



Clinical
Trials
Research
Unit.

Sheffield Teaching Hospitals **NHS**
NHS Foundation Trust



*A randomised controlled trial evaluating NeuRx/4
Diaphragm Pacing in patients with respiratory muscle
weakness due to Motor Neurone Disease*

**RESEARCH PROTOCOL – HTA/PUBLIC VERSION
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**Please note, some information has been removed in “v8 16May14 for public” due to
confidential data not yet published.**

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

DiPALS

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

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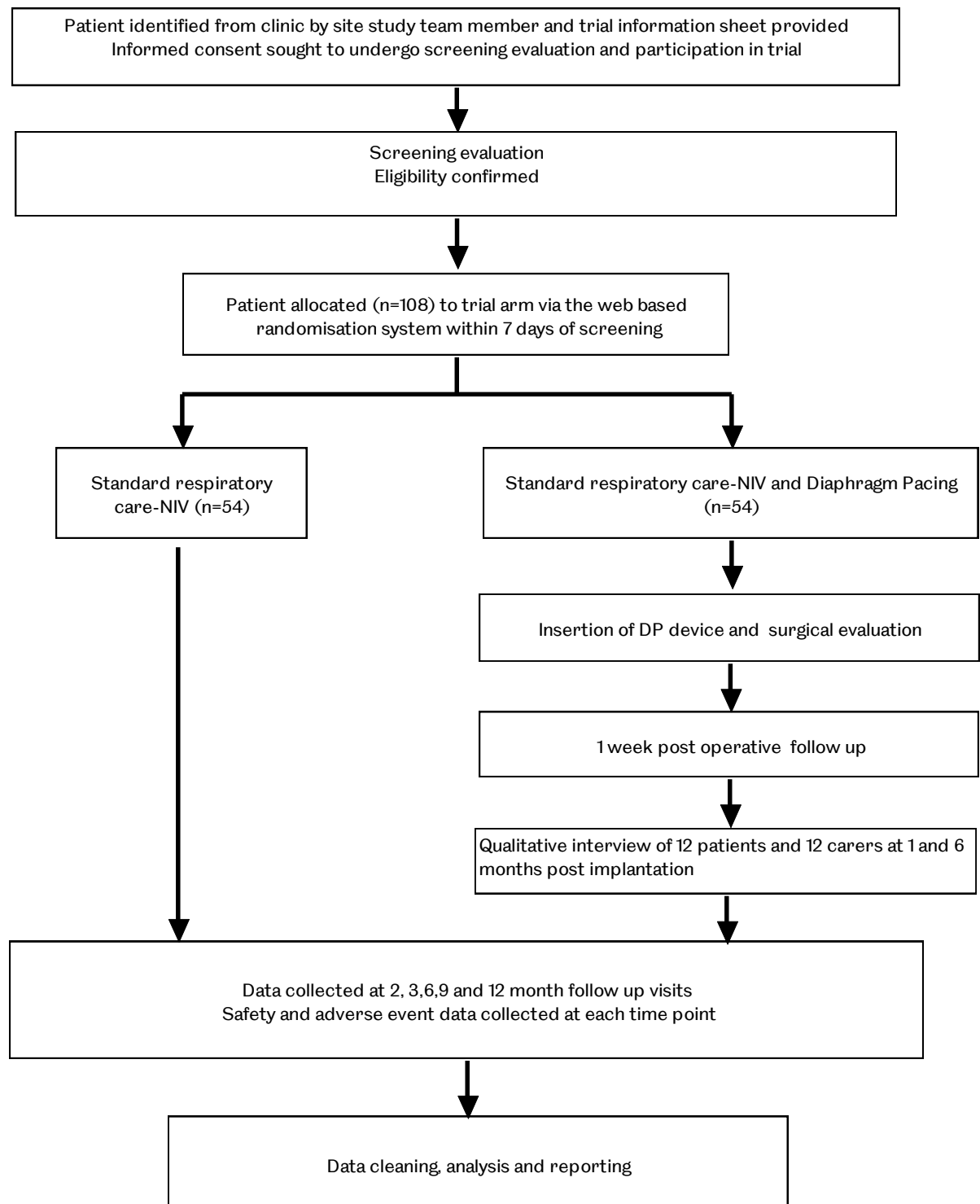
1. Lay Summary

Motor neurone disease (MND) is a devastating illness which leads to muscle weakness and death, usually within 2-3 years of symptom onset. Weakness of breathing muscles including the diaphragm (the main breathing muscle) usually results in death in these patients. Non Invasive Ventilation (NIV) therapy is the current standard treatment to help allow these patients to breathe. Patients wear a face mask over their nose or mouth or both. As they breathe in, the machine gives an extra push of air to support the patient's weak breathing muscles, enabling a bigger deeper breath. Some MND patients however do not tolerate NIV due to the type of mask they have. During the day problems with using NIV include mask interface problems, claustrophobia, feeding and communication. Eventually respiratory muscle weakness will progress to a point at which intermittent/overnight NIV is ineffective.

Diaphragm pacing (DP) is a means of increasing the strength of the main breathing muscle. The NeuRx RA/4 Diaphragm Pacing System has been developed for patients who are unable to control their diaphragms because of stable high spinal cord injuries or because they have a neuromuscular disease such as MND. The pacing wires are inserted into the diaphragm muscle during a small operation and are connected to a small portable box that the patient can easily carry about.

The proposed study will assess if treatment with DP prolongs life and maintains quality of life when given in addition to current standard care with NIV. 108 patients will be recruited to the study in up to 10 NHS sites in the UK. Patients will be randomised to either have NIV or receive DP in addition to NIV. Study participants will be required to complete outcome measures at 5 follow up time points (2, 3, 6, 9 and 12 months). Patients in the DP group will have additional visits for surgery and a 1 week post operative follow up. 12 patients (and their carers) from the DP group will also be asked to complete 2 qualitative interviews. The project is funded by the HTA (Health Technology Assessment) Programme and the Motor Neurone Disease Association.

Figure 1
Trial summary



2. Background

MND is the third commonest neurodegenerative disease with an annual incidence of 2-3 in 100,000 and prevalence of 5-8 per 100,000⁽⁵⁻⁷⁾. Patients experience increasing weakness affecting the limbs, speech and swallowing, and breathing. As the diaphragm and intercostal muscles, the major muscles of breathing, become weak patients initially experience sleep fragmentation and symptoms of carbon dioxide retention. These consist of early morning headaches, unrefreshing sleep and sleepiness during the day^(8, 9). These symptoms severely impact on cognition and quality of life⁽²⁾. When respiratory weakness is severe, patients can be breathless at rest and are prone to recurrent chest infections. Severe respiratory muscle weakness is a poor prognostic sign and once the forced vital capacity (a measure of respiratory muscle strength) reaches less than 50% of the predicted value, mortality at 9 months ranges from 60%-100%^(10, 11).

