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

Background
Amyotrophic lateral sclerosis (ALS), also known as motor neurone disease or Lou Gehrig’s disease, is an uncommon neurodegenerative disease that affects the brain and nerves and causes weakness that gets worse over time.

There is no cure for ALS – the condition is always fatal and significantly shortens life expectancy. Most people with ALS die of respiratory failure within 2–3 years of symptom onset.

Treatments are available which can help to reduce the impact on patients’ daily lives. Non-invasive ventilation is part of the standard care for treating ALS patients who have had respiratory failure, improving survival and quality of life.

Diaphragm Pacing (DP) is a technique which may offer additional or alternative benefits to patients with ALS, in respiratory failure.

The aim of the trial was to establish the safety and efficacy of diaphragm pacing with the NeuRx/4 DP system in patients with respiratory muscle weakness due to ALS.

Methods
The team undertook a randomised controlled trial at seven specialist ALS and respiratory centres in the UK.

Participants were aged 18 years or over, had a diagnosis of laboratory supported probable, clinical probable or clinically definite ALS (stabilised on riluzole for 30 days) and were in respiratory failure.

Half of the 74 participants were randomly assigned to receive either non-invasive treatment alone, while the other half of the cohort received non-invasive treatment along with diaphragm pacing using the NeuRx RA/4 system. Treatment allocation was not masked to patients, carers, or outcome assessors.

Key features
- Three year study, between 2011 and 2014
- 74 participants with ALS in respiratory failure
- Seven specialist ALS sites across the UK
- Chief investigator: Professor Christopher McDermott (MBChB FRCP PhD), Head of Department, Professor of Translational Neurology, Honorary Consultant Neurologist, Sheffield Institute for Translational Neuroscience (SITraN)
- The first randomised control trial of non-invasive ventilation (NIV) alone, versus NIV with pacing

The primary outcome assessed as part of the trial was overall survival – defined as the time taken from allocation to death, from any cause. A number of secondary clinical outcomes were also measured to assess participant quality of life.

NIHR involvement and funding
The study was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. It was also part funded by the Motor Neurone Disease Association of England, Wales and Northern Ireland.

Outcomes and findings
The trial results showed that the addition of diaphragm pacing to standard care with non-invasive ventilation was associated with decreased survival in patients with ALS. The results suggest that diaphragmatic pacing should not be used as a routine treatment for patients with ALS in respiratory failure.
ventilator-dependent chronic respiratory failure caused by motor neurone disease suggests that there are serious long-term safety concerns. Evidence on efficacy is limited and therefore, this procedure should not be used to treat this condition”. Interventionsal procedures guidance IP1566 [IPG593]. There is currently no existing data to show that this device is being used in ALS patients across the UK.

- DiPALS also impacted on a subsequent trial in France (2015): Second Trial of Diaphragm Pacing for ALS Shuts Down - published in The Lancet (November 2016): “An unplanned masked analysis was done after another trial showed excess mortality with diaphragm pacing in patients with hypoventilation (DiPALS). In view of this finding, we analysed mortality in our study and found excess mortality (death from any cause) in our active stimulation group. We therefore terminated the study on July 16, 2015”.

- Comments by ALS patients were also published on the Motor Neurone Disease Association Forum website stating that they will not opt for diaphragmatic pacing as a result of the study results.

Outcomes

Given the outcome of the study, the quality of the study used to approve the device was not only questioned but also the use of the device that was almost at the verge of becoming a standard care treatment for ALS patients with respiratory disorders in the UK was brought a halt, therefore upholding the “do no harm” principle of medicine.

The study has since had a significant impact on national and international guidance and policy documents:

- The National Institute for Health and Care Excellence (NICE) Interventionsal Procedures Programme published a consultation document outlining its recommendations on diaphragmatic pacing based on the study.
- The NICE recommendation states that “Current evidence on intramuscular diaphragm stimulation for

Key publications: