

Facemask Spirometry as a marker of Respiratory Function and Prognosis in Motor Neurone Disease

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Declaration

I declare that the work presented in this thesis is my own, with collaborative support from other research fellows, department of R&D and statisticians. My specific role in each research study is specified below. The doctoral research project was designed by myself and by my clinical research supervisor Dr IE Smith.

Sandip Banerjee

Specific involvement in each study:

Impact of structured follow up on ventilatory support for MND

I retrospectively reviewed the hospital database to identify patients with motor neurone disease (MND) referred for respiratory assessment from 1987 to 2010 in a regional respiratory support centre. I completed the statistical analysis

The role of facemask spirometry in MND

I defined the research proposal. This was followed by setting up the research protocol and submission to regional ethics committee to conduct the study. I performed spirometry with mask and tube/mouthpiece on all patients enrolled in study. I completed the data sheet which was submitted to the R&D department for analysis.

Facemask spirometry as a prognostic tool in MND

I defined the research proposal. This was followed by setting up the research protocol and submission to regional ethics committee to conduct the study. I performed spirometry with mask and tube/mouthpiece on the initial 60 patients enrolled in study.

I completed the data sheet for the first 60 patients enrolled which was submitted to the R&D department for analysis.

A survey of deaths in MND in the era of non-invasive ventilation

This was a survey which involved completion of a structured questionnaire by clinicians, nurses or care co-ordinators involved in the care of the patient with diagnosis of MND who died between October 2010 and December 2011. The questionnaire was devised in conjunction with Dr IE Smith. I received the responses when the survey was completed. Where incomplete details were supplied, I called the person completing the survey for further information. I performed the statistical analysis of the data.

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This work is dedicated to my father, for whom I have the greatest admiration, respect and love.

Abstract

Background:

The assessment and monitoring of respiratory muscle function is clinically relevant in patients with Motor Neurone Disease (MND). Early identification of respiratory muscle dysfunction has therapeutic and prognostic consequences. Current evidence shows that Non-invasive Ventilation (NIV) is associated with improved survival, quality of life and cognitive function. This thesis examines the role of early referral for NIV, serial measurements of vital capacity as a marker of respiratory compromise and advance planning for managing the terminal phase of disease.

Study population and methods:

With an annual incidence of 2.8 per 100,000; 70 new cases of MND per year were predicted in the catchment population. The thesis is set out in 4 phases.

A retrospective case note analysis of the referrals and initiation of NIV in patients with MND between 2000 and 2010 to RSSC, Papworth compared to UK national average.

A prospective study (phase 1) compared mask spirometry with conventional tube spirometry in an unselected MND clinic population grouped according to degree of bulbar involvement. Sixty of the 73 subjects screened were recruited.

A prospective, diagnostic cohort study (phase 2) to assess spirometry measures in predicting outcomes in bulbar and non-bulbar MND subjects. Sixty seven of 78 consecutive subjects with a new or existing diagnosis of MND (not using NIV and without a tracheostomy) were recruited.

A questionnaire survey of all patients (n=70) with probable or definite MND in the East of England region, identified by a network of clinicians, who died between October 2010 and December 2011.

Results:

Phase 1: Mean annual referral numbers were 44 with 31 NIV starters per year (70% of patients referred) rising from 7 to 44 per annum between 2006 to 2010.

Phase 2: Mask spirometry produced higher values than tube spirometry, in patients with FVC < 3 litres. Higher values of FVC were recorded in patients with moderate to severe bulbar involvement, irrespective of FVC.

Phase 3: There was no significant difference between mask and tube spirometry in predicting the onset of ventilatory failure or death. Patients with FVC <70% predicted were more likely to need NIV in a 3 month follow up. The results showed that serial measurements of tube or facemask FVC correlated with progression to respiratory failure or death.

Phase 4: There was no difference in the time and mode of death in patients with NIV compared to those without NIV support. Advanced care plans had been documented in 41%.

Conclusions:

My thesis demonstrated higher referral rates and NIV initiation in MND patients at RSSC, Papworth compared to UK national average, which was due to implementation of a care pathway later confirmed in the NICE guidance. This thesis also confirmed that the rate of decline of FVC, may predict the onset of ventilatory failure, irrespective of bulbar involvement. My questionnaire survey of death in MND confirmed that the dying process is not prolonged for patients who have used NIV at home.

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Abbreviations

ABG	Arterial Blood Gas
ACP	Advanced Care Plans
ALS	Amyotrophic Lateral Sclerosis
ALSFRS r score	Amyotrophic Lateral Sclerosis Functional Rating Scale R score
ATS	American Thoracic Society
BALSFRS r score	Bulbar Amyotrophic Lateral Sclerosis Functional Rating Scale R score
BMI	Body Mass Index (kg/m ²)
BTS	British Thoracic Society
CBG	Capillary Blood Gas
cm H ₂ O	centimetres of Water
CO ₂	Carbon dioxide
CSF	Cerebrospinal fluid
COPD	Chronic Obstructive Pulmonary Disease
EPAP	Expiratory Positive Airway Pressure
ERS	European Respiratory Society
ESS	Epworth Sleepiness Score
FEV ₁	Forced Expiratory Volume in 1 second
FSP	Familial Spastic Paraplegia
FVC	Forced Vital Capacity
HCO ₃	Bicarbonate
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
IPAP	Inspiratory Positive Airway Pressure
IPPV	Intermittent Positive Pressure Ventilation

KPa	KiloPascals
MDT	Multi-disciplinary team
MEP	Maximal Expiratory Pressure
MIP	Maximal Inspiratory Pressure
mm Hg	millimetres of Mercury
MND	Motor Neurone Disease
MVV	Maximal Voluntary Ventilation
NICE	National Institute of Clinical Excellence
NHS	National Health Service
N	number
NIV	Non-invasive Ventilation
O ₂	Oxygen
P	probability
PaO ₂	partial pressure of oxygen in arterial blood
PaCO ₂	partial pressure of carbon dioxide in arterial blood
PEG	percutaneous endoscopic gastrostomy
PFT	Pulmonary Function Test
P _{gas}	gastric pressure
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
P _{oes}	Oesophageal pressure
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSSC	Respiratory Support and Sleep Centre
SF-36	Short form 36
SMA	Spinal Muscular Atrophy

Sn Pdi	Sniff trans diaphragmatic pressure
SpO ₂	pulse oximetry
SVC	slow Vital Capacity
TLC	Total Lung Capacity
TF	Tube feeding
UK	United Kingdom
VC	Vital Capacity
WH	Wisdom Hospice

AIMS

The aims of this thesis were to explore, in patients with motor neurone disease;

(i) the impact of a structured follow up pathway on access to ventilatory support.

