Non-Invasive Ventilation in

Motor Neuron Disease/Amyotrophic Lateral Sclerosis

An Australasian Perspective

By

Wai Kuen Chow

M.B.B.S. F.R.A.C.P

THESIS

FoHS Master of Research

Faculty of Human Sciences

Australian School of Advanced Medicine

Macquarie University

Sydney, Australia

10th October 2014

Table of Contents

SUMMARY

There is a paucity in Australian literature regarding the current practice trends in the use of non-invasive ventilation therapy in patients with motor neuron disease/ amyotrophic lateral sclerosis (MND). The issue of whether non-invasive ventilation support should be provided to patients with irreversible neurodegenerative disease remains debated by some clinicians. An understanding of the practices of Australian and New Zealand specialists with respects to non-invasive ventilation (NIV) in motor neuron disease is thus important.

This study reports the findings of a questionnaire study conducted in Australia and New Zealand via the memberships of the Thoracic Society of Australia and New Zealand, and The Australia and New Zealand Association of Neurologists. It aimed to gain insight into the respiratory and neurologist specialists' current practice and preferences in non-invasive ventilation therapy (NIV) for Motor Neuron Disease (MND) patients. In this study, the rate of NIV therapy use in MND patients by the respiratory physicians and neurologists was 75% and 29% respectively. Sixty percent of neurologists referred symptomatic MND patients to either a respiratory physician or to MND multidisciplinary clinic. There was high variability in the manner patients were assessed as needing NIV therapy, as there was in how patients were monitored on treatment.

DECLARATION OF ORIGINALITY

I certify that the work in this thesis entitled "Non-Invasive Ventilation in Motor Neuron Disease/Amyotrophic Lateral Sclerosis: An Australasian Perspective" has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University.

I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis.

The research presented in this thesis was approved by Macquarie University Ethics Review Committee, reference number: 5201400418 on 9th May 2014.

Dr Wai Kuen Chow

Student ID: 43575609

10th October 2014

CHAPTER 1: INTRODUCTION

1.1 The trend in the use of non-invasive ventilation

The introduction of non-invasive ventilation (NIV) to assist patients with sleep disordered breathing difficulties almost three decades ago was ground breaking. Non-invasive ventilation provided respiratory support via positive pressure ventilation; NIV is delivered through a facial mask to regulate the patients' breathing pattern and to reduce their work of breathing. This mode of non-invasive mechanical ventilation has been widely adopted by patients who develop hypercapnic respiratory failure due to a range of medical conditions. A few examples of the medical conditions include neuromuscular disorders (Duchenne Muscular Dystrophy, Motor Neuron Disease), chronic lung diseases (decompensated Chronic Obstructive Pulmonary Disease, Cystic Fibrosis), restrictive chest wall deformities, Obesity Hypoventilation Syndrome, Congenital breathing abnormalities and spinal cord injury. The provision of ventilatory support with NIV thus plays an important role in the respiratory failure management in acute and chronic situations; and in both hospital based and domiciliary care settings.

A recent questionnaire survey study conducted by Garner et al described the minimum prevalence and the pattern of home mechanical ventilation usage in Australia and New Zealand. This study surveyed 34 centres in both regions, which were identified as servicing greater than five adult patients with more than three months use of home mechanical ventilation. Interestingly, the study described a higher prevalence of home mechanical ventilation usage in Australia (9.8 patients per 100,000 population) and New Zealand (12.0 patients per 100,000 population) when compared to the Europeans (6.6 patients per 100,000 population).

Obesity hypoventilation syndrome was ranked as the first frequent indication (31%, CI 29.3-32.8) for home mechanical ventilation that was managed in New Zealand regions. The neuromuscular group of diseases ranked second (30.2%, CI 28.5-31.9) which was often managed by larger Australian centres.

This study also illustrated that motor neuron disease was the highest proportion (8.4%, CI 7.4-9.5) of the neuromuscular diseases to receive home mechanical ventilation; and was similar to patients with Chronic Obstructive Pulmonary Diseases (8.0%, CI 11.9-14.5) receiving home mechanical ventilation.

The role of non-invasive ventilation use at home to provide mechanical ventilation to motor neuron disease patients with respiratory failure is generally accepted as a standard of care therapy. However, there is a variability in the initiation of non-invasive ventilation therapy to motor neuron disease patients due to their complex spectrum of disease progression, and the variance between states and regions to direct access of non-invasive therapy support service. Perhaps, the inherent grave prognosis of the disease process may also result in a palliative and 'pessimistic' approach to the management of the terminal phases of disease in these patients.

1.2 Incidence and prevalence of motor neuron disease

Statistical data from the *Analysis of Australian Institute of Health and Welfare National Mortality Database* estimated the incidence of motor neuron disease in Australia as being the same as the death rate. In 2011, the incidence of motor neuron disease was 1 in 36,500 or 2.74 cases in 100,000 people. The prevalence was estimated at approximately 1 in 13,000 people; translated to a prevalence of 1,900 people living in Australia with motor neuron disease (population 22,342,000 in 2011).

It was also noted that there had been a steady increase in the number of deaths from motor neuron disease in the last decade. In 2011, there were 790 motor neuron disease related deaths compared to 592 in 2001. The cause of the increase in the number of deaths and incidence is not known.

The *Motor Neuron Disease Association of New Zealand Inc*. reported that there are approximately 300 people living with motor neuron disease; an estimated prevalence of 1 in 15,000 people (population of 4,433,000 in 2012) in New Zealand. There are between 80 -100 new cases diagnosed each year (an estimated incidence of 2.25 cases in 100,000 people); with deaths of approximately 80-100 patients per year. \

The incidence and prevalence of motor neuron disease in both Australia and New Zealand continents allow us to understand the significant impact of this disease burden. These statistics describe the occurrences of motor neuron disease diagnoses, which inevitably will impact socio-economic and health burden within these communities.

CHAPTER 2: LITERATURE REVIEW

2.1 Amyotrophic Lateral Sclerosis/Motor Neuron Disease

Amyotrophic Lateral Sclerosis (ALS) was initially described by Jean-Martin Charcot, a French neurologist and a Professor in anatomical pathology in 1874. He recognised the unrelenting symptoms of progressive muscular weakness with atrophy affecting the whole body to be attributed to upper and lower motor neurons degeneration and death, with gliosis replacing these neurons. In 1939, this disease was well publicised as "Lou-Gehrig's disease" in the United States, named after a popular American baseball player who was diagnosed at the age of 36 during the peak of his baseball career. He later succumbed to the disease two years later. The term Motor Neuron Disease (MND) is sometimes used interchangeably with ALS and is the frequent terminology used in Australia and New Zealand.

MND is a relatively rare disease entity, but it is considered as one of the most common adult-onset neurodegenerative diseases. Over the last few decades, the global incidence has been increasing, and a similarly observed trend is also occurring in Australia. The annual incidence of MND is variable between countries; the current estimated worldwide annual incidence is 3 cases per 100,000 people.[2-8] MND typically affects adults between the ages of 40-60 years, and has a peak incidence in the late 60's to early 70's. There is a slight male preponderance. Motor neuron disease does not discriminate between ethnicity or racial background. The majority of motor neuron disease cases are sporadic, and less than 10% of affected cases have genetic and familial linkages. To date, no direct cause has been found for sporadic MND. Several epidemiological studies have researched whether occupational, environmental or geographical factors are contributory, but there remains no established direct aetiology or risk factors, apart from age and a positive family history. [9-13]

2.2 Spectrum of Motor Neuron Disease

The spectrum of motor neuron disease is defined by the clinical extent and varying pathological involvement of either or both upper and lower motor neurons degeneration of the cortex, brain stem and spinal cord. The most common form of motor neuron disease typically involves both upper and lower motor neuron pathology; and is also known as Amyotrophic Lateral Sclerosis (ALS).[14,15] The typical features of ALS include both upper (spasticity, pathologic reflexes) and lower motor neuron signs (muscle weakness, atrophy, clinical fasciculations) in at least three body regions (upper limb, lower limb, bulbar, thoracic) which progress over a period of six months.[16,17] Several other variants of MND can be classified as:[18]

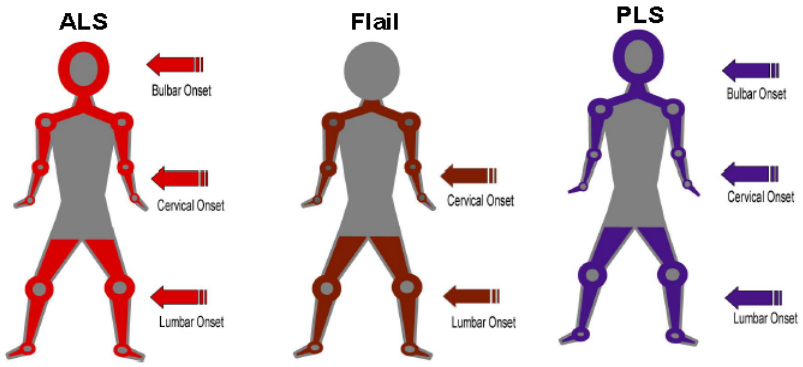
1. *Progressive bulbar palsy or bulbar onset MND* is a progressive upper and lower motor neuron disorder initially affecting the cranial nerves, and is often associated with bulbar dysfunction. Early respiratory dysfunction, speech and swallowing difficulties result in this form of MND have the worse prognosis with a mean survival of 30 months from symptom onset.
2. *Flail limb onset of MND* is characterised by progressive lower motor neuron weakness and wasting affecting the distal parts of the upper or lower limbs, without upper motor neuron and bulbar features. Both flail arm and flail leg syndromes have longer survival when compared to classical ALS syndrome, and tend to have a slower progression towards the development of respiratory muscle weakness.[19,20] This subtype of MND was previously termed *Progressive muscular atrophy*. The course of the disease can be protracted to last as long as 20-30 years.[21]

Primary lateral sclerosis is associated with progressive upper motor neuron syndrome affecting both limbs and bulbar palsies, usually without lower motor neuron features. This subtype characteristically has the slowest progression with six to seven years longer when compared to the classical ALS syndrome.[22]

3. *ALS-plus syndrome*s occurs rarely, and is considered when MND patients have additional features such as fronto-temporal dementia, autonomic insufficiency, parkinsonism, supranuclear gaze paresis and/or sensory deficits. It is associated with significantly shorter survival. [23]

Pictorial representation of MND – with courtesy from AMNDR

AMNDR.org



	Upper Motor Neuron Signs (UMN)	Lower Motor Neuron Signs (LMN)
Bulbar	1. Jaw Jerk Positive 2. Palatal Spasticity 3. Tongue Spasticity	1. Facial Fasciculations 2. Tongue Wasting 3. Palatal Weakness and Fasciculation
Cervical	1. Increased tone 2. Hyper-reflexia 3. Preserved reflexes in wasted muscles	1. Fasciculation's and Weakness 2. Muscle Wasting 3. Absent Reflexes
Lumbar	1. Increase tone and or extensor plantars 2. Hyper-reflexia 3. Preserved reflexes in wasted muscles	1. Fasciculation's and Weakness 2. Muscle Wasting 3. Absent Reflexes

2.3 Respiratory muscle weakness in Motor Neuron Disease

Almost every patient with MND will develop respiratory muscle weakness at some stage during their disease. [24-26] The lung is not directly affected by motor neuron disease, but the mechanics of breathing and the respiratory function supported by major respiratory muscle groups are often involved. The consequences of the affected inspiratory, expiratory and upper airways muscle groups lead to insufficient ventilation (shallow breathing), nocturnal hypoventilation and ineffective cough. The resultant ventilatory and progressive chronic respiratory failure is the most frequent cause of death within three to five years of established MND diagnosis. [14,27]

Symptoms of compromised respiratory function such as tachypnoea, dyspnoea or breathlessness may not be overtly evident especially when MND patients have reduced mobility and exercise tolerance secondary to muscular weakness in both upper and lower limbs. Other symptomatic manifestations such as orthopnoea, choking arousals, unrefreshing sleep, morning headaches, excessive daytime hypersomnolence and fatigue are suggestive of nocturnal hypoventilation related to respiratory muscle weakness. These symptoms may be anticipated as the first sign of inadequate ventilation during sleep, because the diaphragm is the only active inspiratory respiratory muscle during rapid eye movement stage in sleep. [25,28] Therefore, diaphragmatic dysfunction is a notable predictor of dyspnoea, but it is not necessarily a definite indicator of sleep disordered breathing.[25] Patients with MND who report symptoms of respiratory and/or ventilatory dysfunction have a poorer prognosis when compared to those who do not have respiratory symptoms. Typically, the patients with bulbar onset MND have earlier onset of symptomatic respiratory muscle weakness and a rapid decline in its disease progression.[25,29]

The assessment of respiratory muscle weakness with objective physiological testing is therefore of paramount importance in identifying these patients who may require ventilatory support. The serial measurement of vital capacity and forced vital capacity (FVC) by formal pulmonary function testing is a convenient and non-invasive method of evaluating the inspiratory muscle weakness.[30] FVC and other routine measures do not predict the presence or absence of nocturnal hypoventilation.[32] Additional comprehensive testing to include residual volume, maximum voluntary ventilation, maximal inspiratory or maximal expiratory pressure, percentage differences between supine and erect positioning and sniff nasal inspiratory pressure collectively may provide further evidence to support the clinical suspicion.[33] However, the interpretation of these volitional testing results may be imprecise or inadequate in circumstances when patients with bulbar dysfunction have difficulties in sealing the spirometer mouthpiece or when patients' efforts and co-operation are deemed suboptimal.[34]

Alternative invasive assessment of diaphragmatic strength involves placement of a balloon catheter via the nasal passage into both the oesophagus or stomach to measure the transdiaphragmatic pressures, and/or the phrenic nerve stimulation magnetically with recording of the diaphragm electromyogram.[34] These complex tests are usually performed in highly specialised centres that are not readily accessible.

There is a strong correlation between abnormalities of ventilation with respiratory muscle weakness and the degree of sleep disturbance. [26] Sleep presents as a vulnerable period when MND patients are likely to exhibit the earliest indication of breathing regulation difficulties. The evaluation with an overnight oximetry at the patient's home during sleep can detect periods of oxygen desaturations with accompanying tachycardia. This finding raises the suspicion of nocturnal hypoventilation and formal polysomnography can be performed to clarify the aetiology of oxygen desaturations.[24,34] Furthermore, an analysis of arterial blood gas is fundamental in detection of hypercapnic respiratory failure associated with hypoventilation, specifically when carbon dioxide levels are elevated.

