Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Use of non-invasive ventilation to improve survival and quality of life in patients with motor neuron disease

1. Summary of the impact

Motor neuron disease (MND) is a devastating and debilitating disease with poor prognosis; most patients die from progressive respiratory failure within three years of onset. A randomised controlled trial conducted in Newcastle provided robust evidence that non-invasive ventilation for patients with MND can significantly improve quality of life and increase survival (216 days with non-invasive ventilation compared to 11 days without). Findings from this trial underpinned recommendations concerning the use of non-invasive ventilation in MND in clinical guidelines internationally, and use in clinical practice has increased in the UK, across Europe, and in the US and Australasia. In the UK, the number of MND patients successfully established on non-invasive ventilation in 2009 had increased 3.4-fold since 2000 and since 2009 has further increased almost two-fold .

2. Underpinning research

Key Newcastle researchers
(Where people left/joined the University in the period 1993-2013, years are given in brackets)

SC Bourke (1999-2002 & 2005 onwards), Clinical Research Associate 1999-2002, Honorary Clinical Lecturer 2005-2010, then Associate Clinical Lecturer; GJ Gibson, Honorary Professor 1990-2000, Professor of Respiratory Medicine 2000-2009, then Emeritus Professor, TL Williams (2001 onwards), Clinical Lecturer/Senior Lecturer; RE Bullock, Clinical Lecturer.

Background
Motor neuron disease (MND), is one of the most prevalent neurodegenerative diseases of adulthood, with amyotrophic lateral sclerosis (ALS) being the most common form of MND. The International Alliance of ALS/MND Associations reports that around 120,000 people are diagnosed worldwide with MND each year. In the UK, two in 100,000 people are diagnosed with MND annually, and seven out of every 100,000 people currently live with MND in the UK, equating to around 4,300 people. It is a devastating and debilitating disease with a poor prognosis. Progressive weakness of muscles, including those of the limbs, trunk, mouth and respiratory system, and eventual death of the muscle cells results in disability; and ultimately most patients die from respiratory failure within three years of onset. There is currently no cure for MND, and treatment aims only to alleviate suffering and compensate for the progressive loss of bodily functions, including swallowing and breathing. The only drug available for treatment of MND is Riluzole, which offers a modest mean survival benefit of 2–3 months, with no improvement in symptom control.

Research
Respiratory muscle weakness affects most MND patients, causing breathlessness and sleep disruption [R1]. Newcastle research identified this as a strong independent predictor of quality of life in MND patients. Non-invasive ventilation assists breathing via a fitted face-mask through which air is pushed into the trachea of the patient, which in turn means that tracheostomies (surgical opening of the windpipe and insertion of a tube to facilitate breathing) can be avoided. The research, performed by Dr Stephen Bourke and Professor John Gibson in collaboration with colleagues in neurosciences (Professor Pamela Shaw at Sheffield and Dr Timothy Williams) and anaesthesia (Dr Robert Bullock) focused on the long-term use of non-invasive ventilation in MND. While previous nonrandomised studies had suggested that NIV may improve survival and symptom control in patients with MND, these studies were on selected populations and/or did not account for clinical factors such as bulbar function (controls swallowing, breathing and speech), which is known to affect tolerance of non-invasive ventilation, and independently influences survival in patients with MND. Thus, it remained unclear whether non-invasive ventilation *per se* improved patient survival, or if this was due to pre-existing favourable prognostic features. It was

also not clear if non-invasive ventilation improved patients' quality of life [R1].

In 2000, the Newcastle team carried out the first nationwide survey of UK practice on the use of non-invasive ventilation in MND [R2]. Questionnaires were sent to all practising neurologists in the UK, which revealed that only 5.5% of MND patients under review at that time were receiving gnon-invasive ventilation [R2]. Subsequently, 22 patients were included in a non-randomised pilot study, which compared different criteria (including symptoms, lung function, and indices of sleep disordered breathing) for the initiation of non-invasive ventilation [R3]. This study showed significant improvements in patient mental health, quality of life and sleep. It was also reported that orthopnoea (breathlessness when lying flat) was the best predictor of quality of life benefits [R3].

In the subsequent, and first, randomised controlled trial (RCT) to assess the effect of non-invasive ventilation on survival and quality of life in MND, 41 patients (studied between September 2000 and December 2004) were randomly assigned either to receive non-invasive ventilation or to continue without ventilatory support. Overall, 85% of the patients were also receiving riluzole. Initially, patients were monitored closely at regular intervals and were only randomly assigned to a study group when they met one or both of the following criteria: (1) breathlessness lying flat with maximum respiratory pressure (a measurement of muscle strength) less than 60% of that predicted, and (2) suffering from hypercapnia (abnormally high carbon dioxide in the blood due to inadequate breathing) [R4]. Randomisation of patients was performed by a computer programme that included all relevant prognostic factors in its model, e.g. rate of disease progression and bulbar function, in order to ensure that these were similar in the two groups. The findings showed significantly better patient mental health, quality of life and sleep in those treated with NIV, compared to patients that weren't treated with NIV. In addition, for those patients with good bulbar function, median survival was 216 days (once established on non-invasive ventilation), compared to only 11 days in patients treated without ventilatory support [R4].