(ii) compare mask spirometry with conventional tube spirometry in predicting time to ventilatory failure/ need for NIV, and

(iii) identify if NIV and tube feeding lead to a prolongation of the process of dying and if advance care plans influence patient choice in the terminal phase.

Chapter 1. BACKGROUND

1.1 Introduction to Motor Neurone Disease

Motor Neurone Disease (MND) was first described by French Neurologist Charcot in 1874 (Rowland 2001). MND is degenerative disease resulting in progressive weakness and wasting of voluntary muscles, affecting a combination of upper or cortico-spinal motor neurones in the motor cortex and the lower motor neurones in the brainstem and spinal cord. Although at its onset MND may involve selective loss of only upper or lower motor neurones, it ultimately causes progressive loss of both categories of motor neurones (Swash and Charles 2001). Indeed, in the absence of clinical involvement of both motor neurone types, the diagnosis of MND is questionable. Presently, it is incurable with a mean survival of 4-5 years from symptom onset. A committee of the World Federation of Neurology established the El Escorial criteria for diagnosing MND (Brooks 1994). Essential for the diagnosis is simultaneous upper and lower motor neurone involvement with progressive weakness and the exclusion of all alternate diagnoses. The disorder is ranked as 'definite' when three or four of the following are involved: bulbar, cervical, thoracic and lumbosacral neurones. When two sites are involved, the diagnosis is 'probable' and when only one site is implicated the diagnosis is 'possible'.

The diagnosis of MND (Brooks 1994) requires the presence of:

1. Evidence of lower motor neurone degeneration by clinical, electrophysiological and neuro-pathologic examination.
2. Evidence of upper motor neurone signs by clinical examination.
3. Progressive spread of weakness

And the absence of:

1. Electrophysiological or pathologic evidence of another disease process
2. Neuro-imaging evidence of other disease processes that could explain the signs and symptoms

1.2 Pathogenesis of MND

MND encompasses many clinical forms of the disease; amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS) are most commonly described. ALS is the most common and involves loss of both upper and lower motor neurones equally. PMA is a disease predominantly of the lower motor neurones. PLS, the rarest form of the disease predominantly involves the upper motor neurones and is associated with the best prognosis (Wood-Allum 2010). Pseudobulbar palsy is a form of ALS affecting the bulbar region while lower motor neurone disease predominantly affecting upper limbs (flail arm) and lower limbs (flail leg) are also known. Ten percent of MND patients develop associated fronto-temporal dementia (Wijesekera 2009).

The cause for MND is unknown. In a minority of cases there is a familial presentation with clear patterns of inheritance. It is likely that sporadic MND may also involve interactions between several genetic risk factors or between genetic and environmental factors (Turner 2012). The sharp rise in incidence above the age of 50 years suggests the ageing process to be a factor. Men have a 1.5 times higher chance of developing the disease. The exact reason is not known but may be related to men being more likely to sustain physical injury (Kondo 1995). An association with physically demanding occupations has been proposed based on higher incidences amongst sports people and military personnel, but clear epidemiological evidence is lacking (Huisman 2013).

1.3 Genetics of MND

To date the most important clues regarding the pathogenesis of MND have been derived from molecular genetics. In approximately 5-10% of cases, other members of the family are also affected. Familial ALS is a dominant disorder being passed down through the generations and clinically indistinguishable from sporadic disease. The first genetic factor associated with MND was reported in 1991 to lie in chromosome 21 and subsequently identified as the copper/zinc superoxide dismutase genes (SOD1) in which mutations were observed (Siddique 1991). SOD1 is a powerful antioxidant catalytic enzyme responsible for neutralizing potentially harmful free radicals produced as part of normal cellular activity (Rosen 1993). To date more than 150 different

mutations of SOD1 have been described mostly due to single amino acid substitution (Andersen 2006).

The most common gene abnormality associated with MND in Europeans is a massive expansion of C9orf72 gene in chromosome 9. Such mutations are seen in 35% of familial and 5% of sporadic cases of MND. The function of the C9orf72 protein is unknown but loss of this protein is associated with production of aggregate prone proteins (Renton 2011).

Mutations of the TARDBP gene are rare accounting for only 1% of familial ALS but accumulation of TDP-43 protein (the TARDBP gene product) is a feature of 95% of ALS cases whether familial or sporadic. This connection would suggest that the accumulation of TDP-43 is toxic (Sreedharan 2008). In ALS and 60% of cases of fronto-temporal dementia, TDP-43 is lost from the nucleus and forms granular and globular inclusions in the axons. The over expression of TDP-43 leads to accumulation in the cytoplasm and aggregates into a toxic protein which may directly contribute to the death of motor neurones (Vance 2009). Several other genes such as; fused in sarcoma (FUS), valosin containing protein (VCP), ubiquilin 2 (UBQLN2) and sequestosome 1 (SQSTM1) have been implicated in MND. Mutations in these genes lead to delivery of damaged proteins to the cellular recycling system with resultant accumulation of TDP-43 which subsequently causes neurodegeneration (Polymenidou 2011).

1.4 Glutamate and Neuronal Toxicity

There is evidence that excitotoxic damage to the motor neurones may have an important role in the pathogenesis of MND (Choi 1992; Shaw 1994). Glutamate appears to play a central role in the pathogenesis. Glutamate, an excitatory neurotransmitter released at the presynaptic neuronal terminals causes activation of the receptors at the post-synaptic membranes. Glutamine synthetase converts glutamate to glutamine, which is returned to the pre-synaptic neurone where glutaminase converts it back to glutamate. This function may be impaired in MND (Choi 1992; Rothstein 1992). This results in excessive stimulation of the excitatory amino acid receptors at the post synaptic terminals, which leads to excessive entry of sodium and calcium into the cells disturbing the ionic homeostasis and is considered

the mechanism of cell death in MND. The exact reason for the dysfunction is not known but age, sex and mechanical injuries are considered as risk factors. One of the transporters responsible for glutamate uptake from the synapse, excitatory amino acid transporters (EAAT2), is reduced in the motor cortex and spinal cord of up to 70% of patients with sporadic ALS (Rothstein 1992). But increased glutamate in the cerebrospinal fluid (CSF) is seen in only 30% of patients (Shaw 1995). Thus glutamate induced toxicity may contribute but is not entirely responsible for MND.

