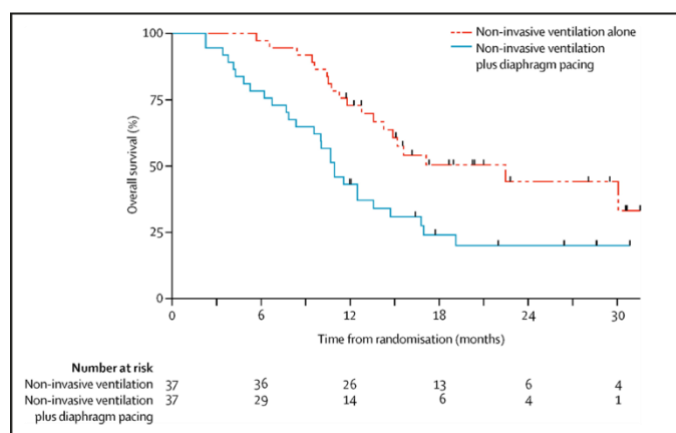


Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: DiPALS: Evidence to inform guidance on the use of diaphragm pacing for patients with amyotrophic lateral sclerosis		
Period when the underpinning research was undertaken: 2011-2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Christopher J. McDermott	Professor of Neurology	2000–present
Dame Pamela J. Shaw	Professor of Neurology	2000–present
Period when the claimed impact occurred: 2014–2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Research undertaken within the University of Sheffield has directly resulted in halting/no-adoption of diaphragm pacing (DPS) for amyotrophic lateral sclerosis (ALS) in the UK, Europe, and Canada, and has prevented DPS becoming an accepted treatment for ALS patients with respiratory insufficiency. The DIPALS trial (led by Sheffield) concluded that the addition of DPS to standard care with non-invasive ventilation (NIV) was associated with decreased survival in patients with ALS. The Sheffield team were pivotal in shaping clinical policy on the use of DPS in ALS patients which has prevented harm to patients worldwide and reduced costs to the NHS.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Amyotrophic lateral sclerosis (ALS), named motor neurone disease (MND) in the UK, is a devastating illness that leads to muscle weakness and death, usually within 2-3 years of symptom onset. Respiratory insufficiency is a common cause of morbidity, particularly in later stages, and respiratory complications are the leading cause of mortality in ALS/MND patients. Non-invasive ventilation (NIV) is the current standard therapy to manage respiratory insufficiency. Some patients do not tolerate NIV due to a number of issues including mask interface problems and claustrophobia. In those that do tolerate NIV, eventually respiratory muscle weakness will progress to a point where NIV is ineffective.</p> <p>The NeuRx RA/4 Diaphragm Pacing System (DPS) was originally developed for patients with respiratory insufficiency and diaphragm paralysis secondary to stable high spinal cord injuries. In 2011, it was given Humanitarian Device Exemption (HDE) by the United States Food and Drug Administration (FDA) for use in ALS/MND. HDE is an approval allowing a medical device to be marketed without requiring evidence of effectiveness. In 2011 the NIHR Health Technology Assessment Programme funded the DIPALS study (ISRCTN 53817913), led by Professor McDermott and implemented by Sheffield researchers with collaborators at seven specialist ALS/MND and respiratory centres in the UK. It was worldwide, the first multicentre, open-label, randomised controlled trial (RCT) designed to determine the safety and efficacy of diaphragm pacing with this system in 108 patients with respiratory muscle weakness due to ALS/MND [R1]. The primary outcome measure was overall survival, defined as the time from randomisation to death from any cause. Analysis was by intention to treat [R1].</p> <p>The DIPALS trial recruited 74 participants diagnosed with ALS/MND that fulfilled the eligibility criteria. They were randomly assigned to receive either NIV alone (n=37) or NIV plus DPS</p>		

(n=37). The Data Monitoring and Ethics Committee (DMEC) recommended suspension of recruitment in December 2013. The participants continued as per the study protocol until June 2014, when the DMEC advised discontinuation of DPS in all patients on safety grounds. Follow-up assessments continued until the planned end of the study in December 2014.