There is no cure for MND. However, an oral medication, *riluzole* (50mg twice daily) is recommended to be commenced promptly at the time of diagnosis, with the aim of slowing the disease progression. It is a safe drug with minimal side effects. There is compelling trial evidence to support the benefits of *riluzole*, as it prolongs median survival by three months following eighteen months of therapy, and can improve one year survival by 15%.[35,36] It is unclear whether the benefits are translated to older, more advanced patients with long standing disease. However, for patients who are on *riluzole* treatment, both bulbar function and limb function decline is delayed.[37]

2.4 Non-invasive positive ventilation therapy and Motor Neuron Disease

Non-invasive ventilation is another therapeutic option that improves survival and quality of life for MND patients with symptoms of respiratory failure and compromise. [38,39] Several controlled trials and one randomised control trial have explored the benefits of non-invasive ventilation.[40-45] The findings of these studies showed strong evidence that the use of non-invasive ventilation reduces the work of breathing, improves gas exchange, improves exercise tolerance and sleep quality. Ultimately, this method of assisted ventilation with bi-level intermittent positive air pressure support improved survival by 48 days and improved quality of life above 75%.[43]

The patient's mental health, energy vitality and general health perceptions were measured against the chronic respiratory disease questionnaire, sleep apnoea quality of life index and short form health survey SF-36. The study by Bourke et al. also showed MND patients with mild bulbar dysfunction had improved median survival of 205 days compared to patients who received standard care.[43]

Despite these studies showing supportive evidence that demonstrated the effectiveness of non-invasive ventilation, this form of assisted respiratory therapy is not consistently advocated. Its utility is not universally considered as standard therapy of care for MND patients and there is a variable trend in its uptake. The first evidence based review guideline published in 1999 by 'The American Academy of Neurology (AAN) Practice Parameter for Amyotrophic Lateral Sclerosis'[46] recommended increased surveillance and vigilance in MND patients for respiratory symptoms of hypoventilation. There was a constellation of respiratory function tests that could be used to monitor progression. The criteria of forced vital capacity below 50% predicted value was emphasised in the guideline to prompt discussion between the physician and the patient regarding non-invasive ventilation counselling.

Furthermore, the recommendation of respiratory symptoms hypervigilance was also echoed in the European Federation of Neurological Societies (EFNS) on the Clinical Management of Amyotrophic Lateral Sclerosis, initially published in 2005, and revised in 2012.[35,38] Their proposed criteria for consideration of non-invasive positive pressure ventilation initiation included symptoms/signs related to respiratory muscle weakness, and/or one of the findings of an abnormal respiratory function test that included forced vital capacity below 80% predicted value, sniff nasal pressure less than 40cms H_20, PiMax less than 60cms H_20, significant nocturnal desaturation on overnight oximetry and morning arterial blood gas PaCO2 greater than 45mmHg.[38]

The Cochrane Database of Systematic Review, 2013 revised the use of mechanical ventilation for amyotrophic lateral sclerosis/ motor neuron disease patients and concluded that non-invasive ventilation therapy has a significant impact in improving and maintaining the quality of life, as well as prolonging the survival of MND patients with milder bulbar dysfunction.[47] The primary role of these guidelines is to provide a succinct proposal of the available evidence based medicine practice to improve patient care outcomes.

Motor neurone disease is a fatal, progressive and unrelenting neurodegenerative disease. It has complex advancement and involvement of upper and/or lower motor neuron degeneration that can be rapid with unpredictable physical functional consequences. The manifestations of respiratory symptoms/signs may not specifically signify respiratory muscle weakness onset, and there is no single respiratory test that can exactly predict the evolution of respiratory function insufficiency. On the other hand, there are some MND patients who can remain asymptomatic despite having very abnormal respiratory physiological testing.

Therefore, the timing of the non- invasive ventilation therapy introduction can be challenging, and considered controversial by some treating specialists for affected patients who have little hope of neurological recovery given the grave prognosis of motor neuron disease.

The current clinical application of the non-invasive ventilation therapy is varied across many continents (Table 1). Over the past decade, there has been an encouraging paradigm shift towards the implementation of NIV therapy for MND patients following the introduction of the clinical care guidelines in 1999. These studies have shown that MND patients receiving NIV therapy often are attending specialised MND care centres.

These patients are more likely to remain on *riluzole* treatment and receive nutritional support via percutaneous gastrostomy especially if patients suffer symptoms of severe bulbar dysfunction. The patients' demographics receiving NIV therapy were usually younger aged, male gender with supportive carer, often with married status. [45,48-50]

Table 1: Summary of the use of NIV therapy across several nations

Author **Country**	**Region/Source**	**Survey period**	**% of MND patients receiving NIV therapy**
Chio [48,51] ITALY	Piemonte and Valle d'Aosta Register for ALS	1995-2004 (n = 1260)	***21%*** (1995-1999 = 25.3%) (2000-2004 = 47.5%)
Lechtzin [45] NORTH AMERICA	ALS Patient Care Database Registry	1996 -2000 (n = 1458)	***15.6%***
Bourke [52] UNITED KINGDOM	Postal survey to neurologists via Association of British Neurologists	2000 (n = 2280)	***5.5%***
O'Neill [53] UNITED KINGDOM	Postal survey to neurologists via Association of British Neurologists (follow up of Bourke study)	2009 (n = 3077)	***14.0%***
Miller [54] NORTH AMERICA	ALS CARE database registry	1996-2004 (n = 5,600)	1997 = ***9%*** 2004 = ***21%***
Colville [55] SCOTLAND (East)	Tayside and North East Fife Local health boards	December 2003 (n = 26)	***3.84%***
Georgoulopoulou [56] ITALY	Modena MND Centre	2000-2009 (n = 193)	***47.7%***
Raaphorst [57] NETHERLANDS	Utrecht Home Ventilation Services	2007-2012 (n = 217)	***51.2%***
Cui [58] CHINA	MND Clinics of Chinese ALS Association	2009-2010 (n = 461)	***34.5%***

The recurring findings of these studies confirm the usefulness of non-invasive ventilation therapy in improving quality of life and prolonging survival. These statistics show progressive acceptance of NIV therapy over recent years and reflect the tolerance of MND patients who were commenced on NIV therapy. The attitudes and perceptions of treating specialists are influential and may bias patient's decision in the acceptance of NIV therapy.

There is a poverty of published literature regarding the current experience and practice trends in the use of non-invasive therapy in MND patients within the Australasian region.

CHAPTER 3: METHODOLOGY

3.1 Aims of study

The aim of this study was to survey all practising respiratory physicians and neurologists within the Australasian region with a postal questionnaire, to gain some insight into their perceptions, practice patterns and knowledge regarding non-invasive ventilation therapy in motor neuron disease. The study also aimed to elucidate any factors that may be influencing the introduction of NIV therapy in MND patients. The issue whether NIV therapy should be initiated in MND patients with limited life expectancy can be challenging. As non-invasive ventilation technology advances, an opportunity to use this therapy should not be overlooked when there is good evidence-based literature to support the effectiveness of NIV therapy. The information gained from this study may form the basis for further research and/or programs in promoting the use of NIV therapy in MND patients. The clinical findings of this study will be analysed for its relevance clinically and statistically, and will be published in a peer review journal as an Australasian perspective in management of motor neuron disease patients with respiratory failure.

3.2 Participants

The postal questionnaire was sent to all respiratory physicians identified through The Thoracic Society of Australia and New Zealand (TSANZ) in June 2014. Due to unforeseeable administrative delays, the postal questionnaire was sent later in September 2014 to all neurologists identified through Australian and New Zealand Association of Neurologists (ANZAN). A cover letter, a consent note with basic demographic information sheet was included with all posted questionnaires, as well as a stamped self-addressed envelope (Refer to Appendix A and B).

Responses were encouraged from clinicians who do not treat MND patients, who are retired or for those who declared no interest or have any clinical relevance to the questionnaire.

Due to the strict regulation (*Australian Privacy Act 1988)* and the protection of specialist members' personal information, the addresses of the questionnaire mail out were not traceable. Therefore, non-responders were not identified to allow second mailing and follow-up reminder note was not dispatched.

3.3 Questionnaire

Ethical and scientific approval was granted for this project to be conducted at Macquarie University by the Macquarie University Human Research Ethics Committee on 9th May 2014. Reference number: 5201400418 (Refer to Appendix D).

A well designed, postal questionnaire that is short with clear and unambiguous questions is a cost effective method of gathering important information.[59,60] The realities of a busy physicians' practice may be prohibitive in their abilities to participate in a postal questionnaire. Feasibly, the highly contentious topic of non-invasive ventilation therapy in MND may be the catalyst to encourage their participation. Other alternative approaches in gathering data include telephone surveys, fax surveys, face to face interview surveys and web based surveys. These alternate strategies were not chosen because they have the disadvantages of portraying a survey as unsolicited, obtrusive and confronting. Furthermore, a paper based questionnaire ensures anonymity, and allows participants to freely express their opinions. There is no clear consensus in the literature that states a specified acceptable response rate as there are often multiple confounders in a survey questionnaire to determine its own credibility.[61,62]

Bourke et al. conducted a postal survey examining the views of British neurologists regarding NIV in MND [52] and found marked variation in the neurologists' practice of the NIV therapy use. He showed an increasing trend in the use of NIV therapy over time when his postal questionnaire survey was re-sent ten years apart (2002 and 2012) to British neurologists. Hence, the reliability of his study's questions could be reproducible which ensured consistency in the measurements of the practice trends in NIV therapy. When dependable reliability and effective validity of the questionnaire is combined, the results can then be interpreted accurately, and the correlation or strength of association between variables can be determined.[63,64] With kind permission from Dr Stephen Bourke, he provided his questionnaire for review (Refer to Appendix E). The questionnaire for this study was designed with adaptations of Dr Bourke's questionnaire (Refer to Appendix C).

The consent note with basic information sheet (Appendix B) obtains consent agreement and collects demographic information such as type of medical speciality, gender, age, consultancy years, type of practice and area of medical practice.

The purpose of the questionnaire was to collect information related to frequency of NIV therapy use, and to gather statistics to understand the preferences of the treating specialists. The questionnaire was based upon a previously validated survey[53] (Appendix C). The questions surveyed were:

1. The number of MND patients:
    i. New patients seen in last 12 months
    ii. Currently managed
    iii. Referred to start NIV therapy in last 12 months
    iv. Successful in being established on NIV therapy
    v. Currently on NIV therapy

2. Yes/No questions pertaining to:

    i. Shared care of MND patients with other specialists
    ii. Direct access to NIV therapy
    iii. Advanced care directives discussion during the planning of NIV therapy

3. Multiple tick box responses to collect information on:

    i. Other Specialities involvement
    ii. Type of respiratory investigations ordered
    iii. The participant's perception of the contra-indications to NIV therapy
    iv. The participant's perception of NIV therapy in MND patients with differing severity of bulbar dysfunction

4. Multiple choice questions with one best option to define the participant's preference in:

i. Next course of action when MND patients have symptoms of nocturnal hypoventilation
ii. Which respiratory symptoms/signs to identify before recommending NIV therapy
iii. A case scenario of typical ALS patient with rapid disease progression with symptoms of respiratory compromise

5. Free writing texts were placed to allow open expressions amongst the yes/no questions. The last page of the questionnaire was positioned to invite participants' comments, and allowed open communication regarding the topic of NIV in MND.

3.4 Data collection

All de-identified responses were assessed confidentially. The responses from the questionnaire was collated and tabulated on an Excel Spreadsheet. Descriptive statistics was used to analyse and quantify the numerical descriptors, such as the mean, mode and median values. Absolute and relative frequencies of the study sample such as percentages, proportions, rates and ratio were studied from the qualitative and quantitative data collected. The calculation of the quantitative data was then used to make inferences to understand the current practice trends of treating specialists who care for MND patients. Further statistical analysis with independent sample t-test to compare two groups of specialists was utilised to compare the results of their responses as the data distribution was determined by two tailed tests

3.5 Limitations of study

One of the major disadvantages of postal questionnaires is the likelihood of insufficient or low response rates which could threaten the study's validity. Indeed the interpretation and conclusions of the questionnaire results correspond to those who responded. The credibility of study results are better supported with higher response rates. However, the absolute number or the size of the sampling population will also influence the integrity of calculated response rate. Steps taken to improve the response rate included inclusion of an introductory cover letter, stamped self-addressed return envelopes, simple questionnaire design and layout without word clutter and the use of Macquarie University logo on the letter head to ensure authenticity of the research study.

Another limitation of questionnaire is the potential for selective participants' bias. Whereby, the respondents are typically highly motivated in the study topic with strong opinions and were willing to devote their time to complete and return the questionnaire. The evaluation of these responses will reflect their beliefs and views one way or another. It can also be difficult to assume that the participants have interpreted the questions as the study had intended. So, commentary opportunities were provided within the questionnaire design to allow respondents to voice their point of views openly. Their comments are likely to provide insightful information that may not have been probed by the designed questionnaire.

CHAPTER 4: RESULTS

Responses were received from 305 of 1635 postal questionnaires distributed (19%). One hundred and ninety nine responses were received from 835 survey questionnaires posted to addresses provided by TSANZ (24%). One hundred and six responses were received from 800 survey questionnaire posted via ANZAN (13%). The Medical Board of Australia (AHPRA), July 2014 publication of medical registrant data showed: 610 respiratory and sleep medicine physicians, 23 paediatricians in respiratory and sleep medicine, 526 neurologists and 28 paediatric neurologists. The questionnaire mailings were likely to have included all practising neurologists and respiratory and sleep physicians in Australia and New Zealand; as well as those who may have retired, advanced physician trainees, and possibly non-clinicians with higher post doctorate degrees. Ninety-four of 199 respiratory responders (47%), and thirty-five of 106 neurology responders (33%) replied with a consent note with the basic demographic information sheet without completing the questionnaire.

4.1 Demographics

There was a male to female ratio of 3.3:1 of respiratory responders without questionnaire. Their mean age was 52.8 (range 29 – 80 years) and the mean years post specialist qualifications (FRACP) was 20.4 years (range 1 – 50 years). Sixty nine percent of respiratory responders without questionnaire worked in the metropolitan area, 31% worked in public practice setting and 21% worked in both private and public practice setting. In the group of neurology responders without questionnaire, the male to female ratio was 2.2:1, with the mean age of 53.3 (range 33 – 87 years) and mean years post FRACP of 19.8 (range 1 – 53 years).

There was no statistical difference between these two groups of specialists (Table 2). Almost all of neurology responders without questionnaire (94%) worked in the metropolitan area and 34% worked in public practice setting.

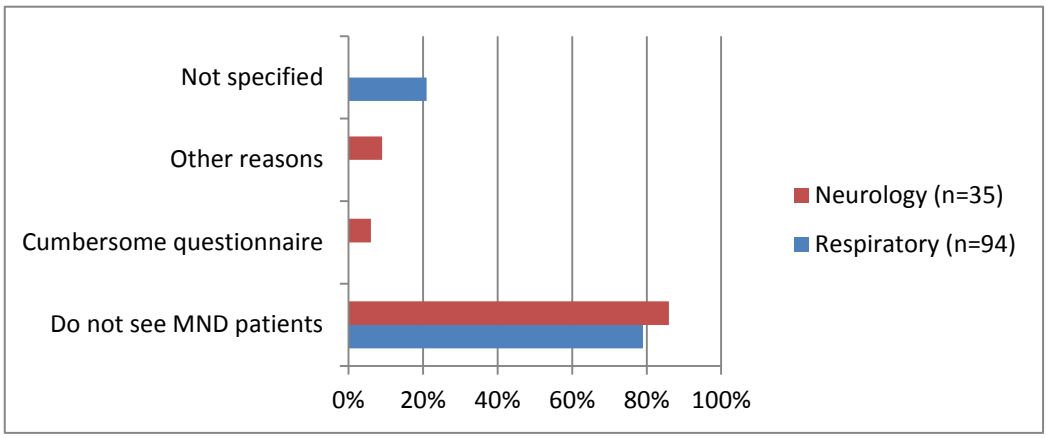
Refer to Appendix F: Table 1 for demographics summary of respondents

Table 2: Comparison of responders without questionnaire

Without Questionnaire:	Respiratory n=94	Neurology n=35	P value
Male:Female Ratio	3.3:1	2.2:1	
Age			
- **Mean (±SD)**	52.8 (±15.4)	53.3 (±15.0)	P = 0.86
- **Range**	29 – 80 years	33 – 87 years	
Years post FRACP			
- **Mean (±SD)**	20.4 (±15.1)	19.8 (±15.9)	P = 0.85
- **Range**	1 - 50	1 - 53	

The most frequent reason for non-completion of the questionnaire was because the respondents did not see MND patients in their daily practice. (Graph 1) Twenty one percent of respiratory respondents who elected not to proceed with the questionnaire survey described reasons of working as a paediatrician, a clinical immunologist, a palliative care physician, an advanced physician trainee, or for having retired. A small number of neurologists found the questionnaire cumbersome. Several neurologists provided explanations that the volume of MND patients seen in their practice was small (2 patients in 12 months) and these patients were then promptly referred to MND multidisciplinary clinics for ongoing management.