1.5 Protein Aggregation

The abnormal clumping of proteins and their aggregates in neurones is commonly seen in neuro-degenerative diseases including MND. This has been seen in cases with SOD1 mutation where SOD1 protein aggregates and in cases with FUS mutation where FUS protein aggregates have been isolated (Polymenidou 2011). It is hypothesized that these aggregates may clog the protein degradation system in the neurones leading to loss of normal activity of the aggregating protein. Altered regulation of gene expression may affect the production of proteins under their control thereby affecting the ability of neurones to withstand insults. Two proteins involved in modulating gene expression, TDP-43 and FUS have been linked to familial MND (Polymenidou 2011). More recently the identification of neurofilament aggregates within motor neurones supports the altered gene expression hypothesis but suggests it is more contributory to motor neurone injury but unlikely to be the primary mechanism in the pathogenesis of MND (Bosco 2010).

1.6 Free radicals, Oxidative stress and MND

In healthy people in the face of stress, the cellular stress response must focus on production of proteins that are critical to cell health but at the same time pause production of non-essential proteins (Weinert 2009). During this normal oxidative stress metabolism, several free radicals are produced. Free radicals are capable of damaging proteins, lipids and nucleic acids. Protein oxidation has been detected in the motor cortex and spinal cord in patients with ALS and mutant transgenic mice (Cluskey 2001). It is also proposed that TDP-43 and FUS protein prevent the mop up of these free radicals, which may initiate the formation of protein aggregates seen in MND patients (Colombrita 2009).

1.7 Impaired Axonal Transport

Motor neurone axons rely on efficient intracellular transport systems which consist of anterograde and retrograde transport systems. The kinesin complex of proteins and dynein-dynactin complex are closely associated with this transport system (Martin 1999). Mutations in kinesin genes are associated with neurodegenerative motor disease in humans such as hereditary spastic paraplegia (Roy 2005). Mutations in dynactin complex cause a lower motor neurone disorder with vocal cord paralysis in humans (Roy 2005). In transgenic mouse models' mutations to this protein complex have been seen although no such findings have been observed in humans (De Vos 2008).

1.8 Inflammatory dysfunction and Contribution of Non-neuronal cells

There is considerable evidence that inflammatory processes and non-neuronal cells may play an active part in the pathogenesis of MND. Microglial and dendritic cell activation is a prominent pathology in human (and mouse models) of MND. The activated non-neuronal cells produce inflammatory cytokines such as interleukins, cyclo-oxygenase 2 (COX-2), tumour necrosis factor alpha (TNF α) and monocyte chemo-attractant protein 1 (MCP-1). There is evidence of upregulation of these proteins in the CSF of patients with MND (Henkel 2004).

The final process of cell death is thought to closely resemble the programmed cell death pathway (apoptosis). Biochemical markers of apoptosis are detected in the terminal stages of human ALS including the caspase family of proteolytic enzymes, apoptosis inhibitor family of proteins (IAPs) and anti-apoptotic and pro apoptotic oncogenes (Pasinelli 1998).

1.9 Histopathological Features

The pathologic hallmark of MND is death of the lower motor neurones consisting of the anterior horn cells in the spinal cord and the brainstem innervating bulbar muscles and upper motor neurones in the motor cortex descending via the pyramidal tract to synapse with lower motor neurones. The degeneration and loss of motor neurones with astrocytic gliosis along with the presence of intraneuronal inclusions in

degenerating neurones and glia make the pathological hallmark (Wijesekera 2009). Upper motor neurone pathology is shown by destruction of betz cells in the motor cortex (Brodmann area 4), astrocytic gliosis involving both the grey matter and the subcortical white matter of the motor cortex and axonal loss within the descending pyramidal pathway associated with myelin pallor and gliosis of the corticospinal tracts (Wijesekera 2009). Lower motor neurone pathology generally affects the ventral horn of the spinal cord and brainstem. The number of lower motor neurones can be reduced by up to 50% at autopsy (Wharton 2003). The remaining neurones are atrophic and contain intra-neuronal inclusions such as Bunina bodies, ubiquitinated inclusions and hyaline conglomerate inclusions. Bunina bodies are small eosinophilic intracytoplasmic inclusion bodies that stain positive for cystatin and are present in 70-100% of cases with ALS (Koichi 2008). TDP 43 is the major protein constituent in ubiquitinated inclusions that result in filamentous or spherical intra-neuronal inclusions. They can be seen in 95% of cases (Neumann2006).

Frequently at the onset of MND selective loss of function either of upper or lower motor neurones may occur although ultimately progressive loss of both categories of motor neurones will develop. Variants of MND predominantly involve subsets of motor neurones. In bulbar palsy and spinal muscular atrophy (SMA), the lower motor neurones of the brainstem and spinal cord respectively are most severely affected. In Pseudo-bulbar palsy, primary lateral sclerosis (PLS) and familial spastic paraplegia (FSP) upper motor neurones innervating the brain stem and spinal cord are primarily affected. The death of the lower motor neurones in the brain stem and spinal cord leads to denervation and consequent atrophy of the corresponding muscle fibres. As denervation progresses, muscle atrophy is readily recognised by muscle biopsy and on clinical examination. The loss of the cortical motor neurones results in thinning of the cortico-spinal tracts present in the internal capsule, brainstem and lateral and anterior white matter columns of the spinal cord. The loss of fibres in the lateral columns leads to fibrillary gliosis leading to rigidity of muscles and eventually of all the limbs. The combined loss of function of the upper and lower motor neurones causes a mixture of spastic paralysis and flaccid muscular weakness and wasting (Campbell 1984).

The disease process spares the sensory, autonomic and oculomotor neurones. Hence patients retain control of their bladder, bowels and eye movements until late in the disease (Choi 1992).

On light microscopy, the entire sensory apparatus and the regulatory mechanism for the control and co-ordination of movements appear to remain intact.

1.10 Epidemiology

The incidence of MND is reported to be between 1.5 and 2.7 per 100000 population/year (average 1.89/100000/year) in Europe and North America (Worms 2001). The prevalence ranges from 2.7 to 7.4 per 100000 in western countries (average 5.2 per 100000). The lifetime risk for sporadic MND by the age of 70 years has been estimated to be between 1 in 400 to 1 in 1000 (Worms 2001). A consistent finding across studies is the excess of males affected with an M: F ratio of 1.5:1. The mean age for onset varies between 55-65 years with a median age of 64 years (Alonso 2009). Only 5% of cases present before the age of 30 years. Approximately two thirds of patients have a spinal onset form of the disease. Bulbar onset is commoner in women and in older age with 43% of patients above the age of 70 years presenting with bulbar symptoms compared to 15% below the age of 30 years (Haverkamp 1995). A review in 2005 found the mortality rates in ALS ranged from 1.54 to 2.55 per 100000/year (Sejvar 2005).

