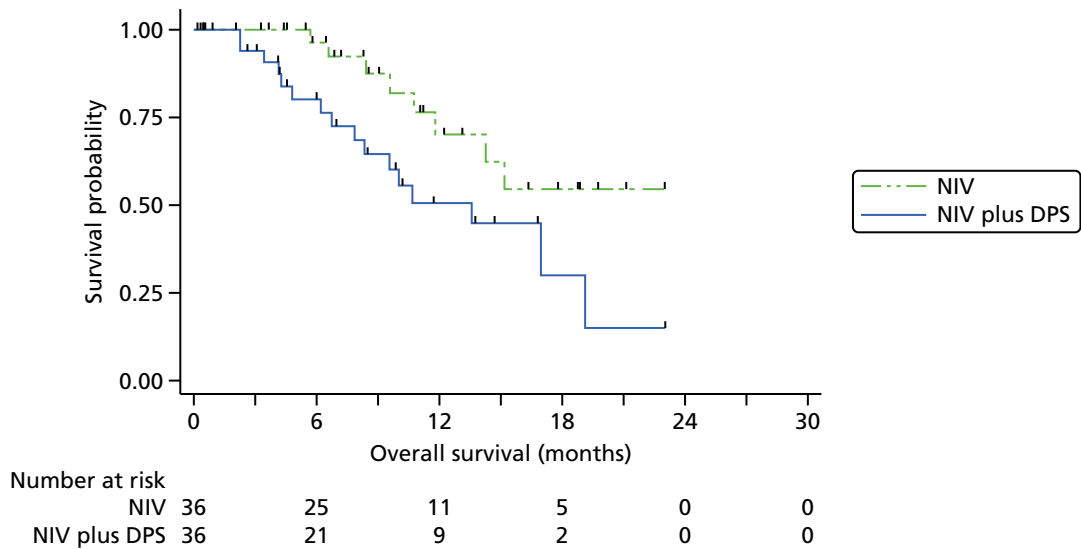


FIGURE 4 Survival at 10 December 2013.

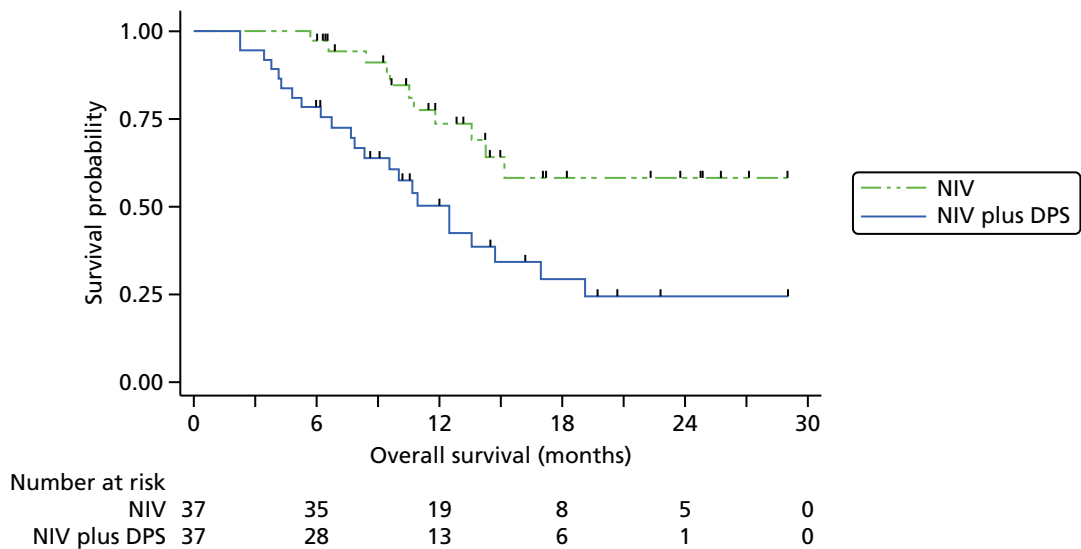


FIGURE 5 Survival at 10 June 2014.

The results of these are given in this section. In all cases the results were not adjusted for other covariates, as the small number of participants in each subgroup means that more complex models are likely to be unstable. Subgroup analyses were by univariate Cox regression, and tests of interactions were derived by adding treatment, subgroup and their interaction to the model. It should also be noted that small subgroup sizes results in wide CIs and low statistical power both for the main effects and interactions.

Overall survival by baseline bulbar function

The subgroup analysis by bulbar function was originally defined to look at survival in severe (functional score of 0–4) and mild/moderate (functional score of 5–12) separately. As all but five participants were in the latter group, we have chosen to split the mild and moderate subgroups out, but retain severe bulbar function as its own (small) category.

Overall survival was inferior in the NIV plus DPS arm in both mild and moderate subgroups, although the difference was statistically significant only in the former. There were too few participants in the severe subgroup to allow a meaningful interpretation to be made. Overall, there was little evidence of a differential effect of DP according to bulbar function with a non-significant p -value for the interaction between bulbar function and group (likelihood ratio test $\chi^2_{(2)} = 3.44$; $p = 0.18$) (Figure 6).

Overall survival by non-invasive ventilation tolerance

The subgroup analysis by NIV use was again originally defined to look at survival in two subgroups: NIV tolerant (≥ 4 hours typical daily use) and NIV intolerant (< 4 hours). Post hoc, we have split the latter category further into low NIV use (1–3.9 hours daily, which might confer some benefit) and non-NIV use (< 1 hour daily, which confers virtually no benefit). The rationale is to allow better assessment of the relationship between pacing and outcome. Pacing has been suggested as possibly having particular benefit among patients who do not tolerate NIV, and this analysis allows us to put that hypothesis to the test. Moreover, the difference in survival may (theoretically) be attributed to participants in the NIV plus DPS arm using pacing in place of NIV; this allows us to compare users within each NIV use subgroup.

We categorised average daily NIV use into < 1 hour, 1–3.9 hours or ≥ 4 hours in order to assess whether or not the difference between groups in overall survival was similar. The Kaplan–Meier graphs are shown in Figure 7. In six participants there were inadequate data from which to assess NIV usage, and small numbers hamper interpretation, but survival in the NIV plus DPS was not superior to NIV alone in any subgroup, with the largest difference (in favour of NIV) among the subgroup of participants who did not use NIV. As with bulbar function there was no evidence of a differential effect according to NIV use at conventional statistical levels (likelihood ratio test $\chi^2_{(2)} = 4.14$; $p = 0.13$).

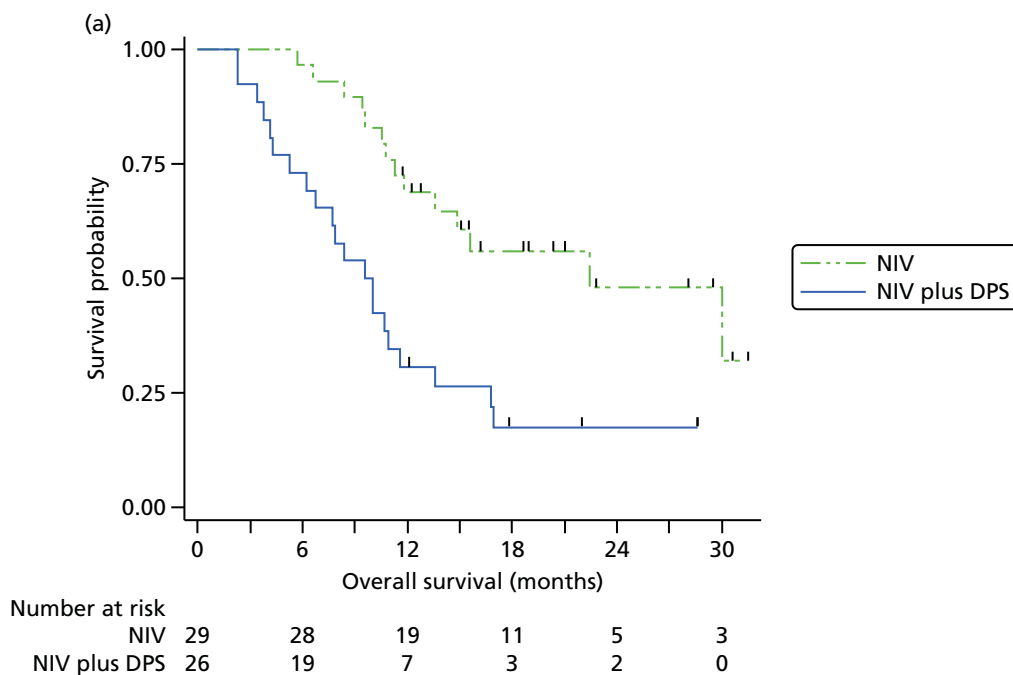


FIGURE 6 Overall survival by bulbar function. (a) Mild bulbar impairment; (b) moderate bulbar impairment; and (c) severe mild bulbar impairment. (*continued*)

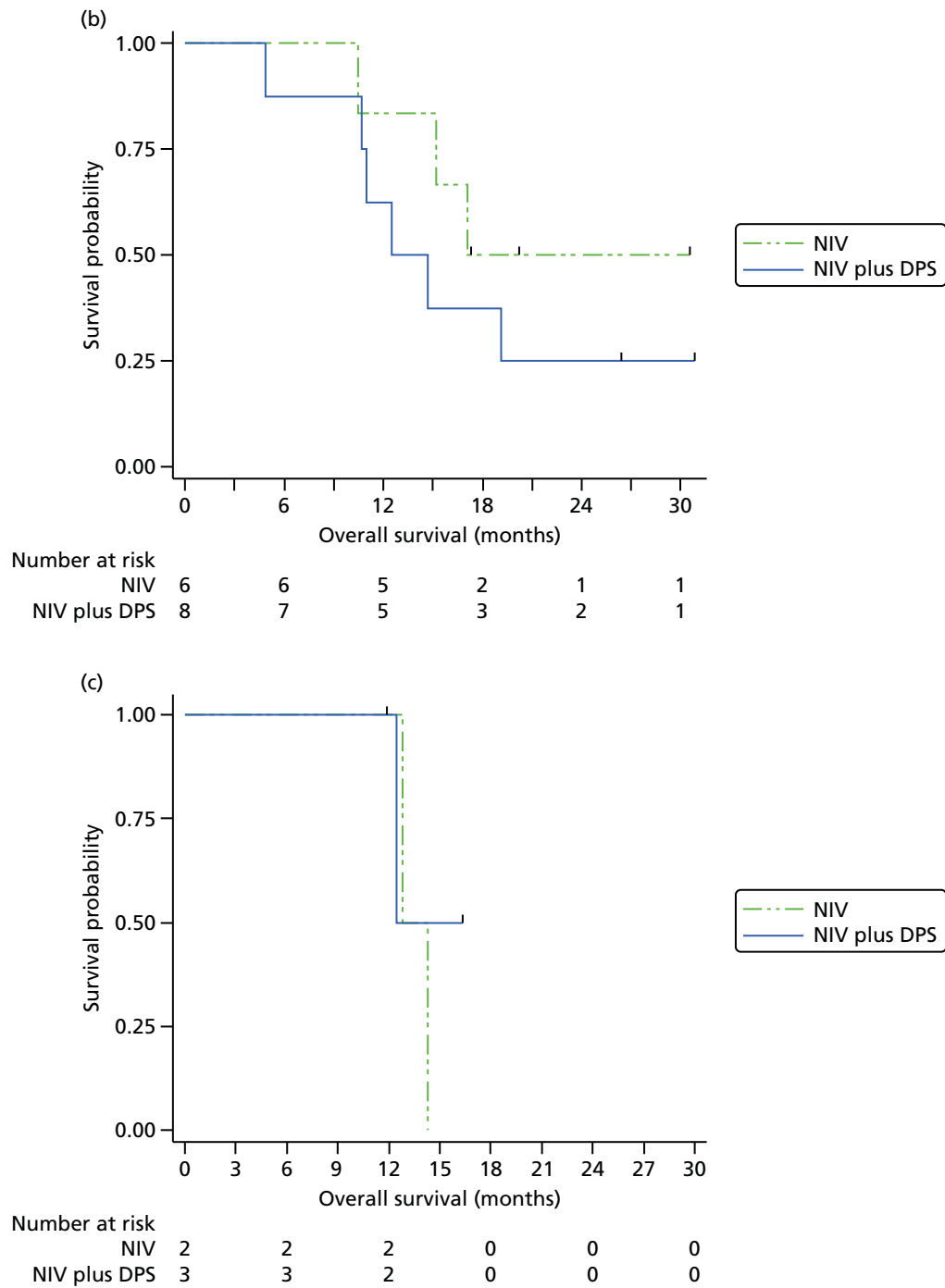


FIGURE 6 Overall survival by bulbar function. (a) Mild bulbar impairment; (b) moderate bulbar impairment; and (c) severe mild bulbar impairment.

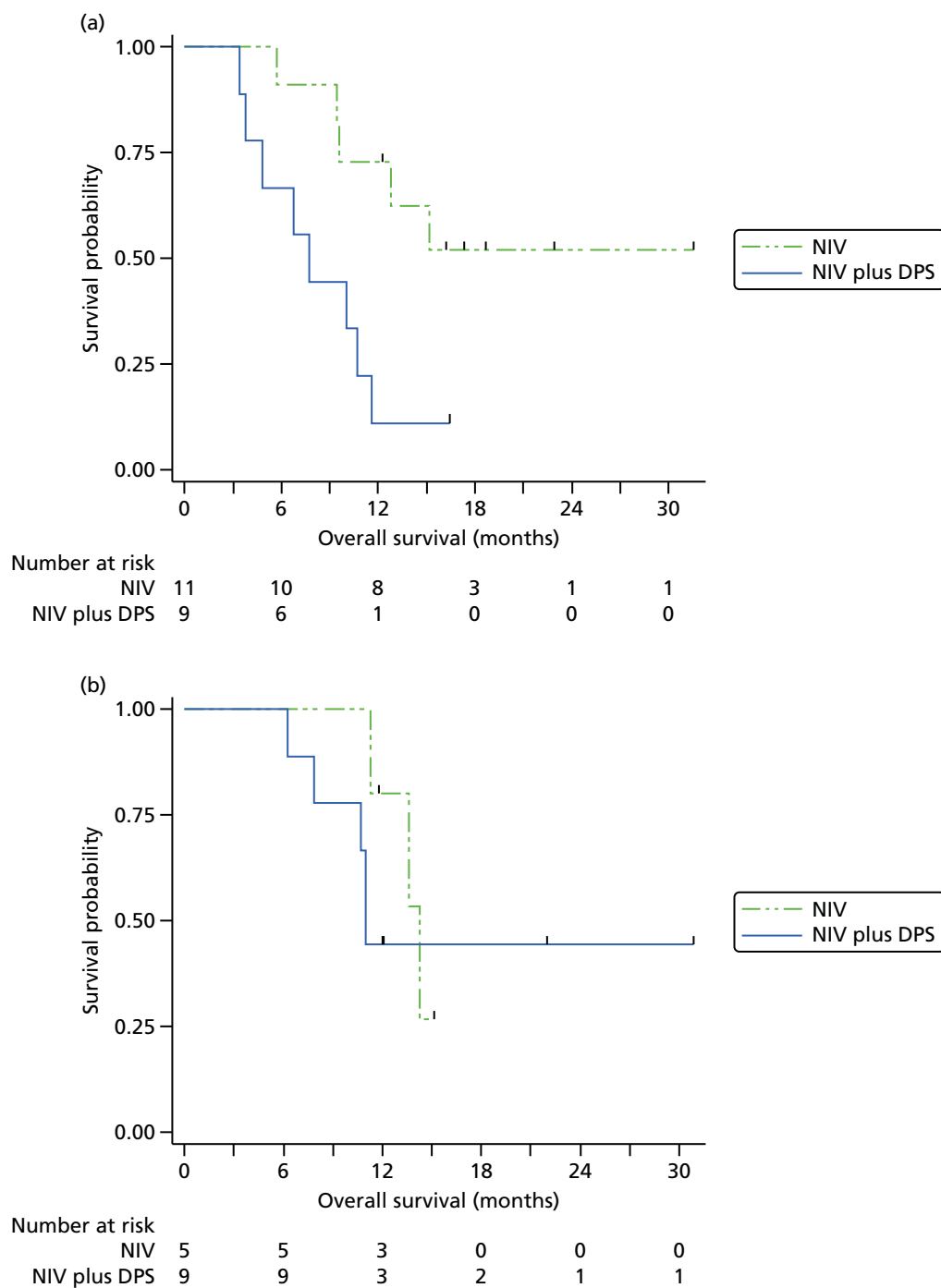


FIGURE 7 Overall survival by NIV use. (a) Non-use (< 1 hour); (b) low use (1–3 hours); and (c) NIV tolerant (≥ 4 hours). (*continued*)

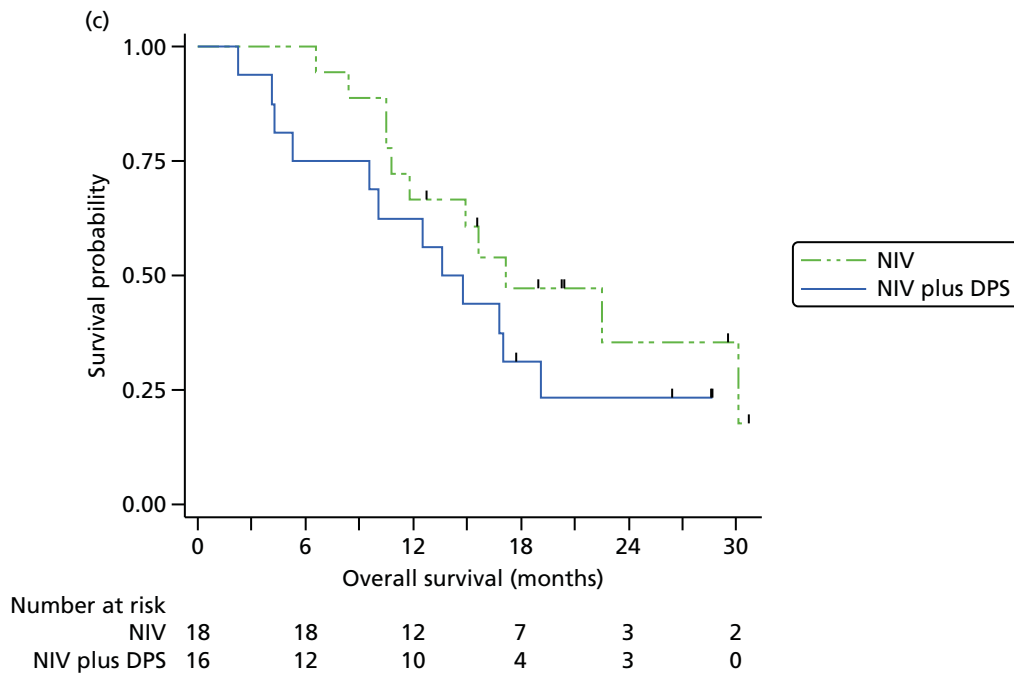


FIGURE 7 Overall survival by NIV use. (a) Non-use (< 1 hour); (b) low use (1–3 hours); and (c) NIV tolerant (≥ 4 hours).

Per-protocol analysis of overall survival

Protocol compliance was based on excluding participants who:

- were randomised in error (i.e. in breach of inclusion/exclusion criteria)
- did not tolerate NIV (< 4 hours' average daily use)
- did not undergo successful DP implantation
- were non-users of DP.

This subgroup was very similar to that shown in the 'tolerant' (≥ 4 hours) subset in subgroup analysis. No participants were erroneously randomised and only one non-user of the pacing device was NIV tolerant, meaning that the total number included reduced from 34 to 33. The HR for NIV plus DPS compared with NIV in this subgroup was 1.92 (95% CI 0.81 to 4.56; $p = 0.141$).

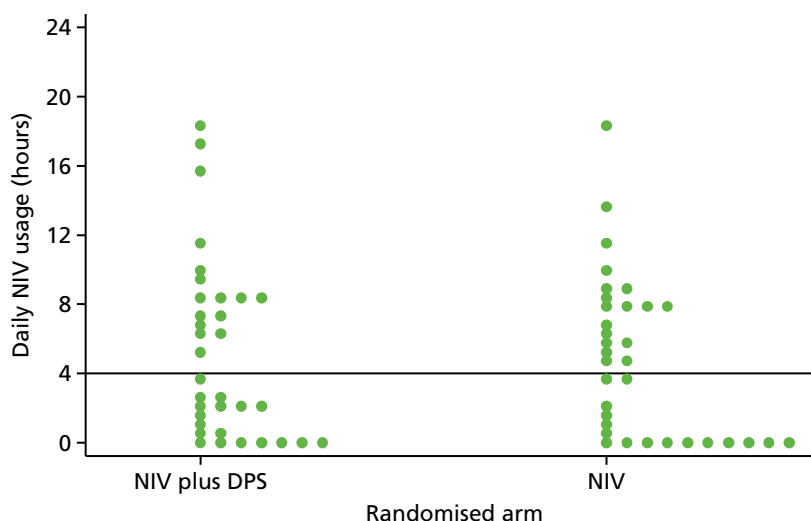
Non-invasive ventilation and pacing usage

Non-invasive ventilation use

Non-invasive ventilation was initiated in 70 out of 74 patients. In total, 57 patients were initiated within 2 weeks of randomisation, a further six within 1 month and the remaining 7 between 3 and 11 months. NIV usage was similar between the two groups (*Table 5* and *Figure 8*).

TABLE 5 Average daily NIV usage after initiation

Variable	Trial arm	
	NIV plus pacing (<i>n</i> = 37)	NIV (<i>n</i> = 37)
Number of patients with data	34	34
Average daily usage (hours)		
Mean	5.2	4.8
Median (IQR)	3.2 (0.5–8.2)	4.6 (0.0–7.8)
Number (%) by subgroup		
< 1 hour	9 (26%)	11 (32%)
1–3.9 hours	9 (26%)	5 (15%)
≥ 4 hours	16 (47%)	18 (53%)

**FIGURE 8** Average daily NIV usage after initiation.

Pacing use

Five pacing group participants did not undergo surgery because of a rapid decline in respiratory function below the safety threshold for surgery (*n* = 1), patient choice (*n* = 2) and the DMEC intervention (*n* = 2); and a sixth patient chose to stop pacing within 1 month of implant following technical problems with the device. All participants who went to surgery had a successful implantation, with a stimulatable diaphragm. When used, the median daily usage was 4.6 hours (IQR 3.0–8.4 hours). Participants pacing were largely able to achieve the target pacing settings within 15 days of surgery and continued to successfully titrate over the course of the study as per the study protocol. Pacing was well tolerated, with only two patients choosing to formally discontinue pacing after implantation, one at 6 months and one at 12 months. The DP settings and usage are described in *Table 6–8*.

TABLE 6 NIV settings at initiation and at final visit

Variable	First recorded setting			Last recorded setting		
	NIV plus pacing		NIV	NIV plus pacing		NIV
	Median (IQR)	Minimum–maximum	Median (IQR)	Median (IQR)	Minimum–maximum	Median (IQR)
Target daily usage (hours)	5 (4–8)	0–8	4 (4–5)	8 (5–8)	0–24	5 (4–8)
Minimum volume assured pressure support (cmH ₂ O)	5 (5–5)	5–12	5 (5–5)	5 (5–5)	5–12	5 (5–5)
Maximum volume assured pressure support (cmH ₂ O)	20 (20–25)	16–25	25 (25–25)	20 (18–25)	16–30	25 (20–25)
Inspiratory positive airways pressure (cmH ₂ O)	12 (10–14)	5–16	12 (10–12)	12 (12–16)	5–18	12 (10–12)
Expiratory positive airways pressure (cmH ₂ O)	4 (4–4)	2–8	4 (4–4)	4 (4–4)	2–6	4 (4–4)
Target tidal volume (ml)	500 (500–550)	400–550	500 (470–500)	550 (500–570)	500–670	500 (450–500)
Respiratory rate (b.p.m.)	12 (10–12)	6–16	12 (10–12)	12 (10–12)	8–16	12 (10–12)

b.p.m., beats per minute.

TABLE 7 NeuRX RA/4 DPS settings

Variable	Initial recommended setting	First recorded setting			Last recorded setting		
		Median (IQR)	Minimum–maximum	Number (%) with settings \geq initial recommended setting	Median (IQR)	Minimum–maximum	Number (%) with settings \geq initial recommended setting
Amperes (mA) ^a	10	10.8 (10–13)	6–19	26 (81%)	12.4 (10–16)	6–23.3	27 (84%)
Pulse (microseconds) ^a	100	100 (98–110)	83–150	23 (72%)	119 (100–145)	83–160	25 (78%)
Respiratory rate (b.p.m.)	12	12 (12–12)	10–14	29 (91%)	12 (12–12)	10–16	30 (94%)
Inspiratory interval (seconds)	1.1	1.1 (1.1–1.1)	1.1–1.2	32 (100%)	1.1 (1.1–1.1)	1.1–1.2	32 (100%)
Pulse frequency (Hz)	12	15 (12–15)	12–20	32 (100%)	15 (12–15)	10–20	31 (97%)
Pulse ramp (seconds)	10	10 (0–10)	0–10	27 (84%)	10 (10–10)	10–10	32 (100%)

b.p.m., beats per minute; Hz, hertz.
a Average across four channels, the other settings are single readings.

TABLE 8 Pacing usage

Variable	NIV plus DPS (n = 37)
Number of patients using pacing	31
Non-users	6
Did not undergo surgery	5
Withdrew with minimal usage following technical problems	1
Time to surgery (n = 32 implanted), n (%)	
Within 14 days	5 (16%)
15–28 days	12 (38%)
29–56 days	10 (31%)
> 56 days	5 (16%)
Average daily usage when used (hours)	
Mean	6.2
Median (IQR)	4.6 (3.0 to 8.4)

Overall survival by non-invasive ventilation and pacing

The relationship between overall survival and NIV use (categorised as non-use, low use and tolerant over the study period) is covered further in this section. Furthermore, the use of overall survival and NIV use in relation to pacing is investigated in more detail. The role of post hoc and exploratory analyses is to attempt to understand the unexpectedly poor survival experienced by participants in the NIV plus DPS group.

Non-invasive ventilation use and overall survival

The problems in evaluating the association between therapeutic regimens and patient outcomes in an uncontrolled, observational setting are well documented. Using NIV is generally accepted as beneficial,²⁷ but the extent to which a participant uses it depends, to a degree, on prognosis. A patient who uses NIV at low levels may do so because their respiratory physician considers them well enough, or they consider themselves well enough, to have no need for high levels of use. Conversely, ALS patients often use NIV at high levels (≥ 12 hours per day) towards the end of their life. There are other factors besides this which impact on NIV use, but the aforementioned factors illustrate how the true impact of NIV is confounded by prognosis and can thereby be underestimated. With this in mind, the overall lack of association between NIV use and survival in the remainder of this section should not be taken as evidence against NIV being beneficial. Rather, this section attempts to assess whether or not NIV use gave rise to differential treatment effect and, crucially, whether or not some participants in the NIV plus DPS group used pacing in place of NIV.

We also note the difficulties in quantifying NIV use. In some cases there was a lag between NIV initiation and regular use, and in a handful of cases several months passed between initiation and regular use. It could be argued that the analysis should take NIV use starting from the date of first regular use, but the limitation of doing so is that 'regular' use is not unequivocally defined. Some patients started NIV at low levels (1–2 hours per day), whereas others used NIV on trial basis, only to stop (sometimes for several months) before recommencing. Furthermore, the participant diary data were in many cases not recorded in sufficient detail (completeness) to allow a date of 'regular' use to be determined.

Non-invasive ventilation use in the 12-month follow-up period

We first looked at NIV from the point of initiation to the end of the 12 months' follow-up or death, whichever occurred first. Data were available for 68 of the 74 participants over the study duration.

The primary motivation, however, is not to quantify the association between NIV and survival *per se*, but to investigate whether or not the difference between the randomised NIV plus DPS and NIV arms may be affected by NIV rather than pacing alone.

The problem in visualising survival data is that the survival times are censored for a proportion of the participants. The relationship between NIV use and survival can be displayed graphically only if some assumptions are made as to what the censored times would have been, had they been observed. There is necessarily considerable uncertainty in doing so. For the purpose of displaying the data in graphical form we followed the approach proposed by Royston and Parmar²² to estimate the underlying (but unobserved) survival times based on each individual's censored survival time, treatment group and prognostic covariates. A Q-Q plot of the data showed the log-normal survival distribution to give a reasonable fit to the data; therefore, a truncated log-normal regression model was fitted. From this, the overall survival for each individual was being estimated based on their predicted mean survival, their censored survival time, and the root-mean-square error of the model. We fitted two models with minimisation covariates also included in both: first, for all patients and then second, within each group separately. The estimated survival was taken as the average of these two predicted times.

It is important to note that we estimate the survival times only for the purpose of visualising the relationship between NIV, and not for the analysis itself. In all cases, the graphical display distinguishes estimated survival times from observed survival times.

Overall, no relationship was evident between typical NIV use and survival, using either the level of NIV or its categorised version (< 1 hour, 1–3.9 hours or 4 hours). These are demonstrated graphically for the NIV use measured in hours (*Figure 9*), using the estimated/extrapolated survival for censored survival and in a more conventional Kaplan–Meier graph for the categorisation of NIV use (*Figure 10*).

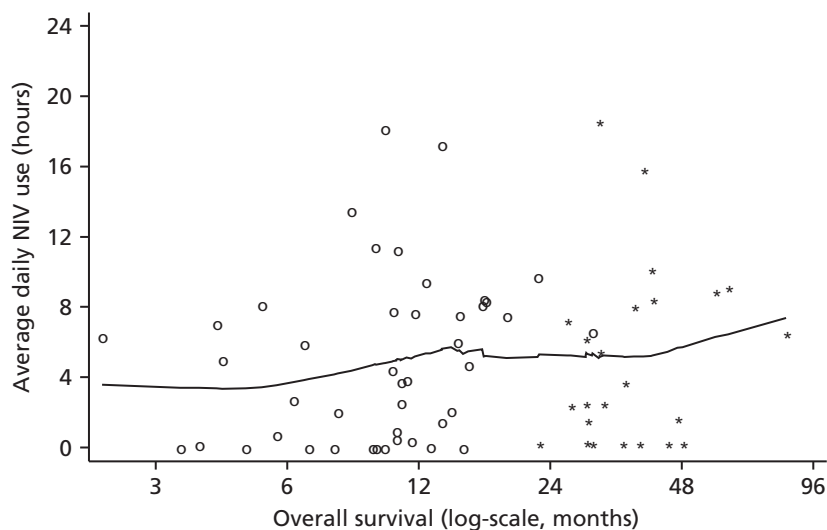


FIGURE 9 Survival by NIV use: NIV use in hours. Censored survival times are estimated based on a censored log-normal distribution using treatment and minimisation covariates. The line is a locally weighted scatterplot smoother (lowess) with a bandwidth of 0.6. Circles denote actual survival times; stars are estimated times.

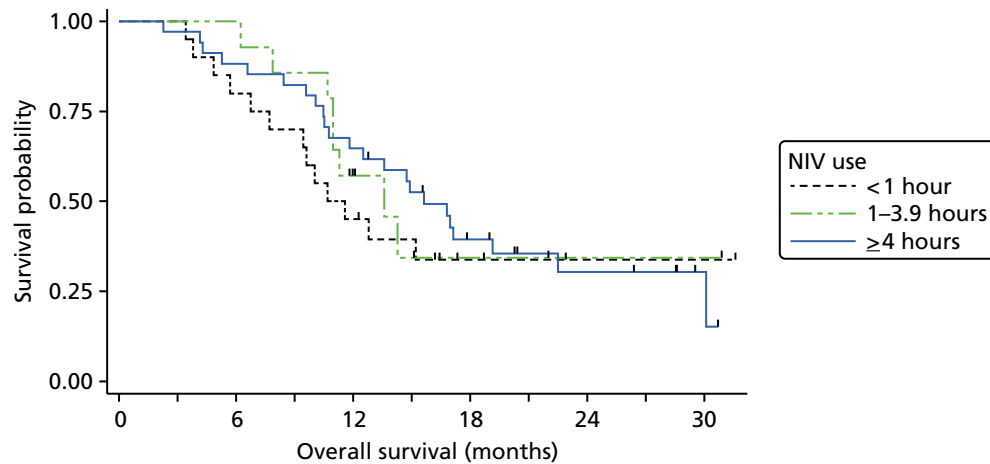


FIGURE 10 Survival by NIV use: NIV use category. Censored survival times are estimated based on a censored log-normal distribution using treatment and minimisation covariates. The line is a locally weighted scatterplot smoother (lowess) with a bandwidth of 0.6.

In the categorised version of NIV there was no association between average daily usage and overall survival, using either the standard log-rank test ($\chi^2_{(2)} = 0.64$; $p = 0.72$) or the log-rank test for trend across the categories ($\chi^2_{(1)} = 0.64$; $p = 0.46$). As shown in *Table 9*, the largest difference between NIV plus DPS and NIV alone was observed in the low-use subgroup ($n = 20$ participants), but the interaction term between treatment group and NIV category was not statistically significant at conventional levels in a Cox regression model (likelihood ratio test $\chi^2_{(2)} = 4.14$; $p = 0.13$).

No relationship was found when looking at the average number of hours (i.e. as a continuous measure) and overall survival. The linear association as derived from a univariate Cox regression model showed a small and non-statistically significant increase in survival with increasing hourly use of NIV (HR 0.98, 95% CI 0.92 to 1.04; $p = 0.52$). The possibility of a non-linear relationship was assessed using fractional polynomials regression, but the best non-linear model still failed to find any association (likelihood ratio test $\chi^2_{(2)} = 1.26$; $p = 0.53$) or of any interaction between treatment and NIV use (likelihood ratio test $\chi^2_{(1)} = 0.68$; $p = 0.41$).

TABLE 9 Overall survival by bulbar function and by NIV use

Variable	Trial arm, number of participants (deaths)		Comparison	
	NIV plus DPS	NIV	HR (95% CI)	p-value
Overall survival by bulbar function				
Overall test of interaction between treatment and bulbar function				
Mild (9–12)	26 (21)	29 (14)	2.99 (1.49 to 6.01)	0.002
Moderate (5–8)	8 (6)	6 (3)	1.95 (0.48 to 7.92)	0.349
Severe (0–4)	3 (1)	2 (2)	0.62 (0.05 to 7.00)	0.697
Overall survival by NIV use				
Overall test of interaction between treatment and NIV use				
Non-use (< 1 hour daily)	9 (8)	11 (5)	3.90 (1.23 to 12.4)	0.021
Low use (1–3.9 hours daily)	9 (5)	5 (3)	1.50 (0.35 to 6.38)	0.584
Tolerant (≥ 4 hours daily)	16 (12)	18 (11)	1.63 (0.70 to 3.78)	0.253

Non-invasive ventilation use in the first 3 and 6 months post randomisation

We also looked at whether overall survival is associated with NIV use in (1) the first 3 months post randomisation or (2) the first 6 months post randomisation. Although this does not use the more complete NIV data over the 12 months' follow-up, focusing on short-/medium-term use might be seen as a surrogate for intention-to-use NIV, as opposed to the level of use necessitated by disease progression. Participants for whom NIV initiation was delayed are included; a participant who was initiated at 4 months would be defined as having zero use within the 0–3 months period.