Graph 1: Reasons given for study non-completion



For the responders completing the questionnaire, the neurology respondents had a greater male to female ratio (4.9:1) when compared to the respiratory respondents (2.3:1). The neurology responders were older with a mean age of 51.9 (range 30- 78 years) in comparison to the respiratory responders with mean age of 45.5 (range 26 – 69 years). The mean years post FRACP for respiratory responders was 13.1 (range 1 – 46 years) and for the neurology responders was 19.3 (range 1 -45 years). There were statistical significance differences in the variation of mean age and mean years post FRACP between these groups (Table 3). Both specialties based their practice in the metropolitan region (respiratory 87%, neurology 82%) with about 50% of them working in both private and public care setting (Table 3).

Table 3: Comparison of responders completing the questionnaire

With Questionnaire:	Respiratory n=105	Neurology n=71	P value
Male:Female Ratio	2.3:1	4.9:1	
Age			
- **Mean (±SD)**	45.5 (±9.3)	51.9 (±11.0)	P < 0.05
- **Range**	29 -69 years	30 -78 years	
Years post FRACP			
- **Mean (±SD)**	13.1 (±10.2)	19.3 (±11.3)	P <0.05
- **Range**	1 - 46	1 -45	

4.2 Practice trends in the care of Motor Neuron Disease patients

The total number of new MND patients seen by respiratory physicians and neurologists in the last twelve months was 478 patients, and 448 patients respectively, assuming non duplication. The neurology responders reviewed more new patients, (mean = 6.3) when compared to the respiratory responders (mean = 4.6 patient). In contrast, the respiratory responders referred more MND patients for NIV therapy (mean = 4.3), than the neurology responders (mean = 3.3). The success rate of NIV therapy use was high in both specialists groups, respiratory (84%) and neurology (79%) (Table 4).

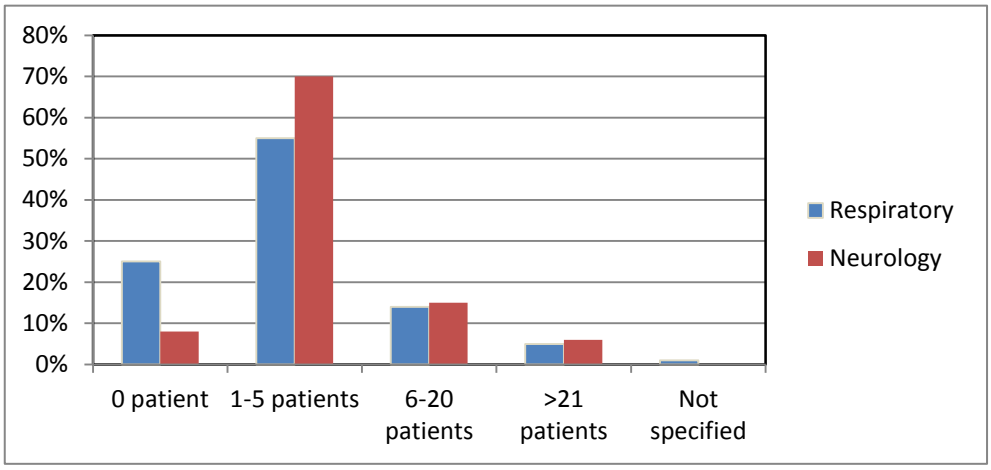
Refer to Appendix G: Table 6 for summary of motor neuron disease patients seen

Table 4: Comparison of new MND patients seen and referral to NIV therapy in last twelve months

In the last 12 months:	Respiratory n=105	Neurology n=71	P value
Number of new MND patients			
- **Total**	478	448	
- **Mean (±SD)**	4.6 (±7.9)	6.3 (±10.5)	P = 0.86
- **Range**	0 - 50	0 - 60	
Referred patients for NIV therapy			
- **Total**	394	198	
- **Mean (±SD)**	4.3 (±12.3)	3.3 (±7.9)	P = 0.58
- **Range**	0 -100	0 - 40	
Successful patients on NIV therapy			
- **Total**	329	157	
- **Mean (±SD)**	4.1(±10.4)	4.5 (±8.2)	P = 0.83
- **Range**	0 - 80	0 -36	
Success rate of NIV therapy	84%	79%	

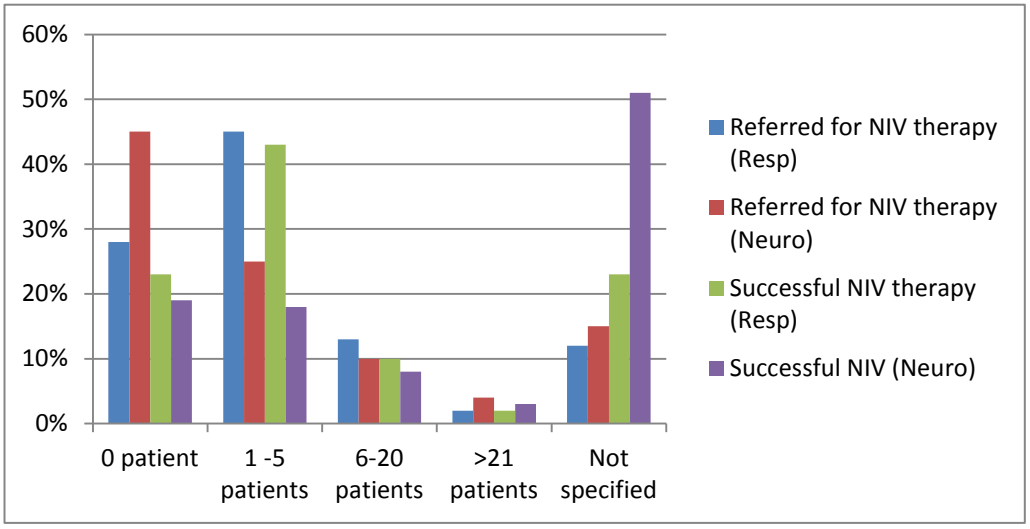
Seventy percent of neurologists and 55% of respiratory physicians reviewed between one to five new MND patients in the preceding twelve months (Graph 2).

Graph 2: New MND patients reviewed in the last twelve months



Forty five percent of respiratory physicians treated between one to five MND patients with NIV therapy in the last twelve months, and 43% of the respiratory physicians reported successful NIV therapy for one to five MND patients. In comparison, twenty five percent of neurologists referred between one to five patients for NIV therapy, and 45% of them did not refer any MND patients to start NIV therapy. Fifty one percent of neurologist responses were incomplete for the number of MND patients for established successful NIV therapy. (Graph 3)

Graph 3: NIV therapy referral in MND patients in the last twelve months



The total number of currently managed MND patients for respiratory physicians was 839 patients, and 629 patients for neurologists, again assuming non duplication. The number of patients reviewed between the respiratory physicians (mean 8.2) and neurologists (mean 9.0) was similar. The respiratory physicians reviewed more MND patients on NIV therapy (mean 8.0) in comparison to neurologists (mean 3.8). The reported current number of patients on NIV therapy for respiratory responders was 631, and 183 patients for neurology responders.

Therefore, the rate of NIV therapy in currently managed MND patients for respiratory physicians and neurologists were 75% and 29% respectively (Table 5).

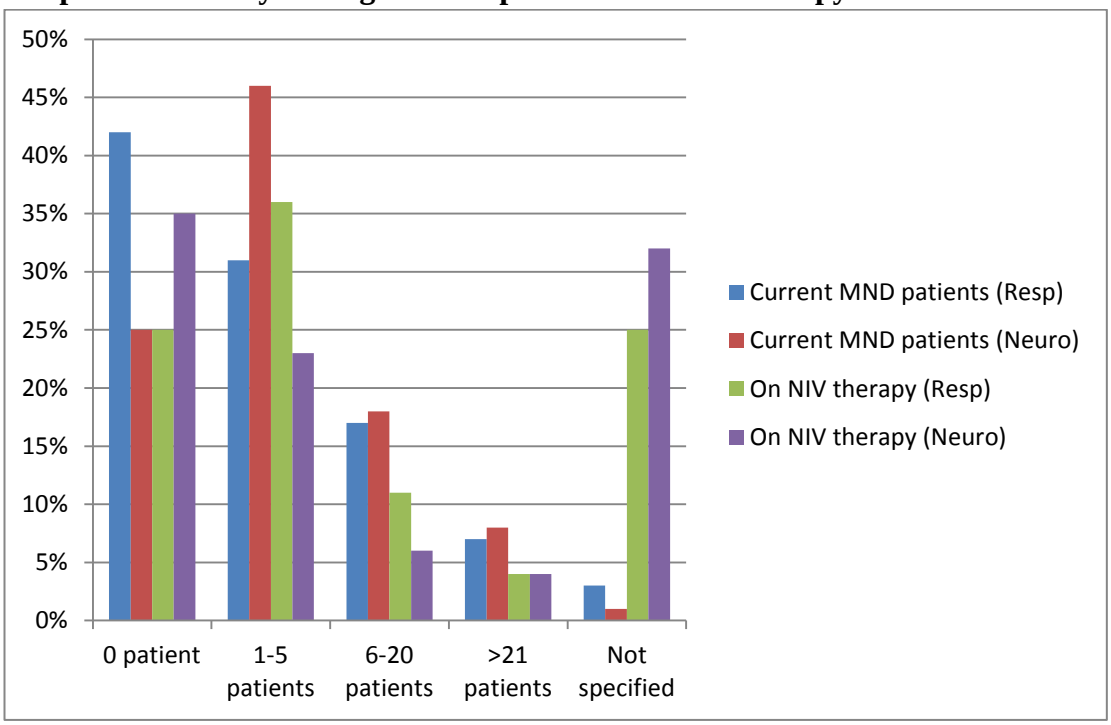
Table 5: Comparison of currently managed MND patients and NIV therapy

Currently managed	Respiratory n=105	Neurology n=71	P value
Number of MND patients			
- **Total**	839	627	
- **Mean (±SD)**	8.2 (±28.5)	9.0 (±22.2)	P = 0.76
- **Range**	0 - 200	0 - 140	
Patients on NIV therapy			
- **Total**	631	183	
- **Mean (±SD)**	8.0 (±28.2)	3.8 (±8.7)	P = 0.32
- **Range**	0 - 200	0 - 40	
Rate of NIV therapy use	75%	29%	

Forty six percent of neurologists reported managing between one to five MND patients currently, and eight percent of neurologists were managing greater than 21 MND patients. A greater proportion of respiratory physicians, 42% were currently not managing any MND patient, and 31% of them currently reviewed between one to five MND patients.

There were a significant proportion of respiratory physicians (25%) and neurologists (32%) who did not specify the number of their MND patients using NIV therapy (Graph 4).

Graph 4: Currently managed MND patients and NIV therapy

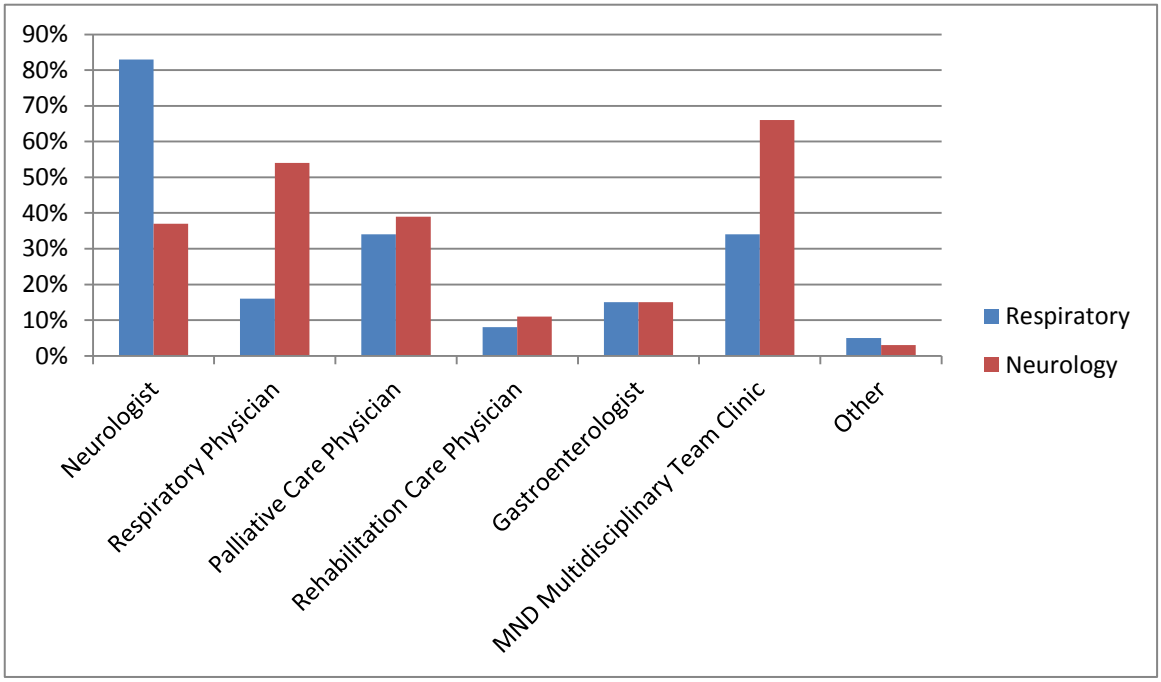


4.3 Shared management of MND patients

The majority of respiratory physicians (85%) and neurologists (95%) referred their MND patients to other specialists and co-share their MND patients care and management. As anticipated, there is an increased trend in referrals between the respiratory physicians and neurologists. Thirty seven percent of neurologists referred to their neurologist colleague often for a second opinion to verify and confirm the diagnosis of motor neuron disease. There was an increased pattern of referral from the neurologists to the MND multidisciplinary team clinic (66%) in comparison to the respiratory physicians (34%). (Graph 5)