The Western Pacific form of ALS is associated with Parkinsonism and Dementia (ALS-PD complex). In the at-risk populations, it has prevalence 50-100 times higher than for ALS elsewhere in the world. These populations include the Chamorro people of Guam and Marianas island, Kii peninsula of Honshu Island and the Auyu and Jakai people of south west New Guinea. The cause of this distribution is not understood (Steele 2008).

Although most cases of MND are sporadic, 5% of cases have a family history of MND. Compared to sporadic cases the age of onset for this 5% is about a decade earlier, males and females are affected equally and survival shorter (Mulder 1986).

1.11 Clinical Features

Approximately two thirds of patients with sporadic MND have a spinal form of the disease at presentation (Wijesekera 2009). The symptoms are related to focal muscle weakness, where the symptoms start either proximally or distally in the upper or lower limbs. MND symptoms usually present in an insidious, progressive fashion, initially ranging from non-specific muscle cramping, twitching, ill-defined weakness and fatigue to gait difficulties or decreased fine motor control. Patients may have noticed fasciculation preceding the onset of weakness and wasting for some months but rarely are these presenting symptoms. The average time from onset of symptoms to diagnosis is about 14 months, about one third of expected survival (Leigh 2003). The onset is usually asymmetrical; the other limbs develop weakness and wasting sooner or later with most patients going on to develop bulbar symptoms and eventually respiratory failure. Gradually spasticity will develop in the weakened atrophic limbs affecting manual dexterity and gait.

A quarter of patients present with bulbar symptoms such as sialorrhoea, dysarthria or dysphagia (Leigh 2003). Patients generally present with dysphagia to solids and liquids before noticing speech disturbance (Hadjikoutis 2000). Limb symptoms can develop simultaneously with bulbar symptoms and in the clear majority of cases will be evident within 1-2 years. A third of patients experience pseudobulbar symptoms i.e. emotional lability resulting in uncontrollable laughter or crying and excessive yawning (Portet 2001).

About 5% of people with MND present with respiratory weakness without significant limb or bulbar symptoms. These patients present with symptoms of type 2 respiratory failure or nocturnal hypoventilation including dyspnoea, orthopnoea, disturbed sleep, morning headaches, excessive daytime sleepiness, decreased concentration and irritability of mood (de Carvalho 1996).

As the disease progresses, patients develop a picture of a combination of upper and lower motor neurone signs affecting the bulbar, cervical, thoracic and lumbar territories. With progression of the disease, continuous physical deterioration results in loss of mobility with most patients becoming wheelchair or bed bound. Impaired swallowing coordination can result in aspiration of oral contents into the airway. When

flaccid paralysis involves the pharynx and larynx, the cough reflex becomes weak leading to increased risk when aspiration of food and saliva occurs (Mitsumoto 1994). Cognitive disorders are observed in 50% of ALS cases (Portet 2001). A small proportion of ALS patients will develop frontotemporal dementia. A significant percentage of non-demented patients will show mild to moderate cognitive changes predominantly of a dys-executive nature. This consists of a group of symptoms due to impairment in activities that include planning, abstract thinking, flexibility and behavioural control. Memory deficits, language involvement and mood disorders also account for or compound cognitive dysfunction in ALS (Goldstein 2013). A common pathogenic mechanism between ALS and frontotemporal dementia has been recently identified (Deng HX 2011). This group identified that mutations in UBQLN2, which encodes the ubiquitin-like protein ubiquilin 2, cause dominantly inherited, chromosome-X-linked ALS and ALS/dementia.

1.12 Clinical features of Variant disorders

Variants of MND have differing clinical presentations, rate of progression and prognosis. Progressive muscular atrophy accounts for 5-10% of cases with MND and identifies a purely lower motor neurone syndrome without accompanying upper motor neurone signs. It is almost always of limb onset, but patients may develop swallowing difficulties eventually. It is reported that 50% go on to develop symptoms and signs of typical ALS picture (Traynor 2000).

The flail arm and flail leg variants also initially present with a predominantly lower motor neurone presentation. In the flail arm, variant weakness and wasting affects the proximal upper limb in a symmetrical pattern leading to severe wasting around the shoulder girdle and the arms hanging flaccidly. The tendon reflexes in the upper limbs are depressed or absent. The lower limbs remain strong for some years along with retained tendon reflexes but eventually spasticity and wasting develops. Swallowing difficulties and diaphragmatic weakness are usually late features. In the flail leg syndrome, weakness and wasting begins in the distal lower limbs in a symmetrical manner. The clinical features are of lower motor neurone syndrome with hypotonia and depressed tendon reflexes. Pyramidal signs are usually absent leading to

considerable diagnostic delay. These two variants show considerably slower progression compared to more typical forms of MND (Traynor 2000).

PLS is a progressive pure upper motor neurone syndrome that cannot be attributed to another disease. Patients present with pure upper motor neurone signs with either absent or minimal lower motor neurone symptoms. It can be difficult to differentiate PLS from ALS during the early stages as some patients with typical MND can present initially with UMN signs alone before going to develop the usual clinical picture of ALS (Pringle 1992).

1.13 Management and Prognosis

The management of MND has evolved over the last 2 decades. Although still incurable, MND is not untreatable and interventions that prolong survival have been developed. These however do not arrest progression of the disease and its management has become increasingly complex and may raise difficult practical and ethical issues about quality of life and end of life decisions (Leigh 2003). The pathophysiology of MND is poorly understood and no specific biologic markers have been identified to monitor disease progression or identify therapeutic efficacy. Several reports have suggested that with serial observations of one or more parameters, the rate of progression can be predicted in patients with MND (Almeida, 2010; Qureshi 2006). To date an optimal and consistent testing format has not been definitively identified and tested on many patients. Although simple clinical tests that generate valid reproducible data sensitive to early progression of disease are being identified (Leonardis 2012).

1.14 Disease modifying treatment

There is evidence that chronic glutamate excitotoxicity contributes to neuronal death in MND and this resulted in clinical trials with Riluzole, a drug with complex effects, which appears to block the presynaptic release of glutamate (Rothstein 1996). The first randomised controlled trial comparing 100 mg of riluzole to placebo identified a significantly lower mortality in the Riluzole group compared to placebo at 12 months but the differences were not significant at 15 or 18 months (Bensimom 1994). A larger RCT compared 50 mg, 100 mg and 200 mg with placebo over a median follow-up of 18 months (Lacomblez 1996). There was a 2.3-month median survival benefit and a

lower mortality in riluzole treated patients at 9, 12 and 15 months (Lacomblez 1996). A post hoc analysis identified no beneficial effects on bulbar function but a small positive benefit on limb function (Riviere 1998). Thus, MND specific therapy can at best slow disease progression but cannot stabilise or improve the underlying disease pathology. These studies showed no correlation between site of onset and benefit of Riluzole (Traynor 2001; Meininger 2000). A population based study showed a six-month survival benefit that was significant in bulbar onset and elderly patients but not so in limb onset MND patients (Zoccolella 2007). Another study identified no survival benefit when vital capacity was less than 50% (Meininger 2004). Cochrane review concludes that Riluzole (100 mg) does provide modest survival benefit of 2-3 months in patients with MND with symptoms onset of less than 5 years, forced vital capacity greater than 60% and age less than 75 years (Miller 2012).