An important advance in the management of respiratory symptoms in MND has been the demonstration of the beneficial effects of non invasive ventilation (NIV). A randomised controlled trial demonstrated a median survival benefit of approximately 7 months ($p=0.006$), in MND patients using NIV who had good bulbar function⁽³⁾. This survival benefit was accompanied by a significant and sustained improvement in quality of life. As experience with NIV has developed, areas of continuing need have been identified which are not sufficiently addressed by NIV alone:

- a) MND patients with significant compromise of bulbar function do not tolerate NIV and in the above trial of NIV, no survival benefit was demonstrated for this group⁽³⁾.
- b) Similarly some patients fail to tolerate NIV due to claustrophobia and mask interface problems. In addition although the NIV systems are ideal for overnight use, during the day the mask interface can interfere with communication and feeding and the ventilator itself, although small, does restrict mobility.
- c) Eventually respiratory muscle weakness progresses to a point at which intermittent/overnight NIV is ineffective.

There is therefore, a need for additional complementary respiratory support to further aid respiratory muscle weakness and so potentially provide a further prolongation of good quality of life.

Diaphragm pacing (DP) is a technique initially developed for the treatment of respiratory muscle weakness in patients with spinal cord injury⁽¹²⁾. In this patient group it has allowed patients to reduce their time on mechanical ventilation or even remove the need for mechanical ventilation⁽¹³⁾. The NeuRX RA/4 System is a four channel percutaneous neuromuscular stimulation system. Intramuscular electrodes are implanted laparoscopically in the diaphragm, with leads tunnelled to an exit site on the abdomen. A small external stimulator delivers the stimulus pulses and provides respiratory timing. It is hypothesised that the benefits of DP in MND are due to restoration of the coordination of respiration, lost as a result of upper motor neurone dysfunction, as well as conditioning of diaphragm muscle. In a healthy diaphragm slow twitch type I muscle fibres predominate. Disuse and suppression of the diaphragm activity, due to artificial ventilation, has been demonstrated to lead quickly to atrophy and to a predominance of fast type IIb muscle fibres⁽¹⁴⁾.

Type IIb muscles fibres lead to inefficient uncoordinated diaphragm contractions. In MND a similar process is likely to occur due to disuse (secondary to UMN dysfunction) and

suppression of diaphragm activity due to NIV. DP may condition the diaphragm with a conversion back to efficient type I muscle fibres ⁽¹⁵⁾.

The anticipated benefits of DP in the MND patient group are: survival benefit; improved quality of life; reduction in need for NIV; a less intrusive method of providing respiratory support compared to NIV. DP is not currently routinely performed in the NHS. If proven to be beneficial DP may become standard care for MND patients with respiratory insufficiency.

Diaphragm Pacing

The NeuRx R/A4 device, has been utilized in over 300 patients to date, including two separate investigational device exemption (IDE) trials. There are over 275 patient years of cumulative use of the device with the initial spinal cord injured (SCI) patient utilizing the device continuously for 10 years.

Efficacy evidence

A pilot feasibility study of 16 patients with MND implanted with DP demonstrated provisional safety and tolerability data and a decline in forced vital capacity of 0.9% per month following implantation, compared to 2.4% per month before the procedure (15). One hundred and six MND patients have been implanted with the NeuRX RA/4 Device in a U.S. Food and Drug Administration (FDA) prospective multi-centre trial. Full publication of the results is awaited. The planned primary analysis of this study was the change in rate of decline of FVC between lead-in (3 months) and DP treatment (12 months) phases for patients not using NIV. This study will provide an indication of potential benefit of DP but an RCT is needed comparing current standard care with DP plus standard care. Additionally FVC is at best a surrogate marker for survival. However, information with regard effectiveness and safety of DP in MND can be extracted from this study.

Safety and tolerability of DPS

A total of 167 implantations in Spinal Cord Injured patients and 142 in MND patients have taken place (309 total) with no major complications (personal communication from Synapse Biomedical). Detailed safety data has been published on 51 patients with MND who have undergone the implantation procedure (49 in the FDA trial or pilot and 2 compassionate use cases). In the trial/series the FVC at implantation ranged from 45%-89%, whereas the compassionate cases had an FVC of 26% and 28%. All patients were extubated without difficulty and there was no 0 day or 30 day mortality (18).

Device related

Mild to moderate infection at the percutaneous exit site was reported in 8/106 patients. Three patients had a recurrence of infection 1-3 months after the first report. All were described as mild except one which was described as moderate in severity. None were considered serious.

In the 106 patients implanted overall, there were no serious adverse events involving discomfort from stimulation and no reports of severe discomfort. Mild discomfort was reported in 25 patients (24%) and moderate discomfort was reported in 2 patients (1.9%).

In the 106 patients implanted there were no serious adverse events involving malfunctioning device components. No patient had to return for surgical correction of malfunctioning electrodes. In the cases of the diaphragm electrodes, all malfunctions occurred external to the body at the connector holder. In the 106 patients, there were 26 reports of anode malfunction in 21 patients (20%) and 45 reports of electrode malfunction in 31 patients (29%).

These malfunctions were corrected when the patients returned to the study sites. For DiPALS, replacement components if needed will be provided at no cost by Synapse Biomedical. In practical terms in MND, malfunctioning components resulted in a loss or diminution of conditioning therapy until the malfunction was corrected. While the proportion of patients experiencing anode or lead malfunction at some point in their DP use is substantial, malfunction tends to occur relatively late when it does occur and it can be resolved. Also, in contrast to SCI patients, the MND patients are using DP for diaphragm conditioning, not for primary ventilatory assistance.

Based on the experience in the FDA study, design improvements have been implemented in an effort to improve reliability or to simplify malfunction resolution. These changes focus on the cable to electrode interface. This includes making the cable more robust by improving the strain relief at the electrode connector end, creating a strain relief boot for the electrode lead wires as they exit the connector block, and providing a back-up surface anode in the patient kit. All of these changes do not modify the function of the device, but are rather intended to improve reliability as part of continuous improvement efforts in the design and development process.