However, the findings were similar to those reported for 12-month NIV use above. Overall survival was weakly associated with NIV use, but was not statistically significant: the HR for 3-month use was 0.96 (95% CI 0.87 to 1.05; $p = 0.33$) and for 6-month use was 0.98 (95% CI 0.91 to 1.07; $p = 0.68$). Non-linear associations derived from fractional polynomial regression also failed to reach statistical significance (likelihood ratio test for 3-month follow-up: $\chi^2_{(2)} = 2.95$; $p = 0.23$; 6-month follow-up likelihood ratio test $\chi^2_{(1)} = 0.89$; $p = 0.64$). Again, no interaction was found between treatment group and NIV use over either period.

Pacing use and overall survival

We assessed the relationship between pacing use and overall survival. Unlike NIV, no normative data exist for pacing use; consequently, we did not categorise pacing usage into groups. The caveats that apply when assessing the relationship between NIV and survival also apply here.

Figure 11 shows average pacing use against overall survival, again estimating survival times as described in *Non-invasive pacing and overall survival*. As with NIV, no discernible relationship was evident. The HR for each additional hour of use was 1.01 (95% CI 0.94 to 1.09; $p = 0.707$); if non-implanted patients were excluded, the HR was 1.00 (95% CI 0.92 to 1.09; $p = 0.931$). Non-linear models, again derived using fractional polynomials, did not improve the fit of the model.

Non-invasive ventilation, pacing and overall survival

The final analyses looked at the association between NIV and pacing use within the 37 participants randomised to receive the intervention. A potential theory was that participants in the NIV plus pacing arm may have used pacing in place of NIV. If so, this could partly explain the between-group differences, as NIV use is known to prolong survival.

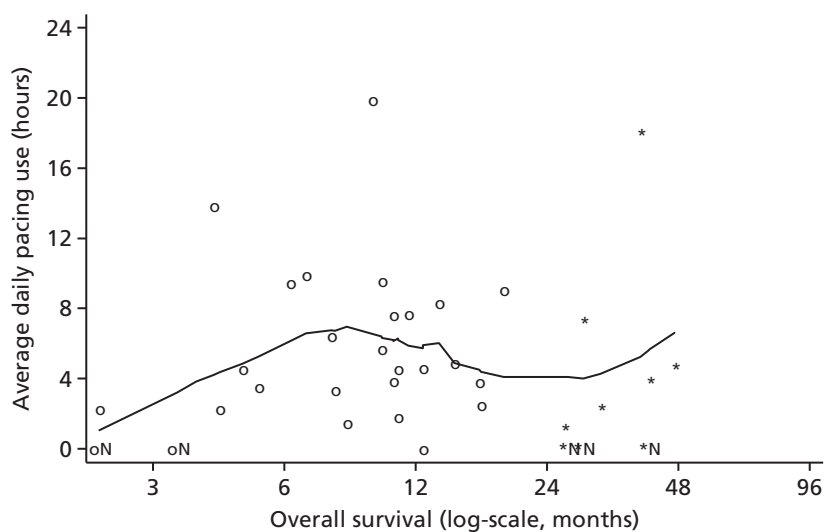


FIGURE 11 Survival by pacing use. Censored survival times are estimated based on a censored log-normal distribution using treatment and minimisation covariates. The line is a locally weighted scatterplot smoother (lowess) with a bandwidth of 0.6. Circles denote actual survival times; stars are estimated times. N, not implanted.

Nevertheless, this theory was not borne out by the data. The average use of pacing and NIV is shown in *Figure 12*; the relationship between the two measures was positive rather than negative, suggesting participants who use NIV more also tended to use pacing more. We also split the NIV plus DPS arm into NIV-tolerant users (≥ 4 hours per day on average) and NIV-non-tolerant users (< 4 hours per day on average), with the Kaplan–Meier curves as shown in *Figure 13*. Participants in the NIV plus DPS arm who used NIV for an average ≥ 4 hours a day had a better survival than those who did not, but their survival remained lower than the NIV alone group. Neither comparison was statistically significant at the 5% significance level; however, the small numbers in each subgroup mean that the statistical power is low for this comparison.

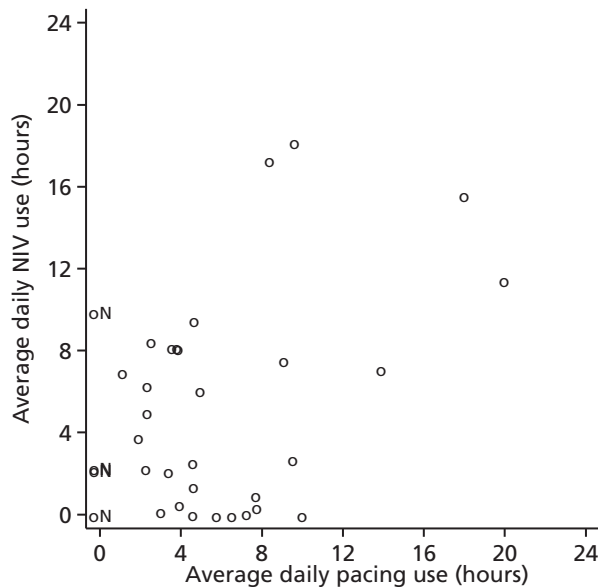
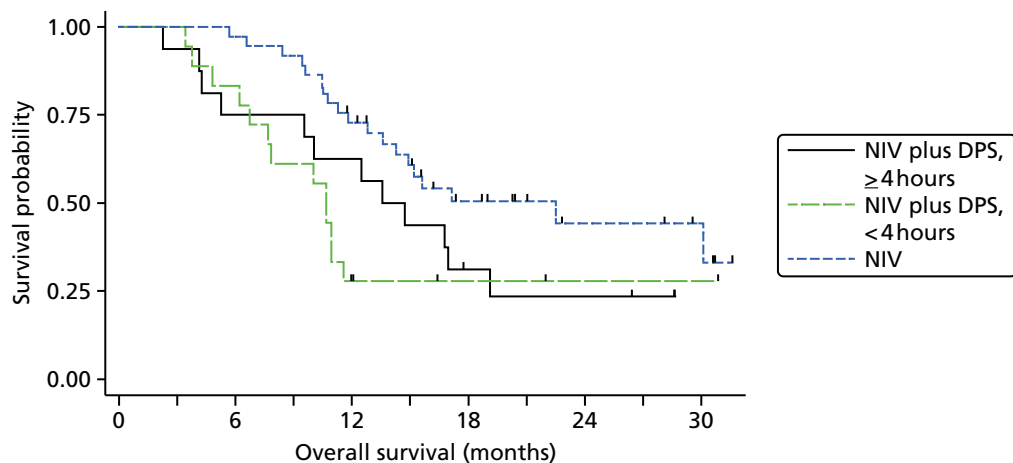


FIGURE 12 Relationship between NIV and pacing use. N, not implanted.



	0	6	12	18	24	30
Number at risk						
NIV plus DPS, ≥ 4 hours	16	12	10	4	3	0
NIV plus DPS, < 4 hours	18	15	3	2	1	1
NIV alone	37	36	26	13	6	4

FIGURE 13 Overall survival by pacing and NIV use.

Secondary outcomes

Tracheostomy and tracheostomy-free survival

Tracheostomy-free survival is defined as the time to death or tracheostomy, whichever comes first.

One tracheostomy was reported: one participant in the NIV plus DPS arm underwent a tracheostomy 31 months after randomisation. The TFS is, therefore, very similar to overall survival, with a HR adjusted for minimisation covariates being 2.42 (95% CI 1.28 to 4.59; $p = 0.007$).

Participant quality of life

European Quality of Life-5 Dimensions, three levels

The participant health utility as measured by EQ-5D-3L is shown in *Figures 14 and 15*. Among those surviving to 12 months and with complete data, the difference in EQ-5D-3L scores was -0.18 (95% CI -0.44 to 0.08 ; $p = 0.164$). However, over the follow-up period as a whole, the EQ-5D-3L score declined quicker in the NIV plus DPS arm than in the NIV alone arm, with the longitudinal analysis providing an average difference across time of -0.13 (95% CI -0.25 to -0.00 ; $p = 0.042$). Imputing missing data made no material difference to the conclusions. The preplanned analysis of EQ-5D-3L scores according to NIV tolerance and bulbar function was not undertaken because of small numbers (especially in the NIV plus DPS arm) and the apparent deficit in overall survival.

A further analysis of EQ-5D-3L scores included both surviving and non-surviving participants, with a score of 0 assigned to the latter from the point of death onwards. Doing so demonstrated a lower QoL both at 12 months (mean difference -0.12 , 95% CI -0.24 to -0.01 ; $p = 0.040$) and also longitudinally (mean difference -0.14 , 95% CI -0.24 to -0.04 ; $p = 0.001$).

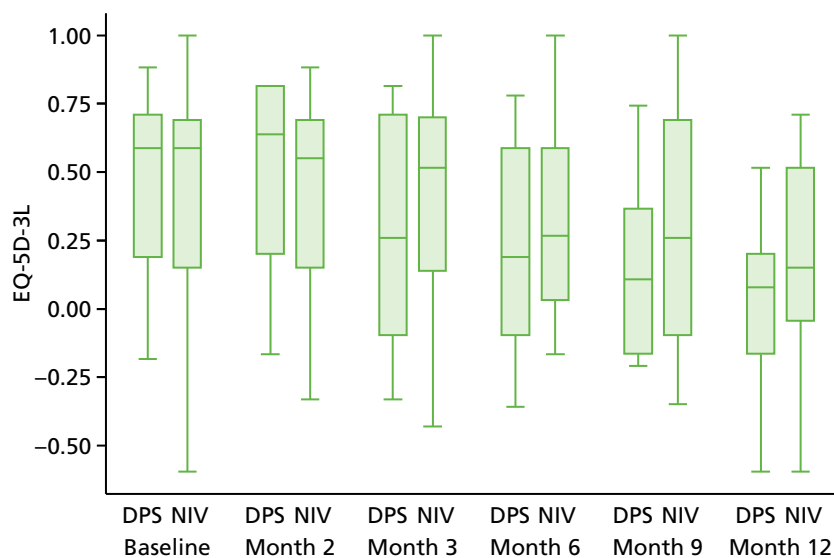


FIGURE 14 The EQ-5D-3L health utility among surviving participants over time: EQ-5D-3L health tariff.

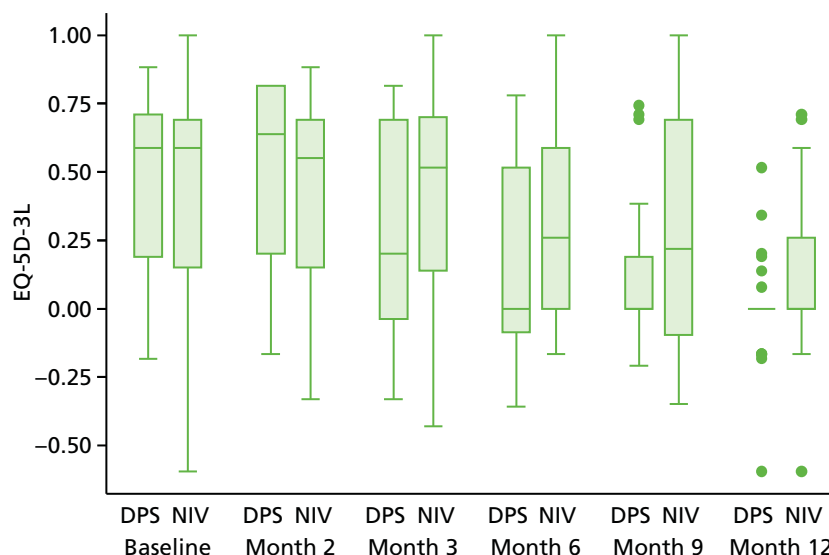


FIGURE 15 The EQ-5D-3L health utility among surviving participants over time: patient EQ-5D-3L health tariff, deaths imputed as zero.

The findings of the EQ-5D-3L thermometer scale were consistent with those for the main EQ-5D-3L questionnaire (Table 10). All longitudinal analyses were repeated using an unstructured correlation matrix, as the random intercept model makes the assumption of a common correlation between repeated measures, irrespective of their proximity in time. Although correlation decreased with time, the estimated difference between intervention and control was virtually unaltered.

TABLE 10 Quality of life

Instrument	End of follow-up analysis				Longitudinal analysis	
	Trial arm		Comparison		Comparison	
	NIV plus DPS (n = 37)	NIV (n = 37)	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Number (%) of participants alive at 12 months	16 (43)	27 (73)	–	–	–	–
Patient QoL						
EQ-5D-3L health state (% complete ^a)	131/178 (74)	161/209 (77)	–	–	–	–
Complete case, mean (standard error)	0.02 (0.09)	0.19 (0.08)	–0.18 (–0.44 to 0.08)	0.164	–0.13 (–0.25 to 0.00)	0.042
With imputation for surviving participants, mean (standard error)	0.02 (0.09)	0.13 (0.08)	–0.11 (–0.39 to 0.16)	0.410	–0.12 (–0.24 to 0.00)	0.056
With imputations for all participants, ^b mean (standard error)	0.01 (0.03)	0.11 (0.05)	–0.12 (–0.24 to 0.01)	0.040	–0.14 (–0.24 to 0.04)	0.001

TABLE 10 Quality of life (continued)

Instrument	End of follow-up analysis				Longitudinal analysis	
	Trial arm		Comparison		Comparison	
	NIV plus DPS (n = 37)	NIV (n = 37)	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
<i>EQ-5D-3L thermometer scale</i> (% complete ^a)	132/178 (74)	160/209 (77)	–	–	–	–
Complete case, mean (standard error)	34.4 (6.3)	42.3 (5.1)	3.4 (–14.5 to 21.2)	0.699	–8.3 (–17.4 to 0.8)	0.074
With imputation for surviving participants, mean (standard error)	36.0 (6.6)	40.0 (5.2)	1.3 (–17.6 to 20.1)	0.893	–5.6 (–14.5 to 3.2)	0.212
With imputation for all participants, ^b mean (standard error)	14.8 (3.9)	27.4 (4.8)	–13.4 (–25.9 to 0.9)	0.036	–12.0 (–20.8 to 3.1)	0.008
<i>SF-36 aggregate physical health score</i> (% complete ^a)	110/154 (72)	133/174 (76)	–	–	–	–
Complete case, mean (standard error)	25.4 (4.2)	21.8 (1.8)	7.4 (–1.9 to 16.8)	0.110	0.2 (–2.2 to 2.5)	0.900
With imputation, mean (standard error)	23.8 (3.2)	20.6 (2.4)	8.7 (–1.3 to 18.7)	0.089	0.3 (–2.0 to 2.7)	0.780
<i>SF-36 aggregate mental health score</i> (% complete ^a)	110/154 (72)	133/174 (76)	–	–	–	–
Complete case, mean (standard error)	44.1 (3.7)	47.0 (4.2)	–7.8 (–20.5 to 4.9)	0.210	–4.1 (–8.6 to 0.3)	0.066
With imputation, mean (standard error)	42.7 (4.2)	47.4 (3.5)	–8.6 (–22.2 to 5.1)	0.218	–3.5 (–7.9 to 0.8)	0.112
<i>SAQLI</i> (% complete ^a)	110/154 (72)	132/174 (76)	–	–	–	–
Complete case, mean (standard error)	4.1 (0.5)	4.2 (0.3)	–0.2 (–1.3 to 1.0)	0.751	–0.3 (–0.7 to 0.1)	0.163
With imputation, mean (standard error)	3.9 (0.4)	4.5 (0.3)	–0.6 (–1.7 to 0.6)	0.329	–0.3 (–0.7 to 0.1)	0.117
Carer QoL						
<i>EQ-5D-3L health state</i> (% complete ^a)	109/178 (61)	148/209 (71)	–	–	–	–
	0.78 (0.11)	0.82 (0.06)	–0.08 (–0.38 to 0.23)	0.600	–0.08 (–0.17 to 0.01)	0.077
<i>EQ-5D-3L thermometer scale</i> (% complete ^a)	110/178 (62)	149/209 (71)	–	–	–	–
	81.3 (7.1)	71.0 (6.4)	12.1 (–13.1 to 37.2)	0.329	–0.2 (–7.4 to 7.1)	0.966
<i>CBI</i> (% complete ^a)	93/154 (60)	121/174 (70)	–	–	–	–
	28.0 (3.2)	29.6 (3.2)	3.1 (–7.5 to 13.8)	0.536	1.2 (–2.7 to 5.0)	0.558

a Completeness is number of questionnaires obtained within time windows as a ratio of the number expected (i.e. not including post death). Denominator includes all participants, although not all participants had assigned carers.

b Imputation comprised a health utility or thermometer score of 0 from the point of death onwards.

Short Form questionnaire-36 items

As expected, overall physical health (as derived from SF-36) is considerably lower than population norms in both groups, although mental health was comparable. No differences were evident between the two groups over the duration of the study. As with EQ-5D-3L, the difference in aggregate mental health scores between the groups was not statistically significant among surviving participants at 12 months (mean difference -7.8 , 95% CI -20.5 to 4.9 ; $p = 0.210$), but was of borderline significance over the duration of the study (mean difference -4.1 , 95% CI -8.6 to 0.3 ; $p = 0.066$). Physical health appeared similar between groups on both scales (Figures 16 and 17). Relaxing the assumption of a common correlation in the longitudinal analyses made virtually no difference to the findings, with the correlation being relatively constant with time.

Sleep Apnoea Quality of life Index

Sleep apnoea appeared similar at all time points between the two groups (Figure 18).

Carer quality of life

The carer QoL is presented in Table 10 and, graphically, in Figures 19 and 20. There was little in the way of difference between the groups.

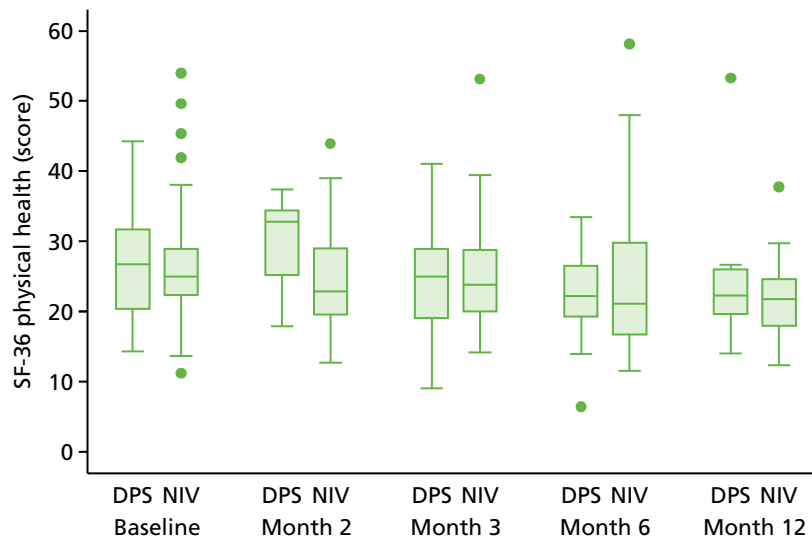


FIGURE 16 The SF-36 aggregate physical health component.

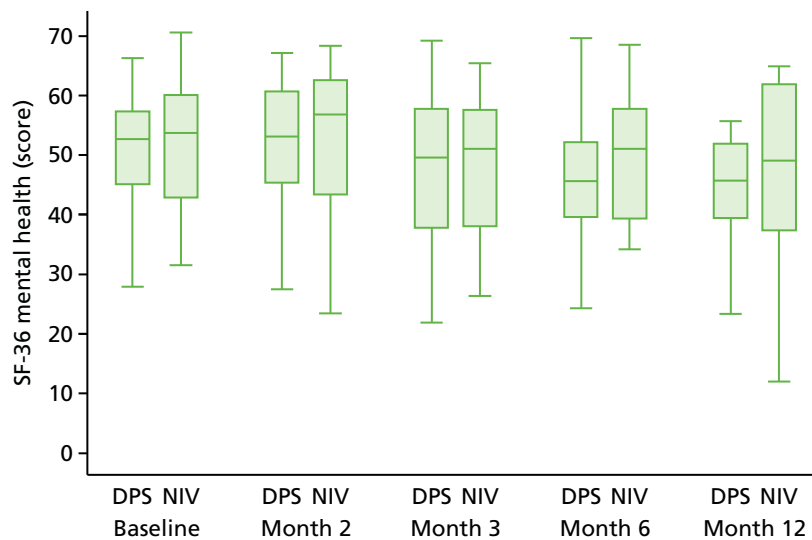


FIGURE 17 The SF-36 aggregate mental health component.

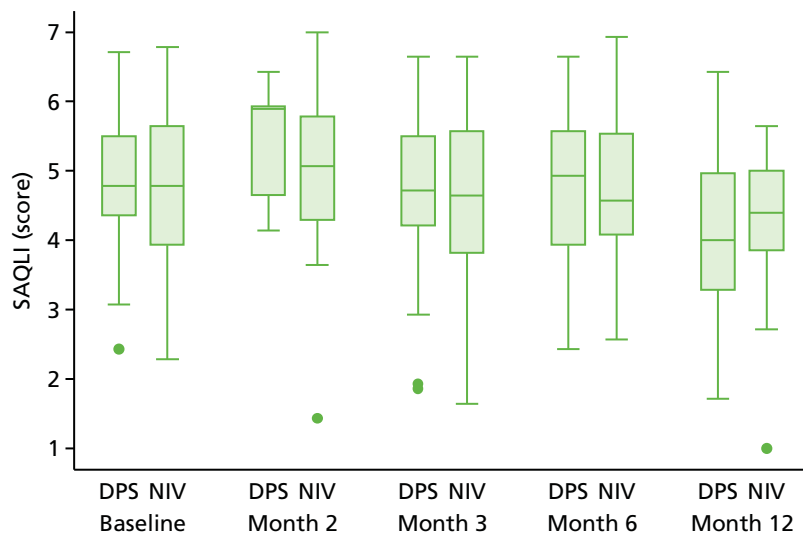


FIGURE 18 Sleep Apnoea Quality of Life Index.

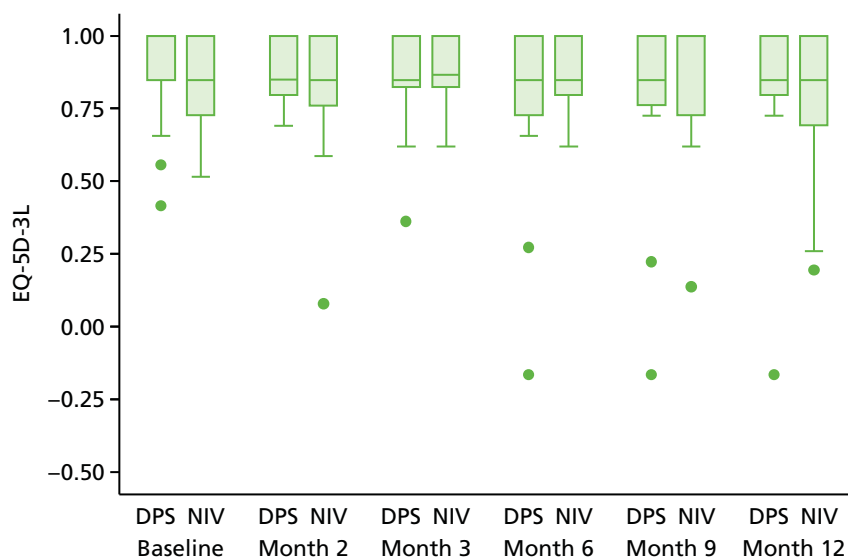


FIGURE 19 Carer EQ-5D-3L health tariff.

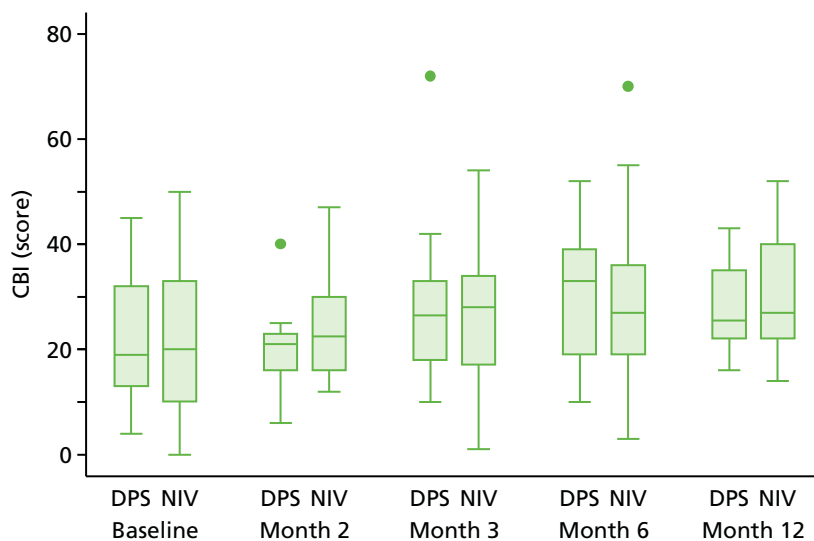


FIGURE 20 Caregiver Burden Inventory.

Relationship between quality of life, pacing and baseline symptoms

We have compared baseline scores with 12-month averages in EQ-5D-3L, SF-36 physical component summary score, SF-36 mental component summary score and total SAQLI and see no relationship between symptoms present and QoL scores. *Figures 21 and 22* show these for SAQLI; similar patterns were observed on other measures.

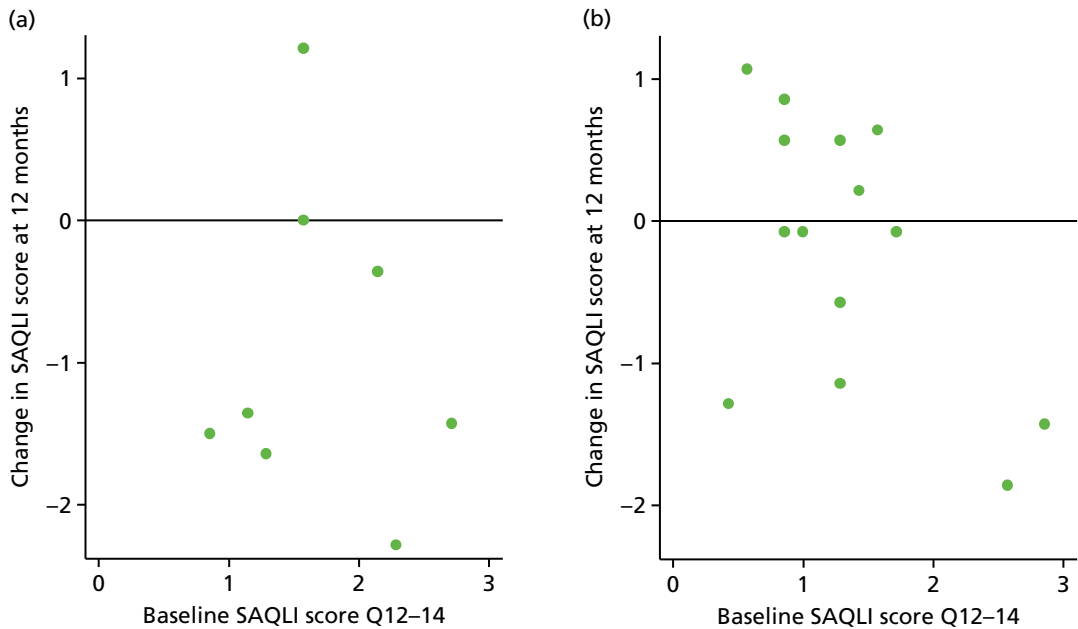


FIGURE 21 Change (12 months–baseline) in SAQLI score in relation to baseline SAQLI score (Q12–Q14). (a) NIV plus DPS; and (b) NIV.

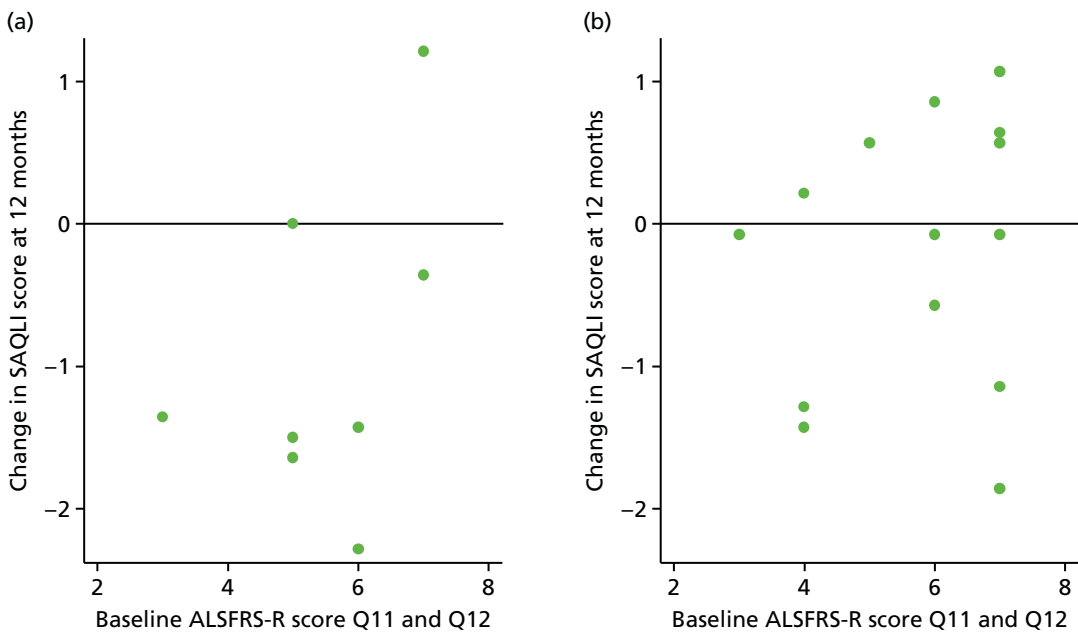


FIGURE 22 Change (12 months–baseline) in SAQLI score in relation to baseline ALSFRS-R sum (Q11–Q12). (a) NIV plus DPS; and (b) NIV.

Resource use

Resource use is shown in *Table 11*. As can be seen, the groups generally used similar levels of resources. The exception was respiratory devices, specifically the cough assist device and suction. The number of users was similar in both groups but the level at which they were used was somewhat greater in the NIV alone group.

TABLE 11 Resource use

Variables	Trial arm			
	NIV plus pacing (<i>n</i> = 37)		NIV (<i>n</i> = 37)	
	Number (%) of patients	Total days	Number (%) of patients	Total days
Admissions				
Admissions following surgery ^a				
ITU	12 (32%)	13	–	–
Non-ITU	32 (86%)	86	–	–
Admissions within 1 week of surgery	2 (5%)	12	–	–
All other admissions	9 (24%)	67	13 (35%)	109
GP/emergency use				
	Number (%) of patients	Total number	Number (%) of patients	Total number
GP appointments	29 (78%)	165	30 (81%)	152
A&E attendances	17 (46%)	23	11 (30%)	14
Minor injuries unit	6 (16%)	9	3 (8%)	11
Respiratory device				
	Number (%) of patients	Monthly use (when used ^b)	Number (%) of patients	Monthly use (when used ^b)
Cough assist use	12 (32%)	4.2	10 (27%)	10.0
Breath stacking	5 (14%)	8.6	6 (16%)	6.7
Suction	7 (19%)	2.4	5 (14%)	9.5
Other resource use				
	Number (%) of patients	Total number	Number (%) of patients	Total number
Physiotherapy	22 (59%)	144	24 (65%)	165
Occupational therapy	22 (59%)	127	24 (65%)	99
Other	13 (35%)	57	16 (43%)	86
A&E, accident and emergency; ITU, intensive care unit.				
a Denominator is all participants but only 32 were implanted, all of whom required postoperative stay.				
b Monthly use defined as total reported uses/total follow-up (in months) among users.				

Safety

Adverse events

A total of 243 AEs were observed, 162 of which were in the NIV plus DPS arm. Taking into account the differential follow-up owing to survival differences, this equates to 5.9 events per person-year in the NIV plus pacing group, compared with 2.5 events per person-year in the control group (Table 12). Eight of the events occurred in patients who had not been implanted.

TABLE 12 Adverse events

Category	Trial arm		NIV	
	NIV plus pacing		Number of AEs	Number (%) of patients with an event
Any AE	162 (8)	29 (78%)	81	23 (62%)
Respiratory	45 (5)	25 (68%)	19	14 (38%)
Type of respiratory event				
Chest infection	20	12 (32%)	11	7 (19%)
Respiratory failure	10 (2)	10 (27%)	5	5 (14%)
Breathless – unclassified	5	4 (11%)	3	2 (5%)
Pneumothorax/capnothorax	5	5 (14%)	0	–
Blocked airway	3 (3)	1 (3%)	0	–
Cough	1	1 (3%)	0	–
Pulmonary embolism	1	1 (3%)	0	–
Pain	23	10 (27%)	10	6 (16%)
Gastrointestinal	17	10 (27%)	12	9 (24%)
ALS symptoms	18 (3)	8 (22%)	7	3 (8%)
Insertion/removal of PEG/PIG	9	5 (14%)	10	9 (24%)
Genitourinary	7	3 (8%)	8	3 (8%)
Infection of PEG/PIG	10	3 (8%)	2	1 (3%)
Dermatological	6	3 (8%)	4	4 (11%)
Wire problems	8	5 (14%)	0	n/a
Cardiovascular system	4	4 (11%)	2	2 (5%)
Psychiatric	5	4 (11%)	0	–
NIV specific	3	3 (8%)	2	2 (5%)
Wire infection	4	3 (8%)	0	n/a
Central nervous system	1	1 (3%)	1	1 (3%)
Other	2	2 (5%)	4	3 (8%)

n/a, not applicable; PEG, percutaneous endoscopic gastrostomy; PIG, per oral image-guided gastrostomy.

a Numbers in brackets denote SAEs among the five NIV plus DPS participants who did not undergo implantation.

Serious adverse events

Serious adverse events are presented in *Table 13*. Again, more SAEs were observed in the NIV plus pacing arm.