1.15 Multi-disciplinary care

Coordinated multi-disciplinary care has become the cornerstone of management of MND (Ng 2011) to target the needs of individual persons. Multidisciplinary care in MND may be defined as an intervention delivered by two or more disciplines, directed by a physician, which is patient centred and responsive to the evolving symptoms of the condition (Ng 2011). Its aim is to maximise the participation of the patient and thereby the quality of life they lead. National Institute of Clinical Excellence (NICE) recommends that a multidisciplinary team (MDT) should include a neurologist, respiratory physician, MND specialist nurse, respiratory specialist nurse, respiratory physiotherapist, respiratory physiologist, palliative care specialist and speech and language therapist (NICE 2016). Increasingly nutritionists and psychologists are being included into the MDT. The MDT can work within an in-patient or out-patient setting depending on the intensity of input required. It can also be delivered in the community or patient's own home and local community (Ng 2011). As the care needs of patients with MND are variable, the actual content of the MDT care can vary from case to case. Evidence for such multi-disciplinary care is growing (Traynor 2003; Chio 2006). Traynor et al, compared patients who attended a multidisciplinary ALS clinic every 6-12 weeks to those who attended a general neurology clinic where patient reviews occurred every 6 months. This study found that median survival for ALS patients was 7.5 months longer for the multidisciplinary ALS clinic cohort as compared to those that

attended a general neurology clinic. Patients with bulbar onset had an even greater survival benefit of 9.6 months. This was the first prospective study that suggested patients with ALS receiving multidisciplinary care may have a better prognosis. Chio et al. (2006), compared specialist tertiary ALS centre care with care given either by a general practitioner, physician or rehabilitation physician. This study identified improved survival, reduced hospitalisation and length of hospital stay in the tertiary ALS centres cohort. Not only does MDT care improve prognosis but Van den Berg et al. (2005) found improved quality of life on Short Form (SF 36) mental health and social functioning domains in their multi-disciplinary cohort but no difference in healthcare costs compared to the general clinic group. Whilst NICE recommends an MDT approach to care for MND patients, the present evidence cannot conclude which specific outcomes are influenced such as survival, dependency, social integration, mood or quality of life are influenced by multidisciplinary care (Ng 2011).

1.16 Ventilatory management

The median survival in MND is reported to vary from 20 to 48 months, although certain tertiary centres report longer survival times (Stambler 1999). Patients usually succumb to respiratory failure. In a few patients, this is usually the presenting feature of the condition. The disease progression can be variable and some progress very rapidly. In patients with minimal respiratory reserve, a minor insult can trigger progression to ventilatory failure. Weakness of the respiratory muscles may gradually develop during the disease. Patients complain of dyspnoea for progressively less physical activity, orthopnoea, nightmares and fragmented sleep, morning headaches, daytime sleepiness, cough impairment and recurrent lower respiratory tract infections. Inspiratory muscle weakness is the main determinant of respiratory failure in MND (Polkey 1998). As the disease progresses, the diaphragm and the intercostal muscles are severely affected. However, Berlowitz et al. (2006), in their retrospective review of MND patients, who underwent full diagnostic polysomnography, identified nocturnal hypoventilation in patients with no diaphragmatic weakness suggesting a dysfunction of their respiratory centre. Their data (from seven years' experience of managing MND patients) found that domiciliary ventilation assistance improved sleep quality and corrected sleep related hypoxia. Assisted ventilation can be provided invasively (invasive mechanical ventilation) and non-invasively (non-invasive ventilation).

In an uncontrolled series, invasive ventilation has been associated with prolonged survival with an average of 5 years and 6% of patients have lived for more than 10 years on invasive ventilation (Bach 1990). Survival appears to be longer in younger patients (age < 60 years) at disease onset (Sivak 1982; Spataro 2012). Tracheostomy tubes provide not only ventilatory support but also access for airway suctioning. Cuffed or uncuffed tubes can be used to provide ventilation based on level of air leaks and hypoventilation (Sancho 2010). However, improvement in quality of life has not been clearly demonstrated (Anderson 2012). Invasive mechanical ventilation is associated with many complications including accumulation of mucus, atelectasis, pneumonia, and chronic colonization with gram negative bacteria, tracheoesophageal fistula, granulation formation, tracheal stenosis, tracheomalacia, haemorrhage, diaphragmatic deconditioning and pneumothorax (Bach 1990) and a high risk of emergency admissions due to respiratory complications. Alternative tracheostomy tubes such as fenestrated and cuff-less tubes can allow patients to inhale and exhale through the fenestration and around the tubes allowing them to speak without severe speech impairment (Anderson 2012). Invasive mechanical ventilation is associated with high healthcare costs and increased family and caregiver burden (Farrero 2005; Moss 1996). In the UK, invasive mechanical ventilation is less likely to be considered for patients with MND than in some countries including Japan and Italy. Intubated patients seem to be more likely to be dissatisfied with their quality of life than patients treated with NIV (Polkey 1999). In the UK, establishing care at home may be problematic and the practice has been not to offer tracheostomy with the intention to palliate symptoms rather than extend longevity. Discontinuation of ventilation is associated with complex challenges to doctors; emotional, practical and ethical issues (Faull 2014). Anxiolytics and opiates are often required to avoid any discomfort to patients. Development of guidelines on NIV withdrawal and consideration of targeted support include education, psychological support and debriefing sessions are valuable (Faull 2014).