The aim of our trial will be to determine whether DP in addition to NIV provides added benefit for patients in terms of survival and quality of life outcomes.

We will conduct this trial in compliance with the protocol, GCP and regulatory requirements.

3. Aims and objectives

Primary research objective

The primary objective of this trial will be to evaluate the effect of Diaphragm Pacing (DP) on survival over the study duration in patients with MND/ amyotrophic lateral sclerosis (ALS) with respiratory muscle weakness.

Secondary research objectives

The secondary objectives will be to evaluate the effect of DP on:

Efficacy endpoints

- Quality adjusted life years (QALYs) as calculated by combining EQ-5D and mortality data ⁽¹⁾
- Quality of life: sleep apnoea quality of life index (SAQLI), and SF-36 ^(2, 3)

- Quality of life of the main carer of the patient (Caregiver Burden Inventory)⁽⁴⁾

For each efficacy endpoint, the treatment effect will be assessed by analysing the difference between groups over the 12-month follow-up period, and the difference at 12 months.

Safety endpoints

- safety (adverse events) and tolerability (patient withdrawal from treatment)

Health economic objectives and resource use

The objective of the health economic analysis will be to assess the cost-effectiveness of DP compared to standard care in patients with ALS/MND.

A cost-utility analysis will be undertaken using the costs, EQ-5D and mortality data from the trial. This will be supplemented with decision analytic modelling to estimate lifetime cost-effectiveness for the patient cohort recruited to the trial.

Qualitative interview

The qualitative interviews will be undertaken to draw directly upon people's own experience and views, within the context of everyday lives, to understand how DP impacts on quality of life over time of both patients and carers.

4. Trial Design

DiPALS is a multi-centre prospective randomised controlled interventional trial. 108 patients will be randomly allocated to receive either standard care (NIV) or standard care with additional DP in up to 10 centres (see Figure 1, page 5). The participants will be male or female above the age of 18 yrs. Use of the device in the management of a patient's respiratory dysfunction (device parameters, frequency and length of sessions) will be managed at all centres. Participants will be requested to attend visits in order to obtain safety, quality of life, survival and health economic follow-up at 2, 3, 6, 9 and 12 months post randomisation. Each site has experience in conducting research in patients with MND 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.

5. Ancillary sub-studies

Qualitative Interviews

The qualitative component will draw directly upon both patient and carer's own experience and views, within the context of everyday lives^(30, 31). An essential part of DiPALS is not only to demonstrate the efficacy of DP but also to ensure that any extension of life is not to the detriment of quality of life. The qualitative component will complement the data collected by

SF36 and SAQLI for this purpose. The qualitative component will provide information not easily obtained from questionnaires that will facilitate the implementation of respiratory care pathways incorporating Diaphragm pacing should the study demonstrate benefit.

Design

A total of 12 patients and 12 carers will be recruited for the qualitative component from those allocated to treatment across all sites. Although eligibility of participants for the main study will have been determined through screening for the trial those selected for interview will reflect the diversity of the MND population. This will involve purposively selecting patients to reflect the variation within the predefined patient prognostic factors. It is anticipated that MND patients will not be able to tolerate an interview in addition to follow up assessments at local sites therefore an experienced research fellow will conduct the interviews at a time and location that is convenient for participants.

Ideally the patients and carers will be interviewed separately because they may have different views but joint interviews will be undertaken if requested by the participants. The research team are experienced in working with MND patients and appreciate the need for sensitivity whilst conducting the qualitative interviews with these vulnerable participants.

Conduct

The in-depth interviews will be undertaken with DP patients 1 and 6 months post implantation. The first interview at 1 month will focus on the intervention and the practicalities of having the implant fitted and adjusting to life using the device. This information will be essential to inform the clinical team of issues related to both understanding the procedure including use of the equipment and any beneficial or adverse impact it may have.

A second interview will be undertaken at approximately 6 months post implantation. This will focus on the impact the intervention has had on QoL. Changes to QoL are reported to occur within this timeframe for all MND patients. Six months is also considered an appropriate time to allow patients receiving DP (and caregivers) to become familiar with the intervention and its impact on QoL. Interviews will provide an opportunity to take account of their views and experience of the intervention.

Analysis

Data from the 48 qualitative interviews will be recorded, transcribed and undergo Framework analysis⁽³²⁾. Although Framework analysis was developed for applied policy it has proved useful in applied health research. Analysis will be ongoing and iterative involving concurrent data collection and analysis, with systematic efforts to check and refine developing categories of data. Themes identified in the early phases of data collection will inform the areas of investigation in later interviews. The emerging analysis will be discussed at regular team meetings to develop recurring themes within the data which will explore respondents' underlying reasoning, discuss deviant cases and reach agreement on recurrent themes and findings.

6. Selection of patients

Participants will be identified by the neurology or respiratory clinicians at each site. Each potential participant will be given a study patient information leaflet which will detail what will happen if they choose to take part. See section 7, Participant recruitment for full details.

A patient is eligible for the study if all the inclusion and none of the exclusion criteria are met.

Inclusion criteria

1. Age 18 or older
2. Familial or sporadic MND/ALS diagnosed as laboratory-supported probable, probable, or definite according to the World Federation of Neurology El Escorial criteria.
3. Stabilised on Riluzole therapy for at least 30 days
4. Respiratory insufficiency as determined by **one** or more of:
 - a) Forced Vital Capacity (FVC) less than 75% predicted
 - b) Supine vital capacity (VC) less than 75% of sitting or standing VC
 - c) Sniff Nasal Inspiratory Pressure (SNIP) less than 65 cmH₂O men, or 55cmH₂O women in the presence of symptoms
 - d) Sniff Nasal Inspiratory Pressure (SNIP) less than 40 cmH₂O (see exclusion criteria 9 below)
 - e) PaCO₂ > 6kPa (daytime) or PaCO₂ >6.5 kPa (overnight)
 - f) Significant overnight O₂ desaturation (>5% of night with SpO₂ <90% during overnight oximetry)
5. Bilateral phrenic nerve function clinically acceptable (see page 13)

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 MND/ALS, would increase the risk of general anaesthesia or adversely affect survival over the course of the study.
4. Current pregnancy or breastfeeding
5. Significant decision making incapacity preventing informed consent by the subject due to a major mental disorder such as major depression or 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 three 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. Forced Vital Capacity (FVC) < 50% predicted or SNIP < 30 cmH₂O in patients unable to perform FVC (bulbar patients) – because of potential anaesthetic risk

7. Participant recruitment

Screening

Potentially eligible MND patients with respiratory insufficiency will be identified by either the neurology or respiratory consultants at the site. This will be either at a clinic or from their clinic database. Patients who are attending a routine clinic appointment will be approached about the study at this appointment with the patient information sheet. Patients identified from the clinic list who are due to come in for a visit will be sent an information sheet in the post prior to their appointment. At the appointment the patient will be given an opportunity to discuss the study in more detail and ask any questions. All patients will be given as long as they require to consider the Patient Information Sheet. After this period patients will be approached either by telephone or in clinic and the patient will be given the option to give informed consent to the screening procedures and the trial.