TABLE 13 Serious adverse events

Category	Trial arm		NIV	
	NIV plus pacing	NIV	Number of SAEs	Number (%) of patients with an event
Any SAE	46 (5)	27 (73)	31	19 (51)
Respiratory	29 (5)	21 (57)	13	11 (30)
Type of respiratory event				
Chest infection	10	9 (24)	6	5 (14)
Respiratory failure	10 (2)	10 (27)	5	5 (14)
Breathless – unclassified	2	2 (5)	2	1 (3)
Pneumothorax/capnothorax	3	3 (8)	0	–
Blocked airway	3 (3)	1 (3)	0	–
Pulmonary embolism	1	1 (3)	0	–
Insertion/removal of PEG/PIG	6	4 (11)	9	8 (22)
Gastrointestinal	3	3 (8)	2	2 (5)
Cardiovascular system	3	3 (8)	1	1 (3)
Pain	1	1 (3)	3	2 (5)
Wire problems	2	2 (5)	0	n/a
ALS symptoms	1	1 (3)	0	–
Dermatological	0	–	1	1 (3)
Genitourinary	0	–	1	1 (3)
Other	1	1 (3)	1	1 (3)

n/a, not applicable; PEG, percutaneous endoscopic gastrostomy; PIG, per oral image-guided gastrostomy.

a Numbers in brackets denote SAEs among the five NIV plus DPS participants who did not undergo implantation.

Adverse events related to surgery or pacing

In total, 31 events (in 15 different participants) were adjudged to have had an AE with either a 'definite' or a 'probable' relationship to pacing. These AEs are listed in *Box 1* and *Table 14*. Seven surgical complications or device-related adverse events were recorded on the date of procedure.

Cause of death

The causes of death are presented in *Table 15*. Although participants in the NIV plus pacing arm had shortened overall survival, mortality was not obviously attributable to the procedure or to the pacing. One participant in the NIV plus DPS arm died 45 days after surgery; none of the remaining participants died within 3 months of the procedure.

BOX 1 Adverse events related to surgery or pacing

Surgical complications or device-related adverse events on the date of procedure

Bilateral pneumothorax.

Capno/pneumothorax.

Tension pneumothorax.

Right-sided pneumothorax requiring chest drain.

Lines 1- + 2-captured electrocardiogram trace. Maximum settings established.

Small nick to spleen which caused bleeding. Pressure was applied and bleeding stopped after 5 minutes.

Abdominal pain.

TABLE 14 Adverse events related to pacing

Event	Frequency (if > 1)
Respiratory events related to pacing (n = 5)	
Bilateral pneumothorax ^a (D)	
Tension pneumothorax ^a (D)	
Right-sided pneumothorax requiring chest drain ^a (D)	
Capno/pneumothorax (D)	
Difficulty with breathing (P)	
Wire infections (n = 4)	
Infection to electrode site (D)	4
Wire problems (n = 4)	
Anode wire pulled/fell out ^a (D)	4 (2 SAE)
Anode replaced as the anode was causing the abdominal pain (D)	
Diaphragmatic pacing wire number 1 showing X on pacer. This will need replacing (D)	
Patient feels his skin is being burnt by anode bypass (P)	
Sore pacing wire insertion site (D)	
Pain (n = 12)	
Anode replaced as the anode was causing the abdomen pain (D)	
Pain in back and shoulders (P)	
Pain in ribs (P)	
Shoulder pain (on contraction) (P)	
Shoulder pain on pacing (D)	
Pain to left side of chest on pacing (D)	
Discomfort during pacing (D)	
Back and shoulder pain post operation (D)	
Pain – abdominal (D)	
Pain in left shoulder and stomach when pacer switched on (D)	
Intermittent shoulder pain on pacing (D)	
Right and left shoulder pain on pacing (D)	
Dermatological (n = 1)	
Bypass pad causing contact dermatitis (D)	
Gastrointestinal (n = 1)	
Acute gastric dilatation responded well to decompression with nasogastric tube. Well described following upper gastrointestinal surgery although rare – was slightly higher risk because of bleeding from spleen during surgery ^a (P)	
a SAE.	
Note	
Relationship is (D) = definite or (P) = probable.	

TABLE 15 Cause of death

Cause of death	Trial arm	
	NIV plus DPS (<i>n</i> = 37)	NIV (<i>n</i> = 37)
Total deaths	28	19
Causes of death		
Respiratory failure	16	13
Chest infection	5	2
ALS	6	4
Hypothermia	1	0

Physiological measurements

In the light of the early stopping, the TSC requested additional respiratory function data to be collected to augment that which was already collected at baseline (and for DP, immediately pre surgery). Specifically, we wished to assess (1) whether or not the groups were comparable at baseline; (2) whether or not decline appeared more pronounced in the post-surgery period among the NIV plus DPS group than in the NIV group; and (3) the trajectory across time, in general, to see if it offered any other clues by which to explain the findings. We were able to obtain data for patients at some of the sites for FVC, arterial carbon dioxide and ALSFRS-R.

The purpose of the analysis was not to assess efficacy but to investigate possible treatment harm and, consequently, we analysed the group based on actual exposure (i.e. implanted with the pacing device) as opposed to the more conventional intention-to-treat analyses. Measurements taken more than 45 days prior to randomisation or > 1 month after the end of scheduled follow-up were excluded. A generalised least squares regression model was fitted in which the treatment received, time since randomisation and their interaction were the covariates. No attempt was made to impute missing data.

The figures show some evidence that FVC did indeed decline faster in participants who were implanted than those who were not, with the average rate of decline per month being 2.1% steeper among implanted participants than in those without implantation (95% CI -3.4% to -0.8%; $p = 0.001$). It is not easy to distinguish whether or not the decline is more pronounced in the postoperative period than the preoperative period (and, hence, directly attributable to operation), as the latter is a short period of time. (Figures 23 and 24).

The trajectory for PaCO_2 is shown in Figures 25 and 26. In contrast to FVC, the change in PaCO_2 is more modest, with no obvious change in levels in either group.

Finally the trajectory is shown for ALSFRS-R, a measure of ALS symptomology based on a 12-item questionnaire and ranging from 0 points (most severe) to 48 points (least severe). There was substantial decline in the control group (on average 1.1 point per month), but the rate of decline was greater still among participants who underwent implantation (mean difference 0.4 points per month, 95% CI -0.7 to 0.0 points per month; $p = 0.035$) (Figures 27 and 28).

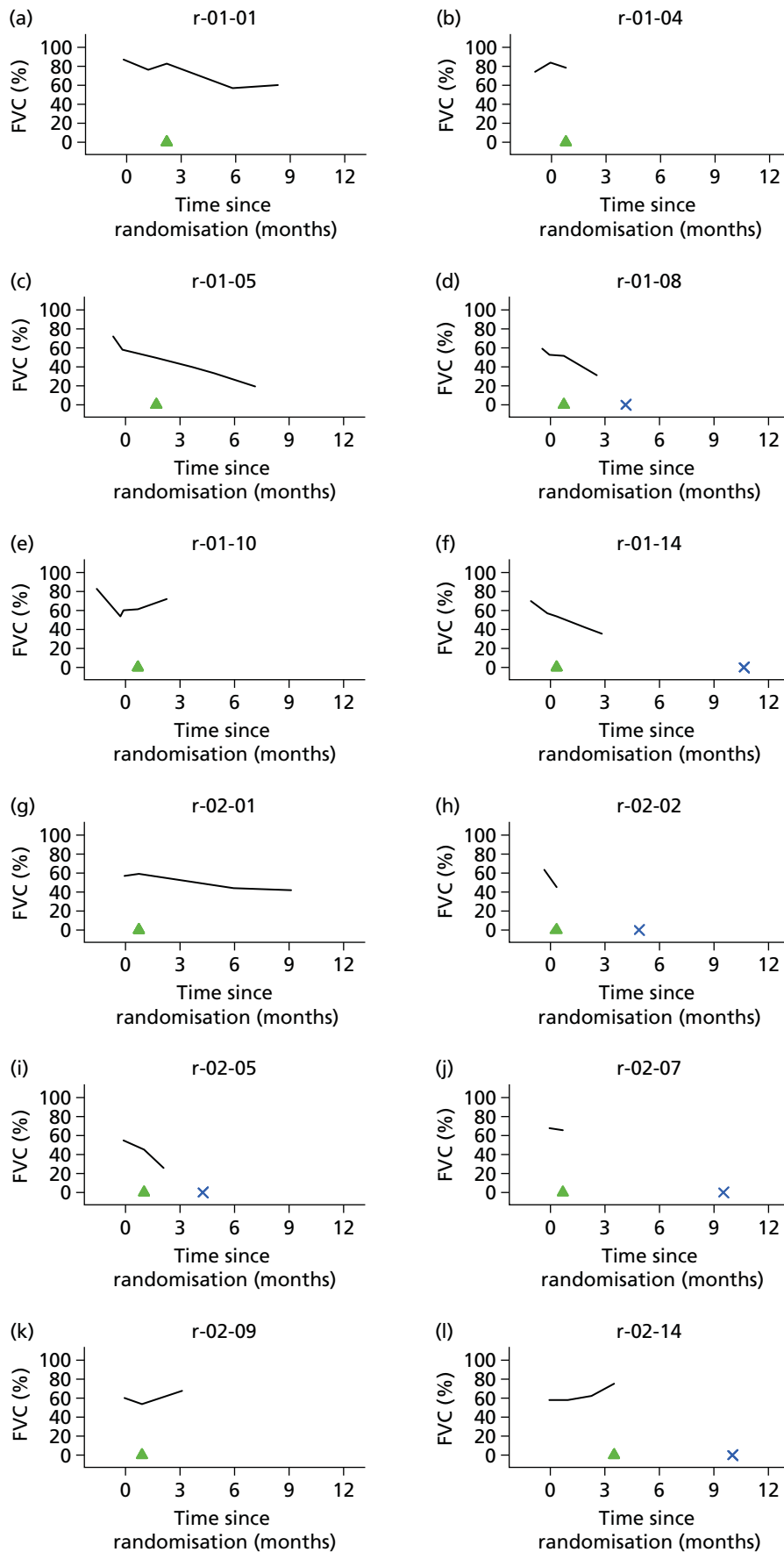


FIGURE 23 Forced vital capacity against time for implanted participants. The triangle denotes date of procedure and the cross denotes date of death. (*continued*)

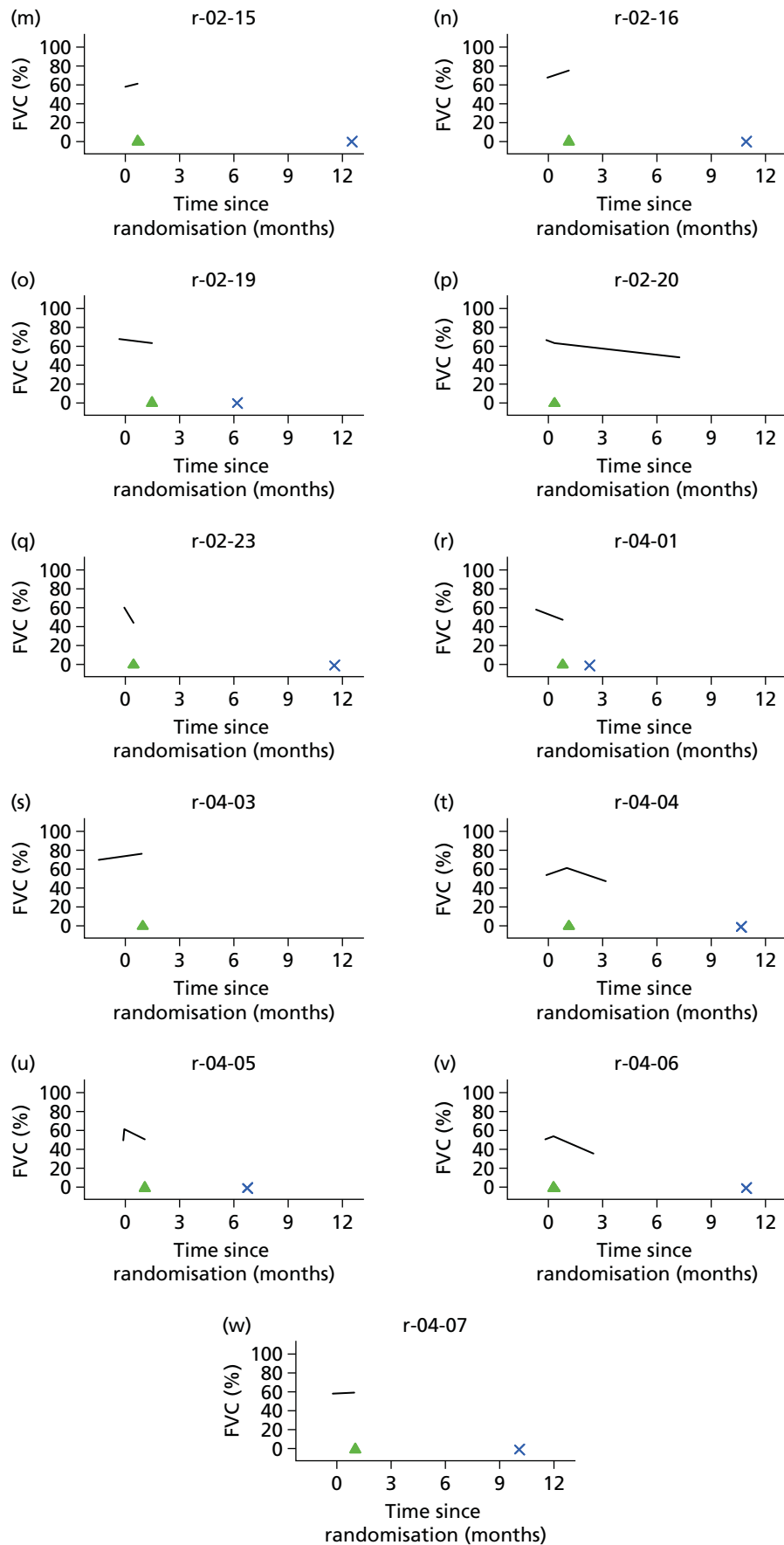


FIGURE 23 Forced vital capacity against time for implanted participants. The triangle denotes date of procedure and the cross denotes date of death.

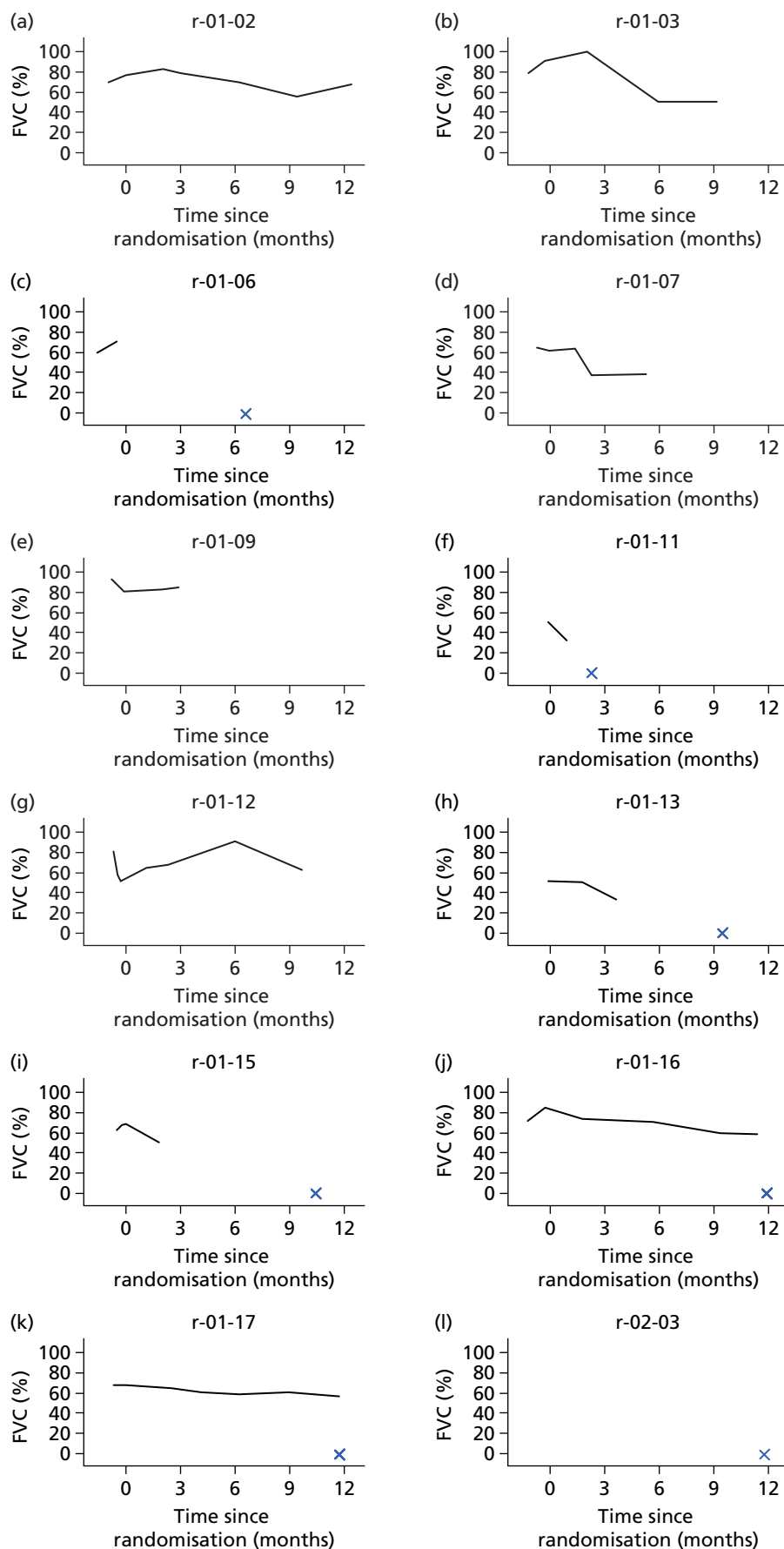


FIGURE 24 Forced vital capacity against time for non-implanted participants. The cross denotes date of death. (*continued*)

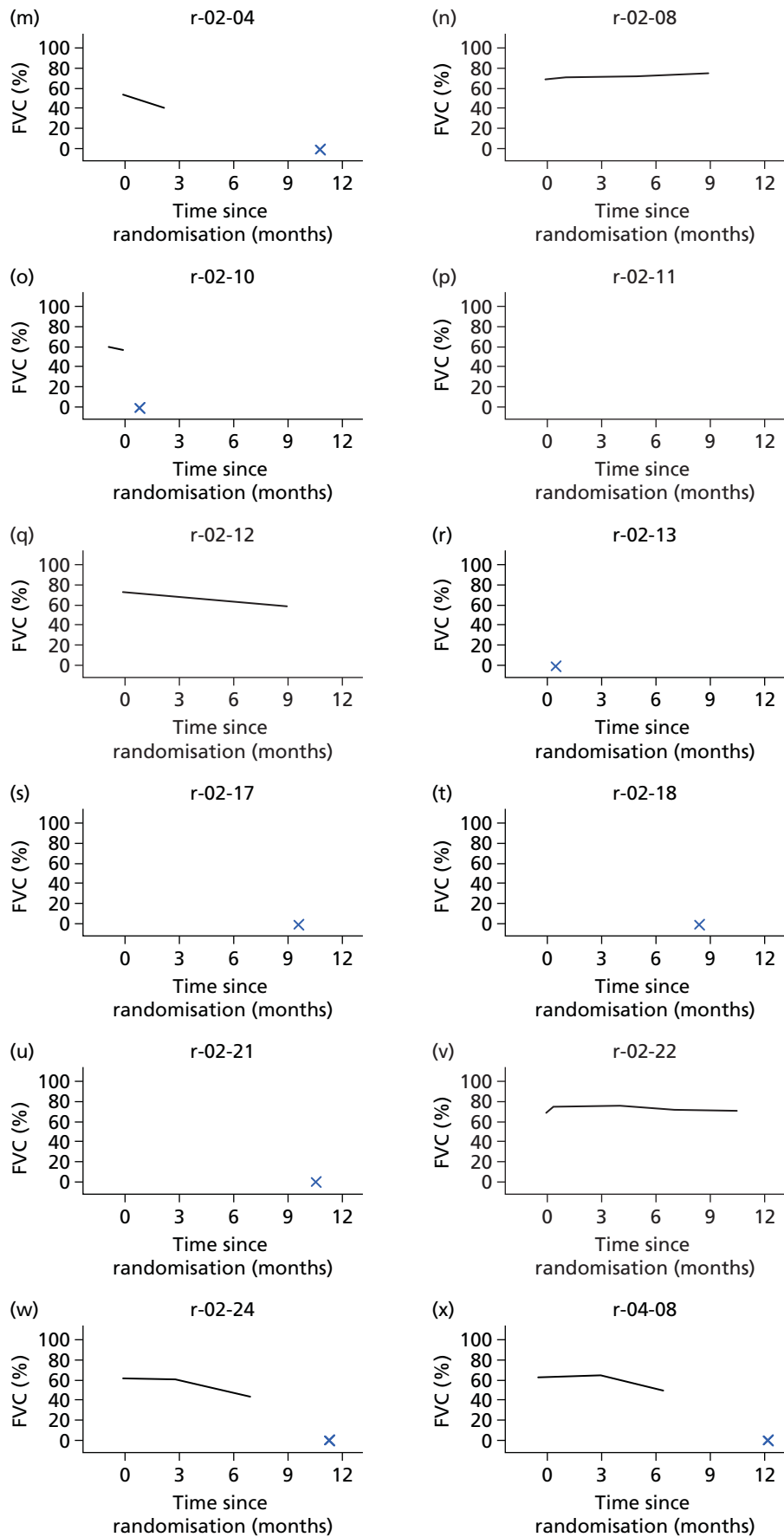


FIGURE 24 Forced vital capacity against time for non-implemented participants. The cross denotes date of death. (continued)

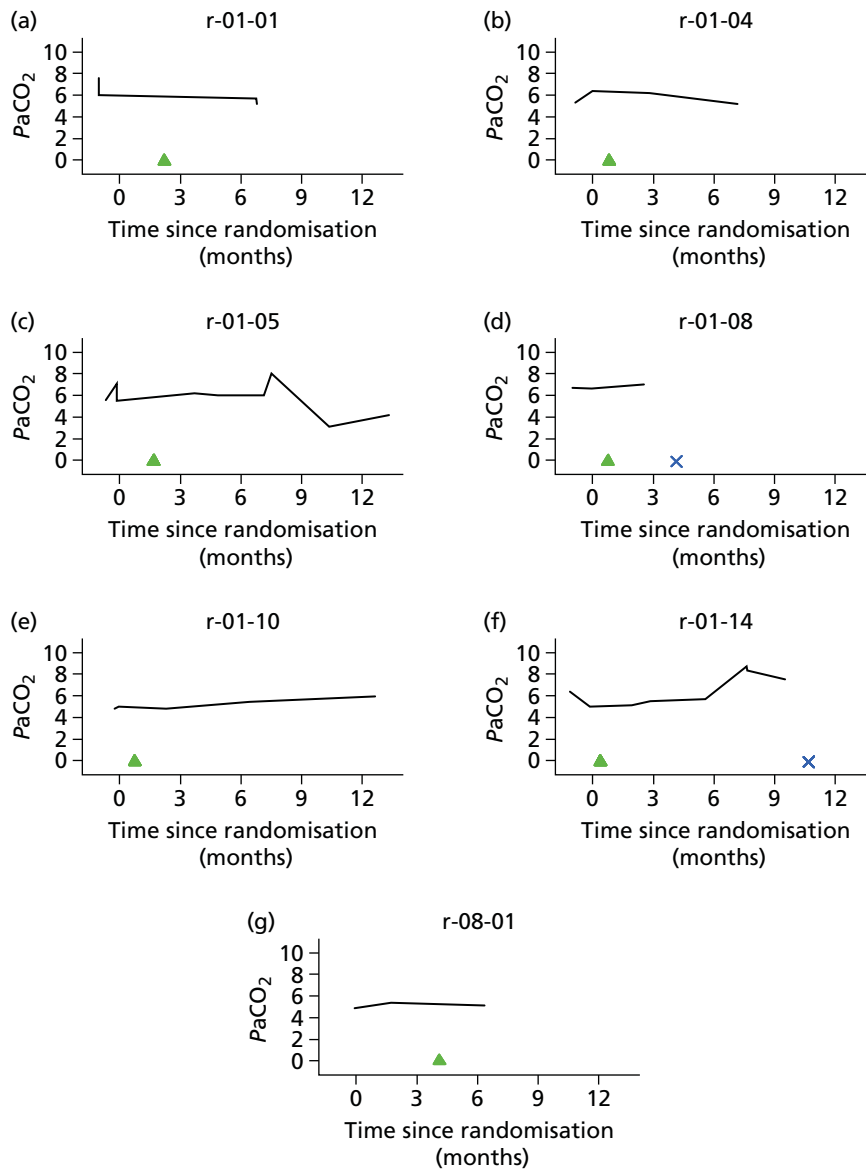


FIGURE 25 The PaCO₂ against time for implanted participants. The triangle denotes date of procedure, the cross denotes date of death.

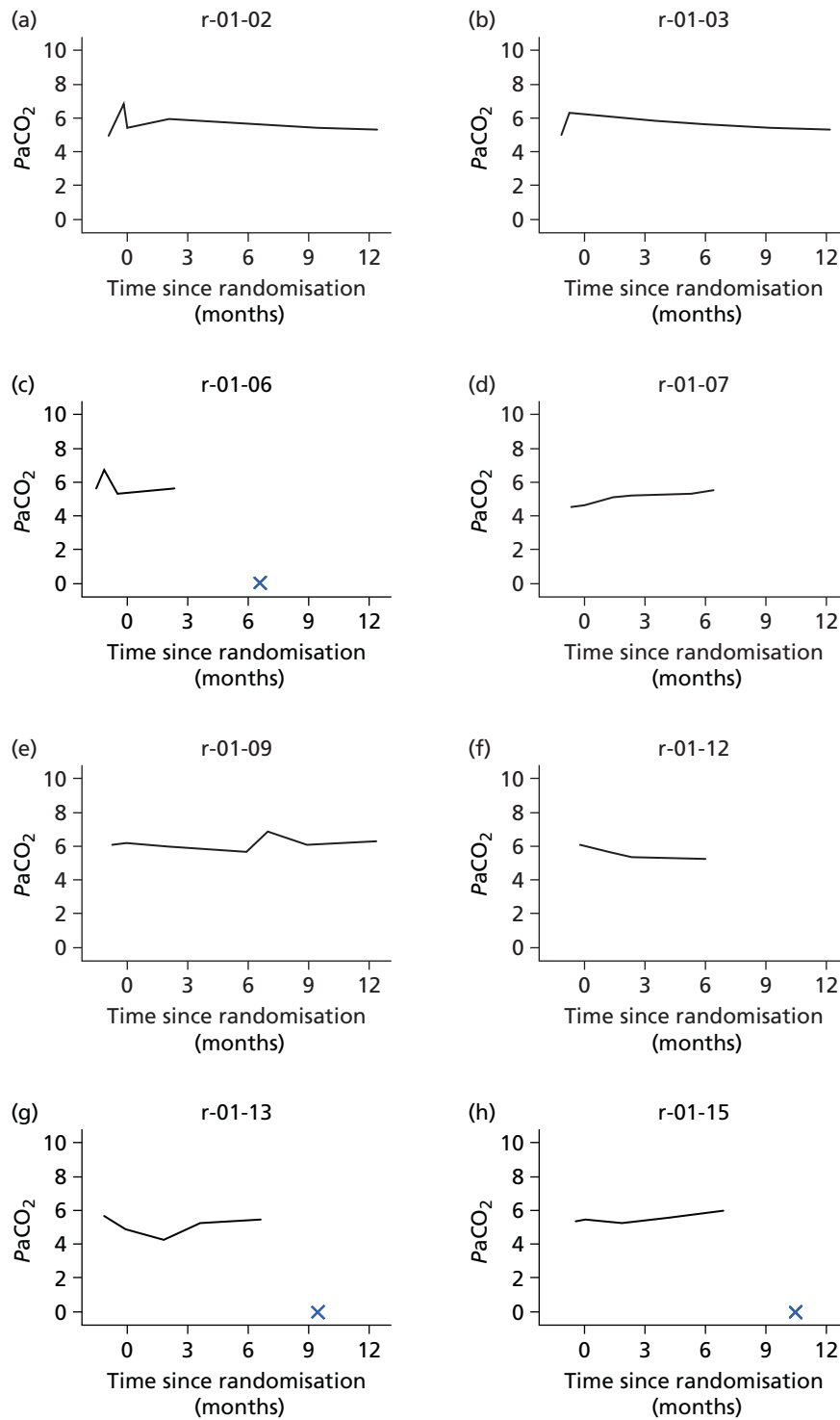


FIGURE 26 The PaCO₂ against time for non-implanted participants. The cross denotes date of death. (continued)

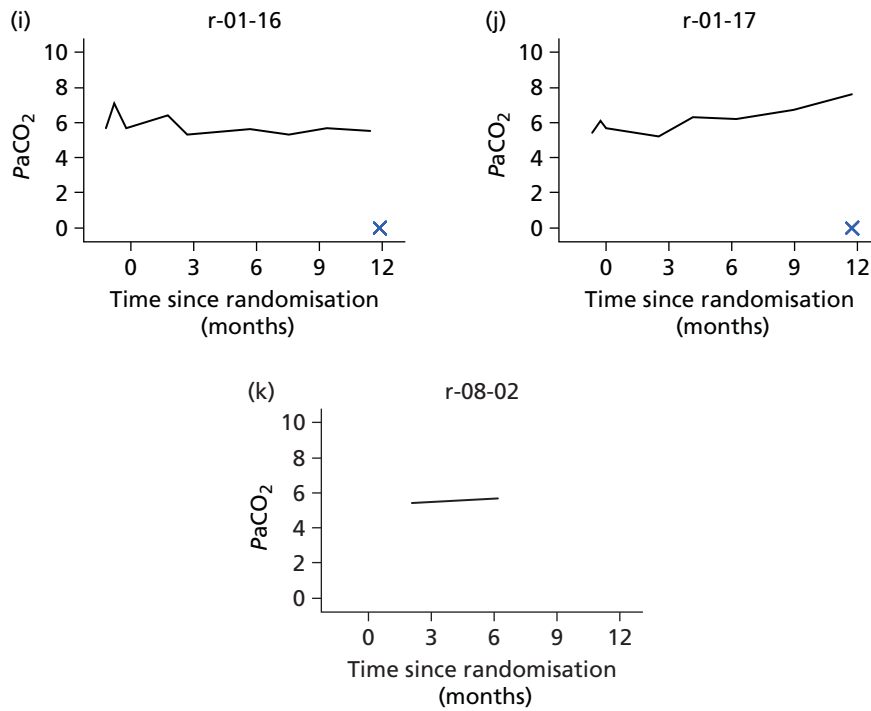


FIGURE 26 The PaCO₂ against time for non-implanted participants. The cross denotes date of death.

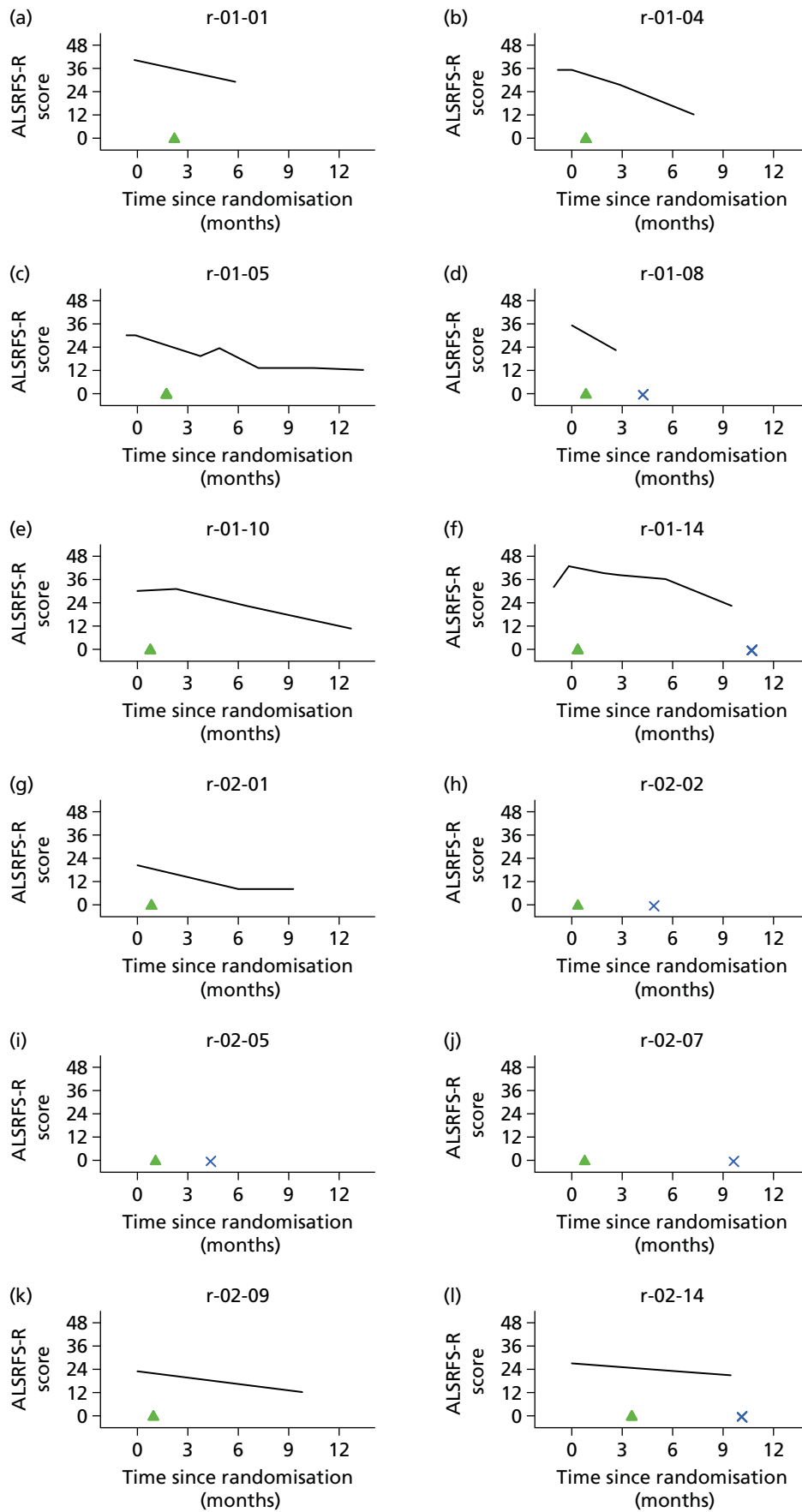


FIGURE 27 The ALSRFS-R score against time for implanted participants. The triangle denotes date of procedure and the cross denotes date of death. (continued)

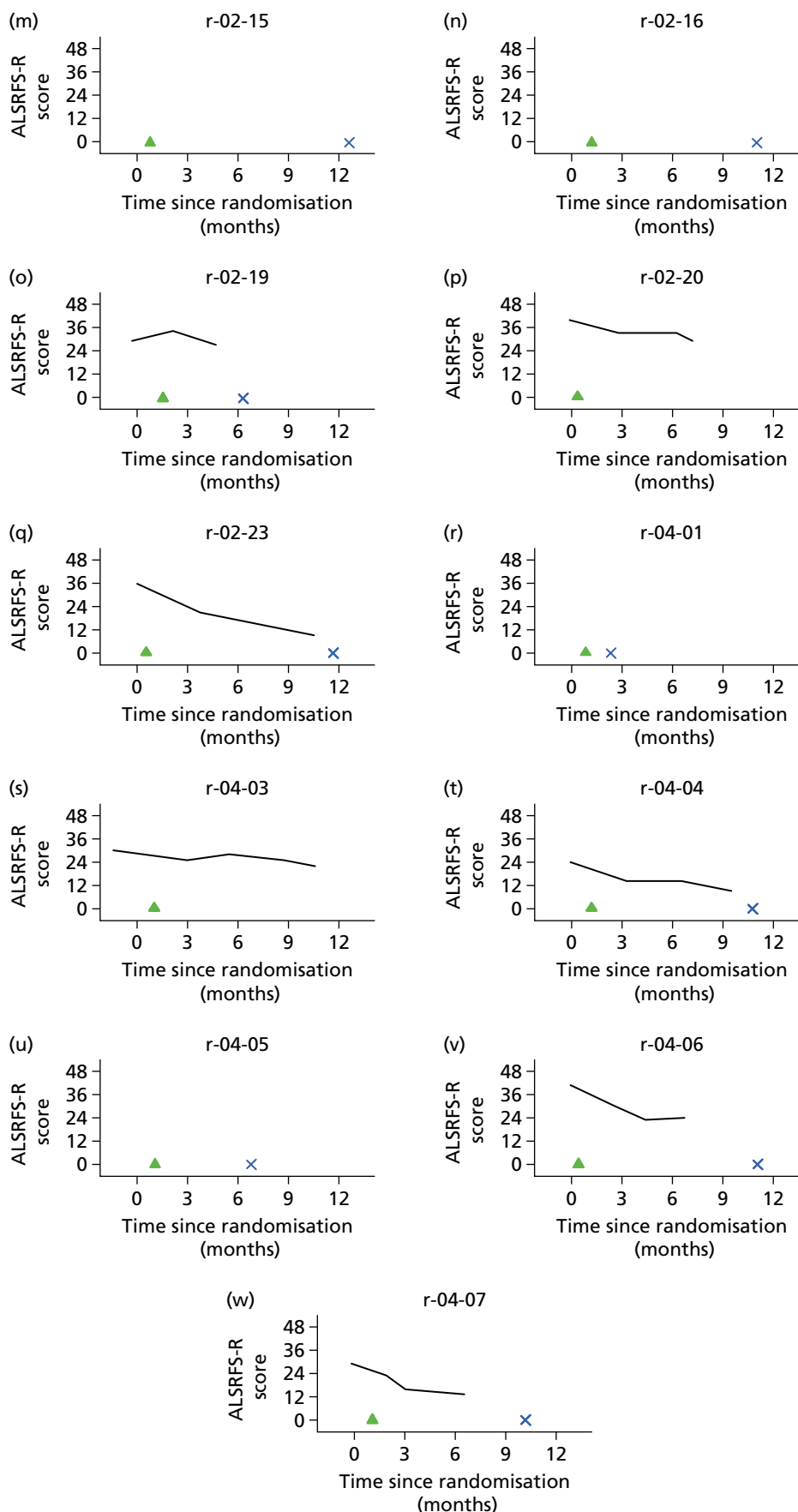


FIGURE 27 The ALSRFS-R score against time for implanted participants. The triangle denotes date of procedure and the cross denotes date of death.