Refer to Appendix H: Table 7 for summary of shared MND patients' management

Graph 5: Patterns of specialists' referral

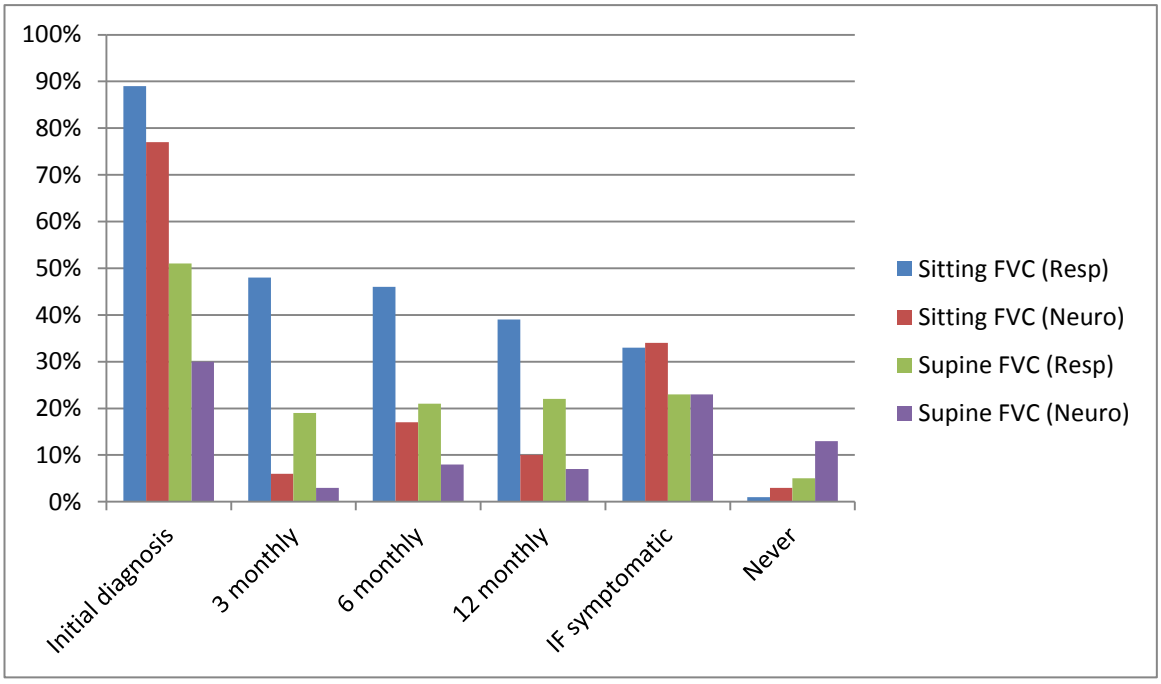


4.4 The use of respiratory investigations

The survey questionnaire showed increased and frequent use of respiratory investigations by respiratory physicians, most commonly carried out during the time of initial diagnosis. Seventy seven percent of neurologists and 89% of respiratory physicians indicated the use of sitting forced vital capacity was performed as part of their routine examination at the time of initial MND diagnosis. A greater percentage of respiratory physicians would continue monitoring forced vital capacity at different time intervals as shown in Graph 6. Although a smaller proportion of neurologists continued monitoring with forced vital capacity at different time intervals, over 30% of neurologists would perform the testing when patients become symptomatic. Similarly, over 30% of respiratory physicians indicated a similar trend in their practice as well (Graph 6).

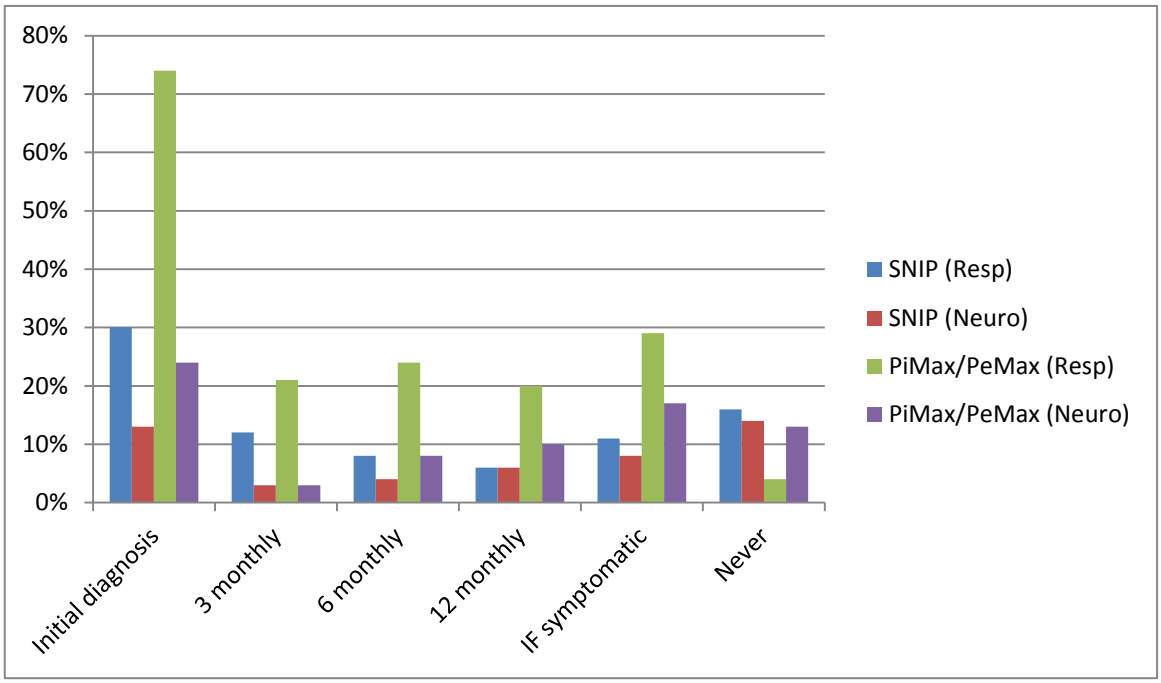
Refer to Appendix I: Table 7 for summary of an indication of respiratory investigations used

Graph 6: Comparison in the use of sitting FVC & supine FVC between respiratory and neurology



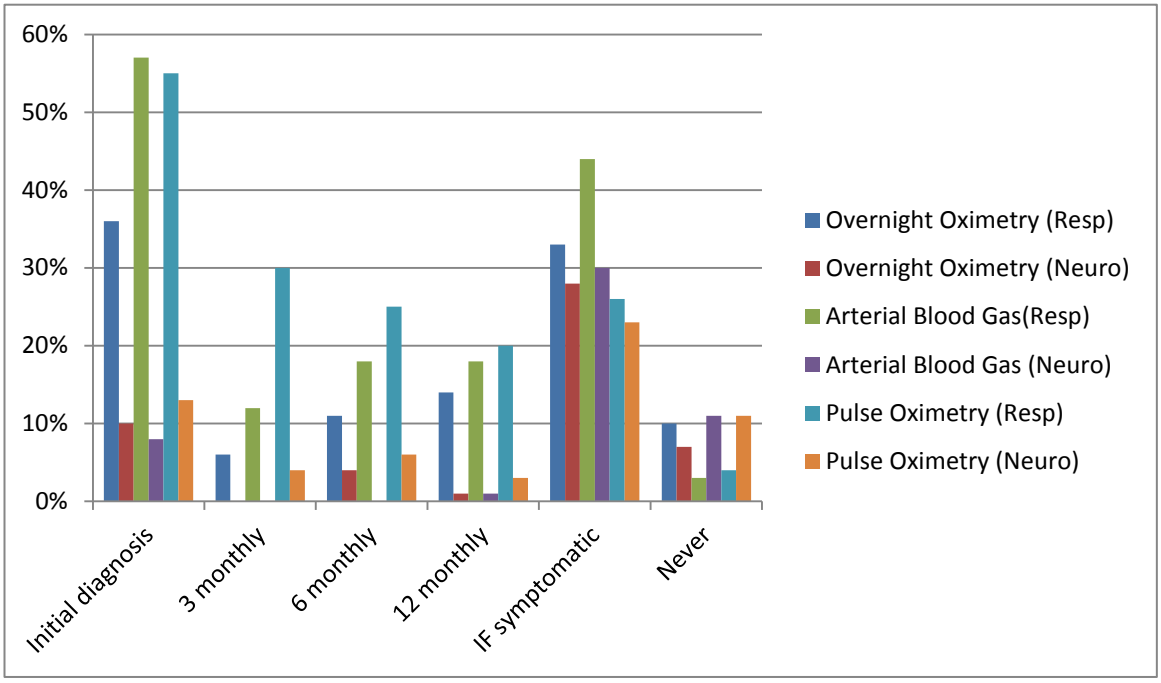
The pattern of routine use of the Sniff Nasal Inspiratory pressure (SNIP) and Maximum inspiratory and expiratory pressures (PiMax/PeMax) was significantly lower in comparison to the use of forced vital capacity. Seventy four percent of respiratory physicians indicated the routine use of SNIP at the time of initial diagnosis with MND, and almost twenty percent of the respiratory physicians were continuing to monitor progression at three, six and, or twelve monthly intervals. In comparison, a smaller percentage of neurologists chose to use SNIP or PiMax/PeMax for monitoring and almost 15% of neurologists never use this testing (Graph 7).

Graph 7: Comparison in the use of SNIP & PiMax/PeMax between respiratory and neurology



More than half of the respiratory physicians indicated the routine use of pulse oximetry and arterial blood gas at initial MND diagnosis. Thirty six percent of respiratory physicians would routinely organise an overnight oximetry study during the time of initial diagnosis. In comparison, almost 30% of neurologists indicated that they would use the pulse oximetry, arterial blood gas and or overnight oximetry only if and when patients display symptoms (Graph 8).

Graph 8: Comparison in the use of overnight oximetry, arterial blood gas and pulse oximetry between respiratory and neurology



4.5 Accessibility to NIV therapy

Ninety percent of respiratory physicians and 65% of neurologists had direct access to NIV therapy (Table 8). Ten percent of respiratory physicians did not have direct access to NIV therapy reported issues relating to lack of NIV therapy expertise and resources in regional area, but will readily refer patients to specialist centres in the metropolitan region.

Table 8: Direct Access to NIV therapy service

	Respiratory n=105	Neurology N=71
YES	95 (90%)	46 (65%)
NO	10 (10%)	24 (34%)
Not specified	0 (0%)	1 (1%)

Similar sentiments were also voiced by the 34% of neurologists who did not have direct access to NIV therapy, and they also commented on having "indirect access" to NIV therapy either via a respiratory physician or to refer to an MND multidisciplinary clinic or a specialised respiratory failure clinic (Table 8).

4.6 Advanced care directives discussion

The majority of respiratory physicians (86%) and neurologists (77%) broached the advanced care directives discussions with their MND patients, and often introducing the issue before the application of NIV therapy. The minority of treating specialists who did not openly discussed the sensitive issue of advanced care directives felt it was not their responsibility when they are not the primary care physician, or when the patients have been referred on to the MND multidisciplinary team clinic or to a specialist respiratory failure clinic (Table 9).

Table 9: Advanced care directives discussion and NIV therapy

	Respiratory n=105	Neurology N=71
YES	90 (86%)	55 (77%)
NO	11 (10%)	10 (14%)
Not specified	4 (4%)	6 (8%)

4.7 Specialists preferences and opinions

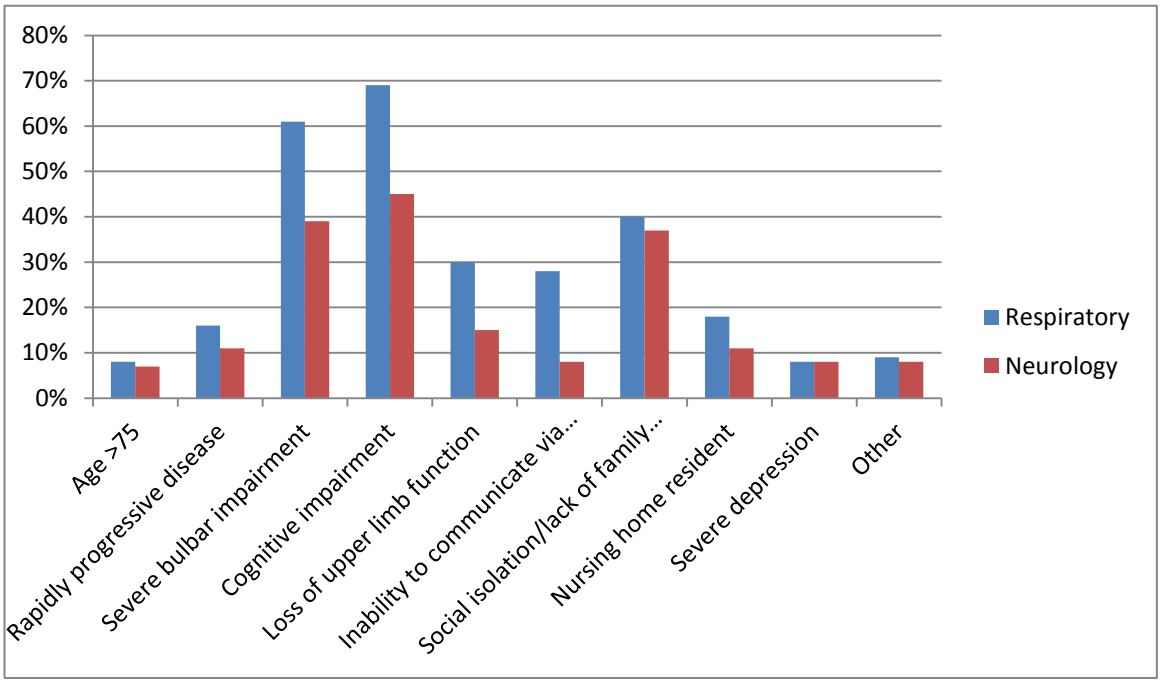
Referral to a formal diagnostic sleep study was favoured by sixty three percent of respiratory physicians when patients complained of respiratory symptoms suspicious of nocturnal hypoventilation. Fifty eight percent of neurologists indicated that a referral to the respiratory physician would be their preferred option. Fifteen percent of respiratory physician would commence NIV therapy empirically, but none of the neurologist chose this option.

Table 10 - *Preference:* Next step when MND patients complain of respiratory symptoms suspicious of nocturnal hypoventilation

	Respiratory n=105	Neurology n=71
REFER		
- **Respiratory physician**	1 (1%)	41 (58%)
- **Formal diagnostic sleep study**	66 (63%)	9 (13%)
- **Ambulatory sleep study (with EEG)**	3 (3%)	0 (0%)
ASSESS with respiratory investigations	18 (17%)	9 (13%)
COMMENCE NIV therapy empirically	15 (14%)	0 (0%)
Do Nothing	0 (0%)	1 (1%)
Other	0 (0%)	10 (14%)
Not specified	2 (2%)	1 (1%)

The three most frequently chosen contraindications to NIV therapy by both respiratory physicians and neurologists were severe bulbar impairment, cognitive impairment and social isolation or lack of family support (no carer). Several other responses from the neurologists and respiratory physicians quoted "no contraindications to NIV therapy". Similar thread of other responses from respiratory and neurology responders also commented that patients' wishes and choices should be considered, as it may be a "contraindication" when patients refuse NIV therapy or if the patient was not tolerant of NIV therapy (Graph 9).

Graph 9: Contraindications to NIV therapy



Refer to Appendix J: Table 11 for Summary of contraindications to NIV therapy.

There was a spread of responses between the respiratory physicians and neurologists in their preferences to decide when NIV therapy should be recommended. Thirty seven percent of neurologists and twenty two percent of respiratory physicians indicated that progressive respiratory symptoms were sufficient grounds to recommend NIV therapy. The respiratory physicians' responses also indicated that coupling of progressive respiratory symptoms with a diagnostic sleep study (30%) and the coupling with increased PCO2 (21%) were also their preferred options. Twenty one percent of neurologists indicated their preference of progressive respiratory symptoms with an abnormal overnight oximetry. Interestingly, 13% of neurologists did not choose an option to describe their preferences (Table 11).