A follow up UK survey carried out in 2009 to assess any changes in respiratory care of MND patients following the trial showed a 3.4-fold increase in the proportion being treated with NIV [R5].

3. References to the research

(Newcastle researchers in bold. Citation count from Scopus, July 2013)

R1. **Bourke SC**, Shaw PJ, **Gibson GJ**. Respiratory function vs. sleep-disordered breathing as predictors of QOL in ALS. Neurology 2001; 57:2040–4. DOI:10.1212/WNL.57.11.2040. **Cited by 67.**

R2. **Bourke SC**, **Williams TL**, **Bullock RE**, **Gibson GJ**, Shaw PJ. Non-invasive ventilation in motor neuron disease: current UK practice. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders 2002; 3:145–149. DOI:10.1080/146608202760834157. **Cited by 21.**

R3. **Bourke SC**, **Bullock RE**, **Williams TL**, Shaw PJ, **Gibson GJ**. Non-invasive ventilation in ALS: indications and effects on quality of life. Neurology 2003; 61:171–7. DOI: 10.1212/01.WNL.0000076182.13137.38. **Cited by 136.**

R4. **Bourke SC**, **Tomlinson M**, **Williams TL**, **Bullock RE**, Shaw PJ, **Gibson GJ**. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurology 2006; 5:140–7. DOI: org/10.1016/S1474-4422(05)70326-4. **Cited by 209.**

R5. O'Neill CL, **Williams TL**, Peel ET, McDermott CJ, Shaw PJ, **Gibson GJ**, **Bourke SC**. Non-invasive ventilation in motor neurone disease: an update of current UK practice. Journal of Neurology, Neurosurgery and Psychiatry 2012; 83:371–376. DOI: 10.1136/jnnp-2011-300480. **Cited by 10.**

Selected funding awards

- 1999-2000 Sleep disordered breathing & the impact of nocturnal ventilatory support & quality of life in motor neurone disease - a pilot study. The Newcastle upon Tyne Hospitals NHS Charities - £41,387
- 2000-2002 Sleep Disordered Breathing and the Impact of Nocturnal Non-Invasive Ventilatory Support on Quality of Life in Motor Neurone Disease. NHS Executive - Northern & Yorkshire - £82,480

4. Details of the impact

Patient Benefits

The research at Newcastle has had a significant impact on the health and welfare of patients with MND, and the randomised controlled trial (RCT) has led to changes in clinical guidelines and clinical practice. The work has provided one of only two evidence-based treatments for patients with MND in recent decades, with Riluzole being the other. However, Riluzole offers only a modest survival benefit, with no improvement in symptom control. As testified by an Associate Professor at the Respiratory Institute of the Cleveland Clinic, Ohio, the Newcastle studies '*…have shown that the magnitude of the survival impact of noninvasive ventilation exceeds that of pharmacologic intervention (with riluzole), such that future trials have to factor in the survival benefit of NIPPV* [non-invasive positive pressure ventilation]' [EV a].

The Newcastle RCT was considered Class 1 research when reviewed within guidelines on the treatment of patients with MND, produced by both the American Academy of Neurology [EV b] and the European Federation of Neurological Societies [EV c], and it was the only RCT selected as fulfilling the rigorous criteria for entry into a Cochrane review of the subject of mechanical ventilation for MND patients [EV d]. The research clearly demonstrated the survival benefit offered by non-invasive ventilation to those patients with good bulbar function compared to standard non-ventilatory treatment. It also demonstrated a significant and sustained improvement of quality of life for patients treated by non-invasive ventilation. Respiratory muscle weakness causes hypoventilation and sleep disruption and, as a consequence, patients with MND often suffer from morning headaches, lethargy, fatigue, poor concentration, and poor appetite [EV e]. Non-invasive ventilation can significantly reduce these symptoms, such that the longer survival of MND patients given non-invasive ventilation is accompanied by improved symptoms. Since non-invasive ventilation is provided through a portable ventilator, patients are treated in their own homes [EV e] with support from specialist home ventilation services, which are available in the UK and elsewhere.

The potential benefits of non-invasive ventilation are recognised by the *MND Association*, who quoted the Newcastle-based research in a press release [EV e] ahead of a Westminster Hall debate in 2009 on the availability of non-invasive ventilation to people with MND. The RCT [R4, section 2] was directly referred to during the debate [EV f]. Specifically, it was stated that: '*Clinical research published in 2006 showed that non-invasive ventilation typically increased the median survival period for people with motor neurone disease by seven months*' and '*…the typical survival period is 14 months, so seven months would be a material change in someone's survival, and a major change in their quality of life and that of their carers*' [EV f].