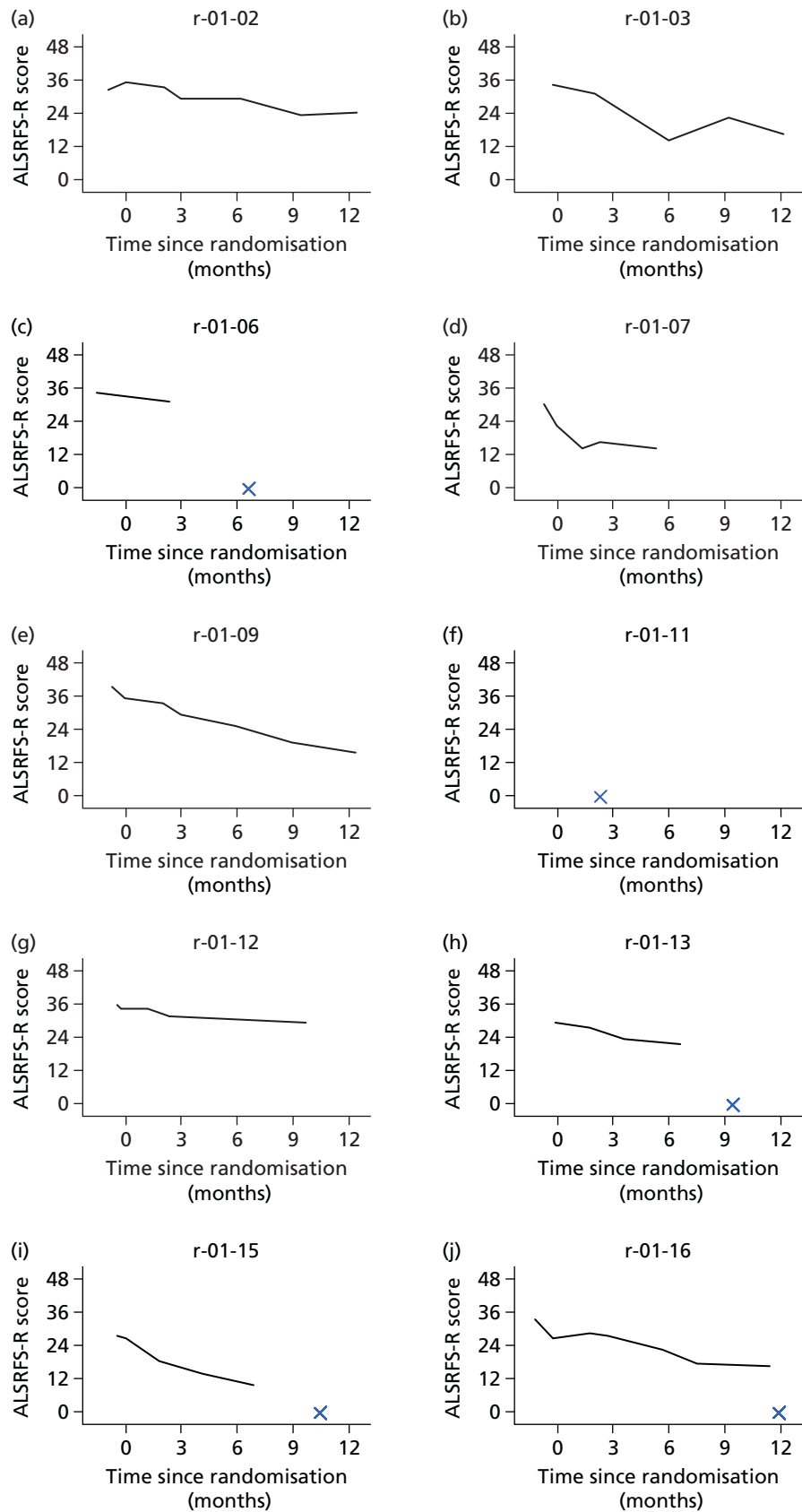


FIGURE 28 The ALSRFS-R score against time for non-implanted participants. The cross denotes date of death. (continued)

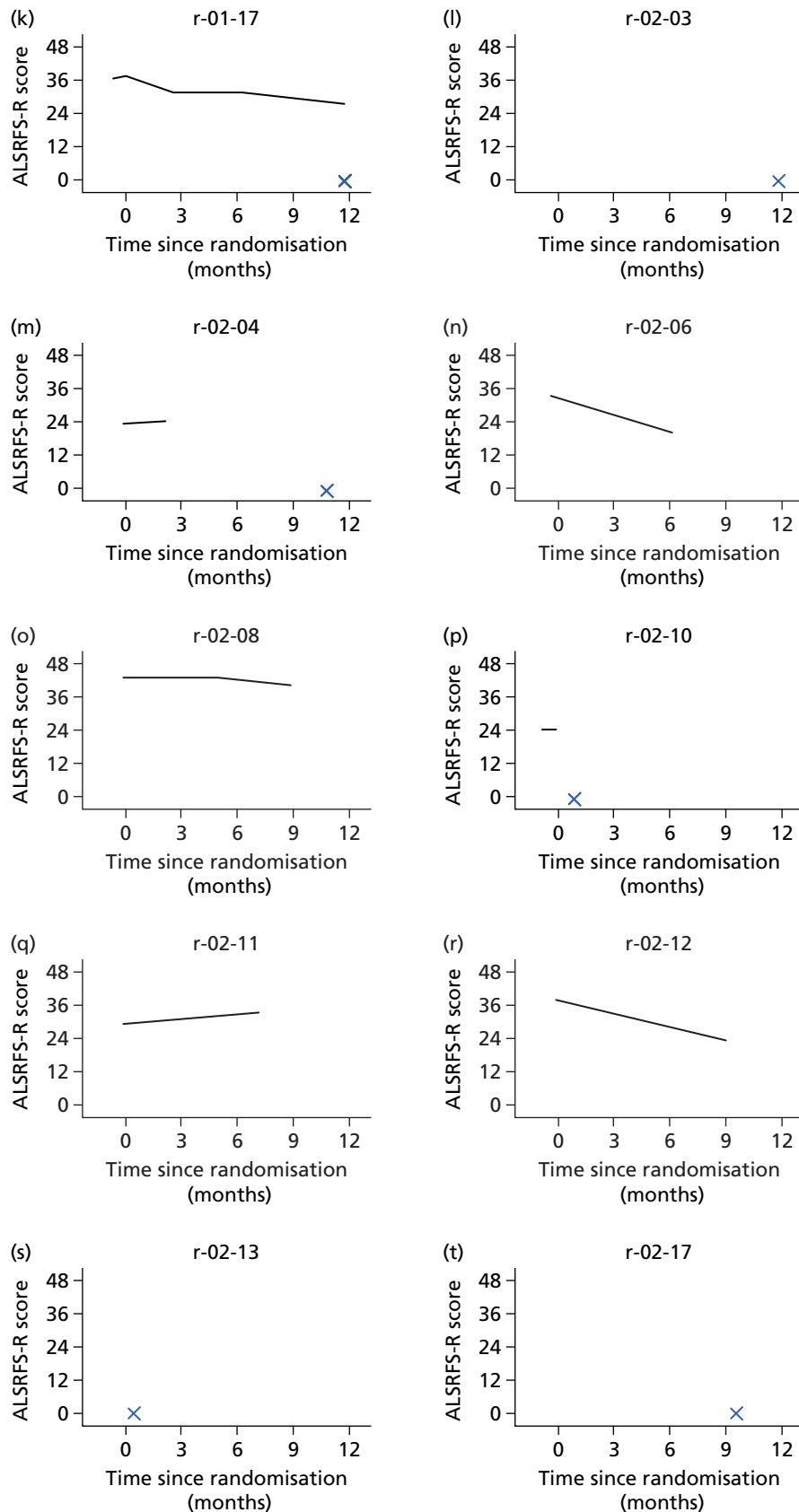


FIGURE 28 The ALSRFS-R score against time for non-implanted participants. The cross denotes date of death. (continued)

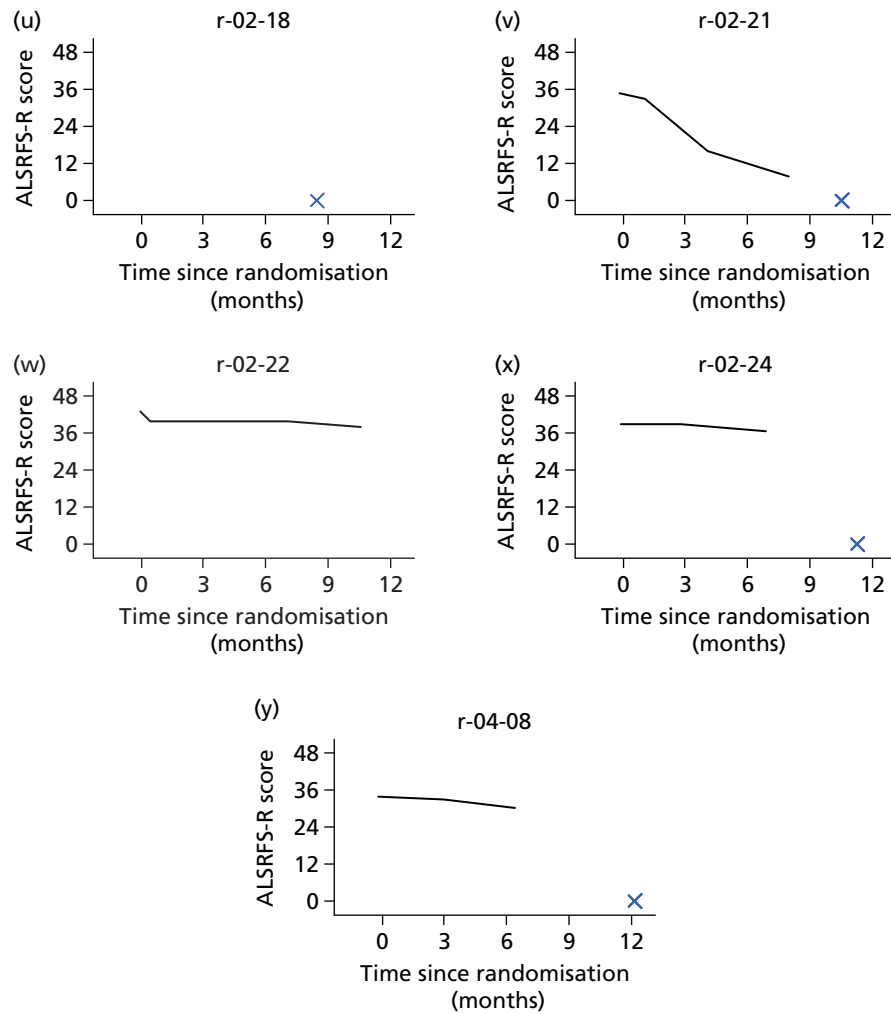


FIGURE 28 The ALSRFS-R score against time for non-implanted participants. The cross denotes date of death.

Chapter 5 Qualitative substudy

A qualitative longitudinal study formed a subelement of the trial design. This was an essential part of the DiPALS trial, as it is important not only to investigate the efficacy of DP but also to ensure that any extension of life was not to the detriment of QoL. The qualitative substudy therefore was designed to complement the data collected via the SF-36 and SAQLI by providing additional depth of insight into patient and carer perceptions and experiences of the DPS intervention.

The aim of the qualitative component was to evaluate the acceptability and perceived impact of the intervention on patients with ALS and their family.

Outcomes

The primary end point was the perceptions of patients and carers regarding acceptability and impact of the device.

Qualitative substudy methods

Sampling

We purposively selected participants for the qualitative element of the study from those randomised to the pacing intervention arm of the trial. We intended that our sample would include diversity in terms of patient sex, age, ALS type, and across the different ALS centres taking part in the trial.

Potential participants for the qualitative substudy were identified following randomisation. They were approached by study leads at the research centres at the first follow-up appointment after surgery. The qualitative study component was outlined to potential participants, and an information sheet related to this component was also provided (see *Appendices 7 and 8*). If they were willing to take part, contact details were provided to a qualitative researcher who was independent of the main trial team.

It was expected that ALS patients would not be able to tolerate an interview in addition to other trial assessments when they attended follow-up visits at local sites. Therefore, an experienced research fellow (SB) conducted semistructured interviews at a time and location that was convenient for participants.

Data collection

Qualitative interviews with patients and carers were carried out at two time points: 1 month following initiation of the pacing intervention and, when possible, 6 months later. Interviews were conducted in patients' homes lasting 45–60 minutes and were based around a predefined interview schedule (see *Appendix 18*).

Prior to the interview taking place the researcher checked the contents of the patient information sheet with participants, answered any questions, and a consent form was signed. Participating carers were interviewed together with patients or separately, as preferred by respondents. During the interviews a total communication approach was used for participants with impaired speech, whereby use of gesture, writing, communication aids and forced alternative responses were used to facilitate responses.

Interviews were audio-recorded. The first interview was carried out 1 month following implantation, and focused on expectations and experiences of the surgery, learning to operate the system, and perceptions regarding any impact on life. The second interview, undertaken when possible approximately 6 months post implantation, was considered an appropriate time to allow patients using DPS (and caregivers) to become familiar with the intervention and to have gained an understanding of potential impacts.

Therefore, the second interview explored experiences of the system, views regarding DP versus NIV, perceptions of any effects, and reflections in hindsight on taking part in the trial.

Data analysis methods

Interviews were transcribed verbatim and transcript data were analysed using techniques of thematic analysis, where similar concepts or ideas across the interviews are brought together and assigned a code. Relationships between codes are then examined to develop a network of themes and subthemes recurring across the data. Systematic coding and retrieval of data was supported by the ATLAS.ti software (version 7, ATLAS.ti Scientific Software Development GmbH, Berlin, Germany). Data were shared and discussed at several qualitative team meetings to establish consensus for the coding network.

Participant characteristics

Fourteen patients and eight carers took part in the qualitative substudy. Eight patients were male and six were female; 10 were aged in their sixties, and four were aged in their fifties. On the ALS FRS-R at entry into the study, 11 patients were in the mild impairment range for bulbar function and three were in the moderate bulbar impairment range. In terms of limb function, one patient scored > 9 , 12 scored 5–8 (moderate impairment), and one scored < 5 . Patients were under the care of five different ALS centres. Nine participants were interviewed at both time points, two patients had died in the interval period and two patients preferred not to be followed up because of disease progression. One further person was not using the system at initial visit, or subsequently, and declined follow-up.

Usage of the diaphragm pacing system

At first visit, all but one of the participants had the DPS in use (although one system had technical issues with a broken wire and had not been used for a few days). Ten participants were using DPS during the daytime. Two preferred to use it overnight, and another used it during both day and night. Nine patients had it in operation for 1.5–2 hours per day (in a number of half-hour sessions), with one person reporting 5 hours, and three people estimating at least 6–8 hours' daily use. Seven patients were also using NIV overnight, and one used NIV in the daytime for short periods. Five participants were struggling to use, or were unable to use, NIV, and one person was awaiting initiation on NIV.

At the 6-month follow-up, use of DPS among this sample of participants during the daytime ranged from 20–24 hours (two patients) to 2–5 hours (five patients). Five patients used NIV overnight, two used it for 20–24 hours; two participants used it for 7–9 hours overnight, one occasionally and another rarely.

Results

Patient and carer experiences

Participants described the process from initial approach to be involved in the study, to ongoing usage of the pacer and perceived outcomes. The recurring themes and subthemes are presented in *Figure 29*. Owing to the extensive volume of material we focus on the themes most frequently found and include a number of verbatim quotes to illustrate key points.

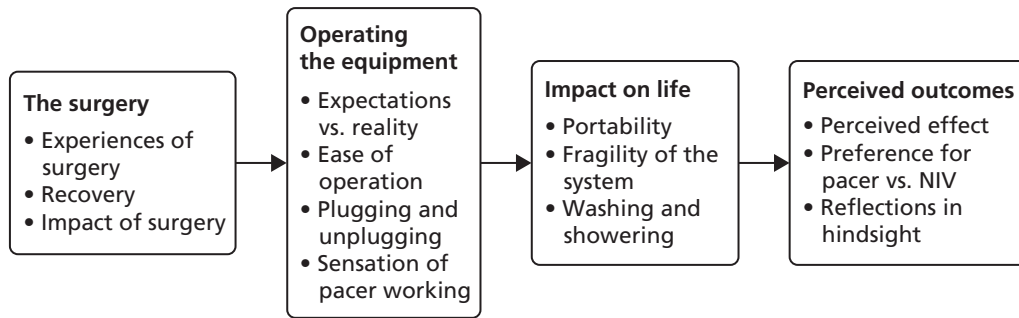


FIGURE 29 The patient journey trialling DP.

The surgery

Experiences of the surgery

The prospect of surgery (in particular having a general anaesthetic) was described as a concern for some:

I was more concerned about being put to sleep rather than the surgery.

I was a bit concerned about having the op, yeah; any operation you have, as an ALS patient there is going to be some side effect.

There was obviously the consideration I might not go under and come out properly.

He did have a few worries about it.

She's bad, she always has been with gas.

Whereas other patients reported little apprehension:

I would say the operation seems quite straightforward.

As far as I'm concerned it's just a minor operation.

Recovery

Several patients mentioned their expectation that they would stay in hospital only overnight following the surgery. All but two, however, had stayed longer:

Coming home it took about four days I think.

It might've been a week and a day.

A day, two days . . . but it turned out to be longer than that.

There were reports of postoperative pain for around half of patients:

My right shoulder, when I came out from anaesthetic, you know, that was killing. I couldn't move.

I got pain in my shoulders, which they said was referred pain.

He did have painkillers in the first few days, he did have a lot of . . . I think there was quite a bit of pain.

I had a lot of pain, yeah; had this terrible pain on this side.

Impact of surgery

Four participants mentioned that the surgery had impacted adversely on their ALS symptoms:

It took him a while to seem to pick up after it, which I didn't expect.

It wasn't bad; the only thing it did do . . . sent my ALS out of kilter.

Since coming out of hospital I've definitely felt weaker.

If you have any kind of procedure you are going to take a few steps backwards and you're going to have to recover again.

Operating the equipment

Expectations versus reality

Participants described their reaction on first seeing the system. All had seen either the equipment or pictures of it at their consultation prior to agreeing to take part and, for most, expectations were not different from reality:

It was what I expected really; I just expected what I'd got.

However, some patients described how they had struggled to visualise exactly what it would look like:

They kept saying well it's like a pacemaker . . . and we didn't know really to be honest.

I mean when you wake up and see it on you, it's a bit of a shock.

I didn't know what I was expecting.

A lot more (incisions) than what I expected . . . they'd said keyhole I think I just got an idea of a cut here and a cut here.

I don't know what to expect, basically; I wasn't sure what it would, cos even looking at a picture you're not sure what it's going to look like on you.

The main area of surprise seemed to be regarding the narrow width of the wires:

You kind of think oh wires out your tummy you just expect something that you plug into a computer.

And the wires, cos they're more like threads . . . you always think wires are thicker don't you.

There were no instances of patients expressing concerns regarding having technology within and, attached to, their bodies. This perhaps is to be expected from individuals who had agreed to take part in the trial. Participants, although recognising it could be a little strange, mostly seemed to have taken having the system fitted in their stride:

Really weird to have a plug into you; it's a bit science fiction really.

I've got all these bits of wires in me now.

They're (family) fascinated with it, I'm actually quite OK with it.

It's not the nicest thing hanging from your diaphragm but . . .

I said yeah, you know, no problem; something to get your head around.

There is something there still physically on your, attached to you.

He (patient) loves the technology.

Ease of operation

There was consensus among participants that the system was easy and trouble-free to operate:

It was a piece of cake, no problems.

It's easy to manage, there's nothing to do other than make sure the cable's connected properly.

It's so easy to manage; it is a very simple device to use.

That's easy, yeah, just press two buttons, even I can do that.

It's really simple.

A small number of patients with severe limb impairment needed assistance to switch the device on and off.

Plugging and unplugging

Plugging the external lead on to the receiver on the body was described as being potentially awkward:

The actual fitting of the pacer on to this is very awkward for somebody with ALS. It's very small and it's very hard to get in exactly the right place.

You put it in, it doesn't click, so you keep trying, trying, trying, you know, so it is a bit annoying actually.

She had a job trying to fit it because it was the other way round, it took her some time.

Sometimes it goes in really easily.

It is a bit of a struggle to get it in.

The difficulty in attaching the lead to the connector was described as being made more challenging owing to the siting of the connector:

If it were a little bit lower down maybe they could do it themselves.

Because where it is it's quite hard to see, especially for a lady.

If it were a bit lower down it'd just go in.

You can't see a thing cos it's under my bust.

I think the location of the wire is such a way that I can't even look at it properly.

Sensation of the pacer working

Patient reports of the sensation of the pacer working varied considerably. The majority of participants described it as a noticeable, but not painful, feeling:

If I'm watching something, if I'm talking to somebody, you forget about it.

It's hard to describe; it's quite strong and almost like beats.

It's a bit like a needle scratching down your stomach.

It's like really, really strong butterflies.

It just like your heart ticking away, you know it's there but you don't know it.

Just a little electric pulse.

Like a flutter, fluttering feeling.

It's not painful; within a day you don't really notice it.

I would not say it's pleasant, I mean it is definitely unpleasant, but it is not unbearable.

You do feel something but it's not uncomfortable; he initially used to say ouch, but now he's stopped doing that.

Others, in contrast, experienced higher levels of discomfort:

It's like getting shocked with an electric fence.

it affects the left shoulder; it is a bit painful when you inhale.

The most excruciating pain she's ever experienced in her life, no exaggeration.

Because of the discomfort and pain that he's had, he hasn't been using it as he should be.

It can be very uncomfortable; this is very painful.

For three participants, the level of pain experienced limited the length of time that they were able to use the system. At follow-up interview, these individuals had continued to attempt to use the pacer despite their discomfort. One person had found that if it was much more tolerable when lying down at night .

Impact on life

The system was not reported to have an adverse impact on life (apart from those experiencing significant pain):

My life just goes on normally, I work around it.

No it doesn't have any effect; I can just sit and have it on.

We just fit it round our routine.

You just sit back and watch something else and do something and suddenly half an hour is gone.

Only one patient highlighted that making time for several interventions impacted on their day:

It has now structured our whole day . . . cos we can't do this at night with three hours on that, two hours on this, feeds. The entire day is structured out by these things now.

Another patient reported that the system set off security alarms in shops, so this affected where they went.

Portability

Several participants mentioned that they had been surprised at the size of the external battery unit, and some that they struggled to put it in a clothing pocket:

It was bigger than I was expecting; well I'd seen it on my [tablet] but of course on there it looks quite small.

It is a little bit on big side, for what's in it; I would think they could have made that like half size of that.

I wouldn't like it in my pocket; it might come out.

A bit big even for our pockets.

I'm not sure where box is going to go.

It needs a bag provided, you know.

It needs either a waist strap or a shoulder strap or just something to carry it around in.

The solution that most adopted was to use a waist bag or 'bum bag':

We just altered a bum bag, didn't we, to use.

I'd certainly say well try a bum bag.

My wife thought of that, because it was getting a bit awkward, what do you do with this thing and this box, so she said OK, we can use this bag so we took it out and then she put, put a hole in the side.

Fragility of the system

The system was perceived to require careful handling, with worries regarding pulling or catching and then breaking the external wires and connector, or dropping the external unit. Patients were anxious that if the wires broke that they would need to undergo further surgery, and that if they pulled on the wires that the internal mechanism would be damaged:

Those wires so minute you know you could look at them and they break.

I'll have to make it really secure so I can't catch it and pull it.

Because I'm liable to drop it, the flex might just drop and I don't want it to pull on it.

Well I don't know how strong the wires are, are they strong enough, I mean if I pull it will it come out.

You're careful with it, cos obviously it's quite delicate.

It could slip off, you could knock it.

I think the only thing that is a concern is just if you pulled on the wires.

But if ever I pull it it's like pulling wires out of your flesh isn't it really.

The wires could catch on clothing or catch in fingers:

You can catch it quite easily; when you bend over they catch.

I have to be a bit careful I caught it my pyjamas over the thread the other day.

Night-time was a particular concern in terms of pulling the wires:

She was worried if she turned over and pulled it.

I'm a bit worried about sleeping with it cos I turn quite a bit at night.

These worries were not unfounded, with two patients in the sample having to suspend use of the pacer shortly after initiation because of broken wires:

One of the wires is broken.

The reason the wire came out was I was sitting on the bed and the phone rang and I had on it and I forgot so it went to the floor.

Washing and showering

There was variation in level of patient and carer concern regarding getting the system wet. For most individuals, showering with the connectors exposed was not of concern after the incisions had healed:

Not too worried because the wires have to be kind of watered because it's in your body and there's fluids there all the time.

I don't think about it.

She's been in the bath of couple of times it's no bother.

It's fine now; I just shower like you would normally.

Three participants were more cautious and, at follow-up interview, had continued to ensure that the connector was kept dry:

They say there's no problem if you wet it but he knows that electricity and water don't mix.

Even now I put a piece of plastic on it.

Some people say don't get it wet, other people say it doesn't matter; my advice was just cover it when you shower.

Perceived outcomes

Perceived effect

At first interview, 4 of the 14 patients reported that they had noticed some improvement to their breathing or had a stronger voice, changes that they attributed to using the pacer. Of the nine who could be followed up, two perceived that the pacer had been of benefit to their breathing. The most frequent responses to questions regarding any perceived benefit were uncertainty, and hope that benefit may be in the longer term:

There's very little I can attribute to this.

I can't actually tell if it's helping me to breathe easier or not.

I don't know.

You don't know if it's working or not.

Hopefully the diaphragm will benefit from that exercise and stand me in good stead later on in life that's the only way I'm looking at it.

The progressive nature of the disease meant that it was challenging for patients and carers to ascertain where a patient would have been if they had not trialled the pacing:

I don't know how to tell if the having pacer has and will make a difference.

We don't know how quickly deterioration would be anyway.

He hasn't seemed to have improved any but then again he could have been worse than this if he'd not had the machine on so it's really hard to compare isn't it.

I don't know whether it's because of diaphragmatic pacing or whether they think that it would be the same.

It's hard to tell because we, we feel he's deteriorated quickly anyway.

Preference for pacing versus non-invasive ventilation

Although there was very limited evidence of perceived benefit, patients generally reported that the pacer was preferable to NIV:

I much prefer this [pacer], I have a problem with the other one [NIV].

If that works is it possible I won't have to have the NIV.

If they could just replace the mask with that.

Definitely the pacer, because the pacer that is brilliant, the mask is a nightmare.

If I had a choice it'd be this one [points to pacer].

There was a recognition, however, that benefits were more easily attributable to using NIV:

I can't say that if I'm battling to breathe and I put this thing (pacer) on I get instant relief whereas if I put the NIV on, the minute I put it on I can feel it taking over.

I don't have enough confidence in this [pacer] to tell me it's replacing that [NIV].

I think I'd go for the pacer rather than the mask but I feel that the mask does more good.

I'd have the breathing mask because it makes me sleep and I feel better in the morning cos I've had a good night's sleep but I'd pick the pacer if it did the same thing as the breathing mask.

Some patients emphasised that the two interventions were operating differently:

When you get up in the morning you can feel fresh in a way, this is a completely different device which agitates your diaphragm.

To be perfectly honest, with this disease I think you need what you need; they're not doing the same thing; there's good things and bad things about both.

Reflections in hindsight

Participants were asked what they would say to another patient with ALS who was considering having the pacing system, and their reflections on taking part in the study. None of the patients at the first interview reported that they regretted having the pacer fitted:

So far we have no regrets.

If you've got a chance of it go for it.

With this disease, there are so few things that anybody can do for you that, to be perfectly honest, if you get chance or something then I'd grab it with open arms.

Well I'd say go for it, you've got nothing to lose.

At second interview these views were unchanged:

Well tell 'em to have it, I mean everything that helps to keeping your breathing is obviously good, the only thing is you don't know if it is helping you or not.

They should go for it.

You don't have any regrets do you . . . absolutely none; like everything it's got to be an individual decision because with ALS whatever you do you know that there's a finite about what you can do but in this instance I would say have a go.

Chapter 6 Discussion

Main findings

The main finding was that DP had a deleterious effect on overall survival. In the DP plus NIV arm compared with the NIV alone arm, the observed reduction in overall survival was 11.5 months and the reduction in survival from symptom onset was 17 months.

The impact on QoL was at best minimal, with no statistically significant differences observed between the arms in patient or carer preplanned QoL measures SF-36, EQ-5D, SAQLI and CBI. The lack of benefit on the SAQLI is particularly noteworthy, as the one RCT of NIV demonstrated improved QoL and respiratory symptoms using this inventory.¹ A planned cost–utility analysis did not go ahead following the lack of efficacy. However, we analysed the EQ-5D-3L scores, as this is a valid QoL tool in its own right. The patient health utility (EQ-5D-3L) was slightly lower in the NIV plus pacing group than in the NIV alone group, especially when a score of 0 was imputed to EQ-5D-3L following death. Differences were modest at any individual time point, but longitudinal analysis demonstrated statistically and clinically significant differences on all patient EQ-5D-3L questionnaires, indicating that at least on one measure, the addition of DP, was associated with a reduction the QoL of patients.

There were more AEs in the NIV plus DPS arm, and many of these were related to the surgery, for example postoperative pain. The type and frequency of the AEs are consistent with those published for ALS, and device-related AEs (e.g. discomfort on pacing or wire failure) were less common than observed in the SSPB, as submitted to the FDA.¹¹ There are three immediate plausible explanations for the latter finding: (1) improvements in using the device with time, (2) patient under-reporting or (3) the fact that AEs were reported over a longer follow-up (in our study, AEs were reported up to death or 1 year post randomisation, whichever came first). Nevertheless, the low rate of pacing-related AEs support our assertion that the implantation procedures and management of the NeuRX RA/4 DPS was conducted in accordance with previous reports and the manufacturer's recommendations.

More deaths were observed in the NIV plus pacing arm; however, the causes of death were similar across the arms and consistent with expected causes of death in ALS. This observation suggests that the NeuRX RA/4 DPS is not modifying the disease phenotype of ALS leading to death through some unusual mechanism. The causes of death would support the hypothesis that the disease course is accelerated by the intervention. It is perhaps important to emphasise that postoperative mortality was not encountered, with only one participant death within 3 months of implantation (and this was 45 days after the procedure). This rules out the direct effects of the implantation procedure itself as the cause of the observed harm in the NIV plus pacing arm.

A full health economic analysis of the cost-effectiveness of the NeuRX RA/4 DPS was planned. Given the lack of efficacy and apparent harm, this analysis did not go ahead. We have, however, compared the health-care resource use between the two arms. This is helpful in exploring if there were differences in other treatments or resources that could have impacted on the results. We found no difference in the way participants accessed health care. Similarly, access to other respiratory interventions, such as cough assist, breath stacking and suction, was comparable. There was a tendency for patients in the NIV arm to use cough assist and suction more frequently, whereas those in the NIV plus pacing arm used breath stacking more. The impact of these differences cannot be quantified, but they are unlikely to explain the differences in survival we observe.