Table 11: *Preference*: Descriptive criteria in recommending NIV therapy

	Respiratory n=105	Neurology n=71
Progressive respiratory symptoms	23 (22%)	26 (37%)
Progressive respiratory symptom & abnormal overnight oximetry	12 (11%)	15 (21%)
Progressive respiratory symptoms & increased PCO_2	22 (21%)	1 (1%)
Progressive respiratory symptoms & increased PCO_2 & abnormal overnight oximetry	12 (11%)	1 (1%)
Progressive respiratory symptoms & diagnostic formal polysomnography	32 (30%)	8 (11%)
Aysptomatic but progressive decline FVC<50% & increased $PC0_2$	2 (2%)	6 (8%)
None of the above	0 (0%)	9 (13%)
Not specified	2 (2%)	5 (7%)

To further interrogate the specialists' preferences of the use of NIV therapy in an MND patient, a fictional case scenario was described:

"Case scenario: Mr MND is 65 year old retired politician with flail arm variant of amyotrophic lateral sclerosis. Twelve months following his diagnosis, he has no functional hand movements, with progressive lower limb weakness. His speech is dysarthric, and his swallowing is moderately impaired. Following commencement of Cipramil, his mood is less labile. He has a caring wife who is his primary carer, and is living in a single storey home. He is noticeably breathless during conversations and complains of orthopnoea, unrefreshing sleep and morning headaches. The recent overnight oximetry showed repetitive oxygen desaturations, with 20 events below 85%, from a baseline of 93%. His FVC has been trending downwards, currently at 50% predicted."

There was no correct or incorrect answer. Fifty eight percent of neurologists indicated that they would refer on to a MND multidisciplinary team and 25% of them would plan to commence NIV therapy as an inpatient. In contrast, 41% of respiratory physicians would plan to commence NIV therapy as inpatient, while 25% would refer to MND multidisciplinary care team and another 26% chose to further investigate with a formal diagnostic sleep study. A small minority, 6 % of respiratory physician and 3% of neurologists referred the case onto the palliative care physician. (Table 12)

Table 12: *Preference:* Next step in managing a case scenario of a patient with typical ALS progression with nocturnal hypoventilation

	Respiratory n=105	Neurology n=71
REFER		
- **MND multidisciplinary care team**	26 (25%)	41 (58%)
- **Formal diagnostic sleep study**	27 (26%)	4 (6%)
- **Palliative care physician**	6 (6%)	2 (3%)
COMMENCE NIV therapy as inpatient	43 (41%)	18 (25%)
Do Nothing and review in 3 months	0 (0%)	1 (1%)
Not specified	3 (3%)	5 (7%)

This survey questionnaire demonstrated that 50% of respiratory physicians have the opinion that NIV therapy should be offered to MND patients with mild bulbar dysfunction, and a further 13% of them believed that NIV therapy should be offered to MND patients with bulbar dysfunction ranging from mild to severe. Forty one percent of respiratory physicians would consider commencing NIV therapy in selected patients, with moderate to severe bulbar dysfunction. Forty three percent of respiratory physicians understood that NIV therapy is proven to increase survival in MND, and further 6% believed the effectiveness of NIV therapy across all range of bulbar severity. A small percentage of respiratory physicians (19%) indicated that there was no role for NIV therapy in MND management. (Table 13)

Similarly, almost fifty percent of neurologists indicated that NIV therapy should be offered to MND patients with mild bulbar dysfunction and to those who have moderate to severe bulbar dysfunction. Thirty five percent of neurologists understood the role of NIV therapy in increasing survival in MND patients with mild bulbar dysfunction, and a further 15% of them indicated NIV therapy is proven to increase survival in MND patients with moderate to severe bulbar dysfunction. Only a tiny percentage of neurologists (7%) indicated that there was no role for NIV therapy in MND management. (Table 13)

Table 13: *Opinion:* Role of NIV therapy in patients with bulbar dysfunction

City or Town	Respiratory n=105	Neurology N=71
NIV therapy has no role in MND management		
- **Normal to mild bulbar dysfunction**	1 (1%)	2(3%)
- **Moderate to severe bulbar dysfunction**	19 (18%)	3 (4%)
- **Whole spectrum of bulbar dysfunction**	0 (0%)	0 (0%)
NIV therapy should be considered in carefully selected MND patients		
- **Normal to mild bulbar dysfunction**	14 (13%)	12 (17%)
- **Moderate to severe bulbar dysfunction**	43 (41%)	19 (27%)
- **Whole spectrum of bulbar dysfunction**	24 (23%)	15 (21%)
NIV therapy should be offered		
- **Normal to mild bulbar dysfunction**	52 (50%)	21 (30%)
- **Moderate to severe bulbar dysfunction**	5 (5%)	10 (14%)
- **Whole spectrum of bulbar dysfunction**	14 (13%)	14 (20%)
NIV therapy is proven to increase survival in MND patients		
- **Normal to mild bulbar dysfunction**	45 (43%)	25 (35%)
- **Moderate to severe bulbar dysfunction**	1 (1%)	3 (4%)
- **Whole spectrum of bulbar dysfunction**	5 (5%)	8 (11%)

CHAPTER 5: DISCUSSION

Currently, there is limited Australian literature on the use of NIV therapy in patients with MND. The aim of this research study was to gain insight into the respiratory physicians and neurologists' current preferences, opinions and practice trends in management of their MND patients with NIV therapy. To our knowledge, this postal questionnaire is the first study to be conducted in Australia and New Zealand.

5.1 The practice trends

The overall response rate from 1635 postal questionnaire was modest (19%), and the interpretations of the results were limited to this small cohort of specialists' responses. Almost half of the 199 respiratory responders and one third of the 106 neurology responders indicated that they do not encounter MND patients in their daily medical practice. They had similar demographic characteristics with a mean age of early fifties, had an average twenty years of consultant physician practice and worked predominantly in the metropolitan areas. These data were not unexpected as MND is not a common disease, with a low incidence of 2.74 cases in 100,000 people.

The rest of the 50% respiratory responders and almost 70% of neurology responders were involved in the management of MND patients. Their differences in demographic characteristics were statistically significant ($p<0.05$). The mean age for the respiratory responders were almost five years younger than the neurologists mean age of 52. The respiratory responders were six years less experienced when compared to the neurologists of 19.3 consultancy years. Nearly fifty percent of both respiratory and neurology responders worked in the public and private care setting within metropolitan regions. The questionnaire did not identify whether MND patients were managed in the specialists' private or public practice setting.

Both respiratory and neurologists specialists were currently reviewing an average of eight to nine MND patients; and they saw an average of five to six new MND patients in the preceding 12 months. The practice of managing greater than twenty one MND patients was not common, as approximately five percent of specialists had implied in their practice pattern. This fact highlighted the subspecialty nature of managing MND patients with NIV therapy. There was one outlier response form a respiratory responder who reported their management of 200 current MND patients; 100 patients referred to NIV therapy in last 12 months with 80% success rate, and seeing 50 new MND patients in the last twelve months. This is an interesting revelation of one physician who had dedicated their practice to the specialised management for MND patients, most likely in a MND multidisciplinary care team setting.

Almost every respiratory physician had direct access to NIV therapy service, unless they were working in smaller regional hospitals or in the rural regions, where NIV therapy expertise and support were lacking. Approximately one third of the neurologists reported no direct access to NIV therapy but could easily refer the MND patients to clinics supported by an MND multidisciplinary team or to respiratory physicians. A few neurologists working in rural and regional regions also echoed the lack of resources and facilities to support NIV therapy administration. It had always been a challenge to ensure equitable delivery of medical care and attention delivered to patients living in the outskirts.

A significant proportion of respiratory physicians (86%) and neurologists (77%) would appropriately start timely discussions regarding advanced care directives, and most preferred to initiate the discussion prior to the commencement of NIV therapy. There was a minority of specialists who did not feel comfortable in breaching the issue of end of life care. They believed it was the responsibilities of the primary physician – who could be the neurologist, or respiratory physician, or palliative care physician and or the MND multidisciplinary care

team. The reluctance or the avoidance of addressing the sensitive issue of terminal care with the MND patient requiring NIV therapy can potentially lead to unrealistic expectations of survival and confusion.

5.2 The use of respiratory investigations

Spirometry with the measurement of forced vital capacity was the most frequently used respiratory investigation by both respiratory physician and neurologist alike. The respiratory physicians were more inclined to continue serial monitoring of forced vital capacity, pulse oximetry, maximum inspiratory and expiratory respiratory pressures at frequent intervals. The three most frequently used tests if patients were symptomatic by both respiratory physicians and neurologist were sitting forced vital capacity, overnight oximetry and arterial blood gas analysis. Thirty percent of respiratory physicians and 13% of neurologists indicated the use of Sniff Nasal Inspiratory Pressure at the time of initial diagnosis. The neurologists tended to order respiratory investigations at the time of initial diagnosis and repeating the testing again when patients became symptomatic. On the other hand, the respiratory physicians were more likely to arrange regular spirometry testing with pulse oximetry and reserve the analysis of arterial blood gas when patients became symptomatic.

When confronted with a hypothetical MND patient with symptoms suggestive of nocturnal hypoventilation, almost 60% of neurologists would initiate the referral to a respiratory physician or to an MND multidisciplinary team. The respiratory physicians' responses were divided between commencing NIV therapy (41%), referring for a formal diagnostic sleep study (26%) and referring to MND multidisciplinary care team (25%). Some of the responses from the respiratory physicians were inclined to arrange a formal diagnostic sleep study for symptomatic MND patients. If the waiting period to secure a formal diagnostic sleep study was short, then confirmatory testing would be ideal.

However the common presentation of a physically disabled MND patient with respiratory compromise waiting for a confirmatory testing may not be justifiable. The waiting time for formal diagnostic sleep study was prohibitive to NIV therapy commencement and MND patients could die in the interim.

5.3 NIV therapy in MND

Both respiratory and neurologists were referring an average of three to four patients in the last twelve months for NIV therapy, and both specialists reported a high success rate of approximately 75-85% in the establishment of NIV therapy. As expected, the respiratory physicians were currently managing twice as many MND patients on NIV therapy as the neurologists. Referrals to other specialities were also notably increased in their management of MND patients. Over 90% of neurologists shared the care of their MND patients, usually referred on to the MND multidisciplinary care team (66%), or to the respiratory physician (54%) and palliative care physician (39%). Over one third of the neurologists would also refer to their colleagues for a second opinion – to confirm the diagnosis of MND.

There was also an increased trend to co-share the management of MND patients amongst the respiratory physicians. Over 80% of respiratory physicians manage their MND patients with the neurologists. One third of the respiratory physicians also referred onto the palliative care physician. The survey showed that the neurologists (66%) were more likely than the respiratory physicians (34%) to refer onto a MND multidisciplinary team clinic for ongoing management of MND patients. The questionnaire did not evaluate the accessibility to MND multidisciplinary team clinic and it was not clear whether common knowledge could be assumed for understanding the existence of specialised MND clinics.

The estimated rate of NIV therapy use in current MND patients, reported by the respiratory physicians and neurologists was 75% (631/839) and 29% (283/627) respectively. The specialists' responses relied on their anecdotal recollections and some under or over reporting of cases was likely. Nevertheless, the rate of NIV therapy usage was disparate between the two specialties. The respiratory physicians were more inclined to treat and manage symptomatic MND patients requiring NIV therapy, therefore the higher percentage in the use of NIV therapy. In contrast, the neurologists were more likely to continue the management of MND patients who have minimal respiratory complaints and would refer on their symptomatic MND patients requiring ventilatory support.

This study illustrated the Australasian NIV therapy usage rates of respiratory physicians and neurologists are higher than previously thought. It compared favourably to other international usage rates defined in the literature (see Table 1). A recent questionnaire study to centres managing home mechanical ventilation in Australia and New Zealand by Garner et al[1] showed that motor neuron disease constituted only 8.4% (95% CI 7.4-9.5) of home mechanical ventilation usage.

Being a rare illness, there is a paucity of reliable and reproducible data on the frequency and utility of NIV in the setting of MND. As can be demonstrated from this survey's data set, there is significant disparity between specialties in the use of NIV, the assessment criteria used to initiate NIV, and effective monitoring of its use.

A National Registry of MND in Australia, the Australian Motor Neurone Disease Registry (AMNDR) monitors the progress and therapy of MND patients (www.amndr.org). Data that is centralised allows insight into therapy in specialist MND clinics. Our data differs from AMNDR substantially, as nearly of all the data in AMNDR is derived from six specialised multidisciplinary clinics in Australia. Comparison of our data with detailed analysis from

AMNDR data will allow observations regarding the variable use of NIV in specialist setting such as the clinics reporting to AMNDR versus the general community care by neurologists and respiratory physicians.

The three most frequent contra-indications to NIV therapy reported by both respiratory physicians and neurologists were cognitive impairment, followed by severe bulbar dysfunction and social isolation. Although these factors were considered as deterrents to NIV therapy, the presence of these factors were more likely to influence the patients' tolerance and acceptance of NIV therapy. This study showed that the respiratory physicians were less likely than the neurologists to advocate NIV therapy in MND patients with moderate to severe bulbar dysfunction (Graph 10). The survival advantage for patients with severe bulbar dysfunction on NIV was not clearly evident, as demonstrated in the randomised study by Bourke et al[43], but these patients had improved sleep related symptoms with persistent use of NIV therapy.

In comparison, a similar questionnaire study performed by Bourke et al[52,53] collected a higher response rate of 63-76% from neurologists, identified through the Association of British Neurologists. Indeed, their repeated questionnaire after one decade showed encouraging results of 2.6 fold in increased referrals and 3.4 fold in increased proportion of patients successfully established on NIV therapy. Several similarities and differences were observed between these studies. Our study found that 25% of Australasian neurologists' were referring 1-5 MND patients for NIV therapy referral in twelve months, and a similar rate of 20% was observed of the British neurologists. It appeared that the most common perceived deterrent to NIV therapy by both British (45%) and Australasian (45%) neurologists was cognitive impairment. Although a higher proportion of Australasian (39%) neurologists believed severe bulbar impairment to be a contra-indication to NIV therapy compared to British (20%)

neurologists. There was a higher rate of referral to palliative care physician by the Australasian neurologists (40%) when compared to British (10%) neurologists. These comparison findings indicated that the Australasian neurologists practice trends of NIV therapy management was indifferent to their British colleagues.

There were several limitations to this study. The modest questionnaire response rate may not be reflective of all practising respiratory and neurologist specialists. However, this study captured responses from treating physicians who were actively involved in the care of MND patients. The low response rate of questionnaire may be improved by re-sending a second mail out with a reminder letter. Alternatively, an internet based questionnaire survey may possibly increase the number of responses. However, due to regulated restriction of specialists' personal information and addresses, it was not possible to track or identify responders and non-responders. The scope of this study focussed on the opinions of the neurologists and respiratory physicians only, as they were the two most likely physicians who would be at the forefront in the assessment and management of MND patients with respiratory failure. The opinions of other specialists such as palliative care physicians, rehabilitation physicians and general medical practitioners were not surveyed as they generally do not see as many MND patients. However, their involvement in the overall management in the care of MND patients is vital in supporting MND patients' functionality within the community.