Clinical Practice

The Newcastle led survey carried out in 2009 found that the number of MND patients referred for non-invasive ventilation within the UK had increased 2.6-fold compared to the number of referrals in 2000 (from 234 to 612), and the number of patients successfully established on non-invasive ventilation had increased 3.4-fold (from 126 to 444) [R5, section 3]. Since the incidence of MND has remained stable over that time, these figures indicate that there has been a substantial change in clinical practice and an improvement in the referrals process [R5, section 3]. In addition, the access to non-invasive ventilation services by neurologists has improved, as 10.1% reported no service available in 2000 compared with only 1% in 2009 [R5, section 3]. In 2010, NICE published guidelines on the use of NIV in the management of MND, with Dr Bourke on the guideline development group [EV g]. Within the UK, the wider implementation of these guidelines continues to increase the use of non-invasive ventilation for MND and addresses any current variations in clinical practice. This is evidenced by two surveys carried out by the MND Association on patients living with MND in England, Wales and Northern Ireland. Data from patient questionnaires showed that NIV use by MND patients has increased from 13.2% (62 out of 469 patients) in 2009 to 24.6% (192 out of 779 patients) in 2013 [EV h].

The clinical impact of this research is clearly evident beyond the UK; the use of non-invasive ventilation in patients with MND has expanded in the US, Australia and across Europe, where clinical guidelines now include evidence-based recommendations for its use. As identified by the clinical and academic director of the national referral centre for chronic respiratory failure and

home ventilation at St Thomas' hospital '*…the trial by Bourke et al has driven forward the use of non-invasive ventilation in both the European and North American Centres*' [EV i].

The *American Academy of Neurology* cite the work by the Newcastle group in the opening paragraph of their 2009 Practice Parameter update (an influential US clinical practice guideline), stating that since the publication of the previous guidelines '*…there have been some important new studies, including a randomized controlled trial of non-invasive ventilation in ALS.*[2]' (where '2' refers to R4 in Section 3) [EV b].

The RCT also has an important position in the *European Federation of Neurological Societies* 2012 *guidelines for the diagnosis and management of ALS* [EV c], in which NIV is advised for the management of respiratory dysfunction in all MND (ALS) patients with good bulbar function [EV c, p.371]. The following quote and recommendation are taken directly from the guidelines (in which '*[140]*' refers to R4 in section 2): '*Non-invasive positive-pressure ventilation increases survival and improves patients' quality of life and is the preferred therapy to alleviate symptoms of respiratory insufficiency [47, 49, 137–142] (of which [140] is Class I)*' [EV c, p.372]. Further, it is stated in the recommendations that '*NIPPV [non-invasive positive-pressure ventilation] can prolong survival for many months' and '…may improve the patient's quality of life*' [EV c, p.372].

In addition, guidelines published in 2010 by the *New South Wales Agency for Clinical Innovation* highlight that "*…the role of NIV remained unclear until a randomised controlled study by Bourke et al [139]*" (where [139] refers to the RCT) and that *'…nocturnal ventilation is used in patients with motor neurone disease to improve symptoms and quality of life*', (again citing R4, section 3) [EV j, p.39-40]. The objective of these guidelines is to provide information to optimise the management of individuals with disorders likely to lead to the development of chronic respiratory failure and aims to assist clinicians in informed decision-making [EV j].

5. Sources to corroborate the impact

EV a. Testimonial: Associate Professor of Medicine, Cleveland Clinic, Ohio, USA. (Held at Newcastle, available on request)

EV b. Miller RG et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2009; 73:1218–26. DOI: 10.1212/WNL.0b013e3181bc0141

EV c. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. European Journal of Neurology 2012;19:360–75. DOI:10.1111/j.1468-1331.2011.03501.x

EV d. Radunovic, A et al. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease (Review).The Cochrane Collaboration, 2009; 4:CD004427. DOI: 10.1002/14651858.CD004427.pub2

EV e. http://centrallobby.politicshome.com/members/member-press/member-press-details/newsarticle/the-benefits-of-non-invasive-ventilation-systems-1///sites/motor-neurone-disease-association/

EV f. http://www.publications.parliament.uk/pa/cm200809/cmhansrd/cm090331/halltext/90331h0001.htm

EV g. National Institute for Health and Clinical Excellence. Motor neurone disease – the use of non-invasive ventilation in the management of motor neurone disease, 2010. www.nice.org.uk/cg105

EV h. Motor Neurone Disease Association: Tracking Surveys, 2009 and 2013 (July). (Copies held and available on request. Contact: Director of Care (South), MND Association)

EV i. Testimonial: Clinical & Academic Director, Lane Fox Respiratory Unit, St Thomas' Hospital; National referral centre for chronic respiratory failure/home ventilation, UK. (Held at Newcastle, available on request).

EV j. ACI, NSW Agency for Clinical Innovation. Domiciliary non-invasive ventilation in adult patients – a consensus statement. http://www.aci.health.nsw.gov.au/search-results?mode=results&queries_keyword_query=non+invasive&x=0&y=0