Survival in relation to non-invasive ventilation and diaphragm pacing use and compliance

One concern was that perhaps patients in the NIV plus pacing arm would reduce NIV use in favour of DP use. If this occurred, then the negative impact of not using NIV, a proven intervention to prolong life, may have caused the survival difference between arms. Somewhat paradoxically, NIV use was similar in both arms, and, when modelled, NIV use did not influence survival, although this is likely to reflect increasing use of ventilation as prognosis deteriorates. We explored whether or not bulbar function at the time of randomisation and whether or not NIV tolerance influenced survival. In the RCT,¹ NIV individuals with poor bulbar function did not experience the survival benefits that those with good bulbar function obtained. Bulbar dysfunction is one obstacle to successful NIV use, but there are others, and indeed, some patients with significant bulbar dysfunction can manage NIV. Therefore, looking at NIV tolerance is likely to be the most informative. The impact of bulbar function at the time of randomisation was negligible among the subgroup of patients who were intolerant of NIV and had a trend towards worse survival in the NIV plus pacing arm than in the NIV arm. Although the numbers are small, this would suggest that DP should not be considered an alternative in patients not able to tolerate NIV. This is particularly disappointing, as despite all efforts there is a consistent 20% or so of individuals with ALS who cannot get on with NIV and would benefit from an alternative means of respiratory support.^{2,3}

Diaphragm pacing was well tolerated, with the majority of patients reaching the set targets for pacing. We explored whether or not the amount of DP use influenced survival and did not find an association. One might have expected, given the overall findings, that the more an individual used DP, the worse the outcome would be. We did not observe such a dosing effect. The study was not designed to look for a dosing effect and one needs to be cautious in interpreting observational data. However, this observation would lend soft support to the hypothesis that the indirect effects of surgery itself may have been the major contributor to the harm.

Qualitative study

The inclusion of qualitative data relating to patient and carer experiences involved in trials is important, as it ensures that research does not focus only on intervention effectiveness, but also considers elements of implementation and acceptability to participants. The use of a qualitative substudy is a significant strength of this trial, as it provides a comprehensive analysis and interpretation of patient perspectives.

The qualitative data provide valuable insights into the views and experiences of patients and carers following their decision to take part in the trial of DP. For most participants there were few factors adversely impacting on their use of the intervention, although some patients in contrast described severe pain or discomfort.

The qualitative data confirm previous reports of pain experienced by some users of DP and highlight the wide variation in experiences: a longer than expected hospital stay; the perception among some that the surgery had negatively impacted on their functioning; the perceived ease of operation; issues of portability; and concern regarding fragility of the device.

In general, the participants found the device to be acceptable in terms of ease of operation and limited impact on QoL. The majority of users described hoped-for rather than perceived benefit. Although the majority of participants were uncertain regarding any benefit obtained, none appeared to regret their decision to trial the device. They described the limited options available to people with ALS and their willingness to try any available interventions.

Although the data offer important insights into patient and carer views and experiences of DP, the qualitative data may be limited by the small sample size and by the fact that these participants had been invited and agreed to participate in a clinical trial. We were successful in achieving a sample relatively balanced by participant sex; however, other differences between our qualitative substudy sample and wider groups of patients with motor neurone disease may need consideration.

Understanding the results

There has been a presumption that DP offers probable benefit; however, the mechanism by which such benefit is conferred is unclear and unproven. One potential mechanism put forward is that DP reverses an effect on the diaphragm muscle fibres whereby a shift from a predominance of efficient type I fibres to inefficient type IIb fibres occurs.¹² This hypothesis is extrapolated from observations in a population receiving closed-system invasive ventilation support and it is not known whether or not NIV has a similar effect on the diaphragm muscle fibres.²⁸ A further hypothesis is that DP leads to conditioning of the diaphragm muscle (i.e. increase in muscle mass). There are a few case reports of this, although the functional consequence of this is unknown should it occur.²⁹ Improved compliance of the lungs and prevention of basal collapse; restoration of the co-ordination of breathing, lost as a result of upper motor neurone dysfunction; and increased tidal volumes are other potential as yet unproven mechanisms. Unhelpfully, we can be no more certain as to why DP may be harmful. The possibilities are a direct effect of pacing (i.e. electrical stimulation) on either the muscle or the phrenic motor neurones. The physiological effects of pacing have not been studied in humans. In canines and rodents, it is clear that neuromuscular damage can be induced depending on the parameters of pacing and that the effects observed differ between healthy and disease models.^{8,9} A simpler explanation may be that pacing causes excessive muscle fatigue or that asynchrony between pacing induced diaphragm contraction, patient- and/or NIV-triggered breaths is an issue.

Undertaking surgery in patients with ALS and respiratory failure does present some challenges and angst among health-care professionals. Our study confirmed the finding of others that general anaesthesia can be undertaken safely in terms of perioperative mortality, with no deaths within 30 days of the implantation procedure and only one within the first 3 postoperative months.⁷ However, there is evidence that the consequences of surgery and general anaesthesia may be less immediate and not apparent initially. A retrospective review of ALS patients undergoing surgery for any reason demonstrated an apparent acceleration of ALS disease progression post surgery, suggesting a potential disease-modifying effect, albeit one that is not well understood.¹⁰ Direct effects of anaesthetic agents and surgical stress, with the release of systemic pro-inflammatory cytokines, are postulated to contribute to the observed effect. It is possible that such indirect effects of surgery are contributing to the survival differences in the DiPALS trial; however, this is far from certain. In an attempt to minimise patient burden and focus on survival and cost-effectiveness, during the grant peer-review process secondary outcome measures detailing progression of ALS (ALSFRS-R score) and respiratory function (FVC) were removed from the protocol. When the negative outcome was identified, the TSC requested that an attempt was made to retrospectively collect any functional data on participants during the follow-up period. Clearly, this is an unplanned and retrospective analysis on incomplete data and conclusions based on this analysis need to be cautious. The baseline data at randomisation demonstrate the two arms to be balanced in terms of respiratory function and ALSFRS-R score. However, it does appear that there was a change in the rate of decline of FVC and ALSFRS-R score following implantation. This finding, however, would be consistent with either an indirect effect of surgery or a direct effect of pacing, as described in the *Discussion*.

The results of the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial in context

Our findings are at odds with the FDA summary of SSPB, which reported a survival advantage for DP of 16.1 months from symptom onset and 9 months from the point of NIV initiation, compared with NIV alone, in a historical cohort.^{11,30} This compares with our findings of a reduction in survival in the NIV plus DPS group by 17 months from symptom onset and 11.8 months from randomisation. The median survival from symptom onset in DiPALS was 45 months in the NIV arm, 28 months in the NIV plus pacing arm and 56 months in the SSPB pacing study.

This raises several possibilities, which include that there are differences between the populations in the DiPALS trial and in previous cohort studies; the DP intervention has been delivered differently; or other treatments that impact on survival are different between the DiPALS trial and previous studies. We will discuss these three possibilities next.

The Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial population compared with other studies of diaphragm pacing

The population in the DiPALS trial other than having a male preponderance is relatively typical of an ALS population with age, proportion of limb to bulbar onset, rate of decline of ALSFRS-R score, all as would be expected.³¹ The complete data set, including baseline study population characteristics, from the uncontrolled multicentre cohort study which led to FDA approval on humanitarian grounds of the NeuRX RA/4 DPS (HDE), has to date not yet been published. Therefore, it is not possible to compare the populations and, therefore, it is challenging to fully understand the differences in the reported outcomes. The broad inclusion criteria for the pilot and pivotal phases of the cohort study were evidence of residual bilateral phrenic nerve function and a FVC of < 85% at screening and > 45% at DPS implantation, but specific details, such as the mean age, FVC and bulbar function of the recruited population, are not publicly available.¹¹ The FVC inclusion is higher than the 75% used in the DiPALS trial and if a significant number of patients lay in the 75–85% range for FVC, then this would contribute to some of the difference observed. More immediately, however, it is noteworthy that of the 144 patients enrolled only 106 were implanted and 84 included in the analysis of overall survival. The reasons for these exclusions are not provided, but we speculate that these may, again in part, explain the disparity. The cohort study contained a lead-in phase of 3 months before implantation during which time patients were monitored. The details of 38 patients who did not undergo implantation are not reported. It seems likely that some have been excluded because they rapidly deteriorated, but this is not clear and there may have been other criteria used. Of the 106 implanted, the data of only 84 patients contribute to the SSPB report, two patients having been lost to follow-up and 20 not meeting the HUD criteria. This cohort is therefore a highly selected group and may not be generalisable to the wider ALS population. In contrast, our trial used an intention-to-treat approach in which all consenting participants were analysed, including patients who subsequently declined rapidly in either group. Therefore, we suspect baseline difference in the study populations may be a major cause of observed survival differences.

Outside ALS, DP is licensed for patients with spinal cord injury in several territories including the USA and Europe. As with ALS, the marketing licence was granted on humanitarian grounds and on the basis of a small ($n = 50$) cohort study of patients with spinal cord injury resulting in a poorly controlled diaphragm and requiring continuous mechanical ventilation.^{11,30} Forty-eight of the 50 had achieved a successful outcome, defined as a continuous period of at least 4 hours without the assistance of a mechanical ventilator; one participant was unable to achieve diaphragmatic pacing. The average follow-up was 1.4 years, during which four deaths were reported, none of which was considered to be related to the device.¹¹ Thus, as with the ALS cohort data, there is limited evidence to support or refute the safety of DP.

Delivery of diaphragm pacing in the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial compared with other studies

The device manufacturer (Synapse Biomedical) provided training for surgeons and site staff in all aspects of the intervention, as is standard practice when it supplies the NeuRX RA/4 DPS within a service. For example, an experienced surgeon from Synapse Biomedical attended the implantation procedure and proctored the local site surgeon until he or she was competent to insert the devices. At all surgeries Synapse Biomedical staff were present to provide standard technical support. It is likely that the implantation procedures, which followed the manufacturer's recommendations, were comparable to those undertaken during the earlier cohort study. Supporting this is the fact that the number of surgical complications was lower than previously reported and there was no mortality within the 30-day perioperative period. All diaphragms were stimlatable at surgery supporting our combined clinical and ultrasound assessment of residual phrenic nerve function. No surgeries needed to be abandoned, as planned in the protocol, if on intraoperative mapping of the diaphragm stimulation was not achievable. Following implantation the majority of patients became regular users (mean daily use 6.2 hours) and titrated their use over the course of the study, in line with the protocol and the manufacturer's recommendations. There were six non-users in the NIV plus pacing arm: five of these did not undergo surgery and one stopped pacing after pulling the wires out after 1 month. The overall survival analysis in the DiPALS trial was by intention to treat; however, if these non-users were excluded, then the HR remained significant (HR 2.71, 95% CI 1.39 to 5.27).

Other confounders

Interventions proven to influence survival in ALS are riluzole, multidisciplinary team care and NIV.^{1,4-6} Riluzole use was equal across groups, as this was one of the inclusion criteria. NIV use was comparable across both arms. All participating centres deliver multidisciplinary team care and were specialist centres for treating patients with ALS and respiratory failure. The health-care resource use indicated patients accessed care in a similar manner, regardless of treatment group.

Limitations

Given that patients allocated DP underwent surgical intervention, it was unavoidable that participants were unblinded as to the intervention. The study assessors were also unblinded to the intervention. The trial statistician was unblinded, but withheld accumulating data from the study team. As the primary outcome measure was objective (overall survival), the risk of bias is small, but there is an unavoidable risk of bias in the subjective patient-reported secondary outcome measures. We considered inserting the DP devices in the control group but not connecting them (sham pacing), to reduce the risk of bias and also to be able to offer DP to control subjects at the end of the 12-month follow-up period, but concluded that implanting control subjects appears less reasonable if one considered a possible negative outcome. The effect of DP on the ongoing use of NIV was a concern and we asked the question of whether or not patients stopped using the NIV system, which has established survival benefit, in favour of the DP system. However, our data show that this was not the case, with similar daily periods of NIV use across both groups.

There are imbalances between the treatment arms in our study, the most notable of which is that the NIV plus pacing arm was slightly older. We have adjusted the HRs for this (and other) covariates, but also propose that it is unlikely that such a small age difference would have a large impact on ALS survival. Older age is negatively associated with survival, but less so within the ALS population, in which prognosis is poor across all demographics; certainly, we are unaware of any previous work that has identified age as having an impact that could explain a difference of this magnitude. Similar numbers of patients across each group are reported to receive additional respiratory interventions. However, there are differences in the frequency of cough assist use and breath stacking use, among those given devices, across the

treatment groups. The effects of these differences are unknown but, again, are unlikely to explain the observed poor survival in the NIV plus pacing group.

Developments since the completion of the Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis trial

Recently, a second randomised trial [Early Stage Amyotrophic Lateral Sclerosis Phrenic Stimulation (RespiStimALS); NCT01583088] has also stopped early citing 'absence of benefit [and] a statistically significant excess mortality in the group of patients receiving active stimulation'.^{32,33} There are two notable differences between this study and the DiPALS trial. First, DP implantation was carried out prior to respiratory failure, with the primary end point being the time to requiring NIV. Second, all participants underwent surgical procedure, but with the control group having a 'sham' procedure in which pacing was not instigated until after NIV had started. The fact that an excess mortality was observed in the intervention arm offers compelling evidence that pacing is actively harmful as opposed to surgery. Subsequently, a third randomised study of DPS (NCT01938495) in the USA has suspended enrolment pending further follow-up data from patients already randomised in the study.

Chapter 7 Conclusions

Meaning of the study and implications for clinicians or policy-makers

Diaphragmatic pacing should not be used as a routine treatment for all patients with ALS in respiratory failure. We cannot exclude the possibility that it is beneficial in a subgroup of patients; however, this should not be assumed. Our findings demonstrate that insertion of the NeuRX RA/4 DPS for pacing is harmful when instigated at the point at which an individual with ALS develops respiratory failure. These findings are further supported by a second RCT in which implanting was performed earlier in the disease trajectory, which also stopped early because of excess mortality in the pacing arm (NCT01583088).³²

A poor prognosis and the absence of curative therapy understandably encourage a 'nothing to lose' approach among patients and some clinicians alike, with an attendant lowering of the standards of evidence required to adopt a new intervention. Our trial demonstrates the potential for harm that can arise from adopting this approach.

Recommendations for future research

The findings of our trial, and also those of Gonzalez-Bermejo,³² are at odds with the promising survival data presented in a previous cohort¹¹ and, anecdotally, a small number of individual cases using diaphragmatic pacing in our own clinics. Before any further study of DP in ALS is undertaken in the patient population, we would encourage a meta-analysis of all current trial data on DPS in ALS. This may help to identify whether or not there are any specific circumstances in which a patient may benefit from DP, such as those with predominant upper motor neuron disease. In addition, the emerging findings within ALS should prompt some consideration of the evidence for DP use among patients with spinal cord injury. If any further studies take place in the future, they should include measures to understand the mechanism by which harm or benefit occurs as a result of DP.

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Publications

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Data sharing statement

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Appendix 1 Changes to protocol

TABLE 16 Changes to protocol

Changes to protocol	Progress report	Date	Approved by
Version 1			
Version 1 (original submitted to REC) was amended to version 2, on 3 August 2011, following comments from the REC to incorporate the following: <i>Each site has experience in conducting research in patients with ALS and their carers. These healthcare professionals are trained in counselling patients and carers at various stages of the disease. Carers who experience any distress at any time will be dealt with effectively</i>	1 (dated 23 January 2012)	17 August 2011	NRES Committee East of England – Cambridge Central
Version 2			
Version 2 was amended to version 3, on 24 August 2011, as part of a substantial amendment (approved by REC on 20 September 2011), which required some modification to the eligibility criteria. There was also clarity required to ensure that the Ionising Radiation section of the Integrated Research Application System form was completed, as participants require an ultrasound at screening and a radiography postoperatively	1 (dated 23 January 2012)	20 September 2011	NRES Committee East of England – Cambridge Central
Version 3			
Version 3 was amended to version 4, on 10 January 2012, as part of a minor amendment (approved by the sponsors on 12 January 2012). This was an update to clarify that NIV and DP patients both receive their diaries on NIV initiation. As this was just a minor change to the order of giving the diary out, it was reviewed and approved by the sponsor	2 (dated 13 July 2012)	20 January 2012	NRES Committee East of England – Cambridge Central
Version 4			
Version 4 was amended to version 5, on 30 October 2012, with the following key changes: 1. The 'trial treatment' section of the protocol (page 15) was amended from 'NIV initiation to occur within 1–2 weeks after randomisation' to 'NIV initiation will occur as per usual clinical practice at the study site after randomisation' 2. Within 'trial treatment' the sentence 'a provisional date for implantation will be allocated at randomisation (within 2–3 weeks)' was amended to 'for those randomised to the DP arm, a provisional date for implantation will be allocated after randomisation. The date of surgery should ideally be within 8 weeks of randomisation' 3. On page 16 of the protocol, the 'participant flow' diagram was amended. NIV and pacing arm boxes were amended to take out 'NIV initiation should occur before DP insertion'	3 (dated 14 January 2013)	4 December 2012	NRES Committee East of England – Cambridge Central

continued

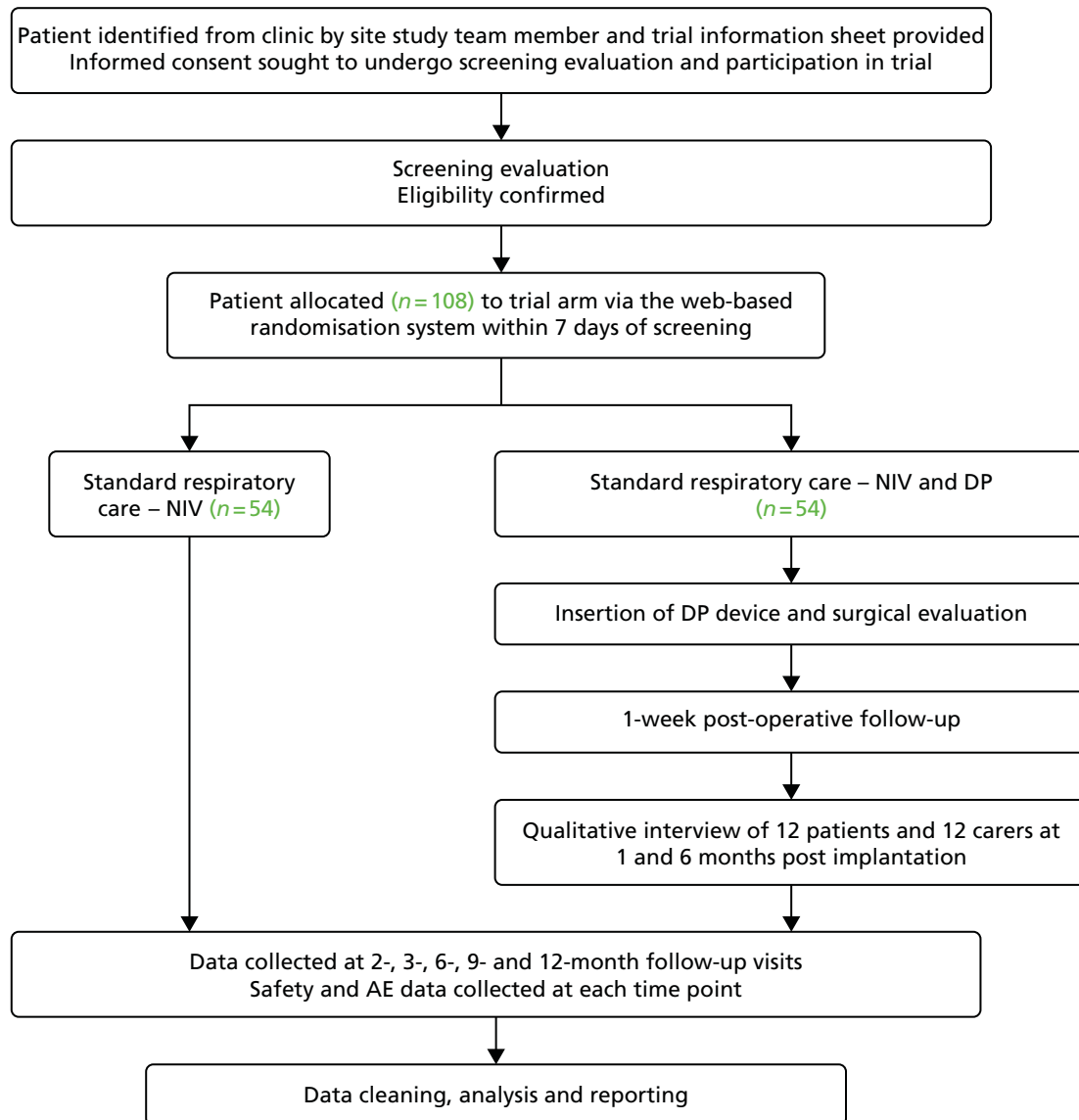
TABLE 16 Changes to protocol (continued)

Changes to protocol	Progress report	Date	Approved by
Version 5			
Version 5 was amended to version 6, on 21 May 2013, with the following changes:	5 (dated 31 January 2014)	8 July 2013	NRES Committee East of England – Cambridge Central
<ol style="list-style-type: none"> 1. Table 1 (page 13) was amended to clarify that blood gases were required only in order to assess eligibility for 4e of the eligibility criteria. As only one of the inclusion criteria (4a–e) needs to be fulfilled, blood gases only need to be performed if a patient was to be entered onto the trial based on 4e 2. On page 18 the sentences ‘A member of Synapse will attend each procedure until sites become competent with use of the device to manage patients independently. The local site PI will be responsible, after liaising with local site staff, for deciding when site staff are competent in performing the intervention without any input from Synapse. The Surgeon at the site will self-certify their competency to perform the operation independently at this stage.’ were added, as it is common practice for sites, once competent, to not need Synapse assistance for intervention 3 3. On page 19 the sentence ‘Pacing may be deferred until the 1-week postoperative appointment to allow patients to adjust to having the device fitted in the immediate postoperative period.’ was added. This was to match practice at all sites, as was recognised that deferring pacing start enables the patient to recover after their operation. In addition to this, in the data collection table (page 21) ‘post or e-mail’ was added to some of the data collection tools to help optimise data collection when it is difficult for patients to attend in person 			
Version 6			
Version 6 was amended to version 7 on 7 October 2013. The protocol was amended to allow respiratory tests up to 2 weeks pre consent, as was standard practice	5 (dated 31 January 2014)	29 October 2013	NRES Committee East of England – Cambridge Central
Version 7			
Version 7 was amended to version 7.1 on 5 November 2013. The data collection table was amended to include data that would be collected from NIV machines and diaries	5 (dated 31 January 2014)	15 November 2013	NRES Committee East of England – Cambridge Central

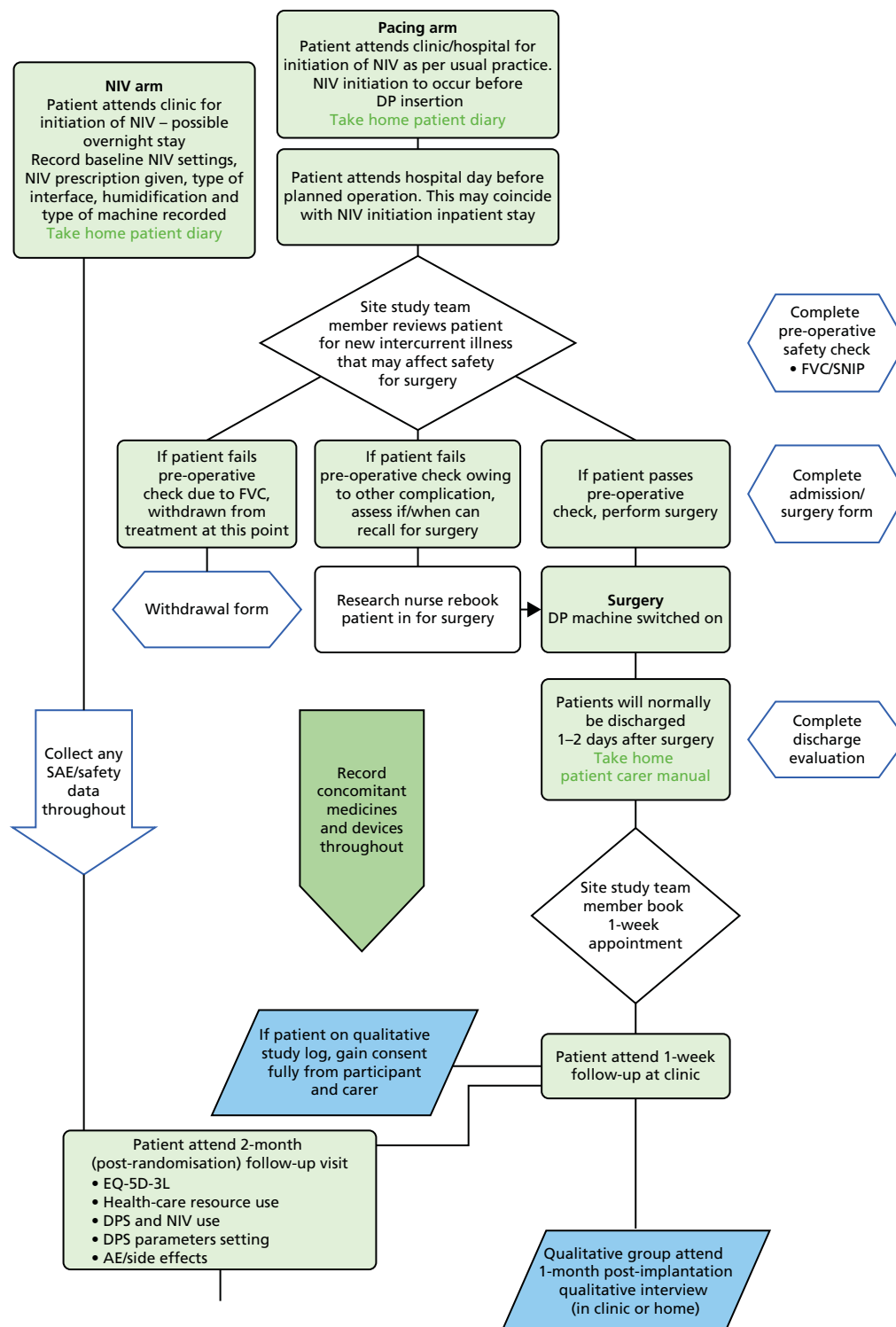
TABLE 16 Changes to protocol (*continued*)

Changes to protocol	Progress report	Date	Approved by
Version 8			
Version 7.1 was amended to version 8, on 16 May 2014, with the following changes:	6 (dated 21 July 2014)	25 June 2014	NRES Committee East of England – Cambridge Central
<ol style="list-style-type: none"> 1. An additional sentence ‘** Data on any respiratory tests routinely performed as part of the participants management of ALS will be collected over the participant’s involvement in the trial’ was added to the protocol. This was to add the collection of FVC/SNIP, etc., over the course of 12 months which would help determine which participants are clinically deteriorating faster than others in the study and to aid with the analysis 2. ‘NIV initiation will occur as per usual clinical practice at the study site after consent has been obtained.’ This was changed from ‘after randomisation’ in the protocol. This was a clarification in the protocol to allow participants in the study to be given standard treatment, that is NIV in each arm from after consent has been obtained in the screening phase. As the screening process could take a few weeks, this amendment was necessary so as to prevent any standard treatment being withheld from participants in both arm as they clinically required it 3. Next to ALSFRS-R in the screening table, the text ‘and routine data’ was added to cover some additional ALSFRS-R information we wished to collect. This was routine clinical information completed by the participants as part of their standard care and would help determine the rate of deterioration of participants in the trial 4. Figure 2 ‘screening and randomisation’ had the label ‘*Note, NIV initiation can occur at any point in the screening phase after consent has been obtained’ added to clarify the point above 			
NRES, National Research Ethics Service.			

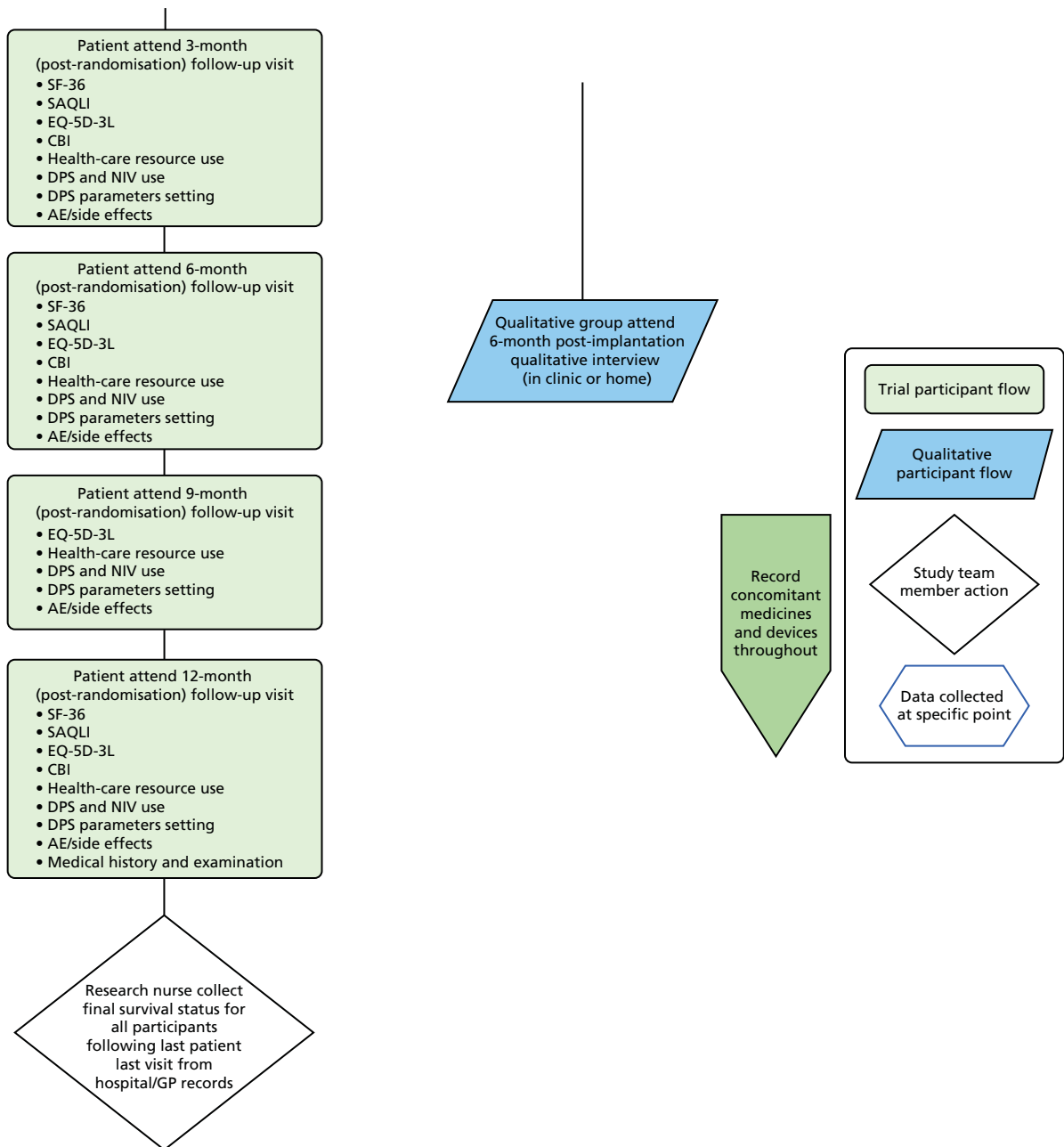
Appendix 2 Trial summary



Appendix 3 Participant flow in each trial arm

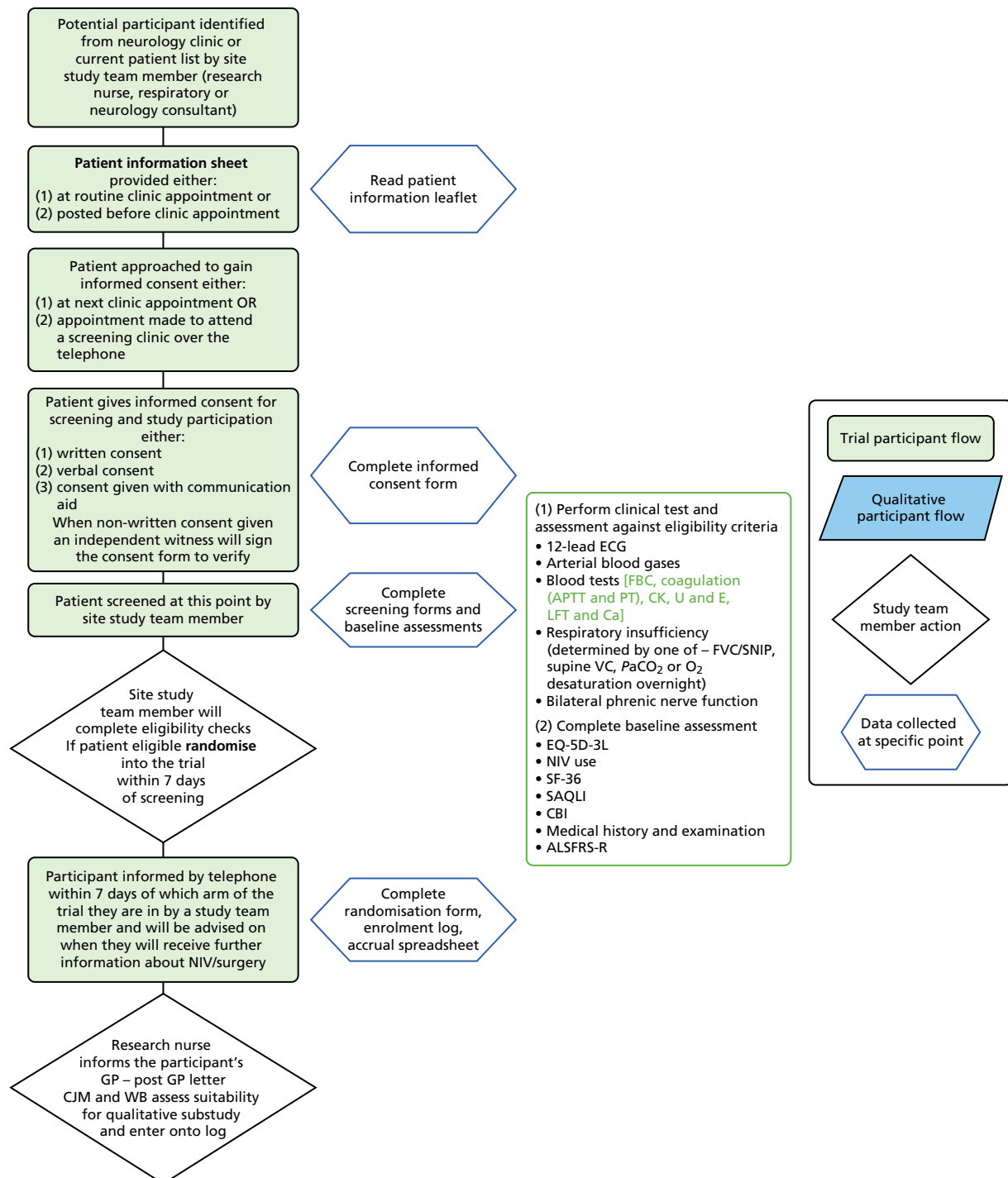


The carer will be asked to complete the EQ-5D-3L, the CBI and the qualitative interviews. Note that NIV initiation can occur at any point in the screening phase after consent has been obtained. (continued)



The carer will be asked to complete the EQ-5D-3L, the CBI and the qualitative interviews. Note that NIV initiation can occur at any point in the screening phase after consent has been obtained.