Consent will be obtained as either:

1. Full written consent or
2. Verbal consent given or
3. Consent given via the use of a communication aid.

Where non written consent is obtained an independent witness will be asked to sign the consent form to verify the consent taken.

If the patient consents to the study a member of the site study team (research nurse, respiratory or neurology consultant) will initiate the screening process. The process will involve assessing patient eligibility both against non clinical and clinical criteria and obtaining baseline assessments. Please also refer to data collection (pg 16) for more detail. Patients who decline participation will be asked for a reason for their non participation to help determine common reasons. This will help aid the recruitment strategy as the trial progresses. We will collect basic details (age, gender, reason for exclusion) on all eligible patients to allow completion of the CONSORT flow chart.

Table 1: Clinical Tests at screening

Test	Result available
12 lead ECG	Immediately
Arterial blood gases (performed if required to assess PaCO ₂ level; 4e inclusion criteria)	Immediately
Blood tests	2 -3 days
**Respiratory insufficiency (determined by either SNIP, FVC, PaCO ₂ or O ₂ desaturation overnight)	Immediately. Results from tests up to 2 weeks prior to consent may be utilised as eligibility criteria.
*Clinical assessment of Bilateral phrenic nerve function	2-3 days

*Clinical assessment indicating acceptable bilateral phrenic nerve function consists of either:
a) absence of paradoxical abdominal wall movement during a sniff manoeuvre and recording less than 10% decline of FVC when moving from sitting to supine position, OR

b) 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 (sharp inhalation through the nose).

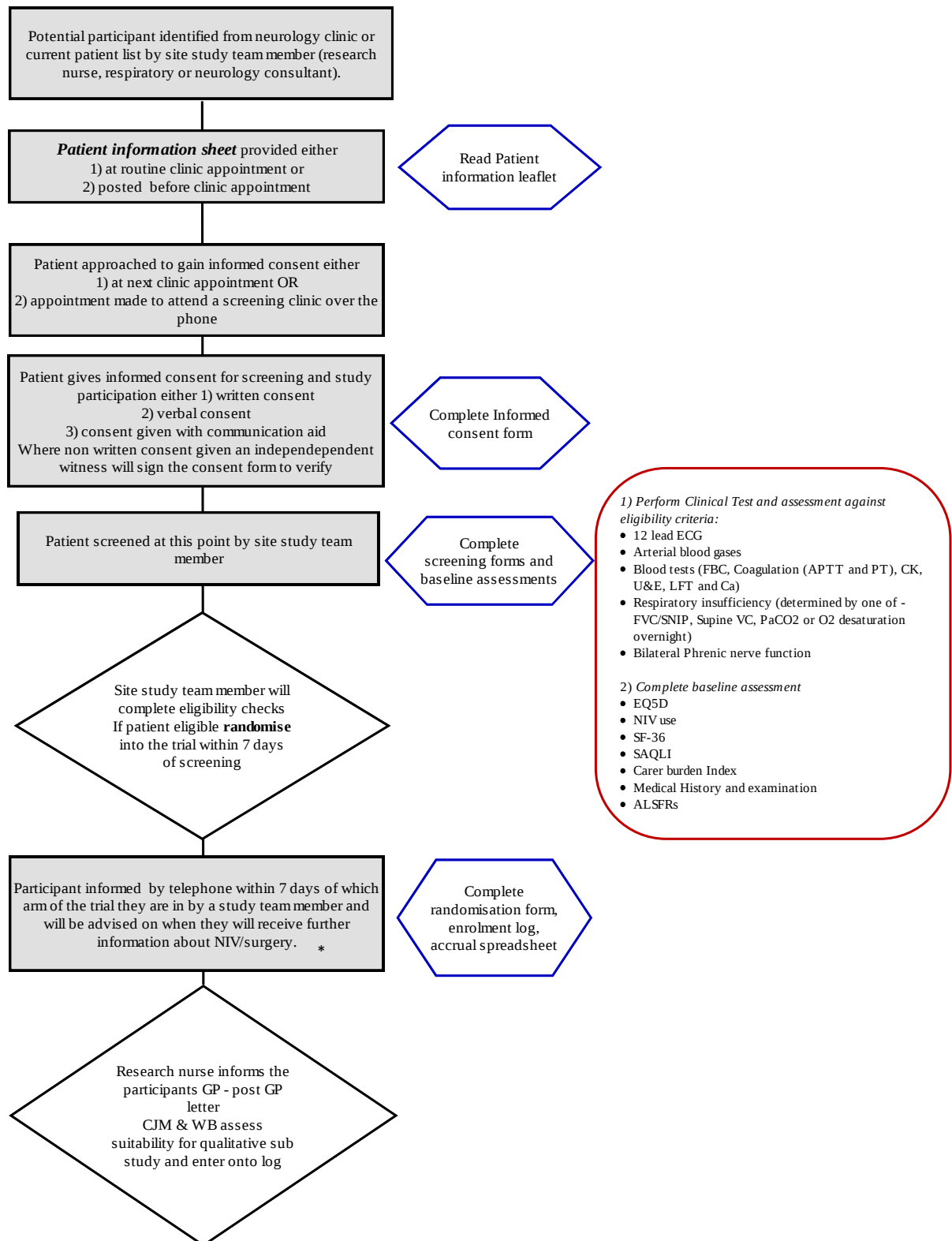
** Data on any respiratory tests routinely performed as part of the participants management of MND will be collected over the participant's involvement in the trial

A member of the site study team will use the results of the tests in order to assess patient eligibility against the inclusion and exclusion criteria. If the patient meets all the inclusion and none of the exclusion criteria (listed above) then they will proceed to randomisation. A member of the site study team will randomise the participant within a week of screening. The patient will be entered onto the study enrolment log.