The European Federation of Neurological Sciences (EFNS) recommends that invasive mechanical ventilation should be considered only for patients with severe bulbar weakness and those intolerant of, or who decline NIV. Invasive mechanical ventilation is sometimes considered when NIV and mechanical insufflation-exsufflation have

failed to maintain oxygen saturation above 95% (Bach 2004). Invasive mechanical ventilation is more common in Japan and Italy (Borasio, 1998). Patients who chose invasive mechanical ventilation are often younger with young children, higher education, higher household income and higher level of optimism with belief in an imminent cure (Spataro 2012). Until the mid-nineteen nineties', MND patients who did not wish to prolong their lives with mechanical ventilation died from ventilatory failure. Bach et al, first reported in 1993 that daily usage of NIV in MND patients delayed or eliminated the use of tracheostomy. Pinto in 1995 carried out a single centre study which included 20 consecutive patients with bulbar features and probable or definite diagnosis of MND. The first ten were treated conservatively with sedatives, oxygen, bronchodilators and physiotherapy. The next ten were provided with bilevel positive pressure ventilation. The study showed a significant difference in survival in favour of patients using NIV. This study showed no significant improvement in quality of life in patients receiving NIV and there were other difficulties with the study. The use of oxygen and sedatives may have accelerated patients' decline. The mean hours of use of NIV were only a few hours and some patients only used it in the daytime. Aboussouan et. al. (2001), in a retrospective case series of 60 patients initiated on NIV sought to determine whether this intervention improved spirometric measures of lung function, survival and quality of life. The data suggested that in patients intolerant to NIV, there was a higher prevalence of moderate to severe bulbar symptoms. Lower mean NIV use (2.6 hours/day compared to 8.7 hours/day) was associated with lower median survival (of 5 months compared to 20 months). This study showed a persistent linear decline in FVC irrespective of the intervention with NIV. Because the rate of decline was not significantly affected by NIV, they speculated that unloading of the inspiratory muscles may lead to deconditioning of muscles translating into decreased maximal inspiratory pressures and spirometric measures of lung function. The study therefore suggested that early intervention with NIV was not indicated. Kleopa et al. (1999) reported retrospective data and proposed that NIV not only prolonged survival but also slowed the decline in pulmonary function. This was the first large scale study to show a positive effect of NIV in patients with MND. NIV tolerance (hours of use > 4hrs) was associated with longer survival. There was no apparent difference in survival in both bulbar and limb onset MND patients tolerant of NIV. They proposed that correction of hypoxia and fatigue was responsible for the lasting beneficial effects of

NIV on pulmonary function and survival. NIV may improve lung compliance by preventing micro-atelectasis and nocturnal hypoventilation thereby preventing the blunting of the central respiratory drive seen with hypercapnoea. A retrospective review of case notes of patients with MND between 1980 and 2000 (at the National Hospital for Neurology and Neurosurgery, London and Lane Fox Unit, St Thomas' Hospital, London) admitted with acute respiratory failure and requiring tracheal intubation, ventilatory support and admission to the Intensive Care Unit (ICU) identified the need for long-term ventilatory support. Seventy percent of the patients were established on invasive positive pressure ventilation through an uncuffed tracheostomy. Most patients remained hospitalised for over 10 weeks and were eventually discharged either to local hospitals or nursing homes. Very few were discharged to the patient's own home. There was variation in the time to death between those who had a previous diagnosis of MND as compared to those who were admitted with respiratory failure with no previous diagnosis of MND (Bradley 2002). This review highlighted concerns regarding the absence of detailed discussion with the patient and family regarding quality of life on respiratory support and disease progression leading to a 'locked-in syndrome'. These findings support previous conclusions that serial monitoring and offering ventilatory support to patients electively, allows them to discuss these issues with their family, come to terms with the disease and increase familiarity and motivation with the equipment and thereby possibly improve compliance (Aboussouan 1997; Cazzolli 1996). However, some patients may present with respiratory failure before detailed discussions have been possible. In these cases, the authors recommend the use of an uncuffed tracheostomy to allow the patient to remain independent while receiving long term continuous domiciliary support using IPPV (Bradley 2002).

In 2006, a randomised controlled trial included patients presenting with orthopnoea and a maximal inspiratory pressure ($P_{i_{max}}$) less than 60% predicted or symptomatic daytime hypercapnoea for NIV. The patients with normal or moderate bulbar involvement showed benefits in quality of life and survival (median 205 days vs 11 days in controls on supportive care). For patients with severe bulbar impairment, NIV use did not result in survival benefit but improved quality of life in emotional, social function and physical domains (Bourke 2006).

In a non-randomised series, Mustafa et al. (2006), showed a median survival of 18 days along with poor quality of life in those with respiratory muscle weakness who declined NIV. In comparison, patients who accepted NIV had a median survival of 298 days along with improvement in quality of life measures within 1 month of initiating NIV. A significant correlation has been found between survival and number of hours of NIV use. Kleopa et al. (1999) reported improved survival and a slower decline in FVC in patients who accepted and used NIV for more than 4 hours a day. Aboussouan et al. (2001) showed a 6-fold higher risk of death in patients intolerant of NIV. In this study tolerance was once again defined as sleeping with the device for at least 4 consecutive hours a night. The patients tolerant of NIV had a significantly higher Forced Vital Capacity (FVC) and Maximal Expiratory Pressure (MEP) values at NIV adaptation (Aboussouan 2001). American Academy of Neurology (AAN) published criteria for initiating NIV in patients with respiratory symptoms suggestive of nocturnal hypoventilation such as orthopnoea, morning headaches, frequent awakenings and excessive daytime sleepiness in the presence of FVC less than 50% of the predicted value, maximal inspiratory pressure (MIP) < 60 cm H₂O, sniff nasal inspiratory pressure (SNIP) < 40 cm H₂O or abnormal oximetry.

The American College of Cardiology proposed in addition a PCO₂ \geq 6 kPa), nocturnal O₂ desaturation <88% for more than 5 consecutive minutes (Miller et al. 2009). Studies by Jackson et al. (2001) and Lechtzin et al. (2007) suggested earlier initiation of NIV may be beneficial.

Lechtzin et al. (2007) retrospectively reviewed cases where NIV was used for at least 4 hours a night. The patients with FVC > 65% were categorised as early starters and revealed a median survival from diagnosis to death of 329 days longer than those with FVC < 65%.

Jackson et al. (2001) carried out a prospective 3-month study where patients were randomised to an early group and late group starter for NIV. The early group were immediately started on NIV when overnight oximetry revealed at least one cumulative minute of oxygen saturation below 90% and at least 2 significant symptoms of nocturnal hypoventilation. The late group were initiated on NIV when FVC dropped below 50% predicted. Early starters showed improvement in the pulmonary symptom

score and vitality subscale of the SF-36. Carratu et al. (2009) showed improved survival for patients initiated on NIV with FVC > 75%.

Gruis et al. (2006) identified potential intolerance in patients with lower FVC at the time of NIV initiation. Sivak et al. (2001) identified longer survival in patients with VC > 45% when NIV was instituted.

The decision of when to initiate NIV is crucial due to the risk of sudden death and mechanical ventilation initiation without proper planning. Pulmonary function tests are used as a guide to begin assessment at regular intervals to identify when NIV is required. Symptoms of alveolar hypoventilation such as orthopnoea, hypersomnolence and disturbed sleep pattern may represent useful indicators of when NIV should be considered. Sleep disordered breathing has been observed at an early stage of the disease and might be the earliest indication of respiratory insufficiency (Kimura 1999).