Appendix 4 Screening and randomisation



The carer will be asked to complete the EQ-5D-3L, the CBI and the qualitative interviews. Note that NIV initiation can occur at any point in the screening phase after consent has been obtained. APTT, activated partial thromboplastin time; Ca, calcium; CK, creatine kinase; ECG, electrocardiogram; FBC, full blood count; LFT, liver function test; PT, prothrombin time; U and E, urea and electrolytes; VC, vital capacity.

Appendix 5 Patient information sheet: patient

What is the purpose of the study?

Motor neurone disease (ALS) affects approximately 2 people in every 100,000 in the UK. One of the main symptoms of ALS is breathlessness. The muscles that people use to help them breathe (the main muscle being the diaphragm) become weak and so patients cannot breathe as well as they once could. This study will determine if adding a new treatment to the usual treatments for ALS breathing problems are of benefit to patients.

What are we studying?

One of the treatments available is a face mask attached to a machine that helps them to breathe more effectively. This is called non-invasive ventilation or NIV. This is a common treatment for breathing problems in people with ALS. The mask fits over the nose or mouth or both. As you breathe in, the machine gives an extra push of air to support the breathing muscles enabling a bigger deeper breath.

Another possible treatment is Diaphragm Pacing (DP). DP is a new technique to help increase the strength of the diaphragm muscle contraction and consequently improve breathing.

The purpose of this study is to find out if having the DP Device fitted as well as receiving NIV offers added benefits, such as prolonging life and improving quality of life, to treatment just with NIV. We do not know if adding DP treatment to standard NIV will be beneficial and this is why we are asking for your help.

Why have I been chosen?

You will have been advised that NIV is a potential treatment option for you to help with your breathing. We would now like to invite you to participate in this study. You do not need to make a decision immediately as to whether or not you want to take part.

If you participate we would also like to invite your main carer to participate in this study. Their involvement would be limited to questionnaires and interviews. If you do not wish your carer to participate or they do not wish to participate you may still enter the study. We are contacting people in a number of NHS hospitals including Sheffield, Manchester, Oxford, Birmingham and Newcastle to take part.

Do I have to take part?

No. It is up to you to decide if you want to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you and your carer to sign a consent form. You are free to withdraw at any time, without giving a reason. If you wish to withdraw, you and your carer will both be withdrawn from the study. We will ask you if you are happy for us to use the information that you have already given us. Withdrawal from the study will not affect your ongoing care.

What will happen to me if I take part?

If you decide to take part and give consent to the trial, you will first undergo some screening assessments at X hospital to see if you are suitable to participate in the trial. These will include: a heart tracing (ECG), blood tests and an

ultrasound scan to evaluate the movement of your diaphragm, a check of the strength of your breathing muscles using sniff and blowing tests. If your centre usually assesses breathing muscle strength using overnight monitoring of oxygen and carbon dioxide levels in your blood, this may also be performed. You and your main carer will be asked to complete some baseline questionnaires at that visit.

Once we have determined that you are eligible to take part you will be put into one of two treatment groups at random as below:

Group 1 – Non Invasive Ventilation (NIV); in this group patients will be given NIV alone

Group 2 – Diaphragm Pacing (DP) plus Non Invasive Ventilation (NIV); this group of patients will be given DP alongside NIV.

You will be given NIV regardless of which group you are allocated to. NIV has already been proven to prolong life and improve quality of life in people with ALS. An appointment will be made with your respiratory or neurology consultants to start NIV. If you are allocated to receive DP, you will need to attend hospital for some additional hospital visits both to get the DP device fitted and also 1 week after surgery to check the device. The admission for surgery to insert the DP device may occur at the same time as the NIV admission depending on local arrangements. NIV should be available in the anaesthetic recovery room after the device is fitted. You should expect to be in hospital for approximately 2 days. A representative from the company who make the device may be present during your operation to help guide the Surgeon with putting the system in place and setting it up. You and your carer may be invited to participate in interviews. 12 patients and their carers will be chosen to take part in the interviews at 1 and 6 months after implantation. The purpose of the interviews is to explore in detail the effects that DP is having. If chosen, you will have the option to opt out of the interviews at the time.

Surgical Implantation (DP group)

If you are receiving DP, you will be admitted to X hospital prior to surgery, for a final review by the surgical team to consider any additional assessments as necessary. You will receive general anaesthesia and will not be awake or able to feel anything during the procedure. During the procedure, approximately 6 small cuts of about ½ an inch long are made in the abdomen. This is to allow passage of the key hole surgery camera, lights and surgical instruments through the abdominal wall.

The surgeon will place the wires in each side of the diaphragm muscle. The wires from the diaphragm will travel under the skin a short distance and then will be passed through the skin onto the surface of the abdomen. The wires will be trimmed so that the ends sticking out of your skin are only 2 - 6 inches in length. You will stay in hospital overnight and should be able to return home the next day. An x-ray will be taken following the surgery to check the position of the wires and to make sure no air has travelled above the diaphragm and into the chest.

If damage to the motor nerves to the diaphragm is too severe it may not be possible to stimulate the diaphragm with the diaphragm pacing system. The scan of the diaphragm performed during screening is an attempt to confirm that diaphragm nerve damage is not too severe. However it is only possible to be certain at the time of the operation. If during the operation it is clear that the diaphragm cannot be stimulated then the operation will be stopped and the device will not be inserted.

Trial Procedures

DP group

DP training will occur prior to discharge. Training is the process of teaching you and your caregiver the correct care and use of the stimulator, and how to record information in your study diary.

You will be given a patient diary to take home with you. In this you will be asked to record the amount of time you have spent on DP and/or NIV. There will also be an option to record any problems you might have experienced. 1 week after implantation you will need to return for assessment at the clinic. You will undergo a surgical evaluation and a safety check to see how the DP device is working.

DP use should not be painful. Your study doctor will set the device at a level which causes maximum stimulation of the diaphragm without discomfort. We recommend that patients start using DP pacing for 30 minute sessions through the day. These sessions can then be gradually increased. Patients should also build up to using DP at night whilst asleep. Your study doctor will advise you on the timings of your DP use and will record your target DP use in your diary. Quality of Life questionnaires will be administered at each subsequent visit – 2, 3, 6, 9 and 12 months into the trial.

NIV group

You will be given a patient diary to take home with you. In this you will be asked to record the amount of time you have spent on NIV. There will also be an option to record any problems you might have experienced. Quality of life questionnaires will be administered at each subsequent visit – 2, 3, 6, 9 and 12 months into the trial. At the end of the trial, patients in the NIV group will not receive DP as DP is not currently a treatment available for patients as part of usual standard care.

What are the benefits?

Research suggests that patients with ALS may benefit from Diaphragm Pacing, in addition to NIV, by slowing the progression of breathing muscle weakness, but also by an improved quality of life. DP may reduce the need for you to have NIV and may also prove to be a less intrusive method of supporting breathing function when compared to NIV.

What treatment may be withheld?

No treatment will be withheld as a result of your involvement in this trial.

Are there any risks or discomforts?

Operation site infection, diaphragm muscle injury and a pneumothorax (see explanation below) are potential complications with the DP implant technique. Infections at the operation site are a possibility, but to date this has not been an issue. If an infection does occur, and it cannot be treated without removal of the electrodes, then the electrodes will be removed.

Air may track from the abdominal cavity to the space around the lungs during the procedure, and this is classified as a pneumothorax. This often occurs during any routine key hole abdominal procedure. If present, it is easily sucked away with a needle and syringe at the completion of the operation.

One of the reasons for undergoing this procedure is that your breathing muscles are weak. A general anaesthetic in patients with weak breathing muscles carries an increased risk of complications including pneumonia. Following the operation there may be an increased risk of requiring additional breathing support with invasive ventilation.

The x-ray to check the placement of the DP wires exposes you to a small amount of radiation. This is equivalent to about 8 days average natural background radiation. The Health Protection Agency describe this level of radiation dose as 'Negligible Risk'. You would not receive this x-ray if you were not taking part in this study.

Will I be able to keep my pacing device at the end of the trial?

Yes. If you want to keep the device at the end of the trial you will be able to.

What happens if I don't want to continue with the study?

You are free to withdraw from the study at any time and this will not affect your clinical care. If you decide to withdraw we can cut the wires at the surface of the skin because they are safe to be left inside your body. However we can remove them completely under local anaesthetic if you chose to.

Will it cost me any money?

No. Any expenses incurred as a result of extra visits over and above usual clinic attendances will be reimbursed.

What happens if something goes wrong?

Any complaints should be addressed to your local doctor in the first instance (contact details are given at the end of this information sheet). If you have any concerns about the study you should ask to speak to the researchers who will do their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from [insert site specific details].

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be identified. Some parts of your medical records and the data collected for the

study will be looked at by authorised persons from the University of Sheffield organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research. We will write to your GP to let him or her know that you are participating in this study, as they are involved in the management of your care, and so it is important that they know what is happening.

What will happen to the results of the study?

We will publish the results in a scientific journal and produce a report that is freely available to anyone who wishes to read it. You will not be personally identified in any report or publication we produce. Please contact us using the details below if you would like to see a summary of the results when the trial is completed.

Who is organising and funding the research?

The research is organised by the University of Sheffield and funded by the Department of Health and the Motor Neurone Disease Association.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Cambridge Central Research Ethics Committee.

Further information can be obtained from:

<insert local PI name>

<insert local PI address>

<insert local PI telephone number>

Or contact the Chief Investigator:

Dr Christopher McDermott

Chief Investigator

Sheffield Institute for Translational Neuroscience

University of Sheffield

XXXX

XXXX

XXXX

Tel: XXXX

Appendix 6 Patient information sheet: carer

What is the purpose of the study?

Motor neurone disease (ALS) affects approximately 2 people in every 100,000 in the UK. One of the main symptoms of ALS is breathlessness. The muscles that people use to help them breathe (the main muscle being the diaphragm) become weak and so patients cannot breathe as well as they once could. This study will determine if adding a new treatment to the usual treatments for ALS breathing problems are of benefit to patients.

What are we studying?

One of the treatments that is available to patients is a face mask attached to a machine that helps them to breathe more effectively. This is called non-invasive ventilation or NIV. This is a common treatment for breathing problems in ALS. The mask fits over the nose or mouth or both. As you breathe in, the machine gives an extra push of air to support the breathing muscles enabling a bigger deeper breath.

Another possible treatment is Diaphragm Pacing (DP). DP is a new technique to help increase the strength of the diaphragm muscle contraction and consequently improve breathing.

The purpose of this study is to find out if having the DP Device fitted as well as receiving NIV offers added benefits, such as prolonging life and improving quality of life, to treatment just with NIV. We do not know if adding DP treatment to standard NIV will be beneficial and this is why we are asking for your help.

Why have I been chosen?

Your relative will have been advised that NIV is a potential treatment option for them to help with their breathing and we have invited them to take part in this study. We would now like to invite you, as their main carer, to participate in this study. You do not need to make a decision immediately as to whether or not you want to take part.

Your involvement will be limited to questionnaires and interviews. We are contacting people in a number of NHS hospitals to take part including Sheffield, Manchester, Oxford, Birmingham and Newcastle.

Do I have to take part?

No. It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you and your relative to sign a consent form. You are free to withdraw at any time, without giving a reason. We will ask you if you are happy for us to use the information that you have already contributed. Withdrawal from the study will not affect your relative's ongoing care.

What will happen to me if I take part?

You will be asked to complete the following questionnaires:

1. The EQ5D – this is a 5 point questionnaire which will be collected at each of the follow up time points. The information will be based on your understanding of your relative's health.

2. The caregiver burden inventory – this is a questionnaire which gives a measure of impact that your care giving has on aspects of your life such as physical and emotional well being and your life in general.

Questionnaires will be administered at the first visit then at 2, 3, 6, 9 and 12 months visits into the trial.

You and your relative may be invited to participate in interviews. 12 patients and their carers will be chosen to take part in the interviews at 1 and 6 months after implantation. The purpose of the interviews is to explore in detail the effects that DP is having. If chosen, you will have the option to opt out of the interviews at the time.

What are the benefits?

Potential benefits associated with the trial have been explained to your relative. We do not anticipate any direct benefits for carers involved in the study.

Are there any risks or discomforts?

Potential risks and discomforts associated with the trial have been fully explained to your relative. We do not anticipate that participating in this study poses any physical risk for you. We appreciate that you may find it upsetting completing any questionnaires about your relative's experiences. If you become upset we will stop and let you decide what you want to do. If you wish to postpone the assessments, this can be arranged. If you feel you want to withdraw from the study altogether you can do so without your relative's care being affected in any way.

What happens if I don't want to continue with the study?

You are free to withdraw from the study at any time. If you withdraw we will ask whether we can keep the data we have already collected from you. Alternatively if it is your preference all data can be destroyed. This will not affect your relative's participation in the study or the treatment that your relative receives.

Will it cost me any money?

No. Any expenses incurred as a result of extra visits over and above usual clinic attendances for your relative will be reimbursed.

What happens if something goes wrong?

Any complaints should be addressed to your local doctor in the first instance (contact details are given at the end of this information sheet). If you have any concerns about the study you should ask to speak to the researchers who will do their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from [insert site specific details].

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. Data collected for the study will be looked at by authorised persons from the University of Sheffield organising the research. They may also be looked

at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

What will happen to the results of the study?

We will publish the results in a scientific journal and produce a report that is freely available to anyone who wishes to read it. You will not be personally identified in any report or publication we produce. Please contact us using the details below if you would like to see a summary of the results when the trial is completed.

Who is organising and funding the research?

The research is organised by the University of Sheffield and funded by the Department of Health and the Motor Neurone Disease Association.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Cambridge Central Research Ethics Committee.

Further information can be obtained from:

<insert local PI name>

<insert local PI address>

<insert local PI telephone number>

Or contact the Chief Investigator:

Dr Christopher McDermott, Chief Investigator

Sheffield Institute for Translational Neuroscience

XXXX

XXXX

XXXX

XXXX

Tel: XXXX

Appendix 7 Patient information sheet: patient qualitative

What is the purpose of the study?

Motor neurone disease (ALS) affects approximately 2 people in every 100,000 in the UK. One of the main symptoms of ALS is breathlessness. The muscles that people use to help them breathe (the main muscle being the diaphragm) become weak and so patients cannot breathe as well as they once could. This study will determine if adding a new treatment to the usual treatments for ALS breathing problems are of benefit to patients.

What are we studying?

As you are aware, we are studying two different treatments in the two groups of this trial:

Arm 1 – Non Invasive Ventilation (NIV); in this group patients will be given NIV alone

Arm 2 – Diaphragm Pacing (DP) plus NIV; in this group patients will be given DP alongside NIV.

The purpose of this study is to find out if having the NeuRx/A4 Device fitted as well as receiving NIV may offer added benefits, such as prolonging life and improving quality of life, to treatment just with NIV. We do not know if adding DP treatment to standard NIV will be beneficial and this is why we are asking for your help.

In this part of the study we are asking participants who have had the DP device fitted to take part in 2 interviews. We would like to draw directly on your and your carer's own experiences and views of having DP within the context of everyday lives. Interviews will provide an opportunity to take account of your views and experience of the device.

Why have I been chosen?

As you are aware, you are already part of the DiPALS study. When you initially gave consent, you agreed to be contacted for the interview stage of the project. We would now like to invite you to participate in these interviews. You do not need to make a decision immediately as to whether or not you want to take part. We would also like to invite the individual you identify as your main carer to participate in this study. However if you do not wish for us to invite them or they decline to participate you may still participate in the interviews.

We are conducting these interviews on 12 patients and their carers in this group. We are contacting people in Sheffield, Manchester, Oxford, Birmingham and Newcastle to take part.

Do I have to take part?

No. It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you and your carer to sign a consent form. You are free to withdraw at any time, without giving a reason. If you wish to withdraw, you and your carer will both be withdrawn from the study. We will ask you if you are happy for us to use the information that you have already contributed. Withdrawal from the study will not affect your ongoing care.

What will happen to me if I take part?

You have now had the DP device fitted and have been identified as somebody we would like to interview for this part of the research. If you consent, an experienced researcher will conduct the interviews at a time and location that is convenient for you. There will be 2 interviews for both you and your carer. The first will be 1 month after your operation and the second 6 months after your operation.

The first interview at 1 month will focus on the DP device and the practicalities of having the implant fitted and adjusting to life using the device.

The 6 month interview will focus on the impact the device has had on your quality of life. This will allow enough time for you and your carer to become familiar with the device and its impact on your life.

Ideally we would like you and your carer to be interviewed separately but joint interviews can be undertaken if this is your wish. The interviews will take about half an hour, but might be shorter if you feel tired. If you decide that you do not feel well enough then the interview can be postponed until you feel better.

Are there any risks or discomforts?

We do not anticipate that participating in this part of the study poses any physical risk, but we appreciate that you may find the interview tiring. If you become tired during any of the assessments or interviews, we will stop and let you decide what you want to do. If you wish to postpone the assessments and interviews, this can be arranged. If you feel you want to withdraw from the study altogether you can, and your care will continue as normal.

What happens if I don't want to continue with the study?

You are free to withdraw from the study at any time and without giving a reason. This will not affect your clinical care.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. Interviews will be tape recorded and then transcribed to assist with analysis. Anything you say in your interviews will be treated in the strictest confidence, and although we might use direct quotes in anything we write as a result of this study, these will also be anonymised. These recordings and transcripts will be kept secure within the department and accessed only by the research team. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

What happens if something goes wrong?

Any complaints should be addressed to your local doctor in the first instance (contact details are given at the end of this information sheet). If you have any concerns about the study you should ask to speak to the researchers who will do

their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from [insert site specific details].

What will happen to the results of the study?

We will publish the results in a scientific journal and produce a report that is freely available to anyone who wishes to read it. You will not be personally identified in any report or publication we produce. Please contact us using the details below if you would like to see a summary of the results when the trial is completed.

Who is organising and funding the research?

The research is organised by the University of Sheffield and funded by the Department of Health and the Motor Neurone Disease Association.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Cambridge Central Research Ethics Committee.

Further information can be obtained from:

<insert local PI name>

<insert local PI hospital name>

<insert local PI hospital address>

<insert local PI telephone number>

Or contact the Chief Investigator:

Dr Christopher McDermott

Chief Investigator

XXXX

XXXX

XXXX

XXXX

XXXX

Tel: XXXX

Appendix 8 Patient information sheet: carer qualitative

What is the purpose of the study?

Motor neurone disease (ALS) affects approximately 2 people in every 100,000 in the UK. One of the main symptoms of ALS is breathlessness. The muscles that people use to help them breathe (the main muscle being the diaphragm) become weak and so patients cannot breathe as well as they once could. This study will determine if adding a new treatment to the usual treatments for ALS breathing problems are of benefit to patients.

What are we studying?

As you are aware, we are studying two different treatments in the two groups of this trial:

Arm 1 – Non Invasive Ventilation (NIV); in this group patients will be given NIV alone

Arm 2 – Diaphragm Pacing (DP) plus NIV; in this group patients will be given DP alongside NIV.

The purpose of this study is to find out if having the NeuRx/A4 Device fitted as well as receiving NIV may offer added benefits, such as prolonging life and improving quality of life, to receiving NIV alone. We do not know which treatment is better and this is why we are asking for your help.

In this part of the study we are asking the carers of patients who have had the DP device fitted to take part in 2 interviews. We would like to draw directly on both of your experiences and views of having DP within the context of everyday lives. Interviews will provide an opportunity to take account of your views and experience of the device.

Why have I been chosen?

As you are aware, you and your relative are already part of the DiPALS study. When you initially gave consent, you agreed to be contacted for the interview stage of the project. We would now like to invite you to participate in these interviews. You do not need to make a decision immediately as to whether or not you want to take part.

We are conducting these interviews on 12 patients and their carer's in this group. We are contacting people in Sheffield, Manchester, Oxford, Birmingham and Newcastle to take part.

Do I have to take part?

No. It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. If you wish to withdraw, your relative may remain in the study if they wish. We will ask you if you are happy for us to use the information that you have already contributed.

What will happen to me if I take part?

Your relative will have now had the DP device fitted and have been identified as somebody we would like to interview for this part of the research. If you consent, an experienced researcher will conduct the interviews at a time and location that is convenient for you. There will be 2 interviews for both you and your relative;

the first one 1 month after your relative's operation and the second one 6 months after their operation.

The first interview at 1 month will focus on the DP device and the practicalities of having the implant fitted and adjusting to life using the device.

The 6 month interview will focus on the impact the device has had on your quality of life. This will allow enough time for you and your relative to become familiar with the device and its impact on your life.

Ideally we would like you both to be interviewed separately but joint interviews can be undertaken if this is your wish. The interviews will take about half an hour, but might be shorter if your relative feels tired.

Are there any risks or discomforts?

We do not anticipate that participating in this part of the study poses any physical risk, but we appreciate that you may find it upsetting talking about your relative's experiences. If you become upset during the interview, we will stop and let you decide what you want to do. If you wish to postpone the assessments and interviews, this can be arranged. If you feel you want to withdraw from the study altogether you can do so without your relative's care being affected in any way.

What happens if I don't want to continue with the study?

You are free to withdraw from the study at any time and without giving a reason.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. Interviews will be tape recorded and then transcribed to assist with analysis. Anything you say in your interviews will be treated in the strictest confidence, and although we might use direct quotes in anything we write as a result of this study, these will also be anonymised. These recordings and transcripts will be kept secure within the department and accessed only by the research team. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

What happens if something goes wrong?

Any complaints should be addressed to the local study doctor in the first instance (contact details are given at the end of this information sheet). If you have any concerns about the study you should ask to speak to the researchers who will do their best to answer your questions [contact number]. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from [insert site specific details].

What will happen to the results of the study?

We will publish the results in a scientific journal and produce a report that is freely available to anyone who wishes to read it. You will not be personally identified in any report or publication we produce. Please contact us using the

details below if you would like to see a summary of the results when the trial is completed.

Who is organising and funding the research?

The research is organised by the University of Sheffield and funded by the Department of Health and the Motor Neurone Disease Association.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Cambridge Central Research Ethics Committee.

Further information can be obtained from:

<insert local PI name>

<insert local PI hospital name>

<insert local PI hospital address>

<insert local PI telephone number>

Or contact the Chief Investigator:

Dr Christopher McDermott

Chief Investigator

Sheffield Institute for Translational Neuroscience

University of Sheffield

Appendix 9 Consent form: patient

Patient Identification Number:

PATIENT CONSENT FORM

THE DiPALS TRIAL

Diaphragm Pacing in Motor Neurone Disease

Please
initial
box

1. I confirm that I have read and understand the information sheet dated.....
(version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I have been given enough information about the study and had enough time to come to my decision
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Sheffield, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
5. I agree to be contacted for the qualitative interview*
6. I agree to my GP being informed of my participation in the study.
7. I agree to take part in the above study.
8. I understand that a representative from the device manufacturers may be present during my operation

Participant:

Signature:

Print Name: Date:.....

Investigator: I have explained the above study to the participant and obtained consent

Signature:

Print Name: Date:.....

Witness:

Signature:

Print Name:

Date:.....

Relationship to participant:

1 copy for participant; 1 for site file; 1 (original) to be kept in patient's medical notes.

*Only 12 of 108 participants and their carers will be selected for the interviews

Appendix 10 Consent form: carer

Relative's Patient Identification Number:

CARER CONSENT FORM THE DiPALS TRIAL

Diaphragm Pacing in Motor Neurone Disease

Please
initial box

- 1. I confirm that I have read and understand the information sheet dated.....
(version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- 2. I have been given enough information about the study and had enough time to come to my decision
- 3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
- 4. I agree to be contacted for the qualitative interview*
- 5. I agree to take part in the above study.

Carer:

Signature:

Print Name: Date:.....

Investigator: I have explained the above study to the participant and obtained consent

Signature:

Print Name:	Date:.....
-------------------	------------

1 copy for carer; 1 for researcher site file; 1 (original) to be kept in relative's medical notes.

*Only 12 of 108 participants and their carers will be selected for the interviews

Appendix 11 Consent form: patient qualitative

Patient Identification Number:

PATIENT QUALITATIVE CONSENT FORM **THE DiPALS TRIAL**

Diaphragm Pacing in Motor Neurone Disease

Please
initial box

1. I confirm that I have read and understand the information sheet dated.....
(version.....) for the above study, have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I have been given enough information about the study and had enough time to come to my decision.
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Sheffield, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
5. I agree to the use of anonymised quotes from the interviews.
6. I agree to take part in the above study.

Participant:

Signature:

Print Name:

Date:.....

Investigator: I have explained the above study to the participant and obtained consent

Signature:

Print Name:

Date:.....

Witness:

Signature:	
Print Name:	Date:.....
Relationship to participant:	

1 copy for participant; 1 for site file; 1 (original) to be kept in patient's medical notes.

Appendix 12 Consent form: carer qualitative

Relative's Patient Identification Number:

CARER QUALITATIVE CONSENT FORM THE DiPALS TRIAL

Diaphragm Pacing in Motor Neurone Disease

Please
initial box

- 1. I confirm that I have read and understand the information sheet dated.....
(version.....) for the above study, have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- 2. I have been given enough information about the study and had enough time to come to my decision.
- 3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
- 4. I agree to the use of anonymised quotes from the interviews.
- 5. I agree to take part in the above study.

Carer:

Signature:

Print Name: Date:.....

Investigator: I have explained the above study to the participant and obtained consent

Signature:

Print Name: Date:.....

1 copy for participant; 1 for site file; 1 (original) to be kept in relative's medical notes.

Appendix 13 Statistical analysis plan

Statistical analysis plan – before data was unblinded



Sheffield Teaching Hospitals 
NHS Foundation Trust



*A randomised controlled trial in patients with
Respiratory Muscle Weakness due to Motor
Neurone Disease of the NeuRx/4 Diaphragm Pacing
Trial*

Statistical analysis plan version 1.0, 30 October 2012

Authored by

Mike Bradburn
Trial statistician
CTRU, University of Sheffield

___/___/___
Date

Approved by

Chris McDermott
Chief investigator
SITraN, University of Sheffield

___/___/___
Date

Lyn Taylor
TSC statistician
SCHARR, University of Sheffield

___/___/___
Date

Carolyn Young
TSC Chair
The Walton Centre, Liverpool

___/___/___
Date

DiPALS statistical analysis plan version 1.0 FINAL

DiPALS statistical analysis plan version 1.0 FINAL

List of abbreviations used

AE	Adverse event
ALS	amyotrophic lateral sclerosis
ANCOVA	Analysis of Covariance
CI	confidence interval
CTRU	University of Sheffield Clinical Trial Research Unit
DMEC	Data Monitoring and Ethics Committee
DP	Diaphragm pacing
EQ-5D	EuroQol health utility questionnaire
FVC	forced vital capacity
GCP	Good Clinical Practice
ITT	intent-to-treat
MND	Motor neurone disease
NIV	non invasive ventilation
PH	Proportional hazards
PP	per-protocol
QoL	Quality of life
SAE	Serious adverse event
SAQLI	sleep apnoea quality of life index
SF-36	Short form-36 questionnaire
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale

DiPALS statistical analysis plan version 1.0 FINAL

Introduction, study design and key trial objectives

Study outline

The DiPALS study is a two-arm, parallel group, open-label randomised controlled clinical trial in patients with motor neurone disease (MND) or amyotrophic lateral sclerosis (ALS) with respiratory muscle weakness. Patients will be allocated to either non invasive ventilation (NIV) with diaphragm pacing (DP), or to NIV alone. NIV alone is the current standard care, and is the control group.

This statistical analysis plan is written in conjunction with the International Conference on Harmonisation topic E9 (Statistical principles for clinical trials, 1998), applicable standard operating procedures from the University of Sheffield Clinical Trials Research Unit (CTRU) and trial documents referenced in section 6. The trial will be conducted in accordance with Good Clinical Practice (GCP) in Clinical Trials.¹

Outcome measures

The primary objective of this trial will be to evaluate the effect of DP on overall survival.

Secondary objectives will be to evaluate the effect of DP on the following:

- Quality adjusted life years (QALYs, not covered in this document)
- Quality of life: sleep apnoea quality of life index (SAQLI), and the Short Form-36 (SF-36) version 1.
- Quality of life of the main carer, measured by Caregiver Burden Inventory (CBI).
- Safety and tolerability.
- Health economic objectives and resource use (not covered in this document).
- Qualitative user perspectives (not covered in this document).

Randomisation

Patients will be allocated to their treatment by minimisation which is carried out via a web-based interface hosted by the CTRU. The minimisation factors are baseline bulbar function (mild, moderate, severe), forced vital capacity (FVC) at baseline (50-59%, 60-69%, 70+%), age (<=39, 40-79, 80+) and sex.

Interim analyses, data monitoring committees etc.

Three committees will be established to govern the conduct of this study:

- Trial Steering Committee (TSC)
- Independent Data Monitoring and Ethics Committee (DMEC)
- Trial Management Group (TMG)

Periodic efficacy and safety analyses will be provided to the DMEC. These summaries will have the treatment groups labelled as "A" and "B", but may be fully unblinded at the discretion of the DMEC. The TSC and TMG will see overall results only.

DiPALS statistical analysis plan version 1.0 FINAL

Sample size calculation

The sample size calculation is based on log-rank test, using Simpson's rule ² as implemented in Stata version 11.1 ³ to allow for the unequal length of follow-up. The study duration comprises an 18-month recruitment period and a 12-month follow-up period, giving a maximum follow-up of 30 months and a minimum of 12 months. Assuming control group survival proportions of 45%, 20% and 10% at the minimum, average and maximum follow-up times respectively, a hazard ratio of 0.45 and an additional 10% loss-to-follow-up, a total of 108 patients (54 per group) are needed to ensure a power of 85% using a two-sided type I error of 5%. The control group figures are conservative estimates based on the sole randomised controlled trial of NIV, which is now considered standard care in the UK. A study carried out in the United States has estimated a one year survival of 86% after study entry for patients using DP and NIV. We have estimated the sample size on a conservative (but clinically important) 1-year difference in survival of 45% versus 70%, which produces the estimated hazard ratio of 0.45. It is anticipated that we will have complete survival data on all subjects recruited, based on previous experience in MND trials.

With regard to quality of life data we anticipate a low level of missing data due to loss to follow up. We have reviewed the patients who were initiated on NIV in the year up to Jun 2009 and we have maintained contact with 100% of those patients surviving at 12 months. The appointment of a research nurse at each study site will enable home visits if necessary to collect the quality of life data. We have however allowed for a 10% loss to follow up in the sample size/power calculation.

Additional patients may be recruited if less than 54 patients receive their allocated treatment.

Data sources, data and analysis populations

Data sources

The data used in this study will come from data entered onto the following sources:

- Case Report Form (CRF) version 1, 11 November 2011
- Screening log version 1, 26 October 2011
- NIV group patient diary version 2, 3 August 2011
- DP group patient diary version 2, 3 August 2011

The database will be stored on the CTRU database (PROSPECT) with the exception of the randomisation list which is held on the CTRU's randomisation system. Electronic data will be extracted from the system during the trial for the purpose of checking (validating) and trial progress reports; however, access to any data which would unblind the study (randomised group, resource usage) will be limited to members independent of the trial (e.g. DMEC statistician). Personal records will not be made available to CTRU staff.

Protocol Deviations

The following will be classified as protocol deviations in the statistical analysis:

1. Patients who are randomised in error (any of the inclusion/exclusion criteria are breached)
2. Patients who do not tolerate NIV
3. (DP group only) Patients who do not have a successful DP implantation
4. (DP group only) Patients who do not use DP

DiPALS statistical analysis plan version 1.0 FINAL

The above criteria will be used in explanatory analyses. All are objective criteria which will be determined from the clinical database and verified by the CI at database lock and before analysis is undertaken. Criteria 2 will also be used as a basis for subgroup analyses.

Analysis populations

Three analysis sets will be used:

Name	Patients included	Treatment group
Intent-to-Treat (ITT)	All patients for whom consent is obtained and who are randomised into the trial	As randomised
Per Protocol (PP)	The subset of the ITT patients who do not violate the protocol, as defined in section 2.2.	As randomised
Safety	All patients who proceed to NIV, with or without DP	As treated

All summaries will be based on the ITT set, with the following exceptions:

- Effectiveness analyses will also be undertaken on the PP set. Additional analyses to assess the impact of compliance, for example complier-average causal effect (CACE) methodology, may also be undertaken if there are a substantial number of withdrawals from treatment or crossing between groups.
- Analysis of adverse events (AEs) will be undertaken on both the ITT and safety sets. In the latter, patients will be analysed by the treatment they were using at the point of the adverse event.

Outline of analyses

General considerations

Data will be reported and presented according to the revised CONSORT statement.^{4,5}

Complete details of data derivations and methods of handling multiplicity, multi-centre data and missing data are covered in section 4. No interim analyses or early stopping are planned.

All summaries will be provided on the full analysis set using an intention to treat (ITT) approach. If loss-to-follow-up and/or treatment crossover is greater than 5%, sensitivity analyses will be performed to assess the robustness of the results. If important discordances are observed between these and the ITT approach, both analyses will be reported.

All summary tables will present summary statistics within each treatment group and overall unless stated otherwise.

Summaries of continuous variables will comprise the number of observations used and either i) mean, standard deviation, median, minimum and maximum, or ii) median, inter-quartile range, minimum and maximum as appropriate for the distributional form of the data.

Summaries of categorical variables will comprise the number of observations used, and the number and percentage of observations in each category.

Summaries of time-to-event outcome data will comprise the median and inter-quartile range of survival within each group, the hazard ratio and its 95% confidence interval.

DiPALS statistical analysis plan version 1.0 FINAL

Summaries of QoL outcomes will comprise the following:

- A summary (mean, standard deviation, median, minimum and maximum) of the QoL, by treatment group and time point.
- The least squared mean QoL change from baseline at each time point, together with its standard error, by treatment group and time point.
- The least squared mean difference between treatment groups, together with its 95% confidence interval and p-value, by time point
- The overall comparison between the treatment groups, together with its 95% confidence interval and p-value, and a test for interaction between treatment group and time. Both are based on longitudinal modelling.

All treatment comparisons will use the NIV only group as the reference (comparator), all statistical exploratory tests of main effects will be two-tailed with alpha = 0.05; and all confidence intervals (CIs) will be two-sided, 95% intervals. As there is controversy with regards to the operating characteristics of minimisation, a permutation test will be used to confirm the p-value from the primary endpoint.⁶ Since interaction tests have low statistical power, additional consideration will be given to p-values below 0.1 when testing interactions (treatment x centre and treatment x subgroups).