Secondly, the questionnaire design was limited to interrogating specialists' practice and preferences in broad principles of NIV therapy. It did not include other important aspects of NIV therapy in MND management, such as accessibility to MND multidisciplinary clinic, health and social economic costs of NIV therapy and whether patients' preferences influenced the specialists opinions or vice versa. This data was not included in order to maintain

consistency and reproducibility with the questionnaire that this survey was based upon. Lastly, the interpretation of questions could vary between respondents. It would be difficult to verify the accuracy of the anonymous responses. Furthermore, although non-duplication of patient numbers reported was assumed, there is always the possibility that a proportion of patient numbers reviewed were duplicated in the reporting of neurologists and respiratory physicians alike. It would be difficult to differentiate and or match the number of patients reviewed as recalled by the specialists, unless specific patient information and data was provided, recorded and cross referenced. Nevertheless, the findings of this study have shown, as anticipated, a higher proportion of MND patients requiring NIV therapy were managed by respiratory physicians in comparison to neurologists.

The comparison of opinions on NIV therapy in MND patients between respiratory physicians and neurologists in this study provided the first reported observation in Australasian region on their awareness in whether NIV therapy was pro-actively advocated or not. The complex assessment of an MND patient with progressive respiratory failure requiring NIV therapy would ideally be performed by specialists with convenient access to NIV therapy support and resources. However, access to NIV therapy may not be equitable to all MND patients, especially to those living in the remote rural Australasian regions.

CHAPTER 6: CONCLUSIONS

This survey shows that both respiratory physicians and neurologists are relying on one another jointly in managing MND patients on NIV therapy. The Australasian rate of NIV therapy use in MND managed by respiratory physicians is high (75%) with eight out of ten MND patients being successfully established on NIV therapy. The severity of bulbar impairment, cognitive impairment and social isolation are the three main barriers to NIV therapy that are perceived by both respiratory physicians and neurologists alike. There is significant variability in how patients are assessed on their eligibility to commence NIV therapy. Further research in the formulation and implementation of practical clinical guidelines of NIV therapy in MND would be beneficial.

APPENDIX A: COVER LETTER TO PARTICIPANTS OF QUESTIONNAIRE

MACQUARIE UNIVERSITY

Friday, 30th May 2014

Research Study:
Non-invasive ventilation in motor neuron disease/amyotrophic lateral sclerosis
An Australian perspective

Dear Doctor

Most patients with motor neuron disease (MND) will eventually develop respiratory failure and may require the assistance of non-invasive ventilation (NIV) during their terminal stages. A randomised control trial by Bourke, et al. [1] concluded that 'in patients with amyotrophic lateral sclerosis without severe bulbar dysfunction, NIV improves survival and quality of life … much greater than that from currently available neuroprotective therapy'.

The practice of NIV therapy initiation in MND patients is variable, and is often dependent on several patient, physician and social factors. We are undertaking a questionnaire to survey the Australian physicians' perspectives and the practice of NIV therapy in patients with motor neuron disease. This questionnaire has been distributed to all Respiratory physicians via The Thoracic Society of Australia and New Zealand, and to all Neurologists via Australian and New Zealand Association of Neurologist.

This questionnaire forms the basis of Dr Wai Kuen Chow's research project to meet the requirements for the Master of Research under the supervision of Prof. Dominic Rowe and A/Prof Alvin Ing of Macquarie University Hospital and Advanced School of Medicine at Macquarie University. The questionnaire has seventeen questions and it should take approximately 10-15 minutes to complete.

We would be very grateful if you could assist in completing the attached questionnaire and return in the envelope provided by **Friday, 20th June 2014**. Please be reassured that your voluntary responses are not identified and will be assessed confidentially. Should you choose not to complete this questionnaire, we would appreciate your feedback by completion of basic information. By analysing your responses, we hope to gain some insight into the Australian practice of clinical application of NIV in patients with MND.

Thank you for your kind co-operation.

Dr Wai Kuen Chow FRACP
Respiratory Physician
Macquarie University Hospital
Tel: 02 9812 3720
Fax: 02 9812 3722
Email: wai-kuen.chow@students.mq.edu.au

Prof Dominic Rowe FRACP
Neurologist
Macquarie University Hospital
Tel: 02 9812 3720
Fax: 02 9812 3722
Email: dominicrowe@mac.com

A/Prof Alvin Ing FRACP
Respiratory Physician
Macquarie University Hospital
Tel: 02 9812 3709
Fax: 02 9812 3844
Email: ajing@med.usyd.edu.au

APPENDIX B: CONSENT NOTE TO PARTICIPANTS OF QUESTIONNAIRE

Basic information:

1. I am a Neurologist □ Respiratory physician □
2. Male □ Female □
3. Age _____
4. Years post completion of FRACP _____
5. Type of Practice: (please tick which that applies)
   - Private Practice Practitioner
   - Public Hospital Practitioner
   - Both Private and Public Practitioner
   - Clinical Academia
6. Area of medical practice:
   - Metropolitan/City
   - Rural
   - Remote Rural

CONSENT:

I agree/disagree to voluntarily participate in this research study. I consent/do not consent in completion of the questionnaire regarding the non-invasive ventilation therapy in motor neuron disease/amyotrophic lateral sclerosis.

The reason for withdrawal is:

- Do not see patients with MND/ALS
- Too cumbersome questionnaire
- Not interested
- Too busy and lacking spare time
- Other ……

Reference:

1 Bourke, S. C. *et al.* Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *The Lancet Neurology* **5**, 140-147, doi:10.1016/s1474-4422(05)70326-4 (2006).

APPENDIX C: QUESTIONNAIRE FOR PARTICIPANTS OF SURVEY

Questionnaire:
Non-invasive ventilation in motor neuron disease/amyotrophic lateral sclerosis
An Australian perspective

1. How many <u>new patients with MND</u> have you seen in the last 12 months? _____
2. How many MND patients do you currently manage? _____
3. What is the average review frequency for these MND patients? _____
4. Do you share the management of these MND patients with other specialist(s)? YES/NO
5. Please tick which other specialists or specialist centres are involved:
   - ☐ Neurologist
   - ☐ Respiratory physician
   - ☐ Palliative Care Physician
   - ☐ Rehabilitation Medicine Physician
   - ☐ Gastroenterologist
   - ☐ Motor Neurone Disease Multi-Disciplinary Team Clinic
   - ☐ Other _____
6. Please indicate which of these *respiratory investigations* do you routinely use?

	Sitting FVC	Supine FVC	SNIP*	PiMax & PeMax**	Overnight oximetry	Arterial Blood Gases	Pulse Oximetry
Initial diagnosis							
3 monthly							
6 monthly							
12 monthly							
IF symptomatic							
Never							

SNIP*: Sniff Nasal Inspiratory Pressure PiMax/PeMax**: Maximum Inspiratory and Expiratory Respiratory Pressures

7. When MND patients complain of respiratory/sleep related symptoms suspicious of nocturnal hypoventilation, what do you do next? (please choose <u>one option</u> that best describes your preference)
   - ☐ Refer to a respiratory physician
   - ☐ Refer for a formal diagnostic sleep study (polysomnography)
   - ☐ Refer for an ambulatory sleep study (with EEG)
   - ☐ Assess with *respiratory investigations* to confirm the clinical diagnosis
   - ☐ Commence NIV therapy empirically
   - ☐ Do nothing
   - ☐ Other _____

8. Please choose <u>one descriptive criteria</u> that best describes your preference in recommending NIV therapy to MND patients.
   - ☐ Progressive respiratory symptoms (orthopnoea, breathlessness, morning headache, daytime sleepiness)
   - ☐ Progressive respiratory symptoms + abnormal overnight oximetry (repetitive oxygen desaturations)
   - ☐ Progressive respiratory symptoms + increased daytime PCO2 on ABGs
   - ☐ Progressive respiratory symptoms + increased daytime PCO2 on ABGs + abnormal overnight oximetry
   - ☐ Progressive respiratory symptoms + diagnostic formal polysomnography
   - ☐ Asymptomatic but progressively declining FVC <50% with increased daytime PCO2
   - ☐ None of the above

9. Do you have direct access to a non-invasive ventilation therapy service? YES/NO
   If No, please state the reason(s) why direct access to NIV therapy is unavailable?
   ……
   ……
   ……
   ……

10. In the last 12 months, how many of your MND patients were referred to start NIV therapy?
    _____

11. Of these patients, how many were successful in being established on NIV therapy?
    _____

12. Of all your patients with MND, how many are currently on NIV therapy?
    _____

13. In your opinion, please tick the relevant contra-indications to NIV therapy in MND patients?
    - ☐ Age >75 years old
    - ☐ Rapidly progressive disease
    - ☐ Severe bulbar impairment
    - ☐ Cognitive impairment
    - ☐ Loss of upper limb function
    - ☐ Inability to communicate via alternate means (iPad/boogie board)
    - ☐ Social isolation/lack of family support (no carer)
    - ☐ Nursing home resident
    - ☐ Severe depression
    - ☐ Other ……

14. Following the onset of symptomatic nocturnal hypoventilation, which of the following statement best reflects your views on the role of NIV therapy in MND patients with differing degrees of bulbar dysfunction? (please tick the boxes as appropriate)

	Normal to Mild Bulbar Function Impairment*	Moderate to Severe Bulbar Function Impairment**
NIV therapy has no role in MND management	☐	☐
NIV therapy should be considered in carefully selected MND patients	☐	☐
NIV therapy should be offered	☐	☐
NIV therapy is proven to increase survival in MND patients	☐	☐

Definition of bulbar impairment based on ALS Functional Rating Scale:

- ***Normal to Mild Bulbar Impairment****: normal speech to intelligible speech with repeating; normal to minimal drooling of saliva, and normal swallowing with some dietary consistency changes.*
- ***Moderate to Severe Bulbar Impairment*****: Loss of useful speech and use of non-vocal communication, excessive saliva drooling, abnormal swallowing requiring supplemental tube feeding or reliant on percutaneous gastrostomy tube feeding.*

15. Do you initiate Advanced Care Directives discussion and planning with your MND patients following the establishment of NIV therapy? YES/NO
    If not, why?
    ……
    ……
    ……
    ……
    ……

16. Case scenario: Mr MND is 65 year old retired politician with flail arm variant of amyotrophic lateral sclerosis. Twelve months following his diagnosis, he has no functional hand movements, with progressive lower limb weakness. His speech is dysarthric, and his swallowing is moderately impaired. Following commencement of Cipramil, his mood is less labile. He has a caring wife who is his primary carer, and is living in a single storey home. He is noticeably breathless during conversations and complains of orthopnoea, unrefreshing sleep and morning headaches. The recent overnight oximetry showed repetitive oxygen desaturations, with 20 events below 85%, from a baseline of 93%. His FVC has been trending downwards, currently at 50% predicted.

    What would you do next? (tick one only)

    - ☐ Refer to MND multidisciplinary care team
    - ☐ Refer for formal diagnostic sleep study (polysomnography)
    - ☐ Refer to palliative care physician
    - ☐ Plan to admit as inpatient to commence NIV therapy
    - ☐ Do nothing and review in three months

17. Other comments

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

Please kindly return both the basic demographic information/consent and the questionnaire in the provided stamped self-addressed envelope.

Thank you for your valuable contribution and participation.

APPENDIX D: ETHICAL AND SCIENTIFIC APPROVAL LETTER

Office of the Deputy Vice-Chancellor (Research)
Research Office
C5C Research HUB East, Level 3, Room 324
MACQUARIE UNIVERSITY NSW 2109 AUSTRALIA
Phone **+61 (0)2 9850 4194**
Fax +61 (0)2 9850 4465
Email ethics.secretariat@mq.edu.au

9 May 2014

Professor Dominic Rowe
Australian School of Advanced Medicine
Faculty of Human Sciences
Macquarie University NSW 2109

Dear Professor Rowe

RE: *Non Invasive Ventilation in Motor Neuron Disease/Amyotrophic Lateral Sclerosis: An Australian Perspective*

Thank you for submitting the above low risk application for ethical and scientific review. Your application was considered by the Macquarie University Human Research Ethics Committee (HREC (Medical Sciences)) out of session.

I am pleased to advise that ethical and scientific approval has been granted for this project to be conducted at:

- Macquarie University

This research meets the requirements set out in the *National Statement on Ethical Conduct in Human Research* (2007 – Updated March 2014) (the *National Statement*).

Details of this approval are as follows:

Reference No: 5201400418

Approval Date: 9 May 2014

The following documentation has been reviewed and approved by the HREC (Medical Sciences):

Document	Version	Date
Macquarie University Ethics Application Form	2.3	July 2013
Macquarie University Participant Information Letter and Consent Form		2 April 2014
Questionnaire Entitled *Non-invasive ventilation in motor neuron disease/amyotrophic lateral sclerosis An Australian Perspective*		
Recruitment Letter to ANZAN Secretariat		
Recruitment Letter to the Thoracic Society of Australia and New Zealand Ltd		

Please ensure that all documentation has a version number and date in future correspondence with the Committee.

Standard Conditions of Approval:

1. Continuing compliance with the requirements of the *National Statement,* which is available at the following website:

   http://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research

2. This approval is valid for five (5) years, subject to the submission of annual reports. Please submit your reports on the anniversary of the approval of this protocol.

3. All adverse events, including events which might affect the continued ethical and scientific acceptability of the project, must be reported to the HREC within 72 hours.

4. Proposed changes to the protocol must be submitted to the Committee for approval before implementation.

5. It is the responsibility of the Chief investigator to retain a copy of all documentation related to this project and to forward a copy of this approval letter to all personnel listed on the project.

Should you have any queries regarding your project, please contact the Ethics Secretariat on 9850 4194 or by email ethics.secretariat@mq.edu.au

The HREC (Medical Sciences) Terms of Reference and Standard Operating Procedures are available from the Research Office website at:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Professor Tony Eyers
Chair, Macquarie University Human Research Ethics Committee (Medical Sciences)

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

APPENDIX E: QUESTIONNAIRE FROM DR STEPHEN BOURKE

Non-invasive ventilation in Motor Neurone Disease / Amyotrophic Lateral Sclerosis

Dear,

In October 2000, the Newcastle MND/NIV group undertook a postal survey of the clinical application of non-invasive ventilation (NIV) in MND in the United Kingdom. This showed that few patients with MND received NIV and that there was marked variation in clinical practice. In view of the body of evidence that has since emerged, we are now undertaking a second survey to get an up to date picture of UK practice, supported by the Motor Neurone Disease Association and the Association of British Neurologists.

We would be very grateful if you could find time to complete and return the attached questionnaire. If you do not see MND patients in your normal practice please simply indicate this on the enclosed return card. A stamped addressed envelope is enclosed. The information you share with us will help to assess current practice within the UK and hopefully lead to improvements in NIV and palliative care services for patients with motor neurone disease.

Many thanks for your time,

Dr Catherine O'Neill, Specialist Registrar in Palliative Medicine
St. Oswald's Hospice, Northumbria Healthcare NHS Trust

Dr. Tim Williams, Consultant Neurologist
The Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr. Tim Peel, Consultant in Respiratory and Palliative Medicine
Northumbria Healthcare NHS Foundation Trust

Professor G John Gibson, Consultant in Respiratory Medicine
The Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University

Dr Christopher McDermott Clinical Senior Lecturer and Honorary Consultant Neurologist
Royal Hallamshire Hospital and Sheffield University.