Patients receiving planned NIV as compared to those without prior pulmonary assessment showed improved survival. This suggests a programmed consultation with the respiratory physician (with evaluation of the clinical status and respiratory function) allows the early identification of patients who may respond to NIV (Sanjuan-Lopez 2014). Volanti et al. (2011) found that tolerance and compliance were better when patients (including those with bulbar onset) and caregivers were provided advanced information, intensive educational training and adaptation that took place in a multi-disciplinary setting.

Attitudes to surveillance for and treatment of ventilatory failure among people with MND have changed over the last 10 years. Bourke et al. (2002) in a postal survey revealed rates of referral and uptake of NIV respectively of 13.6% and 3.5% in MND patients in the UK. This would indicate that 26% of patients referred for respiratory assessment were successfully established on NIV. Most neurologists in the survey had not made a referral for NIV in the preceding year. Increased awareness of the value of NIV culminated in the publication in July 2010 of the NICE guidance designed to increase access to NIV (NICE clinical guideline 105, 2010).

O'Neill et al. (2012) through a postal survey showed a 2.6 and 3.4-fold increase respectively in referrals for respiratory assessment and those currently using NIV in the UK compared to 2000. Of the 612 patients referred for NIV over a 12-month period 444 were successfully established on treatment (73% success rate). The survey also showed that neurologists routinely monitored respiratory function in 20% of cases but 32% still relied solely on symptoms.

1.17 Nutritional management

Around 25-30% of patients with MND have bulbar symptoms at presentation, which include difficulty chewing, swallowing, dealing with saliva and speech or voice changes. Whilst respiratory failure is the primary cause of death in this cohort of patients, aspiration pneumonia, malnutrition and dehydration from difficulty in swallowing can also contribute to poor prognosis. Malnutrition can contribute to respiratory muscle weakness and may have an impact on life span. In 2009, the American Academy of Neurology practice parameter statement recommended that percutaneous endoscopic gastrostomy (PEG) should be offered when there is accelerated weight loss and symptomatic dysphagia (Miller 2009). There is insufficient evidence to indicate whether enteral feeding is beneficial compared to oral feeding for survival. Mazzini et al. (1995) showed a survival benefit of 8 months ($p < 0.03$) in 31 patients who underwent PEG insertion compared to 35 patients who refused the procedure. Similarly, Chio et al. (2006) in their cohort of patients with ALS/MND identified patients not using PEG tube had a hazard ratio (HR) of 3.38 ($p = 0.0006$) for death compared to the patients using PEG. Chio et al. (1999) in a retrospective case series, matched 50 patients with ALS/MND undergoing PEG insertion with 100 historical controls without PEG. The multivariate analyses identified patients with PEG had significantly increased survival in the whole cohort (OR=1.55, $p = 0.02$) and in bulbar patients ($p = 0.02$) but not in spinal onset patients (Chio, 1999). Strong et al. (1999) found a survival advantage of 8 months in patients undergoing PEG feeding only in bulbar onset patients.

However, a prospective study of 244 patients failed to show a survival benefit in the 57 patients who had PEG insertion compared to those with oral feeding (Murphy 2008). Two large MND patient registries, the Scottish Motor Neurone Disease Register

and the ALS-CARE database in the USA do not show a survival benefit from PEG tube feeding even in patients with bulbar onset (Forbes 2004). There are no randomised controlled trials to demonstrate enteral feeding is beneficial. There is currently no consensus about the ideal timing for PEG tube insertion in patients with ALS/MND. There is even some evidence to suggest that PEG tube insertion when FVC < 50% is associated with higher risk (Kasarkis 1999).

1.18 Recommendations for surveillance of ventilatory failure

NICE clinical guideline 105, published in 2010, recommends that a multi-disciplinary team should co-ordinate management and treatment for a patient with MND. The team should include a neurologist, respiratory physician, MND specialist nurse, specialist respiratory physiotherapist, respiratory physiologist, specialist in palliative care and a speech and language therapist. In view of the poor prognosis from the onset of respiratory failure, NICE recommends follow-up every 3 months for patients considered for NIV (NICE clinical guideline 105, 2010). Clinical vigilance, serial measurements of lung functions, monitoring nocturnal ventilation and planning are essential components of respiratory surveillance in this patient group. As NIV tolerance is an important component of improved survival, it is recommended that information and support through discussing non-invasive ventilation with patients is considered soon after diagnosis, when monitoring respiratory functions, when symptoms deteriorate or if patients ask for information. As part of the respiratory assessment, respiratory function tests should be performed every 3 months which include one or both;

- FVC or VC
- Sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory mouth pressure (MIP) and
- Oxygen saturation measured by pulse oximetry (SpO₂)

Arterial blood gas testing should be performed if the SpO₂ is \leq 92% in the presence of known lung disease or \leq 94% with no lung disease. If the patient develops sleep related symptoms overnight oximetry should be undertaken. At the onset of symptoms and signs of respiratory failure or arterial blood gas revealing a PCO₂ > 6kPa consideration for a trial of NIV should be made.

1.19 Assessment of Respiratory Muscle Weakness

Declining respiratory muscle strength is the primary mechanism for the development of ventilatory failure and contributes significantly to morbidity and mortality in MND. Respiratory symptoms usually develop late in the disease process and in conjunction with extremity or bulbar muscle involvement. Rarely patients present with respiratory symptoms initially, due to phrenic nerve involvement (De Carvalho 1996). Ventilatory failure can occur either insidiously or acutely often precipitated by infection or aspiration. At the terminal phase an accelerated decline in vital capacity may occur (Lyll 2001). Pulmonary function measurements can augment clinical observations but may not represent a sufficient indication for use of NIV (Sivak 2001). Orthopnoea and sleep related respiratory symptoms have been among the commonest reasons for initiating NIV (Kimura 1999). According to Miller et al. (1999) and Lyll et al. (2001) there is no evidence to support a single best test for detecting impending respiratory failure. Furthermore, there is no test that can reliably predict hypercarbia. In a trial of NIV, patients with normal or moderate bulbar involvement, randomized to standard supportive care, had a median survival of 11 days. Mustafa et al. (2006), showed a median survival of 18 days along with poor quality of life in those with respiratory muscle weakness provided with standard care. Both these studies highlight that survival once symptomatic ventilatory failure develops is short and associated with significant morbidity. The ability to predict the development of hypercarbia would be very valuable in the management of people with MND.

Measures of respiratory function able to predict time to ventilatory failure and/or death would have several potential uses:

- a. accurate information for patients to allow forward planning.
- b. improved scheduling of follow up appointments in people under surveillance for NIV.
- c. surrogate end points for drug studies to shorten study time.