Disposition and data completeness

The following summary will be presented for all patients screened for entry to the study, by centre and overall:

<i>Enrolment</i>	The "CONSORT" diagram comprising the number of people screened, eligible, consented, randomised, receiving their allocated treatment, withdrawing/lost to follow-up, and included in ITT and PP analysis sets.
<i>Characteristics of non-enrolled patients</i>	The age, gender and reason for non-inclusion.

In addition the following by-patient line-listings will be provided

<i>Reasons for non-randomisation</i>	For people screened but not randomised: <ul style="list-style-type: none"> - A list of reasons for non-recruitment (any/all that apply) - A list of reasons for non-consent
<i>Reasons for non-implantation</i>	For people allocated pacing device: <ul style="list-style-type: none"> - A list of reason(s) for not proceeding with surgery (FVC not acceptable, failure of pre-operative checks, withdrawal, unable to stimulate diaphragm, others)

The inclusion of patients in each analysis population is outlined in section 2.3. Where the randomised intervention (as recorded on the randomisation list) differs from the intervention group as recorded on the case record form, the randomisation list will be assumed to be the correct data source. The following summary will be provided, by treatment group and overall:

DiPALS statistical analysis plan version 1.0 FINAL

<i>Attrition, compliance and analysis sets</i>	The number and percentage of patients who <ol style="list-style-type: none"> a. complete each visit b. are lost to follow-up c. do not receive their allocated treatment or switch treatment d. are in each analysis population as defined in 2.3
--	---

During the recruitment and follow-up periods, the following summaries will be made available to members of the TMG, TSC and DMEC.

<i>Data completeness</i>	The number of patients with complete data for each key parameter, by centre.
--------------------------	--

The inclusion of key parameters may be allowed to vary at the request of the TMG, TSC or DMEC during the trial. In order to allow time for data to be entered onto the system, data items will be considered complete if they have been entered within 30 days of scheduled visit date, and otherwise incomplete.

Demographics and baseline characteristics

The following summaries will be presented:

<i>Demographics and vital signs</i>	Centre, Age, gender, ethnic category, height, weight.
<i>MND characteristics</i>	Duration of MND symptoms, type of onset, site of onset, El Escorial diagnosis, bulbar function, ALSFRS _r
<i>Baseline severity</i>	FVC, Supine VC, SNIP, PaCO ₂ , and the number and percentage of patients with respiratory insufficiency, unacceptable phrenic nerve function, ECG abnormality, and blood test abnormality
<i>Physical examination</i>	The number of patients with abnormalities in each body system
<i>Medical history</i>	The number of patients with each medical history, past or present
<i>Pre-operative checks and surgery details</i>	The number and percentage of patients who meet checks for surgery at initial assessment, at repeat assessment, and who fail and are withdrawn by reason (parameter not met); the number and percentage of patients where DP was not fitted because diaphragm could not be stimulated; the number and percentage of patients with complications (by reason); and the number and percentage of patients with a surgical AE (DP only)

In addition, the following by-patient line listing will be provided:

<i>Surgical complications</i>	A list of all surgical complications recorded
-------------------------------	---

Efficacy

Primary endpoint

The primary efficacy endpoint will be overall survival, defined as the duration from randomisation to death of any cause.

The following summaries will be presented:

DiPALS statistical analysis plan version 1.0 FINAL

<i>Overall survival</i>	A comparison of the overall survival by treatment group.
<i>Overall survival by NIV tolerance</i>	A comparison of the overall survival by treatment group and by NIV tolerance subgroup (tolerant versus intolerant)
<i>Overall survival by bulbar function</i>	A comparison of the overall survival by treatment group and by bulbar function subgroup (mild/moderate versus severe)

NIV tolerance is defined in section 3.5.2 and bulbar function is defined in section 4.3.

Analysis will be undertaken by Cox proportional hazards (PH) regression, with covariates including treatment group and the minimisation factors. The model fit will be assessed as described in section 4.4. Kaplan-Meier survival curves will be presented overall and for each subgroup. Differences in survivorship between subgroups will be tested by inclusion of the covariate in the model along with treatment group. Differences in the effect of treatment between subgroups will be tested using an interaction term between the two.

Secondary outcomes

Patient health utility and QoL

The patient will complete EQ-5D and EQ-5D VAS at six time points (screening, 2, 3, 6, 9 and 12 months), and the SAQLI and SF-36 questionnaires at five time points (screening, 2, 3, 6 and 12 months).

EQ-5D and EQ-5D VAS

Both will all be analysed in four ways as described below:

1. All patients, at end of follow-up: A change from baseline to 12-month analysis (all patients; deaths imputed with worst-case).
2. All patients, longitudinal analysis: A repeated measures analysis, in which the trajectory across time is modelled. This will include all patients, including those who die; deaths will have values imputed with death state case (zero) for both EQ-5D and EQ-5D VAS.
3. Survivors, at end of follow-up: A change from baseline to 12-month analysis (surviving patients only)
4. Survivors, longitudinal analysis: A repeated measures analysis, in which the trajectory across time is modelled (surviving patients only).

The 12-month change in EQ-5D and EQ-5D VAS will be compared between groups using analysis of covariance (ANCOVA) in which the treatment group and the baseline score are included as covariates along with minimisation factors. Repeated measures analyses will be undertaken using a generalised least squares model repeated measures ANCOVA with the same covariates.

DiPALS statistical analysis plan version 1.0 FINAL

EQ-5D and EQ-5D VAS will be summarised as described in 3.1 (QoL outcomes), with the following summaries presented:

<i>Health utility, all patients</i>	EQ-5D and EQ-5D VAS
<i>Health utility, survivors</i>	EQ-5D and EQ-5D VAS

The 12-month change in EQ-5D and EQ-5D VAS will be compared between groups using analysis of covariance (ANCOVA) in which the treatment group and the baseline score are included as covariates along with minimisation factors. Repeated measures analyses will be undertaken using a generalised least squares model repeated measures ANCOVA with the same covariates. The model will use an exchangeable correlation matrix structure, and fit of this model will be tested against an unstructured model (and potentially other alternatives) using Hausman's test.

EQ-5D will be further reported by subgroups (NIV tolerance and bulbar function). Testing for differential treatment effect between subgroups would necessitate a 3-way interaction (treatment group x subgroup x time), which given the sample size would produce potentially unstable coefficients. Therefore, the focus here will be on within-group summary statistics and graphical displays, separately by treatment group.

SF-36

The SF-36 will be used to calculate 8 scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, social functioning and role-emotional) and 2 component summary measures (physical health and mental health). Each of the domains will be rescaled to be between 0-100. All 10 summary measures will be summarised by time, but the longitudinal modelling will only be applied to physical and mental health. Unlike EQ-5D, summaries will comprise only patients who are alive at each time point.

The following will be presented:

<i>SF-36</i>	SF-36 domains by time point
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The analysis strategy will match that of the EQ-5D.

SAQLI

This one-domain questionnaire will be analysed in the same manner as SF-36 physical and mental health domains.

Carer QoL

The patient's main carer will complete EQ-5D and EQ-5D VAS at six time points (screening, 2, 3, 6, 9 and 12 months), and the CBI at five time points (screening, 2, 3, 6 and 12 months).

EQ-5D

DiPALS statistical analysis plan version 1.0 FINAL

Where the patient has a nominated carer, they will complete the EQ-5D and EQ-5D VAS at the same time points as the patient. Analysis will be as for patient EQ-5D survivors only: no attempt will be made to impute carer EQ-5D for whom the patient has died.

CBI

This one-domain questionnaire will be analysed in the same manner as carer EQ-5D.

DiPALS statistical analysis plan version 1.0 FINAL

Admissions / resource

The following will be presented by timepoint visit among patients for whom complete diary data are available:

<i>Resource use</i>	<p>The number and percentage of patients having each of the following, and the number and percentage of episodes of each:</p> <p>1) Services</p> <ul style="list-style-type: none"> - hospital admission (with duration) - emergency department attendance - minor injury clinic or walk in centre - general practitioner referral <p>2) Devices</p> <ul style="list-style-type: none"> - use of CoughAssist - use of Breath-Stacking - use of suction <p>3) Health and social care</p> <ul style="list-style-type: none"> - physiotherapist (home visit, outpatient visit) - occupational therapist (home visit, outpatient visit) - other (home visit, outpatient visit) <p>4) Additional care/support</p> <ul style="list-style-type: none"> - formal (e.g. home help) - informal (e.g. family/friends)
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Safety outcomes

Compliance and machine settings (diaphragm pacing)

Compliance and machine settings for both NIV and DP will be collected in and summarised for in each assessment period separately. Assessments are carried out at baseline, 1 week post-surgery (DP group only), and at months 2,3,6,9 and 12. Compliance will be reported by time period between these visits, i.e. 0-2 months, 2-3 months, 3-6 months, 6-9 months and 9-12 months.

The following summaries will be provided, for the DP group only:

<i>DP usage</i>	The number and percentage of DP users and average DP usage, by time period
<i>DP parameter settings</i>	The number and percentage of patients with one or more channel X within each time period; and a summary of each parameter (amplitude, pulse, respiratory rate, inspiratory interval, pulse frequency and pulse ramp) for each channel, and for each parameter the percentage of patients whose parameters changed, within each time period

Patients are defined as DP compliant if their DP usage has reached at least 4 hours per day one month after implantation. The percentage of users in each time period will be defined as

Percentage of DP users =
 $100 \times \text{number of DP compliant patients in time period} / \text{number of patients alive at end of time period.}$

DiPALS statistical analysis plan version 1.0 FINAL

Compliance and machine settings (NIV)

The following summaries will be presented:

<i>NIV usage</i>	The number and percentage of patients who are NIV compliant, average NIV usage and percentage of target usage, by time period
<i>NIV parameter settings</i>	A summary of each parameter (minimum volume assured pressure support, maximum volume assured pressure support, inspiratory positive airways pressure, expiratory positive airways pressure, target tidal volume, respiratory rate, type of machine, type of mask, and humidification), and for each parameter the percentage of patients whose parameters changed, within each time period

NIV compliance is reported by time period defined identically to DP (above) Patients are defined as NIV compliant within a time period if their NIV usage is at least 4 hours per night. The percentage of users will be defined as

Percentage of NIV users =
 $100 \times \text{Number of NIV compliant patients in time period} / \text{number of patients alive at end of time period}$

Percentage of target time used will be defined *among users only* as

Percentage of target usage achieved =
 $100 \times \text{average use in time period} / \text{target usage within period}$

In addition, the following by-patient line-listing will be presented:

<i>Device technical issues</i>	Reported technical problems or other observations on DP and/or NIV, by time period
--------------------------------	--

Adverse events

The safety and tolerability profiles will be reported by analysing the proportion of patients experiencing adverse outcomes. The following summaries will be presented:

<i>AEs</i>	The number and percentage of patients reporting an AE, by type
<i>Serious AEs (SAEs)</i>	The number and percentage of patients reporting an SAE, by type
<i>Treatment-related AEs</i>	The number and percentage of patients reporting a DP-related AE, by type The number and percentage of patients reporting a NIV-related AE, by type

“Related” will be defined as those AEs recorded as definite, probable or possible.

The following by-patient line listings will be presented:

<i>All AEs</i>	A listing of all AEs including <ul style="list-style-type: none"> - Treatment group (if the patient switches treatment groups, details will be included)
----------------	--

DiPALS statistical analysis plan version 1.0 FINAL

	<ul style="list-style-type: none"> - Description - Days from treatment commencement to AE onset (if patient switches treatment group, this will be the most recent treatment) - Severity - Relationship - Outcome - Seriousness
<i>All SAEs</i>	A listing of all SAEs (as “all AEs” with the omission of “serious”)
<i>All treatment-related AEs</i>	A listing of all treatment-related AEs (as “all AEs” with the omission of “relationship”)

Concomitant medications

The following summary will be presented

<i>Concomitant medication</i>	The number and percentage of patients taking each medication
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Detailed statistical methods and calculations

General considerations

4.1.1 Number and timing of analyses – adjustment for multiplicity

The study may stop prematurely on grounds of safety or futility. However, no formal interim analyses will be performed for efficacy, and consequently no adjustment for multiplicity will be made to the significance levels.

4.1.2 Missing, spurious and unused data

Missing data is not expected for the primary outcome (overall survival). If the patient is lost to follow-up, their survival time will be censored at the date last known alive. For the questionnaire-based QoL outcomes, missing data may arise at any timepoint in one of four ways:

- 1) Questionnaire not completed, patient has died
- 2) Questionnaire completed but not in the correct time frame (i.e. outside visit window)
- 3) Questionnaire incomplete (some questions missing)
- 4) Questionnaire not returned (all questions missing)

1) is addressed in section 3.4.2.

2) will be handled by imposing the following visit windows:

Time point	Lower limit	Upper limit
Screening	No limit	Date of randomisation
2 months	Date of randomisation	75 days post randomisation [2 months + 15 days]
3 months	76 days post randomisation	135 days post randomisation [3 + 1.5 months]
6 months	136 days post	225 days post randomisation [6 + 1.5 months]

DiPALS statistical analysis plan version 1.0 FINAL

9 months	randomisation 226 days	post	315 days post randomisation [9 + 1.5 months]
12 months	randomisation 316 days	post	405 days post randomisation [12 + 1.5 months]

Scenario 3) is covered in the individual sections below.

For scenario 4), the same approach will apply to all questionnaires:

- i) If the questionnaire from an adjacent visit falls within the visit window, use this value.
- ii) If i) has not imputed a value, but values are available both before and afterwards, this will be imputed using the trapezoid method:

$$Q_t = [Q_1 \times (t_2 - t) + Q_2 \times (t - t_1)] / (t_2 - t_1)$$

Where

Q_t is the imputed quality of life at time t

(t_1, t_2) are the time points immediately prior to and following time t ($t_1 < t < t_2$) at which valid responses exist

Q_1 and Q_2 are the responses at times t_1 and t_2 .

Illustration

Suppose a patient has data as follows, for which approaches 1), 2), 3) and 4i) have not dealt with.

Time point	EQ-5D
2 months	0.7
3 months	missing
6 months	0.5

The missing value is then calculated by

$$\text{EQ-5D at } t=3 = [0.7 \times (6-3) + 0.5 \times (3-2)] / (6-2) = [0.7 \times 3 + 0.5 \times 1] / 4 = 0.65$$

- iii) If missing data still persist, there is no consensus of how to proceed. Since MND is a deteriorating condition the use of last observation carried forward will lead to an overestimation of QoL and, depending on the drop-out patterns between the two groups, a potentially biased comparison (see, for example Saha and Jones 2009 7). Other approaches, such as multiple imputation or group mean imputation among survivors, have their own advantages and disadvantages. At the time of writing, research is ongoing within SCHARR to assess approaches to precisely this problem. The preliminary report is expected in late 2011, and an amendment to the analysis plan will be made in 2012 to cover this in more detail.

4.1.3 Analysis sets

DiPALS statistical analysis plan version 1.0 FINAL

The ITT will be the primary analysis population for effectiveness outcomes, with the results for the PP being supportive of it. If for any endpoint the populations confer inconsistent results, further analyses will attempt to investigate the reason for this.

4.1.4 Methods for dealing with multi-centre data

The consistency of outcomes among the treatment centres will be assessed by fitting a model which includes an interaction between treatment group and centre. If the test for interaction is not statistically significant the interaction term will be removed. If significant differences are found, further analyses will be undertaken to assess whether this may be due to differences in case mix (i.e. an artefactual centre effect) or not (i.e. real centre effect).

Disposition and data completeness

Recruitment data, data completeness and patient demographic & characteristics will be reported to the TSC, DMEC and TMG in an ongoing fashion.

Demographics and baseline patient characteristics

The baseline date is the date of randomisation. The centre will be defined as the centre at which the patient first attended. Age is defined as (date of baseline – date of birth).

ALSFR is a one-domain questionnaire comprising 24 questions, each of which is scored from 0-4. The overall score is the sum of these. If the questionnaire is incomplete but at least half of the questions answered (i.e. at least 12 of the 24), the overall score will be multiplied up by the formula

Overall score = (24 / Number of questions answered) x (total score among answered questions)

If fewer than 12 questions are answered, the questionnaire will be treated as missing and will not be used in summaries.

The bulbar function score is calculated from the ALSFRS-r. The answers to the first three questions (speech, swallowing and salivation) are summed, and the bulbar function is categorised from this sum into the following: mild (0-4), moderate (5-8) and severe (9-12).

Efficacy

Primary endpoint

The primary endpoint is overall survival, defined as the time between randomisation and death. If no notification of death has been received, the patient will be censored at the date last known alive.

Pre-trial modelling, undertaken at the proposal development stage, found PH to be the best fit to previous data, and therefore a Cox PH regression model will be fitted with ties handled by the Efron method. The PH assumption will be checked by adding time-dependent covariates and graphing scaled Schoenfeld residuals against time.⁸ If PH is found not to fit the data adequately, an AFT alternative will be fitted and the adequacy of its fit assessed using Q-Q plots.⁹ If this too does not fit, a residual life analysis¹⁰ will be used as the basis for summarising the treatment effect

DiPALS statistical analysis plan version 1.0 FINAL

Secondary endpoints

SAQLI (Sleep Apnoea Quality of Life Index)

SAQLI is a one-domain questionnaire comprising 14 questions, each of which is scored from 1-7. The overall score is the average of these. If the questionnaire is incomplete (i.e. less than 14 questions are answered), the overall score will be defined as the average provided at least half of the questions (7 of the 14) have been answered. If fewer than 7 questions are answered, the questionnaire will be treated as missing; no further imputation will be undertaken.

SF-36

Version 1 of the SF-36 will be used. The domain scores will be calculated using the standard RAND organisation algorithm.

CBI

CBI is a one-domain questionnaire comprising 24 questions, each of which is scored from 0-4. The overall score is the total of these. Incomplete questionnaires will be handled in the same manner as SAQLI

Safety

The DP and NIV usage will be based on the values recorded in the CRF, which are in turn estimated from the patient diary. Additional exploratory analyses using the diary usage data may also be undertaken but are not described here.

For each AE, the report will comprise the number and percentage of patients affected, and the number of events (a patient may have more than one occurrence of the same AE)

Modifications to the original protocol analysis statement

Not applicable.

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DiPALS statistical analysis plan version 1.0 FINAL

Statistical analysis plan – after data was unblinded



Sheffield Teaching Hospitals **NHS**
NHS Foundation Trust



A randomised controlled trial in patients with Respiratory Muscle Weakness due to Motor Neurone Disease of the NeuRx/4 Diaphragm Pacing Trial

Statistical analysis plan version 2.0 Incorporating amendment 1, 18 November 2014

Authored by

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DiPALS statistical analysis plan version 1.0 FINAL

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List of abbreviations used

AE	Adverse event
ALS	amyotrophic lateral sclerosis
ANCOVA	Analysis of Covariance
CI	confidence interval
CTRU	University of Sheffield Clinical Trial Research Unit
DMEC	Data Monitoring and Ethics Committee
DP	Diaphragm pacing
EQ-5D	EuroQol health utility questionnaire
FVC	forced vital capacity
GCP	Good Clinical Practice
ITT	intent-to-treat
MND	Motor neurone disease
NIV	non invasive ventilation
PEG	Percutaneous endoscopic gastrostomy
PH	Proportional hazards
PIG	Per-oral image guided gastrostomy
PP	per-protocol
QoL	Quality of life
SAE	Serious adverse event
SAQLI	sleep apnoea quality of life index
SF-36	Short form-36 questionnaire
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Introduction, study design and key trial objectives

Study outline

The DiPALS study is a two-arm, parallel group, open-label randomised controlled clinical trial in patients with motor neurone disease (ALS) or amyotrophic lateral sclerosis (ALS) with respiratory muscle weakness. Patients will be allocated to either non invasive ventilation (NIV) with diaphragm pacing (DP), or to NIV alone. NIV alone is the current standard care, and is the control group.

This statistical analysis plan is written in conjunction with the International Conference on Harmonisation topic E9 (Statistical principles for clinical trials, 1998),³³ applicable standard operating procedures from the University of Sheffield Clinical Trials Research Unit (CTRU) and trial documents referenced in section 6. The trial will be conducted in accordance with Good Clinical Practice (GCP) in Clinical Trials (International Conference on Harmonisation, 1996).³⁴

Outcome measures

The primary objective of this trial will be to evaluate the effect of DP on overall survival.

Secondary objectives will be to evaluate the effect of DP on the following:

- Quality adjusted life years (QALYs, not covered in this document)
- Quality of life: sleep apnoea quality of life index (SAQLI), and the Short Form-36 (SF-36) version 1.
- Quality of life of the main carer, measured by Caregiver Burden Inventory (CBI).
- Safety and tolerability.
- Health economic objectives and resource use (not covered in this document).
- Qualitative user perspectives (not covered in this document).

Randomisation

Patients will be allocated to their treatment by minimisation which is carried out via a web-based interface hosted by the CTRU. The minimisation factors are baseline bulbar function (mild, moderate, severe), forced vital capacity (FVC) at baseline (50-59%, 60-69%, 70+%), age (<=39, 40-79, 80+) and sex. Interim analyses, data monitoring committee, and early termination of DiPALS

Trial governance committees

Three committees will be established to govern the conduct of this study:

- Trial Steering Committee (TSC)
- Independent Data Monitoring and Ethics Committee (DMEC)
- Trial Management Group (TMG)

Periodic efficacy and safety analyses will be provided to the DMEC. These summaries were originally envisaged as semi-blinded summaries with the treatment groups labelled as “A” and “B”, but the DMEC subsequently exercised their discretion to see fully unblinded summaries. The TSC and TMG have seen overall results only and remain blinded.

Early stopping

In December 2013 the DMEC recommended that recruitment to DiPALS should cease on safety grounds, citing a discrepancy in survival between the two arms. In summary, they recommended that:

Recruitment should be suspended with immediate effect

Implantation of new pacing devices be suspended

Other aspects of the trial remain unaltered; in particular, that patients in the pacing arm should be encouraged to continue using their device.

In doing so, they acknowledged the sample size was relatively small (74 randomised, 24 deaths at the point of this recommendation), and that their decision would be reviewed as additional data became available. Their recommendations were upheld by the TSC, who requested the DMEC step up the frequency of their meetings to every three months.

The recommendation to formally stop recruitment was made by the DMEC in June 2014. This time, their recommendations went further:

That participants in the pacing arm be informed of the concern and advised to cease use of their device forthwith (unless the patient and their clinician believed there were just grounds to do otherwise).

That the trial follow-up continue until all participants had either died or completed 12 month follow-up

That the TSC and the trial team remain blind to the outcome data until this time.

The recommendation was accepted by the TSC, with the exception of the last point. The independent TSC members voted unanimously that some preliminary results be presented before the end of follow-up (expected to be December 2014). Although unusual, the reasons for this were that: the safety concern should not be withheld from a wider audience; the pacing device was becoming more widely used; and the information given to trial patients as above had revealed the concern about pacing to the ALS community. They believed there was good ethical reason to present preliminary data to the ALS community at the major annual international conference in December 2014. The DMEC subsequently agreed to this.

The scope of the interim analysis on preliminary data is outlined in section 3.6. At present, the DMEC and the responsible CTRU statistician remain the only persons to have seen unblinded outcome data.

Wider context: other studies of DP and ALS

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Although the specific details (and unblinded data) remain confidential at this stage, the DMEC have indicated survival in the pacing arm is inferior to the control group. A natural follow-on from this is to attempt to reconcile the disparity between our findings and those which were submitted to (and approved by) the FDA. Unusually, the license for DP was granted on the basis of a relatively small, non-randomised cohort of patients with ALS with respiratory failure (“the FDA cohort”), recognising the rarity of the condition and the lack of curative therapies. A part of the analysis will be to compare – informally – the DiPALS trial data against the FDA cohort with a view to understanding the reasons behind the apparently different outcomes.

At present there are no randomised trials of DP in this therapeutic area, although one is planned; a second (albeit in ALS without respiratory failure) is currently ongoing. There is a possibility of future analyses combining data from these studies: these are not covered here.

Sample size calculation

The sample size calculation was based on log-rank test, using Simpson’s rule¹⁸ as implemented in Stata version 11.1¹⁹ to allow for the unequal length of follow-up. The study duration comprises an 18-month recruitment period and a 12-month follow-up period, giving a maximum follow-up of 30 months and a minimum of 12 months. Assuming control group survival proportions of 45%, 20% and 10% at the minimum, average and maximum follow-up times respectively, a hazard ratio of 0.45 and an additional 10% loss-to-follow-up, a total of 108 patients (54 per group) are needed to ensure a power of 85% using a two-sided type I error of 5%. The control group figures are conservative estimates based on the sole randomised controlled trial of NIV, which is now considered standard care in the UK. A study carried out in the United States and France (the aforementioned “FDA cohort”) has estimated a one year survival of 86% after study entry for patients using DP and NIV. We have estimated the sample size on a conservative (but clinically important) 1-year difference in survival of 45% versus 70%, which produces the estimated hazard ratio of 0.45. It is anticipated that we will have complete survival data on all subjects recruited, based on previous experience in ALS trials.

With regard to quality of life data we anticipate a low level of missing data due to loss to follow up. We have reviewed the patients who were initiated on NIV in the year up to Jun 2009 and we have maintained contact with 100% of those patients surviving at 12 months. The appointment of a research nurse at each study site will enable home visits if necessary to collect the quality of life data. We have however allowed for a 10% loss to follow up in the sample size/power calculation.

Data sources, data and analysis populations

Data sources

The data used in this study will come from data entered onto the following sources:

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Case Report Form (CRF) version 3, 4 December 2013

Screening log version 1, 26 October 2011

NIV group patient diary version 2, 3 August 2011

DP group patient diary version 2, 3 August 2011

The database will be stored on the CTRU database (PROSPECT) with the exception of the randomisation list which is held on the CTRU's randomisation system. Electronic data will be extracted from the system during the trial for the purpose of checking (validating) and trial progress reports; however, access to any data which would unblind the study (randomised group, resource usage) will be limited to the CTRU data management team, CTRU trial statistician and members independent of the trial (DMEC). Personal records will not be made available to CTRU staff.

Protocol Deviations

The following will be classified as protocol deviations in the statistical analysis: Patients who are randomised in error (any of the inclusion/exclusion criteria are breached)

Patients who do not tolerate NIV

(DP group only) Patients who do not have a successful DP implantation

(DP group only) Patients who do not use DP

The above criteria will be used in explanatory analyses. All are objective criteria which will be determined from the clinical database and verified by the CI at database lock and before analysis is undertaken. Criteria 2 will also be used as a basis for subgroup analyses.

Analysis populations

Three analysis sets will be used:

Name	Patients included	Treatment group
Intent-to-Treat (ITT)	All patients for whom consent is obtained and who are randomised into the trial	As randomised
Per Protocol (PP)	The subset of the ITT patients who do not violate the protocol, as defined in section 2.2.	As randomised
Safety	All patients who proceed to NIV, with or without DP	As treated

All summaries will be based on the ITT set, with the following exceptions: Effectiveness analyses will also be undertaken on the PP set. Additional analyses to assess the impact of adherence, for example complier-average causal effect (CACE) methodology, may also be undertaken if there are a substantial number of withdrawals from treatment or crossing between groups.

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Analysis of adverse events (AEs) will be undertaken on both the ITT and safety sets. In the latter, patients will be analysed by the treatment they were using at the point of the adverse event.

Outline of analyses

General considerations

Data will be reported and presented according to the revised CONSORT statement.^{16,35}

Complete details of data derivations and methods of handling multiplicity, multi-centre data and missing data are covered in section 4. No interim analyses or early stopping are planned.

All summaries will be provided on the full analysis set using an intention to treat (ITT) approach. If loss-to-follow-up and/or treatment crossover is greater than 5%, sensitivity analyses will be performed to assess the robustness of the results. If important discordances are observed between these and the ITT approach, both analyses will be reported.

All summary tables will present summary statistics within each treatment group and overall unless stated otherwise.

Summaries of continuous variables will comprise the number of observations used and either

- i) mean, standard deviation, median, minimum and maximum, or
- ii) median, inter-quartile range, minimum and maximum as appropriate for the distributional form of the data.

Summaries of categorical variables will comprise the number of observations used, and the number and percentage of observations in each category.

Summaries of time-to-event outcome data will comprise the median and inter-quartile range of survival within each group, the hazard ratio and its 95% confidence interval.

Summaries of QoL outcomes will comprise the following:

A summary (mean, standard deviation, median, minimum and maximum) of the QoL, by treatment group and time point.

The least squared mean QoL change from baseline at each time point, together with its standard error, by treatment group and time point.

The least squared mean difference between treatment groups, together with its 95% confidence interval and p-value, by time point

The overall comparison between the treatment groups, together with its 95% confidence interval and p-value, and a test for interaction between treatment group and time. Both are based on longitudinal modelling.

DiPALS statistical analysis plan version 2 FINAL including amendment 1

All treatment comparisons will use the NIV only group as the reference (comparator), all statistical exploratory tests of main effects will be two-tailed with $\alpha = 0.05$; and all confidence intervals (CIs) will be two-sided, 95% intervals. As there is controversy with regards to the operating characteristics of minimisation, a permutation test will be used to confirm the p-value from the primary endpoint.²⁵ Since interaction tests have low statistical power, additional consideration will be given to p-values below 0.1 when testing interactions (treatment x centre and treatment x subgroups).

Disposition and data completeness

The following summary will be presented for all patients screened for entry to the study, by centre and overall:

<i>Enrolment</i>	The "CONSORT" diagram comprising the number of people screened, eligible, consented, randomised, receiving their allocated treatment, withdrawing/lost to follow-up, and included in ITT and PP analysis sets.
<i>Characteristics of non-enrolled patients</i>	The age, gender and reason for non-inclusion.

In addition the following by-patient line-listings will be provided

<i>Reasons for non-randomisation</i>	For people screened but not randomised: A list of reasons for non-recruitment (any/all that apply) A list of reasons for non-consent
<i>Reasons for non-implantation</i>	For people allocated pacing device: A list of reason(s) for not proceeding with surgery (FVC not acceptable, failure of pre-operative checks, withdrawal, unable to stimulate diaphragm, others)

The inclusion of patients in each analysis population is outlined in section 2.3. Where the randomised intervention (as recorded on the randomisation list) differs from the intervention group as recorded on the case record form, the randomisation list will be assumed to be the correct data source. The following summary will be provided, by treatment group and overall:

<i>Attrition, adherence and analysis sets</i>	The number and percentage of patients who complete each visit are lost to follow-up do not receive their allocated treatment or switch treatment are in each analysis population as defined in 2.3
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During the recruitment and follow-up periods, the following summaries will be made available to members of the TMG, TSC and DMEC.

DiPALS statistical analysis plan version 2 FINAL including amendment 1

<i>Data completeness</i>	The number of patients with complete data for each key parameter, by centre.
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The inclusion of key parameters may be allowed to vary at the request of the TMG, TSC or DMEC during the trial. In order to allow time for data to be entered onto the system, data items will be considered complete if they have been entered within 30 days of scheduled visit date, and otherwise incomplete. Demographics and baseline characteristics

The following summaries will be presented:

<i>Demographics and vital signs</i>	Centre, Age, gender, ethnic category, height, weight.
<i>ALS characteristics</i>	Duration of ALS symptoms, type of onset, site of onset, El Escorial diagnosis, bulbar function, ALSFRS _r
<i>Baseline severity</i>	FVC, Supine VC, SNIP, PaCO ₂ , and the number and percentage of patients with respiratory insufficiency, unacceptable phrenic nerve function, ECG abnormality, and blood test abnormality
<i>Physical examination</i>	The number of patients with abnormalities in each body system
<i>Medical history</i>	The number of patients with each medical history, past or present
<i>Pre-operative checks and surgery details</i>	The number and percentage of patients who meet checks for surgery at initial assessment, at repeat assessment, and who fail and are withdrawn by reason (parameter not met); the number and percentage of patients where DP was not fitted because diaphragm could not be stimulated; the number and percentage of patients with complications (by reason); and the number and percentage of patients with a surgical AE (DP only)

In addition, the following by-patient line listing will be provided:

<i>Surgical complications</i>	A list of all surgical complications recorded
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Efficacy

Primary endpoint

The primary efficacy endpoint will be overall survival, defined as the duration from randomisation to death of any cause.

Primary overall survival analyses

The following summaries will be presented:

<i>Overall survival</i>	A comparison of the overall survival by treatment group.
<i>Overall</i>	A comparison of the overall survival by treatment group and by

<i>survival by NIV tolerance</i>	NIV tolerance subgroup (tolerant versus intolerant).
<i>Overall survival by bulbar function</i>	A comparison of the overall survival by treatment group and by bulbar function subgroup (mild/moderate versus severe)
<i>Overall survival – per protocol population</i>	A comparison of the overall survival by treatment group, with protocol deviations removed.

Note that NIV tolerance is a key subgroup as written in the protocol. In this context, “NIV tolerance” relates to NIV usage; “tolerant” is taken to mean “adherent” or “compliant”, whilst “intolerant”, “non-adherent” and “non-compliant” all suggest “non-usage”.

For the remainder of this SAP the terms “use” or “usage” will be used when describing the extent to which participants use NIV (i.e. hours), whilst the term “adherence” will be termed to categorise NIV as binary (a subjective “yes or no” judgement). The same will be applied to DP usage in the intervention group. Specific details are provided in sections 3.5.2 and 4.5.1.1.

Bulbar function is defined in section 4.3.

Analysis will be undertaken by Cox proportional hazards (PH) regression, with covariates including treatment group and the minimisation factors. The model fit will be assessed as described in section 4.4. Kaplan-Meier survival curves will be presented overall and for each subgroup. Differences in survivorship between subgroups will be tested by inclusion of the covariate in the model along with treatment group. Differences in the effect of treatment between subgroups will be tested using an interaction term between the two

Supportive overall survival analyses – relationship to adherence

Supportive overall survival analyses – relationship to adherence

In light of the early stopping, additional exploratory (observational) analyses will be performed to better understand the mechanism of pacing.

Kaplan-Meier survival curves will be presented overall and for each subgroup listed below. Differences in survivorship between subgroups will be tested by inclusion of the covariate in a Cox proportional hazards model. These analyses are in addition to the pre-planned analyses according NIV adherence (tolerance) and overall protocol compliance (per-protocol) set out above.

<i>Overall survival by NIV adherence and DP adherence</i>	Analysis 1: Comparison of the overall survival in three subgroups: Adherent to pacing (participants randomised to DP)
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DiPALS statistical analysis plan version 2 FINAL including amendment 1

	<p>Not adherent to pacing (participants randomised to DP group only) Control group (participants randomised to NIV group only) Rationale: to help assess whether non-users of DP are have the same survival as those who use DP</p> <p>Analysis 2: Comparison of survival in three subgroups NIV-adherent patients (DP group only) Non NIV-adherent patients (DP group only) Control group Rationale: this will assess the association between NIV compliance and outcomes in DP participants. One plausible mechanism is that DP participants were using DP in place of NIV.</p>
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Differences in survivorship will be investigated by inclusion of the usage as a covariate in a Cox proportional hazards model.