Professor PJ Shaw, Consultant Neurologist
Royal Hallamshire Hospital and Sheffield University

Dr Stephen Bourke, Consultant Respiratory Physician
Northumbria-Healthcare NHS Foundation Trust and Newcastle University

Non-invasive ventilation in Motor Neurone Disease / Amyotrophic Lateral Sclerosis

1. How many new patients with MND have you seen in the last 12 months? ……..
2. How many patients do you have under review with MND (including those diagnosed in the last 12 months who are being reviewed)? .....
3. Of these, how often do you usually review them? ……monthly.
4. If you share care of any of your patients receiving NIV with another neurologist, please indicate:
   - Name of neurologist & centre

     ……
   - Number of patients under shared care …….
5. Please indicate which of these lung function tests you **routinely** assess?

	Spirometry		SNIP*	$P_i$max / $P_e$max**	Pulse oximetry	Arterial blood gases	Non invasive PCO_2 (e.g. TOSCA)
	Sitting	Supine					
At presentation							
Every clinic visit							
Only if symptomatic							
Never							

*SNIP: Sniff Nasal Inspiratory Pressure

**PiMax/PeMax: Maximum Inspiratory and expiratory respiratory pressures

6. If patients have respiratory / sleep related symptoms, do you refer them for any of the following sleep studies?

Nocturnal oximetry	□
Transcutaneous PCO2 with oximetry (eg TOSCA)	□
Limited sleep study (no EEG)	□
Polysomnography (with EEG)	□

Non-invasive ventilation in Motor Neurone Disease / Amyotrophic Lateral Sclerosis

7. What are your main selection criteria for referring / offering MND patients NIV?
   (please tick A, B and/or C and any subsections that apply)

   A) Symptoms **only** (please indicate below): ☐

   B) Symptoms & physiological impairment (indicate below): ☐

Symptoms

- Orthopnoea ☐
- Breathlessness ☐
- Morning headache ☐
- Daytime sleepiness ☐
- Other ……..

Physiology

- Daytime hypercapnia ☐
- Nocturnal hypoxaemia ☐
- Nocturnal hypercapnia ☐
- VC or FVC ☐ State threshold: ……% predicted
- Pimax ☐ State threshold: ……% predicted or .....cm H_2O
- SNIP ☐ State threshold: ……% predicted or .....cm H_2O
- Other ……..

C) With minimal / no symptoms (early intervention): ☐ - based on:

- VC or FVC ☐ State threshold: ……% predicted
- Pimax ☐ State threshold: ……% predicted or .....cm H_2O
- SNIP ☐ State threshold: ……% predicted or .....cm H_2O
- Other ……

8. What access do you have to a non-invasive ventilation service?

   None ☐ Local service ☐ Regional service ☐

9. If you have no access to NIV or regard the available service as inadequate, what are the barriers to effective provision? (please specify)

- Routine monitoring of respiratory function not possible due to service constraints ☐
- Lack of locally accepted criteria for referral for NIV ☐
- No local NIV service ☐
- Insufficient provision of NIV machines ☐
- Inadequate local NIV service provision for other reasons ☐ - please specify
  ……

Non-invasive ventilation in Motor Neurone Disease / Amyotrophic Lateral Sclerosis

10. How many patients under your care with MND have been referred for NIV in the last twelve months? .....

    (Please include patients referred in liaison with, or directly by respiratory physicians / other specialties and state which specialities involved

    None □ Respiratory □ Palliative care □ anaesthetics □ other □)

11. Of these, how many were established successfully on NIV? .....

12. How many MND patients under your care are currently receiving NIV?

    .....

13. How many patients are currently receiving **long term** tracheostomy ventilation:
    - With normal or only moderately impaired bulbar function **initiated**:

      in an emergency n = ….. / electively n = ……
    - With severe bulbar impairment **initiated**:

      in an emergency n =….. ./ electively n =…....

14. For emergency tracheostomies, in what proportion was the diagnosis clear at time of acute presentation? .....

15. Please indicate which of the following would **deter you** from considering NIV:

    I. Rapidly progressive disease □

    II. Limb function:
    - No useful function of upper limbs (help fitting NIV required) □
    - No useful function lower limbs □
    - Completely dependent □

    III. Severe bulbar impairment □

    IV. Unable to communicate by speech or lightwriter □

    V. Cognitive impairment □

    VI. Social isolation / lack of family support □

    VII. Depression / anxiety □

    VIII. Alcohol / drug abuse □

    IX. Other……

Non-invasive ventilation in Motor Neurone Disease / Amyotrophic Lateral Sclerosis

16. Following the onset of symptomatic respiratory compromise, which of the following statements best reflects your views on the role of NIV in patients with differing degrees of bulbar dysfunction:

	Normal or Moderately Impaired Bulbar Function	Severe Bulbar Impairment
Has no role in the management of MND	□	□
Should be considered in exceptional cases only	□	□
Should be considered in carefully selected patients with MND	□	□
Should be offered to most patients with MND	□	□

17. Do your patients receiving NIV have access to the following back-up facilities (please tick appropriate box / boxes)

	Full-time (24 hours, 7 days per week)	Limited (e.g. Mon – Fri: 9am-5pm)
Technical	□	□
Clinical	□	□

Any additional comments: ……

18. Do you use specialist palliative care services for your MND patients? :

a. At end of life: Y □ N □ % patients……..

b. Prior to end of life: Y □ N □ % patients……..

19. In MND patients with respiratory symptoms, please specify which palliative measures you offer:

	Oxygen	Benzodiazepines	Opioids	Other
a. At end of life:	□	□	□	□
b. Prior to end of life (NIV not tolerated or deemed inappropriate):	□	□	□	□
c. Prior to end of life (before trial of NIV in an appropriate candidate):	□	□	□	□

Please specify any other measures……

……

……

Thank you for your time

APPENDIX F: DATA SUMMARY (1)

Table 1: Summary of respondent demographics

	Without Q		With Q	
	Respiratory n=94	Neurology n= 35	Respiratory n=105	Neurology n=71
Gender				
Male	70 (74%)	24 (69%)	73 (70%)	54 (76%)
Female	21 (22%)	11 (31%)	32 (30%)	11 (15%)
Not specified	3 (3%)			6 (8%)
Age				
Range	29 – 80yrs	33 – 87yrs	29 - 69yrs	30 – 78yrs
Mean	52.78	53.34	45.53	51.90
Standard deviation	15.4	15.0	9.3	11.0
Not specified	n=18	n=6	n=7	n=6
Years post FRACP				
Less than 5	12 (13%)	6 (17%)	30 (29%)	8 (11%)
6 – 15 yrs	23 (24%)	7 (20%)	31 (30%)	14 (20%)
16 - 25 yrs	12 (13%)	3 (9%)	22 (21%)	23 (32%)
26 – 35 yrs	6 (6%)	6 (17%)	13 (12%)	12 (17%)
More than 36	19 (20%)	4 (11%)	1 (1%)	6 (8%)
Not specified	22 (23%)	9 (26%)	8 (8%)	8 (11%)
Type of practice				
Private	18 (19%)	6 (17%)	11 (10%)	12 (17%)
Public	29 (31%)	12 (34%)	40 (38%)	16 (23%)
Private & Public	20 (21%)	10 (29%)	50 (48%)	36 (51%)
Academia	11 (12%)	7 (20%)	6 (6%)	7 (10%)
Not specified	19 (20%)	4 (11%)	2 (2%)	6 (8%)
Area of practice				
Metro	65 (69%)	33 (94%)	91 (87%)	58 (82%)
Rural	8 (9%)	0 (0%)	11 (10%)	11 (15%)
Remote	1 (1%)	0 (0%)	2 (2%)	1 (1%)
Not specified	22 (23%)	2 (6%)	3 (3%)	6 (8%)

APPENDIX G: DATA SUMMARY (2)

Table 6: Summary of the motor neuron disease patients seen

	Respiratory n=105	Neurology n=71
New MND patients seen in last 12 months		
Total Sum	**478**	**448**
0 patient	26 (25%)	6 (8%)
1 -5 patients	58 (55%)	50 (70%)
6 – 20 patients	15 (14%)	11 (15%)
More than 21 patients	5 (5%)	4 (6%)
Not specified	1 (1%)	0 (0%)
Currently managed MND patients		
Total Sum	**839**	**627**
0 patient	44 (42%)	18 (25%)
1 -5 patients	33 (31%)	33 (46%)
6 – 20 patients	18 (17%)	13 (18%)
More than 21 patients	7 (7%)	6 (8%)
Not specified	3 (3%)	1 (1%)
MND patients referred to start NIV in last 12 months		
Total Sum	**394**	**198**
0 patient	29 (28%)	32 (45%)
1 -5 patients	47 (45%)	18 (25%)
6 – 20 patients	14 (13%)	7 (10%)
More than 21 patients	2 (2%)	3 (4%)
Not specified	13 (12%)	11 (15%)
Successful MND patients established on NIV in last 12 months		
Total Sum	**329**	**157**
0 patient	24 (23%)	14 (19%)
1 -5 patients	45 (43%)	13 (18%)
6 – 20 patients	10 (10%)	6 (8%)
More than 21 patients	2 (2%)	2 (3%)
Not specified	24 (23%)	36 (51%)
Current MND patients on NIV		
Total Sum	**631**	**183**
0 patient	26 (25%)	25 (35%)
1 -5 patients	38 (36%)	16 (23%)
6 – 20 patients	11 (11%)	4 (6%)
More than 21 patients	4 (4%)	3 (4%)
Not specified	26 (25%)	23 (32%)
Review Frequency (weeks)		
Mean	13.48	13.16
Standard deviation	6.8	4.4
Not specified	32	13

APPENDIX H: DATA SUMMARY (3)

Table 7: Summary of shared MND patients' management

	Respiratory n=105	Neurology n=71
YES	89 (85%)	67 (94%)
NO	7 (7%)	1 (1%)
Not specified	9 (9%)	3 (4%)
Specialists involved		
Neurologist	87 (83%)	36 (37%)
Respiratory Physician	17 (16%)	38 (54%)
Palliative Care Physician	36 (34%)	28 (39%)
Rehabilitation Medicine Physician	8 (8%)	8 (11%)
Gastroenterologist	16 (15%)	11 (15%)
MND Multidisciplinary Team Clinic	36 (34%)	47 (66%)
Other	5 (5%)	2 (3%)

APPENDIX I: DATA SUMMARY (4)

Table 7: Summary of respiratory investigations used

	Respiratory n=105	Neurology n=71
Sitting FVC		
- **Initial diagnosis**	93 (89%)	55 (77%)
- **3 monthly**	50 (48%)	4 (6%)
- **6 monthly**	48 (46%)	12 (17%)
- **12 monthly**	41 (39%)	7 (10%)
- **IF symptomatic**	35 (33%)	24 (34%)
- **Never**	1 (1%)	2 (3%)
Supine FVC		
- **Initial diagnosis**	54 (51%)	21 (30%)
- **3 monthly**	20 (19%)	2 (3%)
- **6 monthly**	22 (21%)	6 (8%)
- **12 monthly**	23 (22%)	5(7%)
- **IF symptomatic**	24 (23%)	16 (23%)
- **Never**	5 (5%)	9 (13%)
SNIP		
- **Initial diagnosis**	31 (30%)	9 (13%)
- **3 monthly**	13 (12%)	2 (3%)
- **6 monthly**	8 (8%)	3 (4%)
- **12 monthly**	6 (6%)	4 (6%)
- **IF symptomatic**	12 (11%)	6 (8%)
- **Never**	17 (16%)	10 (14%)
PiMax & PeMax		
- **Initial diagnosis**	78 (74%)	17 (24%)
- **3 monthly**	22 (21%)	2 (3%)
- **6 monthly**	25 (24%)	6 (8%)
- **12 monthly**	21 (20%)	7 (10%)
- **IF symptomatic**	30 (29%)	12 (17%)
- **Never**	4 (4%)	9 (13%)

Table 7 cont.: Summary of respiratory investigations used

	Respiratory n=105	Neurology n=71
Overnight Oximetry		
- **Initial diagnosis**	38 (36%)	7 (10%)
- **3 monthly**	6 (6%)	0 (0%)
- **6 monthly**	12 (11%)	3 (4%)
- **12 monthly**	15 (14%)	1 (1%)
- **IF symptomatic**	35 (33%)	20 (28%)
- **Never**	10 (10%)	5 (7%)
Arterial Blood Gas		
- **Initial diagnosis**	60 (57%)	6 (8%)
- **3 monthly**	13 (12%)	0 (0%)
- **6 monthly**	19 (18%)	0 (0%)
- **12 monthly**	19 (18%)	1 (1%)
- **IF symptomatic**	46 (44%)	21 (30%)
- **Never**	3 (3%)	8 (11%)
Pulse Oximetry		
- **Initial diagnosis**	58 (55%)	9 (13%)
- **3 monthly**	32 (30%)	3 (4%)
- **6 monthly**	26 (25%)	4 (6%)
- **12 monthly**	21 (20%)	2 (3%)
- **IF symptomatic**	27 (26%)	16 (23%)
- **Never**	4 (4%)	8 (11%)

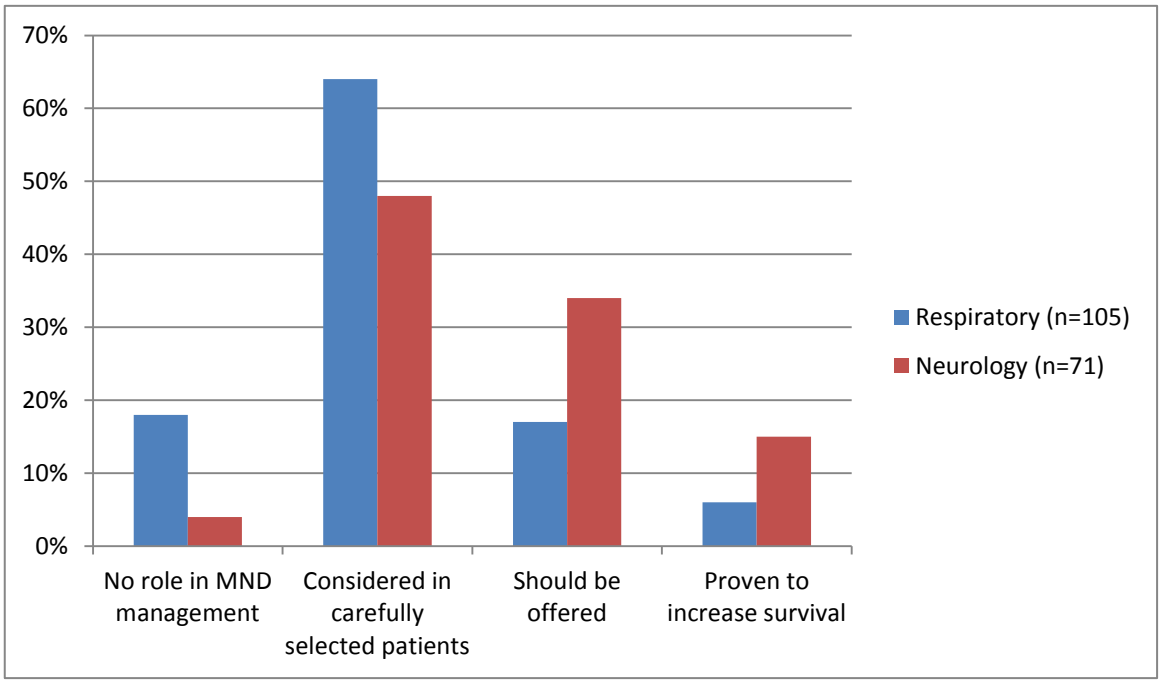
APPENDIX J: DATA SUMMARY (5)

Table 11: Summary of *Opinion*: Contra-indications to NIV therapy

	Respiratory n=105	Neurology n=71
Age >75years	8 (8%)	5 (7%)
Rapidly progressive disease	17 (16%)	8 (11%)
Severe bulbar impairment	64 (61%)	28 (39%)
Cognitive impairment	72 (69%)	32 (45%)
Loss of upper limb function	32(30%)	11 (15%)
Inability to communicate via alternate means	29 (28%)	6 (8%)
Social isolation/lack of family support (no carer)	42 (40%)	26 (37%)
Nursing home resident	19 (18%)	8 (11%)
Severe depression	8 (8%)	6 (8%)
Other	9 (9%)	6 (8%)

APPENDIX J: DATA SUMMARY (6)

Graph 10: The role of NIV therapy in patients with moderate to severe bulbar dysfunction



ACKNOWLEDGEMENTS

I am indebted to my supervisors, Professor Dominic Rowe and Professor Alvin Ing for providing support and guidance throughout the course of this Master of Research study. I am sincerely grateful for their friendly advice and their continuous motivation in inspiring me to pursue further research in motor neuron disease.