Randomisation

Patients will be allocated their treatment by method of minimisation. The minimisation factors will be baseline bulbar function, baseline FVC, age and sex. Patient details (ID, date of birth and the factors above) will be entered into the CTRU web-based randomisation system and the treatment allocation will be returned. Non-deterministic minimisation will be employed by including a random element into the allocation algorithm. The participant will be informed of their treatment allocation within a week of randomisation either by phone or letter. Please refer to figure 2 below for the screening and randomisation process.

Figure 2: Screening and randomisation



*Note, NIV initiation can occur at any point in the screening phase after consent has been obtained

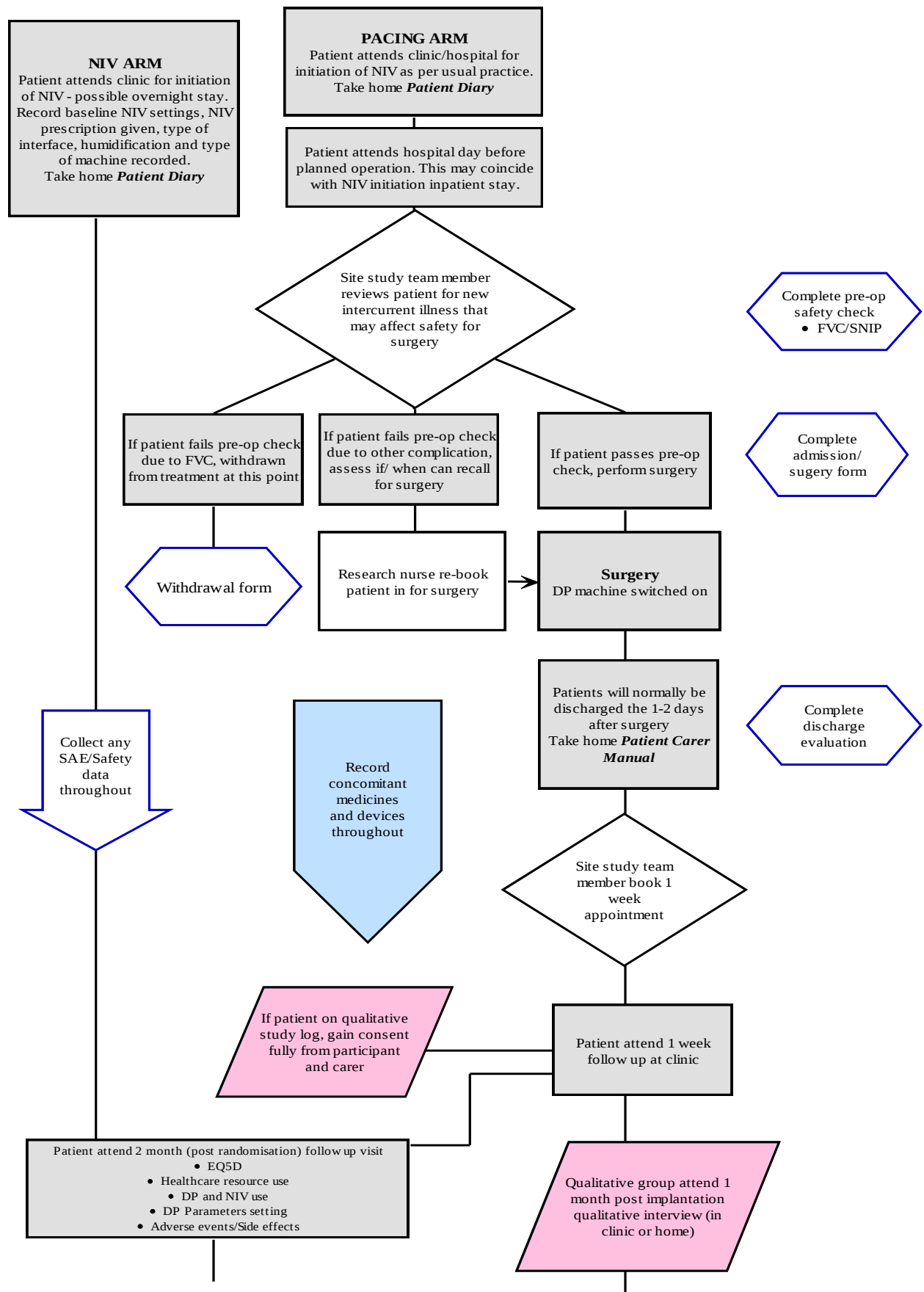
Trial treatment

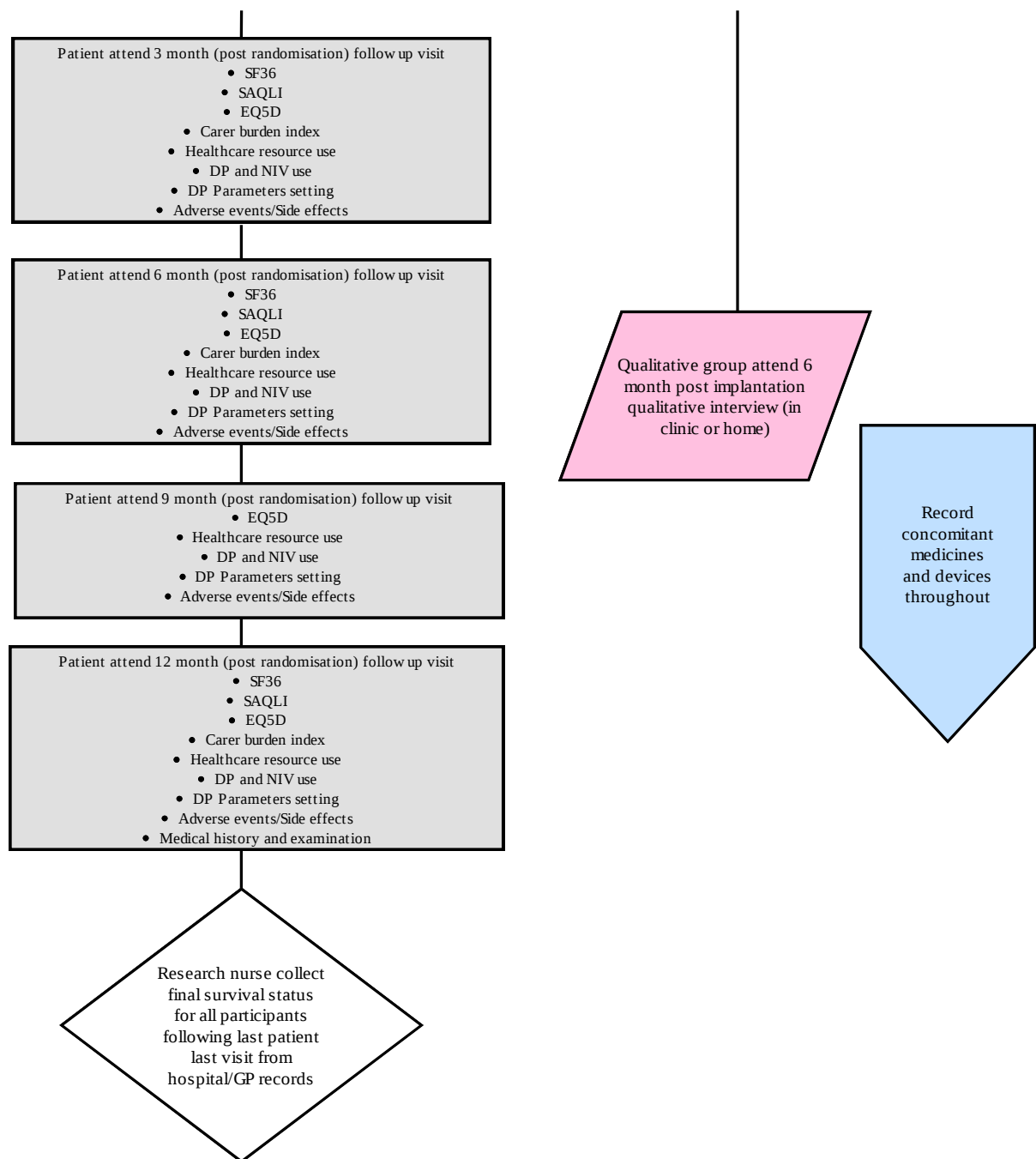
Participants will be randomised to either the treatment arm (n=54) or the control arm (n=54).