<i>Overall survival by typical NIV use</i>	A comparison of the overall survival by treatment group, including a covariate of the number of hours of typical NIV usage in the first i) 3 months and ii) 6 months. This will entail including NIV use in hours as a) a continuous measure and b) by categories.
<i>Overall survival by typical DP use</i>	A comparison of the overall survival including a covariate of the number of hours of typical DP usage in the first i) 3 months and ii) 6 months. This will entail including DP use in hours as a) a continuous measure and b) by categories

The relationship between NIV and DP usage by time point will also be assessed and reported graphically. Since the relationship between typical adherence (in hours) and survival is not expected to be linear, fractional polynomials will be used to assess the fits of quadratic and other non-linear relationships.²⁴ Finally, usage will be defined in categories. For NIV we will follow the approach of Kleopa et al (1999),¹³ who characterised participants as non-adherent (typical usage below 1 hour per day), low-adherent (typical usage 1 to less than 4 hours per day) and good-adherence (typically 4 or more hours per day). Adherence to pacing will also be categorised, but here there is no equivalent published data defining low and good adherence for pacing and so the cutpoints will need adjudication. However, since target usage for pacing on this study is generally lower than NIV target usage in this study, the cutpoints used for low- and good-adherence will be in the region of 1 and 3 hours respectively.

A key question is whether the assessment of adherence should start from randomisation or from first use. Both may be viewed as being of interest, and so exploratory analyses will take adherence as i) starting at randomisation

DiPALS statistical analysis plan version 2 FINAL including amendment 1

(adherence being zero in this period) and ii) starting at initiation (for NIV) or surgery (for pacing).

Participants whose NIV or DP adherence cannot be determined will be excluded from these exploratory analyses.

In doing this, the small number of participants is recognised. Conclusions will be tempered by this limitation, and also the post-hoc nature of the analyses. Nevertheless, given the circumstances of the trial termination there is sufficient interest in this for it to be justified.

Supportive overall survival analyses – analyses at the point of DMEC intervention

The overall survival will also be reported as of the point at which the DMEC made the decision to i) suspend the trial; ii) terminate the trial with advice to stop pacing. In both of these analyses, participants who were randomised to pacing but did not receive it as a result of the DMEC decision (two patients) will be excluded.

Supportive overall survival analyses – tracheostomy free survival

Finally, since “Tracheostomy-free survival” is considered an important outcome, we will look at the incidence of tracheostomy. Tracheostomy-free survival is defined as the time from randomisation to tracheostomy or death, whichever occurs first. However, at the time of writing, no tracheostomies have been performed within the DiPALS trial.

Secondary outcomes
Patient health utility and QoL

The patient will complete EQ-5D and EQ-5D VAS at six time points (screening, 2, 3, 6, 9 and 12 months), and the SAQLI and SF-36 questionnaires at five time points (screening, 2, 3, 6 and 12 months).

EQ-5D and EQ-5D VAS

Both will all be analysed in four ways as described below:

All patients, at end of follow-up: A change from baseline to 12-month analysis (all patients; deaths imputed with worst-case).

All patients, longitudinal analysis: A repeated measures analysis, in which the trajectory across time is modelled. This will include all patients, including those who die; deaths will have values imputed with death state case (zero) for both EQ-5D and EQ-5D VAS.

Survivors, at end of follow-up: A change from baseline to 12-month analysis (surviving patients only)

Survivors, longitudinal analysis: A repeated measures analysis, in which the trajectory across time is modelled (surviving patients only).

DiPALS statistical analysis plan version 2 FINAL including amendment 1

The 12-month change in EQ-5D and EQ-5D VAS will be compared between groups using analysis of covariance (ANCOVA) in which the treatment group and the baseline score are included as covariates along with minimisation factors. Repeated measures analyses will be undertaken using a generalised least squares model repeated measures ANCOVA with the same covariates.

EQ-5D and EQ-5D VAS will be summarised as described in 3.1 (QoL outcomes), with the following summaries presented:

<i>Health utility, all patients</i>	EQ-5D and EQ-5D VAS
<i>Health utility, survivors</i>	EQ-5D and EQ-5D VAS

The 12-month change in EQ-5D and EQ-5D VAS will be compared between groups using analysis of covariance (ANCOVA) in which the treatment group and the baseline score are included as covariates along with minimisation factors. Repeated measures analyses will be undertaken using a generalised least squares model repeated measures ANCOVA with the same covariates. The model will use an exchangeable correlation matrix structure, and fit of this model will be tested against an unstructured model (and potentially other alternatives) using Hausman's test.

EQ-5D will be further reported by subgroups (NIV tolerance and bulbar function). Testing for differential treatment effect between subgroups would necessitate a 3-way interaction (treatment group x subgroup x time), which given the sample size would produce potentially unstable coefficients. Therefore, the focus here will be on within-group summary statistics and graphical displays, separately by treatment group.

SF-36

The SF-36 will be used to calculate 8 scales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, social functioning and role-emotional) and 2 component summary measures (physical health and mental health). Each of the domains will be rescaled to be between 0-100. All 10 summary measures will be summarised by time, but the longitudinal modelling will only be applied to physical and mental health. Unlike EQ-5D, summaries will comprise only patients who are alive at each time point.

The following will be presented:

<i>SF-36</i>	SF-36 domains by time point
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DiPALS statistical analysis plan version 2 FINAL including amendment 1

The analysis strategy will match that of the EQ-5D.

SAQLI

This one-domain questionnaire will be analysed in the same manner as SF-36 physical and mental health domains.

Carer QoL

The patient's main carer will complete EQ-5D and EQ-5D VAS at six time points (screening, 2, 3, 6, 9 and 12 months), and the CBI at five time points (screening, 2, 3, 6 and 12 months).

EQ-5D

Where the patient has a nominated carer, they will complete the EQ-5D and EQ-5D VAS at the same time points as the patient. Analysis will be as for patient EQ-5D survivors only: no attempt will be made to impute carer EQ-5D for whom the patient has died.

CBI

This one-domain questionnaire will be analysed in the same manner as carer EQ-5D.

Admissions / resource

The following will be presented by timepoint visit among patients for whom complete diary data are available:

<i>Resource use</i>	<p>The number and percentage of patients having each of the following, and the number and percentage of episodes of each:</p> <p>1) Services hospital admission (with duration) emergency department attendance minor injury clinic or walk in centre general practitioner referral</p> <p>2) Devices use of CoughAssist use of Breath-Stacking use of suction</p> <p>3) Health and social care physiotherapist (home visit, outpatient visit) occupational therapist (home visit, outpatient visit) other (home visit, outpatient visit)</p> <p>4) Additional care/support formal (e.g. home help) informal (e.g. family/friends)</p>
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DiPALS statistical analysis plan version 2 FINAL including amendment 1

3.4.2.4 Additional outcomes: ALSFRS-r and respiratory function

In the light of the early stopping, the TSC requested additional respiratory function data to be collected to augment that which is already collected at baseline (and for DP, immediately pre-surgery). The following data is now collected: FVC, oxygen saturation, arterial carbon dioxide, SNIP, vital capacity and ALSFRS-r.

The ALSFRS-r score is derived from a questionnaire. In health, a score of 48 (the maximum) is expected, and consequently the overall rate of decline pre-baseline is given by

$(48 - \text{baseline ALSFRS-r score}) / (\text{Date of randomisation} - \text{Date of symptoms onset})$

The remaining five measurements are clinical measurements of lung function.

For each measure, the data will be used to address the following:

Provide summaries of the baseline function by group

Calculate the proportion of patients in the DP arm who decline between baseline and surgery

Respiratory function over time, particularly in relation to surgery for in the DP group.

The reasoning for these is are to assess the following aspects of the study:

To assess whether the groups are comparable. These differences should be small due the minimisation, but may imbalance may occur given the relatively small sample size.

To assess whether the extent to which DP patients decline over the period between randomisation and surgery, and an exploration of the association between this decline and survival. These findings will be compared with the aforementioned FDA cohort study.

n.b. An FVC between 50-75% (or equivalent on other tests) is an entry criteria for DiPALS, additionally, patients with FVC below 45% cannot undergo surgery. The FDA cohort used a similar criteria ($\leq 85\%$ at baseline and $>45\%$ at surgery), but unlike DiPALS excluded those who were never implanted.

The respiratory function over time may shed light on the mechanistic impact of DP in relation to control.

An important note is that problems will occur by virtue of missing data. Some centres do not standardly collect this, and the analyses will be restricted to those which do. More pertinent is the possibility that patients may be too ill to undergo tests; most obviously, the patient may have died. These limitations will not affect i) and will have minimal impact on ii), but iii) in particular will be compromised. Therefore, iii) will comprise mainly of graphical displays depicting change against time, with the date of NIV initiation, DP insertion, withdrawal and death superimposed.

Safety outcomes

Adherence and machine settings (diaphragm pacing)

Adherence and machine settings for both NIV and DP will be collected in and summarised for in each assessment period separately. Assessments are carried out at baseline, 1 week post-surgery (DP group only), and at months 2,3,6,9 and 12. Adherence will be reported by time period between these visits, i.e. 0-2 months, 2-3 months, 3-6 months, 6-9 months and 9-12 months.

The following summaries will be provided, for the DP group only:

<i>DP usage</i>	The number and percentage of DP users and average DP usage, by time period
<i>DP parameter settings</i>	The number and percentage of patients with one or more channel X within each time period; and a summary of each parameter (amplitude, pulse, respiratory rate, inspiratory interval, pulse frequency and pulse ramp) for each channel, and for each parameter the percentage of patients whose parameters changed, within each time period

The assessment of pacing adherence is detailed in section 4.5. Unlike NIV, there is no normative data or robust evidence to support a minimal “therapeutic dose” of pacing, and it is likely that several analyses of adherence will be proposed in addition to those outlined here.

The percentage of users in each time period will be defined as

Percentage of DP users =

$100 \times \text{number of DP adherent patients in time period} / \text{number of patients alive at end of time period.}$

Adherence and machine settings (NIV)

The following summaries will be presented:

<i>NIV usage</i>	The number and percentage of patients who are NIV adherent, average NIV usage by time period, and percentage of target usage, by time period
<i>NIV parameter settings</i>	A summary of each parameter (minimum volume assured pressure support, maximum volume assured pressure support, inspiratory positive airways pressure, expiratory positive airways pressure, target tidal volume, respiratory rate, type of machine, type of mask, and humidification), and for each parameter the percentage of patients whose parameters changed, within each time period

NIV adherence is reported by time period defined identically to DP (above). As a guideline, patients are defined as NIV adherent within a time period if their NIV usage is at least 4 hours per night; this will be adjudicated as set out in section 4.5. The percentage of users will be defined as

Percentage of NIV users =

DiPALS statistical analysis plan version 2 FINAL including amendment 1

100 x Number of NIV adherent patients in time period / number of patients alive at end of time period

Percentage of target time used will be defined *among users only* as

Percentage of target usage achieved =
100 x average use in time period / target usage within period

In addition, the following by-patient line-listing will be presented:

<i>Device technical issues</i>	Reported technical problems or other observations on DP and/or NIV, by time period
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NIV usage data will only be included from the point of NIV initiation onwards, but withdrawal or non-usage of NIV thereafter will be included (as zero).

Adverse events

The safety and tolerability profiles will be reported by analysing the proportion of patients experiencing adverse outcomes. The following summaries will be presented:

<i>AEs</i>	The number and percentage of patients reporting an AE, by type
<i>Serious AEs (SAEs)</i>	The number and percentage of patients reporting an SAE, by type
<i>Treatment-related AEs</i>	The number and percentage of patients reporting a DP-related AE, by type The number and percentage of patients reporting a NIV-related AE, by type

“Related” will be defined as those AEs recorded as definite, probable or possible.

The following by-patient line listings will be presented:

<i>All AEs</i>	A listing of all AEs including Treatment group (if the patient switches treatment groups, details will be included) Description Days from treatment commencement to AE onset (if patient switches treatment group, this will be the most recent treatment Severity Relationship Outcome Seriousness
<i>All SAEs</i>	A listing of all SAEs (as “all AEs” with the omission of “serious”)
<i>All treatment-related AEs</i>	A listing of all treatment-related AEs (as “all AEs” with the omission of “relationship”)

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Concomitant medications

The following summary will be presented

<i>Concomitant medication</i>	The number and percentage of patients taking each medication
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Interim analysis (December 2014)

Following the request of the TSC (see section 1.4.2), the following analyses will be produced for presentation at the 25th International Symposium on MND/ALS in December 2014:

Overall survival

DP and NIV adherence

The analysis will be undertaken using the database as of October 24th 2014. Site staff will be asked to enter all data pertaining to adherence and known deaths by October 17th 2014. Thereafter the database will be exported and the interim analysis commence. A copy of the database as used at this time will be retained, but data entry will continue until the end of study close date (anticipated December 2014).

These analyses will be descriptive rather than definitive, and will entail the following:

Overall survival: Kaplan-Meier survival curves, with hazard ratio as estimated based on a Cox regression model adjusted for minimisation covariates. Two additional, supportive analyses will be performed: i) logrank test (unadjusted), and ii) a Cox regression, stratified by treatment centre.

NIV adherence: the number and percentage of participants deemed adherent with NIV by time period and overall; and a summary of usage hours.

DP adherence: the number and percentage of participants deemed adherent with DP by time period and overall; and a summary of usage hours.

Detailed statistical methods and calculations

General considerations

Number and timing of analyses – adjustment for multiplicity

The study may stop prematurely on grounds of safety or futility. However, no formal interim analyses will be performed for efficacy, and consequently no adjustment for multiplicity will be made to the significance levels.

Missing, spurious and unused data

Missing data is not expected for the primary outcome (overall survival). If the patient is lost to follow-up, their survival time will be censored at the date last

DiPALS statistical analysis plan version 2 FINAL including amendment 1

known alive. For the questionnaire-based QoL outcomes, missing data may arise at any timepoint in one of four ways:

- Questionnaire not completed, patient has died
- Questionnaire completed but not in the correct time frame (i.e. outside visit window)
- Questionnaire incomplete (some questions missing)
- Questionnaire not returned (all questions missing)

1) is addressed in section 3.4.2.

2) will be handled by imposing the following visit windows:

Time point	Lower limit	Upper limit
Screening	No limit	Date of randomisation
2 months	Date of randomisation	75 days post randomisation [2 months + 15 days]
3 months	76 days post randomisation	135 days post randomisation [3 + 1.5 months]
6 months	136 days post randomisation	225 days post randomisation [6 + 1.5 months]
9 months	226 days post randomisation	315 days post randomisation [9 + 1.5 months]
12 months	316 days post randomisation	405 days post randomisation [12 + 1.5 months]

Scenario 3) is covered in the individual sections below.

For scenario 4), the same approach will apply to all questionnaires:

If the questionnaire from an adjacent visit falls within the visit window, use this value.

If i) has not imputed a value, but values are available both before and afterwards, this will be imputed using the trapezoid method:

$$Q_t = [Q_1 \times (t_2 - t) + Q_2 \times (t - t_1)] / (t_2 - t_1)$$

Where

Q_t is the imputed quality of life at time t

(t_1, t_2) are the time points immediately prior to and following time t ($t_1 < t < t_2$) at which valid responses exist

Q_1 and Q_2 are the responses at times t_1 and t_2 .

Illustration

Suppose a patient has data as follows, for which approaches 1), 2), 3) and 4i) have not dealt with.

Time point EQ-5D

DiPALS statistical analysis plan version 2 FINAL including amendment 1

2 months	0.7
3 months	missing
6 months	0.5

The missing value is then calculated by

$$EQ-5D \text{ at } t=3 = [0.7 \times (6-3) + 0.5 \times (3-2)] / (6-2) = [0.7 \times 3 + 0.5 \times 1] / 4 = 0.65$$

If missing data still persist, they will be imputed using multiple imputation using baseline covariates (age, gender, ALSFRS-r and SNIP/FVC group), previous questionnaire values, time point and treatment group.

Analysis sets

The ITT will be the primary analysis population for effectiveness outcomes, with the results for the PP being supportive of it. If for any endpoint the populations confer inconsistent results, further analyses will attempt to investigate the reason for this.

Methods for dealing with multi-centre data

The consistency of outcomes among the treatment centres will be assessed by fitting a model which includes an interaction between treatment group and centre. If the test for interaction is not statistically significant the interaction term will be removed. If significant differences are found, further analyses will be undertaken to assess whether this may be due to differences in case mix (i.e. an artefactual centre effect) or not (i.e. real centre effect).

Disposition and data completeness

Recruitment data, data completeness and patient demographic & characteristics will be reported to the TSC, DMEC and TMG in an ongoing fashion.

Demographics and baseline patient characteristics

The baseline date is the date of randomisation. The centre will be defined as the centre at which the patient first attended. Age is defined as (date of baseline – date of birth).

ALSFRS is a one-domain questionnaire comprising 24 questions, each of which is scored from 0-4. The overall score is the sum of these. If the questionnaire is incomplete but at least half of the questions answered (i.e. at least 12 of the 24), the overall score will be multiplied up by the formula

$$\text{Overall score} = (24 / \text{Number of questions answered}) \times (\text{total score among answered questions})$$

If fewer than 12 questions are answered, the questionnaire will be treated as missing and will not be used in summaries.

DiPALS statistical analysis plan version 2 FINAL including amendment 1

The bulbar function score is calculated from the ALSFRS-r. The answers to the first three questions (speech, swallowing and salivation) are summed, and the bulbar function is categorised from this sum into the following: mild (0-4), moderate (5-8) and severe (9-12).

Efficacy

Primary endpoint

The primary endpoint is overall survival, defined as the time between randomisation and death. If no notification of death has been received, the patient will be censored at the date last known alive.

Pre-trial modelling, undertaken at the proposal development stage, found PH to be the best fit to previous data, and therefore a Cox PH regression model will be fitted with ties handled by the Efron method. The PH assumption will be checked by adding time-dependent covariates and graphing scaled Schoenfeld residuals against time.²⁰ If PH is found not to fit the data adequately, an AFT alternative will be fitted and the adequacy of its fit assessed using Q-Q plots.²¹ If this too does not fit, a residual life analysis.²² will be used as the basis for summarising the treatment effect

Secondary endpoints

SAQLI (Sleep Apnoea Quality of Life Index)

SAQLI is a one-domain questionnaire comprising 14 questions, each of which is scored from 1-7. The overall score is the average of these. If the questionnaire is incomplete (i.e. less than 14 questions are answered), the overall score will be defined as the average provided at least half of the questions (7 of the 14) have been answered. If fewer than 7 questions are answered, the questionnaire will be treated as missing; no further imputation will be undertaken.

SF-36

Version 1 of the SF-36 will be used. The domain scores will be calculated using the standard RAND organisation algorithm.

CBI

CBI is a one-domain questionnaire comprising 24 questions, each of which is scored from 0-4. The overall score is the total of these. Incomplete questionnaires will be handled in the same manner as SAQLI

Safety

NIV and DP usage

The original analyses of DP and NIV usage were to be based primarily on diary data. In the course of the trial however, it became clear that fewer diaries were being completed than expected. As a consequence, alternative approaches to defining usage were required.

NIV usage

DiPALS statistical analysis plan version 2 FINAL including amendment 1

In addition to the patient diary and CRF, NIV usage data can be estimated from the NIV machine itself. The CRF was amended to collect this additional information in 2014.

NIV usage will be collected for each time period, using the following hierarchy:

NIV machine

if i) not available, NIV usage will be taken from the participant diary entries

if i) and ii) not available, NIV usage will be taken from the participants typical usage recorded in the CRF

For the purpose of the analyses, “time period” is defined as the duration between successive visits (0-2, 2-3, 3-6, 6-9 and 9-12 months). Where NIV initiation starts part way through an interval (for example, if NIV started 20 days after randomisation), usage will be defined over the period starting from NIV initiation.

For i), the CRF records the cumulative “blow hour count”, or the number of hours use recorded at each visit date. The average NIV use (in hours) since last visit is then calculated as

$(\text{NIV count at visit} - \text{previous NIV count at previous visit}) / \text{number of days between visits}$

This will be used to calculate NIV usage for time periods for which NIV use is collected both before and after

For ii), the NIV use will be collected from the diary only if the participant has completed at least 80% of the scheduled diary entries. For example, if 95 days have elapsed between the 3&6 month visits, the participant would need to have completed a diary on at least 76 of these. The value taken will be the median value recorded.

For iii), the NIV use will be taken as the value “typical NIV usage” recorded in the CRF.

Based on this, participants will be defined as “adherent” or “not adherent”, blinded to treatment group. The assessment will be made separately by the chief investigator and Dr Stephen Bourke. Cases for which the assessors cannot reach agreement will be referred to the TMG/TSC.

DP usage

DP adherence will be quantified in an analogous manner as NIV, but with two key differences. Firstly, the DP machine does not collect usage data (unlike NIV); DP usage will therefore be taken only from the diary (preferably) or the CRF. Secondly, the qualitative adjudication of adherence by definition cannot be blinded to treatment group. Assessment of adherence to pacing will be made in the same manner as NIV.

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Adverse events

Adverse events will be coded as one of the following categories. Coding will be done by the chief investigator and will be done blinded to the participant's treatment group.

Adverse event categories

- Cardiovascular system
- Central nervous system
- Dermatological
- Gastro-intestinal
- Genito-urinary
- Infection of percutaneous endoscopic gastrostomy (PIG) or per-oral image guided gastrostomy (PEG)
- Insertion/removal of PIG/PEG
- Respiratory, further subdivided into
 - Breathless – unclassified
 - Chest infection
 - Cough
 - Infection
 - Pneumothorax/Capnothorax
 - Pulmonary Embolism
 - Respiratory failure
 - ALS symptoms
 - NIV specific
 - Pain
 - Psychiatric
 - Wire infection
 - Wire problems
 - Other

Additional categories or subcategories may be added at the request of the chief investigator, TSC or DMEC.

For each AE, the report will comprise the number and percentage of patients affected, and the number of events (a patient may have more than one occurrence of the same AE).

Modifications to the original protocol analysis statement

The original analysis plan was written by the trial statistician with access to unblinded, but very limited data: at the time of sign off, one patient death was recorded on the database. The updated analysis plan was written by the same statistician, again with access to unblinded data. The DMEC were asked to approve the plan, and did so (with minimal suggestions) having seen unblinded data summaries throughout the trial progress; all other reviewers/approvers were blinded to the data.

The following have been updated:

Section 1.4: Gives background to the early trial stopping, early data release and other studies of DP in ALS.

DiPALS statistical analysis plan version 2 FINAL including amendment 1

Section 2.1: Updated with new CRF version and details of individuals with data access.

Section 3.4.1: Additional exploratory analyses around the primary endpoint, particularly in relation to compliance/adherence/tolerance

Section 3.4.2: New outcome measures, using routinely collected data from clinic visits, have been added at the request of the TSC

Sections 3.5: Additional details of adherence are provided.

Section 3.6: Details of the interim analyses for presentation at the 25th International Symposium on MND/ALS have been added.

Section 4.1.2 Missing data imputation has been updated. Scenario 4(iii) has been amended.

Sections 4.5: Additional details of adherence and adverse event categorisation are provided.

Appendix 14 Stop pacing patient letter (diaphragm pacing arm)

DiPALS: Diaphragm Pacing plus NIV group

Dear xxxxx

We are writing to update you with important information about the DiPALS study in which you are a participant.

At the last safety meeting the results indicated that pacing was of no benefit to patients with ALS and may in fact be causing harm. **We are therefore asking all patients in the study to stop using their pacing systems immediately.**

- Your local study team will talk to you about how to do this.
- We do not anticipate stopping pacing will lead to any problems for you.
- If you do experience any worsening of symptoms or new symptoms on stopping pacing then please let your study team know.
- The contact details of your study team are xxxxxxxxxxxxxxxx

It is important that you continue to use Non Invasive Ventilation (NIV). This is a safe and effective treatment for breathing problems in ALS patients.

Once you have stopped pacing your study team will organize collection/return of your pacing box. The pacing wires that are attached to you can be dealt with in one of three ways:

1. Left as they are. There is no evidence to suggest the presence of the wires is harmful. It is safe to leave them as they are.
2. The wires can be cut as they leave the skin. You would have no wire visible but the inside part of the wires would be left in.
3. You can be given a local anesthetic in the skin where the wires are located and the wires can be pulled out.

Although we have asked participants to stop pacing it is very important to continue to monitor individuals for safety reasons and to gain as full a picture as possible regarding the effects of pacing in patients with ALS. We therefore ask you to continue with your study visits until your 12 month visit or the planned end of the study.

The full study results are not yet available and will not be available until the end of the year or early next year. However, it is clear that pacing adds no benefit to the group of ALS patients included in the study. We will hopefully have more of an understanding when we have had the opportunity to analyse the full study results.

We understand that this news will lead to worries and many questions. Your study team are available to answer your questions in detail. We have compiled a list of questions and answers to give you some more information, enclosed with this letter.

We would like to take this opportunity to thank you for your contribution to DiPALS. We realize that taking part in clinical studies is itself a burden on individuals and those who support them. DiPALS is an important study and when the full results are available will help doctors and individuals with ALS to be able to make informed decisions about the best treatments for ALS.

Yours sincerely,

Local PI team

Further Questions and answers

Why do I have to stop using my pacing device?

The DiPALS study has a Data Monitoring and Ethics Committee (DMEC). The primary role of the DMEC is to monitor safety of participants taking part in DiPALS. They have analysed the data from the study and have identified that pacing is of no benefit to patients with ALS and may in fact cause harm.

What harm has pacing done to me?

The results suggest that patients who received pacing in addition to Non-Invasive Ventilation did not live as long as patients receiving treatment with NIV alone. The size of the difference in survival will be calculated once we have completed the study. On the data available so far survival is certainly no better in patients receiving pacing and may be worse.

What happens if I feel worse on stopping pacing?

We do not expect this to happen. However if you experience problems on stopping pacing please contact your study doctor. It may be that using your NIV more may help.

I feel pacing helps me and I would like to continue to use it?

The instruction from DiPALS is that all patients stop pacing. Any contrary decision to continue pacing will be taken by your consultant, yourself and local hospital outside of the DiPALS study. The responsibility for continuing pacing will rest with your consultant.

What do I do with the wires attached inside of me now that I have stopped pacing?

The pacing wires that are attached to you can be dealt with in 1 of three ways:

1. Left as they are. There is no evidence to suggest the presence of the wires is harmful. It is safe to leave them as they are.
2. The wires can be cut as they leave the skin. You would have no wire visible but the inside part of the wires would be left in.
3. You can be given a local anesthetic in the skin where the wires are located and the wires can be pulled out.

I have been given NIV as part of the trial. Is that safe?

Yes. NIV is a safe and effective treatment for breathing problems in ALS. You should continue to use NIV as much as possible.

Appendix 15 Stop pacing patient letter (non-invasive ventilation arm)

DiPALS: Non Invasive Ventilation (NIV) group

Dear xxxxx

We are writing to update you with important information about the DiPALS study in which you are a participant.

At the last safety meeting the results indicated that pacing was of no benefit to patients with ALS and may in fact be causing harm. **The safety committee has therefore advised that all patients stop pacing.**

You were not receiving pacing and therefore this decision does not directly affect you. You should however continue to use Non Invasive Ventilation (NIV). This is a safe and effective treatment for breathing problems in ALS patients.

Although we have asked participants in the pacing arm to stop pacing it very important to continue to monitor all individuals for safety reasons and to gain as full a picture as possible regarding the effects of pacing in patients with ALS. We would therefore ask you to continue with your study visits until your 12 month visit or the planned end of the study.

The full study results are not yet available and will not be available until the end of the year or early next year. However, it is clear that pacing adds no benefit to the group of ALS patients included in the study. We will hopefully have more of an understanding when we have had the opportunity to analyse the full study results.

We understand that this may generate many questions. Your study team is available to answer your questions in detail.

We would like to take this opportunity to thank you for your contribution to DiPALS. We realize that taking part in clinical studies is itself a burden on individuals and those who support them. DiPALS is an important study and when the full results are available will help doctors and individuals with ALS to be able to make informed decisions about the best treatments for ALS.

Yours sincerely,
Local PI team

Appendix 16 Stop pacing general practitioner cover letter (diaphragm pacing arm)

Dear Dr XXXX

Your patient has been involved in DiPALS, a study of diaphragmatic pacing as an intervention to treat respiratory problems in motor neuron disease. The Data Monitoring and Ethics committee have advised that all patients should cease pacing immediately. They have indicated that at best pacing is of no benefit but may cause harm. We have enclosed a copy of the letter to participants regarding withdrawal of pacing. The study doctors at the local site will oversee withdrawal of pacing. It is not expected there will be any detrimental effect of doing this. No action is required from you and this communication is for information purposes only.

Yours sincerely

Local PI team

Appendix 17 Pacing discontinuation standard operating procedure

Background

Following the last DMEC meeting held on 23Jun14, after reviewing the unblinded data their key points are as follows:

1. The DMEC recommend that participants in the pacing arm stop pacing.
2. All participants should remain to continue follow up until the last participant's last visit (currently planned for mid-December 2014).
3. On balance, it appears that pacing may be harmful to the study group that have had it implanted
4. The group feel that it is unlikely that there will be any change in the data to suggest otherwise if the participants continued to pace.

The Sponsor (STH), Ethics, HTA, TSC and TMG all informed 23rd June 2014 of DMEC advise. Further guidance issued (24Jun14) from the DMEC to assure the trial team that although they feel it appropriate to discontinue its use in participants they do not think that there is evidence to suggest any acute risk to patients and as such a more gradual planned approach would be acceptable. The central team will submit an amendment to REC to gain approval for both the process and documentation for this procedure.

Process for participants active in study in DP arm

- Local study team to contact participants as soon as practicable by telephone/ home visit or clinic visit and inform them to stop pacing, using information contained in the Stop Pacing Letter to Patients (DP arm) V1 24Jun14. If it is not possible to contact the participant via telephone, the letter should be posted or emailed.
- The local study team should give the participants contact details of their emergency service so that if a deterioration is experienced on stopping pacing the participant knows who to contact 24 hours a day. There is a space on the letter to add your details.
- The local study team should send to the patients GP:
 - 1) a copy of the "Stop Pacing Letter for Patients (DP arm)" V1 24Jun14
 - 2) a copy of the "Stop Pacing GP cover Letter" V1 24Jun14.

- The local study team should arrange to contact the patient by telephone/ home visit or clinic visit 24 hours and 1 week later following pacing cessation to review.
- A discussion regarding patient's wishes regarding wire removal should take place and the patient's wishes be implemented.

Guidance on Managing wires following pacing withdrawal

1. Disconnect device. Return Pacing unit. Internal and external wires left in situ.
2. Disconnect device. Return pacing unit. Internal wires cut as leave body.
3. Disconnect device. Return pacing unit. Wires pulled out under local anaesthetic.

Guidance on continuing pacing beyond study recommendations

The DiPALS instruction is that all patients cease pacing. If a participant wishes to continue pacing, following discussion of the DMEC advice, this is a decision that must have the support of the treating consultant and their employing institution. Such pacing will be occurring outside of the DiPALS study and will not have the support of the DiPALS study team.

For each participant sites are to complete the checklist in Appendix 1 of this SOP once the process is complete and fax/email it back to the study manager.

Participants active in study in NIV only arm

- Local study teams to contact participants via telephone/home visit/ clinic visit and give/send Stop Pacing (NIV arm) letter.

Participants deceased who were in DP/NIV arm

- No action is required until full study results are available

Withdrawal documentation

- Please record any change in condition due to stopping pacing as an adverse event and link to pacing withdrawal in the CRF

- Please complete Appendix 1 DP participant discontinuation checklist

Appendix 1:

DiPALS: DP participant discontinuation check list
(applicable for only patients in the DP arm)

Participant number

Date advice from DMEC to discontinue DP discussed	DATE:
Option for pacing discontinuation chosen	(mark appropriate box with X)
1. Disconnect device. Return Pacing unit. Internal and external wires left in situ	
2. Disconnect device. Return pacing unit. Internal wires cut as leave body.	Date wires cut:
3. Disconnect device. Return pacing unit. Wires pulled out under local anaesthetic.	Date wires removed:
Other: (please provide information where the participant has not wished to choose one of the options above, complications from withdrawal of DP or wire procedures etc.)	

Appendix 18 Qualitative interview topic guide

Topic Guide: 1 month post implantation

The DiPALS Trial.

Diaphragm pacing in motor neurone disease

Study information

- Overview of the study
- Details of funder
- Overview of who is being selected for interview
- Explanation of dissemination strategy and how the study will inform local services

Aim of discussion

- Informal discussion
- Views and opinions
- No right or answers but interested in views and experiences

Confidentiality

- Recording of interviews
- Information will remain anonymous
- Review of information sheet with an opportunity to ask questions
- Signing the consent form

Background Information about the patient/carer

Participant information including name (and how long they have been carer for the individual with ALS)

Awareness of the surgical procedure

- What the surgery involved
- Expectations of what the equipment would do
- Size of equipment and wires involved

Experience of surgery

- Any concerns they had prior to surgery
- Expectation versus reality
- If they were to tell someone else about the procedure what would they tell them
 - Fears, anxiety
 - Pain, discomfort
 - General anaesthetic

Use of equipment in hospital

- Information provided
- Who provided it and when
- Was any of the information provided before the surgery
- Format – written or verbal
- Was it easy to understand
- Was it enough of was there anything else you wanted to know
-

Transition to use at home

- Support available at home
- Did they know who and how to contact them
- Any problems or complications using the equipment
- Who manages the equipment, ensuring it is working properly, dealing with it at home
- How easy is this to do and confidence to take on this role
- Any early impacts on QoL apparent on
- Individual
- Carer
- Family members
- Friends

Topic Guide: 6 month post implantation**The DiPALS Trial.**

Diaphragm pacing in motor neurone disease

Although previously interviewed repeat early information as a reminder and to ensure participants still wish to participate

Study information

- Overview of the study
- Details of funder
- Overview of who is being selected for interview
- Explanation of dissemination strategy and how the study will inform local services

Aim of discussion

- Informal discussion
- Views and opinions
- No right or answers but interested in views and experiences

Confidentiality

- Recording of interviews
- Information will remain anonymous
- Review of information sheet with an opportunity to ask questions
- Signing the consent form

Background Information about the participants

Participant information including name and age

Impact on Quality of life

- Describe any changes that have occurred as a result of having the equipment fitted
- Changes to behaviour both positive and negative
- Does it interfere with certain activities such as dressing, washing etc
- Is there anything that you dislike about the equipment

Experience of using the equipment

- Explain what it's like to use the equipment
- How often and for what duration have you used this (overnight use)
- Any adaptations made to how you were told to use it?
- Barriers to using the equipment
- Follow up at the clinic
- Frequency of support and if any further support is required
- Support from the ALS team
- Any ways the support / information could be improved / adapted
- Support from family and carer
- In the past 6 months how have things changed

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**EME
HS&DR
HTA
PGfAR
PHR**

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