Survival was significantly shorter in the NIV plus DPS group than in the NIV alone group median 11.0 months vs 22.5 months (Fig. 1). Twenty-eight (76%) patients died in the DPS group and 19 (51%) patients died in the NIV alone group. One hundred and sixty-two adverse events (5.9 events per person-year) were recorded in the DPS group, of which 46 events were serious, compared with 81 events (2.5 events per person-year) in the NIV alone group, of which 31 events were serious. Thus, there were twice as many adverse events in the DPS group than in the NIV alone group [Fig. 1, R2, R3].



The Lancet Neurology 2015 14883-892 DOI: (10.1016/S1474-4422(15)00152-0)
Copyright © 2015 DiPALS Study Group Collaborators.
Open Access article distributed under the terms of CC-BY-NC-ND 4.0

Figure 1: Overall survival of patients in DiPALS trial

The conclusions of DiPALS are that addition of DPS to standard care with NIV was associated with decreased survival in patients with ALS/MND, demonstrating that DPS should not be used as a routine treatment for patients with ALS/MND in respiratory failure.

The research was subsequently replicated in a second multicentre, triple-blind RCT in patients with probable or definite ALS/MND in 12 ALS/MND centres in France, RespiStimALS [R2, R3].

3. References to the research (indicative maximum of six references)

- R1. McDermott, C. J., Maguire, C., Cooper, C. L., Ackroyd, R., Baird, W. O.,** Baudouin, S., Bentley, A., Bianchi, S., Bourke, S., **Bradburn, M. J., Dixon, S.,** Ealing, J., Galloway, S., Karat, D., Maynard, N., Morrison, K., Mustafa, N., Stradling, J., Talbot, K., Williams, T., and Shaw, P. J. (2012). Protocol for diaphragm pacing in patients with respiratory muscle weakness due to motor neurone disease (DiPALS): a randomised controlled trial. *BMC Neurology*, 12, 74. <https://doi.org/10.1186/1471-2377-12-74>
- R2. DiPALS Writing Committee, on behalf of the DiPALS Study Group Collaborators** (2015). Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicentre, open-label, randomised controlled trial. *The Lancet Neurology*. 14(9), 883–892. [https://doi.org/10.1016/s1474-4422\(15\)00152-0](https://doi.org/10.1016/s1474-4422(15)00152-0)
- R3. McDermott, C. J., Bradburn, M. J., Maguire, C., Cooper, C. L., Baird, W. O., Baxter, S. K., Cohen, J., Cantrill, H., Dixon, S., Ackroyd, R.,** Baudouin, S., Bentley, A., Berrisford, R., Bianchi, S., Bourke, S. C., Darlison, R., Ealing, J., Elliott, M., Fitzgerald, P., ... **Shaw, P. J.** (2016). DiPALS: Diaphragm Pacing in patients with Amyotrophic Lateral Sclerosis – a

randomised controlled trial. *Health Technology Assessment*, 20(45), 1–186.
<https://doi.org/10.3310/hta20450>

Key funding

DiPALS: A randomised controlled trial evaluating NeuRx/4 Diaphragm Pacing in patients with respiratory muscle weakness due to MND. NIHR Health Technology Assessment Programme 09/55/33, £891,313, April 2011-2014 and Motor Neurone Disease Association of England, Wales and Northern Ireland. Awarded to the University of Sheffield, CI: Prof McDermott.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, public policy and services, practitioners and services.

Main beneficiaries include: ALS/MND patients, practitioners, NHS, and NICE.

Beneficence and non-maleficence are fundamental medical ethical principles. This impact case study highlights the importance of the rigorous safety and regulatory requirements in the UK in upholding these principles. If DPS had been implemented based on FDA approval in the US, it is likely that significant harm would have been caused in a vulnerable patient group where there are limited/no treatment options available. Proving robust evidence of the harm has not only removed the risk of harm, it has also saved the NHS significant funds.