At randomisation arrangements will be made for both NIV and DP insertion for trial participants. NIV initiation will occur as per usual clinical practice at the study site after consent has been obtained. 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. NIV should be available to patients in the anaesthetic recovery room post implantation of the device should this be required.

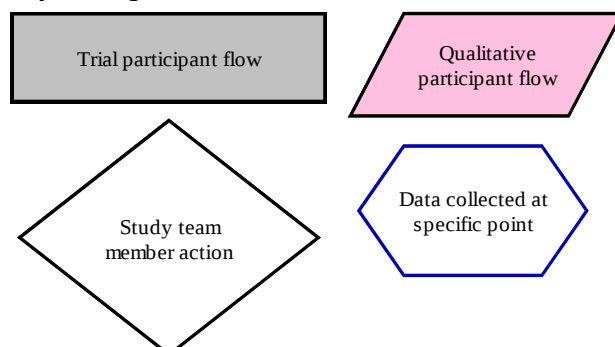
Please see figure 3 overleaf for the participant flow within the trial.

Figure 3: Participant flow in each trial arm





Key for Figure 2 and 3:



Surgical Implantation

In the DP arm participants will be admitted to hospital for insertion of the DP device. A pre-operative safety check will occur either during the admission or in the week leading up to surgery. During the implantation procedure, incisions of 0.5 to 1 inch long will be made in the abdomen. More than one incision will be made so instruments can be passed through the abdominal wall as per standard laparoscopic procedure.

The surgeon will identify the best location to place the electrodes within the diaphragm. A probe will be 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 are identified, the probe will be removed and two electrodes will be placed in each side of the diaphragm muscle. The lead wires from these electrodes will travel under the skin to the abdominal wall. The wires will be trimmed so that the ends sticking out of the skin are only 2 - 6 inches in length. 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. At the end of surgery the clinical station read out should be printed out displaying functioning stimulus connection for each electrode wire. This will be used for surgical quality control.

If the damage to the nerve supply to the diaphragm is too great it is possible that the diaphragm will not be able to be stimulated with the electrodes and diaphragm pacing system. The scan of the diaphragm performed during screening are an attempt to assess whether the diaphragm is stimlatable. However it is only possible to know for sure during the operation. If during the operation it is clear that the diaphragm is not stimlatable then the operation will be stopped and the device will not be inserted.

The training process is simple as the technique is a modification of a standard abdominal laparoscopic procedure. The clinicians who will be performing this procedure in the treatment arm are experienced surgeons who will all be trained in the DP implantation technique until they are competent to perform the procedure. This training protocol has successfully worked in each of the 15 centres in the FDA study. 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.

Evaluation of Electrodes and Training

Evaluation of the electrodes and system will be performed prior to discharge from hospital. A system check of the wires will be completed. Electrode evaluation will be performed by adjusting individual stimulus parameters (pulse amplitude, width, and frequency) using the Clinical station so that a comfortable level of stimulation can be identified for the diaphragm conditioning sessions. During the initial stimulation period, the participant's vital signs will be monitored for any abnormalities. The patient will be given a daily target for the number and length of diaphragm pacing sessions. This will be recorded by the study team member in the patient diary.

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

Prior to discharge, the participant /or carer must demonstrate proficiency in the following:

- Cleaning and care of skin, wires and exit site
- Care and use of the stimulator
- Attachment & detachment of all components
- Completion of Patient Diary

Pacing may be deferred until the 1 week post-operative appointment to allow patients to adjust to having the device fitted in the immediate post-operative period. This is to match practice at all sites as it is recognised this enables the patient to recover after their operation. The initial target for pacing sessions for MND patients is 5 times per day with each session lasting at least 30 minutes. Patients should build up to this target over the first month. In the second month patients should gradually lengthen the training sessions. When using 6-7 hours a day patients should then switch from pacing during the day to using the pacing device overnight whilst asleep. At this stage patients can additionally use the pacing device during the day if they feel benefit but this is not essential. Patients should continue to use their NIV as advised by their study doctor. A Patient Diary will be given to the participant (upon NIV initiation) to take home to record the amount of time spent on DP and/or NIV

Participant compliance

A member of the site study team will be responsible for data collection at the various time points within the trial. Predominantly the research nurses will be involved in coordinating data collection activities and ensure compliance with appointments. Following surgery a 1 week follow up appointment will be booked for participants in the treatment arm before they leave the hospital. At subsequent follow up time points (2, 3, 6, 9 and 12 months) where possible an appointment for the next time point will be scheduled in. The research nurse will telephone the participant 1 week before the appointment as a reminder where resource allows.

Withdrawal

Participants are free to withdraw from treatment or trial at any time. If a participant wishes to withdraw they will be able to speak to a member of the site study team i.e. respiratory or neurology consultants or the research nurse. This will be documented on a participant withdrawal form. Any data already collected during the course of the trial up to the point of withdrawal will be used in the final analysis. We will ask the participant for their permission to continue to collect safety (i.e. adverse event) data and data on survival.

Participants will have the option to withdraw with the following options:

1. Withdraw from treatment but remain within the study. All trial data would continue to be collected at subsequent follow up time points as per protocol.

2. Withdraw from study. Unless the patient objects, any data collected up to this point would be retained and used in the study analysis. The participant agrees to allow contact to give survival and safety data at the usual follow up time points.
3. Withdraw from study entirely. Unless the patient objects, any data collected up to this point would be retained and used in the study analysis. If the patient does not wish to be contacted with regard to safety or survival no further contact with regard to the study will be made.

Data Collection

Once participants have been enrolled and allocated their treatment the data collection process starts. Data collection occurs at baseline, 2, 3, 6, 9 and 12 months for both groups. Additionally the DP group will undergo data collection at the time of surgery and 1 week following surgery. The subgroup of 12 participants and carers who will be undertaking the qualitative sub study will also undergo interviews at 1 and 6 months post implantation. See Table 2 below for full details of the data collection schedule.

Table 2: Data collection

Data collection tool	Time point of study	When collected/given to patient	By who	Why collected
Informed consent form	Recruitment	In clinic, face to face	Neurology or respiratory consultant	Ensure participants have been consented appropriately
Screening and eligibility assessment form	Recruitment/ Screening	In clinic	Neurology or respiratory consultant or research nurse	Ensure protocol violations or deviations are avoided. Include ECG, blood gases, blood test, FVC and phrenic nerve evaluation tests
ALSFRSr	Screening/ routine data	As above	As above	Allows minimisation on bulbar function
Survival	1 week, 2, 3, 6, 9, 12 months, then finally at last follow up for last patient	In clinic, telephone, post or email	Research nurse	Primary outcome measure
*EQ5D questionnaire (patient and carer)	Screening, 2, 3, 6, 9 and 12 months	In clinic or over the phone, post or email	Neurology or respiratory consultant or research nurse	QALYs, secondary outcome measure
SF36	Screening, 2, 3, 6 and 12 months	As above	As above	Generic quality of life, secondary outcome measure
Sleep Apnoea Quality of Life (SAQLI)	Screening, 2, 3, 6 and 12 months	As above	As above	Respiratory specific quality of life, secondary outcome measure
*Caregiver Burden Inventory questionnaire	Screening, 2, 3, 6 and 12 months	As above	As above	Secondary outcome measure
Side effects/ adverse event/concomitant medications and devices forms	All time points as required	As above	As above	AE/SAEs
Healthcare resource use	2, 3, 6, 9 and 12 months	As above	As above	Economic, secondary outcome measure
Patient Diary and case report form incorporating: * NIV use (diary and machine) * DP use and	1 week, 2, 3, 6, 9 and 12 months	In clinic, at hospital or at home	Neurology or respiratory consultant and Patient and Carer	Main outcome Record DP and NIV use

* DP Parameters setting				
NIV use	Screening	As above	As above	Main outcome
Medical history and examination on CRF	Screening and 12 months	In clinic	Neurology or respiratory consultant	Eligibility for trial, safety
Surgery evaluation form/ pre op safety check	Screening, Surgery and 1 week	In clinic or hospital	Neurology or respiratory consultant or Surgeon	Safety and eligibility for surgery
Surgical implantation/ intra operative form	Surgery	In hospital	Neurology consultant or Surgeon	Testing DP device in situ
Discharge evaluation form	Surgery	In hospital	Neurology or respiratory consultant or surgeon	Demonstrate patient and carer competent to use and care for DP device
DP parameters setting	Surgery	Clinic	Neurology or respiratory consultant	Evaluate the DP device, allow optimal use of device
*Qualitative interview (n=12, Patient and carer)	1 and 6 months post implantation	Participants place of choice	Qualitative fellow	Sub study outcome

* The carer will be asked to complete the EQ5D, the caregiver burden inventory and the Qualitative interviews.

Lost to Follow-Up

Unless the participant withdraws from the study entirely (see Withdrawal above) we will continue to collect survival and any safety data/ adverse event data. This will be checked with the participant at the time of withdrawal.

8. Data handling and record keeping

Data input will be the responsibility of the research nurses. Data quality will be the responsibility of the Sheffield CTRU Trial Manager and the Data Management Team. Detailed data management and data quality issues will be set out in a data management and monitoring plan. Data will be collected and retained in accordance with the Data Protection Act 1998. Anonymised trial data will be entered onto a validated database system designed to an agreed specification between the Chief Investigator and Sheffield CTRU. The study manager, data managers, PI's, co-investigators, research nurses and administrators will have access to the anonymised data on the database through the use of usernames and encrypted passwords. The system has a full electronic audit trail and will be regularly backed up. The secure data management system will incorporate quality control procedures to validate the

study data. Error reports will be generated where data clarification is needed. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Trial documents will be retained in a secure location during and after the trial has finished.

All source documents will be retained for a period of at least 5 years following the end of the trial. Where trial related information is documented in medical records those records will be retained for at least 5 years after the last patient last visit.

9. Access to source data

Monitoring and audit by the relevant health authorities will be permitted by the sponsor. These include the Research Ethics Committee and local R&D departments. The sponsor will be allowed to monitor and audit the trial at each site and be allowed access to source data and documents for these purposes.

10. Statistical analysis

Sample size

Sample size – The sample size calculation is based on log-rank test, using Simpson's rule as implemented in Stata version 11.1⁽³⁵⁾ to allow for the unequal length of follow-up.⁽³³⁾ 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. The FDA study of DP in ALS/MND 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.

Data analysis

The primary outcome is overall survival, defined as the duration from randomisation to death. This will be analysed by Cox regression, with covariates including treatment group and the minimisation factors. As a secondary analysis we will also report survival separately for patients who are NIV tolerant and those who are NIV intolerant. The proportionality assumption will be assessed using time-dependent covariates and scaled Schoenfeld residuals⁽³⁶⁾.

The change from baseline for QoL outcomes will be analysed by two methods. The first analysis will compare the change from baseline at 12-months using analysis of covariance (ANCOVA) in which the treatment group and the baseline score are included as covariates along with minimisation factors. The second analysis will assess the QoL over the entire 12-month period by modelling the change from baseline by repeated measures ANCOVA with the same covariates. QoL will be summarised both with imputation for missing data (in particular, assigning a score of zero following the date of death) and without.

The safety and tolerability profiles will be reported by analysing the proportion of patients experiencing adverse outcomes. A description of the statistical analysis of efficacy and safety outcomes will be written in the trial Statistical Analysis Plan by the trial statistician.

11. Economic Evaluation

For the trial, a cost-utility analysis will be undertaken using the costs, EQ-5D and mortality data from trial. The analysis will take a NHS and Personal Social Services (PSS) perspective, with an additional analysis that incorporates carer QALYs within the incremental cost-effectiveness ratio (ICER). This will be supplemented with decision analytic modelling to estimate lifetime cost-effectiveness for the patient cohort recruited to the trial.

Resource use for insertion of the pacing system – theatre time, ward stay and any critical care - will be gathered from theatre and patient administration system (PAS) records. Resource use relating to NIV and other NHS and PSS services will be collected at all follow-up visits. Unit costs for insertion will be based on hospital unit costs. Market prices will be used for the pacing system and its associated costs, with an equivalent annual cost being calculated based on the lifespan of the system based on past experience. NIV costs will be based on business case and contracting information relating to existing NIV services within the participating centres. Other unit costs will be taken from the most recent National Reference Costs, British National Formulary and PSSRU publication ‘Unit costs of health and social care’. The EQ-5D will be completed at baseline and all follow-up visits by patients and the main carer of the patient. QALYs will be estimated using straight line interpolation between data points. Both costs and QALYs will be discounted at 3.5% per annum.

Mean incremental costs and QALYs will be combined into an ICER, and sampling uncertainty represented by plots on the cost-effectiveness plane and associated cost-effectiveness acceptability curves (CEACs). Missing data will be imputed using multiple imputation. An additional analysis will incorporate carer QALYs within the ICER.

A decision analytic model will be constructed that will be validated by replicating the results of the trial, and then results extrapolated to conduct a lifetime analysis. Extrapolation will use transition probabilities estimated from a survival analysis based on the 12 month follow-up data from the trial. Probabilistic sensitivity analysis will be undertaken, with further deterministic analyses using SF-6D utilities and including carer utilities. The feasibility of a mixed treatment comparison that includes DiPALS, the study by Bourke et al (2006) and the ongoing Synapse study will be assessed. This will form the basis of an additional cost-

effectiveness analysis if a valid comparison can be undertaken. As with the trial based analysis, results will be presented in terms of an ICER and CEACs.

12. Safety assessments

All adverse events will be reported in accordance with the CTRU Adverse Event and Serious Adverse Events SOP (PM004).

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event Reporting

Adverse Event (AE) - Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected

Unexpected Serious Adverse Reaction (SUSAR)-Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death
- Is life-threatening* (subject at immediate risk of death)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
- Is another important medical event that may jeopardise the subject***

*"life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse event exclusions

The only adverse event that will be excluded is:

1. Standard or expected disease progression.

Adverse event inclusions

Adverse events which must be reported will include:

1. Chest infection requiring the use of antibiotics
2. Infection at DP site
3. A revision of the DP device

Assessment of Adverse Events

The following criteria will be used when assessing adverse events:

Intensity (severity):

- Mild - does not interfere with routine activities
- Moderate - interferes with routine activities
- Severe - impossible to perform routine activities

Relationship to the trial treatment:

- Unrelated - There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given

- Unlikely - There is little evidence to suggest there is a causal relationship.

There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

- Possible - There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

- Probable - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- Definite - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

- Not assessable - There is Insufficient or contradictory information which cannot be supplemented or verified

Reporting Procedures

All trial participants will be encouraged to contact and inform their site research team if they experience any of the medical problems outlined under SAE's or relevant AE's included (above). Those that are not picked up through general contact will be identified at follow up visits.

A member of the site study team will enquire about any adverse events since the previous visit and record these on the adverse event paper CRF and database. For any Serious Adverse Events an SAE paper CRF and database entry will be completed. The event will be assessed by the local Principal Investigator and the form will be kept in the site file. Serious adverse events will be reported in the periodic safety reports to the research ethics committee.

Research Governance

Trial oversight:

Three committees are being established to govern the conduct of the study:

1. Trial Management Group (TMG)
2. Trial Steering Committee (TSC)
3. Data Monitoring and Ethics Committee (DMEC)

All committees are governed by Sheffield CTRU standard operating procedures. The TMG consists of the Chief and Principal Investigators and key staff within the CTRU. The role of the

TMG is to implement all parts of the trial and to act on the recommendations from the TSC and DMEC.

The TSC consists of the Chief Investigator, key staff within the CTRU (as non voting members), an independent chair and three independent members. The roles of the TSC are to provide supervision of the protocol and statistical analysis plan, provide advice on and monitor progress of the trial, to review information from other sources and to consider recommendations from the DMEC. The DMEC will consist of an independent chair and 2 independent members including a statistician. The DMEC has responsibility for monitoring the results provided by the trial statistician to the plan described in the trial protocol with reference to efficacy and safety, reviewing information from other sources, providing recommendations to the TSC on why the trial might be modified or discontinued in terms of ethics and safety and considering adverse events. There will be no interim analysis for the trial unless the DMEC feels that this is necessary.

Monitoring arrangements

Trial set up and monitoring arrangements have been agreed with the trial Sponsor (Sheffield Teaching Hospitals). Once all research governance approvals and contracts are in place the trial manager will visit each site for an initiation visit. This will be before recruitment starts in order to check the site has all the necessary tools in place ready to start recruitment. Thereafter an annual visit will take place to monitor each site in order to perform source data verification and data completeness checks. A general check of the continued suitability of the site will also be performed.

13. Ethical considerations

The trial will be conducted subject to Research Ethics Committee favourable opinion including any provisions for site specific assessment. The application will be submitted through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information leaflet, consent forms, CRF's and questionnaires will be present in the site files before initiation of the study and patient recruitment.

This trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031).

14. Finance and indemnity

The trial has been financed by the HTA and details have been drawn up in a separate agreement.

This is an NHS sponsored study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial.

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical trial.

15. Reporting and dissemination

Results of the trial will be disseminated in peer reviewed scientific journals and clinical and academic conferences.

Details of the trial will also be made available on the study website. Summaries of the research will be updated periodically to inform readers of the ongoing progress.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

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17. Appendices

CONSORT FLOW DIAGRAM: The DiPALS Trial