I would like to thank Dr Stephen Bourke for providing his questionnaire which was adapted to answer questions pertinent to my research study.

I am thankful for the financial support provided by the MND Research Centre at Macquarie University that funded some of the administrative costs.

I am grateful to Ms Rita Perkons the CEO of TSANZ, and Ms Mandy Jones the EO of ANZAN for facilitating the delivery of the cover letter, consent form and questionnaire to their members.

I owe my deepest gratitude to my husband and children for their love, patience, encouragement and support.

REFERENCES

1 Garner, D. J. *et al.* Home mechanical ventilation in Australia and New Zealand. *Eur. Respir. J.* **41**, 39-45, doi:10.1183/09031936.00206311 (2013).

2 Gordon, P. H. *et al.* Changing mortality for motor neuron disease in France (1968-2007): An age-period-cohort analysis. *Eur. J. Epidemiol.* **26**, 729-737, doi:10.1007/s10654-011-9595-0 (2011).

3 Imam, I., Ball, S., Wright, D., Hanemann, C. O. & Zajicek, J. The epidemiology of motor neurone disease in two counties in the southwest of England. *Journal of Neurology* **257**, 977-981, doi:10.1007/s00415-009-5448-0 (2010).

4 Donaghy, C. *et al.* The epidemiology of motor neuron disease in Northern Ireland using capture-recapture methodology. *Amyotrophic Lateral Sclerosis* **11**, 374-378, doi:10.3109/17482960903329569 (2010).

5 Lai, C. H. & Tseng, H. F. Epidemiology and medical expenses of motor neuron diseases in Taiwan. *Neuroepidemiology* **31**, 159-166, doi:10.1159/000154928 (2008).

6 Forbes, R. B., Colville, S., Parratt, J. & Swingler, R. J. The incidence of motor nueron disease in Scotland. *Journal of Neurology* **254**, 866-869, doi:10.1007/s00415-006-0454-y (2007).

7 Day, T. G., Scott, M., Perring, R. & Doyle, P. Motor neuron disease mortality in Great Britain continues to rise: Examination of mortality rates 1975 - 2004. *Amyotrophic Lateral Sclerosis* **8**, 337-342, doi:10.1080/17482960701725455 (2007).

8 Fong, G. C. Y. *et al.* An epidemiological study of motor neuron disease in Hong Kong. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* **6**, 164-168, doi:10.1080/14660820510028412 (2005).

9 Mulder, D. W. & Kurland, L. T. Motor neuron disease: epidemiologic studies. *Adv Exp Med Biol* **209**, 325-332 (1987).

10 Salazar-Grueso, E. F. & Roos, R. P. Amyotrophic lateral sclerosis and viruses. *CLIN. NEUROSCI.* **3**, 360-367 (1995).

11 Charles, T. & Swash, M. Amyotrophic lateral sclerosis: current understanding. *J Neurosci Nurs* **33**, 245-253 (2001).

12 Park, R. M. *et al.* Potential occupational risks for neurodegenerative diseases. *Am. J. Ind. Med.* **48**, 63-77, doi:10.1002/ajim.20178 (2005).

13 Uccelli, R. *et al.* Geographic distribution of amyotrophic lateral sclerosis through motor neuron disease mortality data. *Eur. J. Epidemiol.* **22**, 781-790, doi:10.1007/s10654-007-9173-7 (2007).

14 Sathasivam, S. Motor neurone disease: Clinical features, diagnosis, diagnostic pitfalls and prognostic markers. *Singapore Med. J.* **51**, 367-373 (2010).

15 Strong, M. J. & Rosenfeld, J. Amyotrophic lateral sclerosis: A review of current concepts. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* **4**, 136-143, doi:10.1080/14660820310011250 (2003).

16 Brooks, B. R. *et al.* El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* **124**, 96-107, doi:10.1016/0022-510X(94)90191-0 (1994).

17 Brooks, B. R., Miller, R. G., Swash, M. & Munsat, T. L. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* **1**, 293-299, doi:10.1080/146608200300079536 (2000).

18 *Motor neuron diseases : causes, classification, and treatments / Bradley J. Turner and Julie B. Atkin, editors*. (New York : Nova Biomedical Books, c2012, 2012).

19 Wijesekera, L. C. *et al.* Natural history and clinical features of the flail arm and flail leg ALS variants. *Neurology* **72**, 1087-1094, doi:10.1212/01.wnl.0000345041.83406.a2 (2009).

20 Czaplinski, A., Steck, A. J., Andersen, P. M. & Weber, M. Flail arm syndrome: A clinical variant of amyotrophic lateral sclerosis. *European Journal of Neurology* **11**, 567-568, doi:10.1111/j.1468-1331.2004.00841.x (2004).

21 Visser, J., de Jong, J. M. & de Visser, M. The history of progressive muscular atrophy: syndrome or disease? *Neurology* **70**, 723-727, doi:10.1212/01.wnl.0000302187.20239.93 (2008).

22 Gordon, P. H. *et al.* The natural history of primary lateral sclerosis. *Neurology* **66**, 647-653, doi:10.1212/01.wnl.0000200962.94777.71 (2006).

23 McCluskey, L. *et al.* ALS-Plus syndrome: Non-pyramidal features in a large ALS cohort. *Journal of the Neurological Sciences*, doi:10.1016/j.jns.2014.07.022 (2014).

24 Bourke, S. C., Shaw, P. J. & Gibson, G. J. Respiratory function vs sleep-disordered breathing as predictors of QOL in ALS. *Neurology* **57**, 2040-2044 (2001).

25 Nichols, N. L. *et al.* Ventilatory control in ALS. *Respir. Physiol. Neurobiol.* **189**, 429-437, doi:10.1016/j.resp.2013.05.016 (2013).

26 Lyall, R. A., Donaldson, N., Polkey, M. I., Leigh, P. N. & Moxham, J. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. *Brain* **124**, 2000-2013 (2001).

27 Eisen, A. Amyotrophic lateral sclerosis: A 40-year personal perspective. *Journal of Clinical Neuroscience* **16**, 505-512, doi:10.1016/j.jocn.2008.07.072 (2009).

28 Arnulf, I. *et al.* Sleep disorders and diaphragmatic function in patients with amyotrophic lateral sclerosis. *Am. J. Respir. Crit. Care Med.* **161**, 849 (2000).

29 MacDuff, A. & Grant, I. S. Critical care management of neuromuscular disease, including long-term ventilation. *Curr. Opin. Crit. Care* **9**, 106-112, doi:10.1097/00075198-200304000-00005 (2003).

30 Chandrasoma, B. *et al.* Pulmonary function in patients with Amyotrophic Lateral Sclerosis at disease onset. *Monaldi Archives for Chest Disease - Pulmonary Series* **77**, 129-133 (2012).

32 Winhammar, J. M. C. *et al.* Nocturnal hypoxia in motor neuron disease is not predicted by standard respiratory function tests. *Internal Medicine Journal* **36**, 419-422, doi:10.1111/j.1445-5994.2006.01102.x (2006).

33 Fitting, J. W. Volitional assessment of respiratory muscle strength. *Monaldi Archives for Chest Disease - Pulmonary Series* **77**, 19-22 (2012).

34 Mustfa, N. & Moxham, J. Respiratory muscle assessment in motor neurone disease. *QJM Mon. J. Assoc. Phys.* **94**, 497-502 (2001).

35 Andersen, P. M. *et al.* EFNS task force on management of amyotrophic lateral sclerosis: Guidelines for diagnosing and clinical care of patients and relatives: An evidence-based review with good practice points. *European Journal of Neurology* **12**, 921-938, doi:10.1111/j.1468-1331.2005.01351.x (2005).

36 Miller, R. G. *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* **73**, 1218-1226, doi:10.1212/WNL.0b013e3181bc0141 (2009).

37 Miller, R. G., Mitchell, J. D. & Moore, D. H. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane database of systematic reviews (Online)* **3** (2012).

38 Andersen, P. M. *et al.* EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) - revised report of an EFNS task force. *European Journal of Neurology* **19**, 360-375, doi:10.1111/j.1468-1331.2011.03501.x (2012).

39 Gruis, K. L., Brown, D. L., Weatherwax, K. J., Feldman, E. L. & Chervin, R. D. Evaluation of sham non-invasive ventilation for randomized, controlled trials in ALS. *Amyotrophic Lateral Sclerosis* **7**, 96-99, doi:10.1080/14660820600640604 (2006).

40 Pinto, A. C., Evangelista, T., Carvalho, M., Alves, M. A. & Sales Luís, M. L. Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: Survival rates in a controlled trial. *Journal of the Neurological Sciences* **129**, 19-26, doi:10.1016/0022-510X(95)00052-4 (1995).

41 Aboussouan, L. S. & Mireles-Cabodevila, E. Respiratory support in patients with amyotrophic lateral sclerosis. *Respiratory Care* **58**, 1555-1558, doi:10.4187/respcare.02710 (2013).

42 Kleopa, K. A., Sherman, M., Neal, B., Romano, G. J. & Heiman-Patterson, T. Bipap improves survival and rate of pulmonary function decline in patients with ALS. *Journal of the Neurological Sciences* **164**, 82-88, doi:10.1016/S0022-510X(99)00045-3 (1999).

43 Bourke, S. C. *et al.* Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *The Lancet Neurology* **5**, 140-147, doi:10.1016/s1474-4422(05)70326-4 (2006).

44 Lechtzin, N. Respiratory effects of amyotrophic lateral sclerosis: Problems and solutions. *Respiratory Care* **51**, 871-881 (2006).

45 Lechtzin, N. *et al.* Use of noninvasive ventilation in patients with amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* **5**, 9-15, doi:10.1080/14660820310017335 (2004).

46 Miller, R. G. *et al.* Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurorehabilitation and Neural Repair* **13**, 93-107, doi:10.1177/154596839901300202 (1999).

47 Radunovic, A., Annane, D., Rafiq, M. K. & Mustfa, N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. *The Cochrane database of systematic reviews* **3** (2013).

48 Chiò, A. *et al.* Epidemiology of ALS in Italy: A 10-year prospective population-based study. *Neurology* **72**, 725-731, doi:10.1212/01.wnl.0000343008.26874.d1 (2009).

49 Chiò, A. *et al.* Phenotypic heterogeneity of amyotrophic lateral sclerosis: A population based study. *Journal of Neurology, Neurosurgery and Psychiatry* **82**, 740-746, doi:10.1136/jnnp.2010.235952

49 Kwiatkowski Jr., T.J., Bosco, D.A., Leclerc, A.L., Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis (2009) Science, 323, pp. 1205-1208; Armon, C., Smoking may be considered an established risk factor for sporadic ALS (2009) Neurology, 73, pp. 1693-1698 (2011).

50 Chio, A. *et al.* Non-invasive ventilation in amyotrophic lateral sclerosis: a 10 year population based study. *Journal of neurology, neurosurgery, and psychiatry* **83**, 377-381, doi:10.1136/jnnp-2011-300472 (2012).

51 Chiò, A. *et al.* Non-invasive ventilation in amyotrophic lateral sclerosis: A 10 year population based study. *Journal of Neurology, Neurosurgery and Psychiatry* **83**, 377-381, doi:10.1136/jnnp-2011-300472 (2012).

52 Bourke, S. C., Williams, T. L., Bullock, R. E., Gibson, G. J. & Shaw, P. J. Non-invasive ventilation in motor neuron disease: Current UK practice. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* **3**, 145-149, doi:10.1080/146608202760834157 (2002).

53 O'Neill, C. L. *et al.* Non-invasive ventilation in motor neuron disease: an update of current UK practice. *Journal of neurology, neurosurgery, and psychiatry* **83**, 371-376, doi:10.1136/jnnp-2011-300480 (2012).

54 Miller, R. G. *et al.* Outcomes research in amyotrophic lateral sclerosis: Lessons learned from the amyotrophic lateral sclerosis clinical assessment, research, and education database. *Ann. Neurol.* **65**, S24-S28, doi:10.1002/ana.21556 (2009).

55 Colville, S., Swingler, R. J., Grant, I. S. & Williams, F. L. R. A population based study of respiratory function in motor neuron disease patients living in Tayside and North East Fife, Scotland. *Journal of Neurology* **254**, 453-458, doi:10.1007/s00415-006-0389-3 (2007).

56 Georgoulopoulou, E. *et al.* The impact of clinical factors, riluzole and therapeutic interventions on ALS survival: A population based study in Modena, Italy. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* **14**, 338-345, doi:10.3109/21678421.2013.763281 (2013).

57 Raaphorst, J. *et al.* Treatment of respiratory impairment in patients with motor neuron disease in the Netherlands: Patient preference and timing of referral. *European Journal of Neurology* **20**, 1524-1530, doi:10.1111/ene.12096 (2013).

58 Cui, F. *et al.* Epidemiological characteristics of motor neuron disease in Chinese patients. *Acta Neurologica Scandinavica*, doi:10.1111/ane.12240 (2014).

59 Hocking, J. S., Lim, M. S. C., Read, T. & Hellard, M. Postal surveys of physicians gave superior response rates over telephone interviews in a randomized trial. *Journal of Clinical Epidemiology* **59**, 521-524, doi:10.1016/j.jclinepi.2005.10.009 (2006).

60 Edwards, P. J. *et al.* Methods to increase response rates to postal questionnaires. *Cochrane Database of Systematic Reviews*, doi:10.1002/14651858.MR000008.pub3 (2007).

61 Krosnick, J. A. Vol. 50 537-567 (1999).

62 Asch, D. A., Jedrziewski, M. K. & Christakis, N. A. Response rates to mail surveys published in medical journals. *Journal of Clinical Epidemiology* **50**, 1129-1136, doi:10.1016/S0895-4356(97)00126-1 (1997).

63 Karras, D. J. Statistical methodology: II. Reliability and validity assessment in study design, Part A. *Academic Emergency Medicine* **4**, 64-71 (1997).

64 Karras, D. J. Statistical methodology: II. Reliability and validity assessment in study design, part B. *Academic Emergency Medicine* **4**, 144-147 (1997).