Preventing harm to ALS/MND patients

The initial impact of the DIPALS study is on the life of ALS/MND patients participating in DPS trials worldwide by ensuring they were not adversely affected by DPS; this is evidenced by the early termination of the Sheffield DIPALS trial and the RespiStimALS trial in France [S1], and the suspension of recruitment of the further 122 participants in the NEALS study in the US [S2]. This has led to the safeguarding of all ALS/MND patients worldwide from possible harm caused by DPS treatment. Approximately 82% of ALS/MND deaths are attributable to respiratory failure. Given that respiratory muscle weakness in ALS/MND will progress eventually to a point where even tolerated intermittent/overnight NIV is ineffective. It is highly plausible that DPS would have become standard care, as an upper estimate, to the 82% of patients with late-stage ALS/MND. Accordingly, the DIPALS trial protected approximately 80-100,000 patients worldwide at the time of the trial from harm. Furthermore, with an incidence rate of ALS/MND of approximately 2 per 100,000 people, the DIPALS study continues to prevent harm to over 5,000 newly diagnosed ALS/MND cases year on year.

Impact on UK guidelines

In 2011, the NeuRx 4/4 DPS received HDE approval from the FDA for use in ALS/MND on the basis of one non-randomised study which compared patients treated with DPS with published historical data for NIV as the control. However, the data from the NeuRx 4/4 DPS trial on which the FDA based their decision was not published, and this was questioned in a cautionary commentary that urged for further RCTs. At the time of the DIPALS trial, the FDA HDE approval on humanitarian grounds was wrongly seen as a proxy for high-quality evidence. As a result, many centres worldwide, including in the UK, were proceeding to offer pacing to ALS/MND patients, despite a lack of robust, independent, high-quality evidence from RCTs to support its use.

In the UK, National Institute for Health and Care Excellence (NICE) approval had not been received, restricting the access for ALS/MND patients with respiratory difficulties to DPS. The DIPALS trial, motivated by the lack of RCTs into use of DPS in ALS/MND, was required in order for NICE to decide on whether to recommend DPS or not. Following the full analysis and reporting of the DIPALS results, the NICE interventional procedures programme published its recommendations on DPS, quoting the DIPALS study. The NICE recommendation followed the

conclusions of the DIPALS study and states “*Current evidence on intramuscular diaphragm stimulation for 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*” [S3]. It is highly likely that if the DIPALS trial had not been conducted that the use of DPS would have grown to the point it was accepted as standard care, and that within a few years it would have been seen as unethical to conduct the DIPALS study.

The Motor Neurone Disease Association (MNDA), the only national ALS/MND charity in the UK and the founding member of the International Alliance of ALS/MND associations (which has 40 member organisations in 34 countries), does not recommend the use of DPS for their members. In their response to the interim report of a UK government initiative designed to enable patients to get quicker access to innovative new diagnostic tools, treatments, and medical technologies, they used the results of the DIPALS trials as a case study to support the position that “*while treatments remain experimental and unproven, we do not support making them routinely available. Such treatments should be made available to patients only via rigorous methodologies in order to make sure that they can be safely used in the wider patient population*” [MNDA Policy Manager, S4].

Impact on clinical practice and guidelines in other European countries

The DIPALS study results informed a Europe-wide halt/no-adoption of DPS in ALS/MND. The European Respiratory Society published a clinical signpost concluding that “*Diaphragm pacing should not be offered to any patient with ALS/MND*”, and the German National Guideline for Treating Chronic Respiratory Failure states “*This approach [DPS] is associated with shortened survival [in ALS/MND] and is therefore obsolete*” [S5].

In 2019, The University of Sheffield surveyed all non-UK members of the European Network for the Cure of ALS (ENCALS), which includes 54 centres covering 24 countries, by questionnaire. Questions covered guidelines and policy related to use of DPS in ALS/MND and any changes due to recommendations from the DiPALS trial. There were 20 respondents from 12 countries. Six centres from Slovenia, Germany, Norway, Sweden, Spain, and France stated definitely that the recommendations from the studies had affected their use of diaphragm pacing in ALS/MND. Fourteen centres (70% of respondents) replied “completely no use” to the question “How have the recommendations of the Diaphragm Pacing studies affected your clinical practice regarding the application of DPS in patients with ALS?” Free text responses included “*Never implemented because of the published results*” and “*We were only preparing to start diaphragm pacing when the results were published. We just decided not to go further with this therapy*” [S6].

Impact on clinical practice and guidelines in North America

Based on the DIPALS study, The Canadian Thoracic Society clinical practice guidelines concluded: “*We do not recommend diaphragm pacing in patients with ALS/MND*” [S7]. In the US, the halting of the DIPALS trial and subsequent publication of results coincides with a sharp decline in implantation of pacing devices in ALS/MND patients [Fig 2, S8].

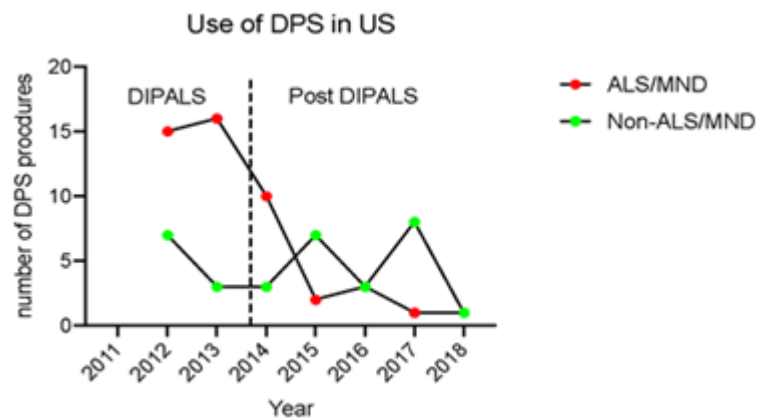


Fig 2: Use of DPS in the US. Data on DPS in the US obtained from the IBM® MarketScan® Research Databases

Impact on health economics

By preventing DPS from becoming standard care, the Sheffield research caused significant savings to health care providers worldwide. As an indication of the scale of savings, using the UK as example, in 2014 the cost of the devices and operation within the NHS was calculated as £18,000/patient compared to the annual cost of NIV of £3,600/patient [S9].

5. Sources to corroborate the impact (indicative maximum of 10 references)

- S1. Termination of the 16 July 2015 of the RespiStimALS. Gonzalez-Bermejo, J., et. Al. (2016). Early diaphragm pacing in patients with amyotrophic lateral sclerosis (RespiStimALS): a randomised controlled triple-blind trial. *The Lancet Neurology*, 15(12), 1217–1227. [https://doi.org/10.1016/s1474-4422\(16\)30233-2](https://doi.org/10.1016/s1474-4422(16)30233-2).
- S2. Halting of the NEALS trial in response to DIPALS. Katz, J., Shefner, J., and Schoenfeld, D. (2017). *Neurology* 88, S3.007.
- S3. NICE decision not to approve diaphragm pacing for ALS patients based on DIPALS trial [IPG593] <https://www.nice.org.uk/guidance/ipg593>. Interventional procedures guidance. Recommendation 1.1 P.4-8.
- S4. MND Association response to the interim report of the Accelerated Access Review pp.2, 'Case study: diaphragm pacing' (<https://www.mndassociation.org/app/uploads/mnd-association-response-to-accelerated-access-review-interim-report.pdf>).
- S5. European and German clinical guidelines: *ERJ Open Research*, 1(2), 00073–02015. <https://doi.org/10.1183/23120541.00073-2015>. *Respiration*, 96(2), 171–203. <https://doi.org/10.1159/000488667> (para 12.2.1.3).
- S6. Responses from the European Network for the Cure of ALS on the use of diaphragm pacing with ALS/MND patients.
- S7. The Canadian Thoracic Society clinical practice guideline which does not recommend the use of diaphragm pacing for ALS/MND patients. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*, 3(1), 9–27. <https://doi.org/10.1080/24745332.2018.1559644>
- S8. Data on DPS in the US obtained from the IBM® MarketScan® research databases.
- S9. DIPALS grant proposal containing the cost associated with using diaphragm pacing or non-invasive ventilation: Device £13k, Synapse Biomedical Inc. + Insertion £3k, Sheffield Teaching Hospitals NHS Foundation Trust + Annual cost of device £667, Synapse, or £2k over remaining life with a median survival of 3 years.