1.20 Spirometry

Spirometry is a physiological test that measures an individual's ability to inhale or exhale volumes of air as a function of time. The primary signal measured may be volume or flow. Spirometry is invaluable as a screening test of general respiratory health in the same way that blood pressure provides important information about general cardiovascular health. Expiratory volumes are conventionally reported. The most commonly used measures are FEV₁, FVC and VC. To measure FVC, the patient inhales maximally, then exhales as rapidly and as completely as possible. Normal lungs generally can empty more than 80 percent of their volume in six seconds or less (Miller, 2005). FEV₁ is the volume of air exhaled in the first second of the FVC manoeuvre. In a relaxed vital capacity manoeuvre, the instruction is to breathe out but not to force the breath. This will give a greater value than the FVC in the presence of airway collapse as seen in emphysema. Spirometric values have good reproducibility and most subjects can follow the instructions and perform the procedures (Brusasco 2005). There are established normal values (Hankinson 1991). Spirometry may be performed either in the sitting or standing position. Sitting is preferable for safety reasons in order to avoid falling due to syncope. There should be no difference in the amount of air the patient can exhale from a sitting position compared to standing as long as they are sitting up straight and there are no restrictions. If a wheelchair is used, the wheels should be locked (Miller 2005). The precision of the test is good. Acceptable repeatability is said to be achieved when the difference between the largest and the next largest FVC is ≤ 0.150 litres. The accuracy of the test, that is how close the result is to the true value, requires maximal effort and a lack of bias. Insisting on repeatable results helps to reduce the risk of sub maximal efforts affecting the accuracy. The intrinsic accuracy of the turbine spirometer used in this thesis has been compared to a rolling seal spirometer (Malmberg 1993). The turbine spirometer recorded FVC values with a mean of 0.64 L (15 +/- 11%) less than the rolling seal spirometer. "The short-term repeatability of the measurements expressed as the coefficient of variation of repeated measurements using the pocket spirometer was 2.2% for FEV₁ and 2.3% for FVC in a series of 10 healthy subjects and 10 patients with COPD." Thus there is likely some under measurement with the turbine device but the ease of use was a major factor in our research plan.

A prospective study of the early stages of development of COPD showed that FEV₁ declines continuously and smoothly over an individual's life. Most non-smokers lose FEV₁ slowly and almost never develop significant airway obstruction. However susceptible smokers will lose FEV₁ at a more rapid rate and develop various degrees of airway obstruction, which ultimately leads to disabling symptoms and can be fatal. This study proved that spirometry could not only be a useful screening test but also a prognostic marker to assess progress of airway obstruction (Fletcher 1977).

Fallat et al. (1979) performed clinical evaluation and pulmonary function tests in 218 patients with MND (with ALS). Serial studies were obtained in 103 patients, in 31 until death. Most patients, regardless of the pattern of motor neurone involvement, had characteristic abnormalities in pulmonary function, including reduced FVC and maximum voluntary ventilation (MVV). It was common for clinical evaluation to report uncompromised function when FVC (and MVV) were as low as 50% of predicted. Spirometry is therefore of value in detecting early involvement of respiratory muscles. Progressively greater reductions in FVC and MVV in all the fatal cases indicated that serial spirometry has prognostic value in ALS.

A study looking at the relationship between respiratory muscle strength and FVC in patients with ALS identified that both measures can assist in early diagnosis of respiratory dysfunction (Schiffman 1993). Case records of 36 patients over a 10-year period identified 31 of 36 patients had respiratory muscle weakness at presentation, although only 7 reported any respiratory symptoms. The rate of decline in FVC was found to be linear, although there was considerable inter-patient variability. Analysis of data from the placebo group of the Amyotrophic Lateral Sclerosis Ciliary Neurotrophic Factor (ALS CNTF) treatment study group (Stambler 1999) found that FVC dropped linearly and the lower the FVC at diagnosis, the shorter was the survival time. Thus, both baseline FVC and the rate of decline in FVC can be predictive of survival time (Fallat 1979; Schiffman 1993).

Fallat et al. (1979) found a non-linear decline in FVC. This pattern was shown in another case series where FVC deterioration followed a curvilinear slope in the later stages of the disease (Marti-Fabregas 1996). The preservation of normal lung volumes despite reduced muscle strength can be explained by the sigmoid shape of the

pressure volume relationship of the relaxed respiratory system. In a retrospective cohort of patients with either a definite or probable diagnosis of ALS, those with a baseline FVC < 75% were shown to have a median tracheostomy free survival of 2.91 years compared with 4.08 years for those with FVC > 75% (Czaplinski, 2006). Baumann et al. (2010) found single measures of seated FVC and supine FVC to be correlated with survival. The rate of change in seated FVC was an independent predictor of survival in ALS. An abnormal baseline FVC and a steeper rate of decline were both predictors of a shorter survival.

However, Fallat et al (1979), suggested that FVC might not fall until there is profound muscle weakness due to the sigmoid relationship of the lung pressure volume curve. Patients with bulbar weakness are often unable to form a tight seal and therefore the FVC values may not reflect the patient's true respiratory muscle strength.

1.21 Sniff Nasal Inspiratory Pressure (SNIP)

Inspiratory muscle weakness is the primary determinant of ventilatory failure in MND (Polkey 1998). VC, FVC, maximal inspiratory mouth pressure (MIP), oesophageal pressure, trans-diaphragmatic pressure and nasal inspiratory pressure during a maximal sniff manoeuvre are volitional respiratory measures that assess respiratory muscle strength. From among these VC, FVC, MIP and SNIP are non-invasive and frequently used in clinical assessments. Sub-optimal results for measurement of FVC and MIP in patients with bulbar or facial weakness have led to a drive for alternative methods to measure respiratory muscle strength that do not require a mouthpiece. Sniffing was identified as a natural manoeuvre to exploit in this context.

In patients with normal bulbar function, VC and SNIP showed a high sensitivity (90%) and specificity (73.5%) in predicting hypercapnoea, a key indication for NIV (Chaudri 2000). However, this was not the case in patients with bulbar involvement. Morgan et al. (2005) showed that the sensitivity of FVC (< 50% of predicted), for predicting 6-month mortality, was 58% with a specificity of 96%, whereas SNIP (less negative than -40 cm H₂O) had a sensitivity of 97% and a specificity of 79%.

A prospective series of 16 patients showed that SNIP was the single respiratory function test found to demonstrate linear decline, sensitivity in mild disease and reproducible in advanced disease (Fitting 1999; Morgan 2005). Lyall et al. (2001) suggested that SNIP as a screening test for the presence of ventilatory failure (at a cut off level of 32% of predicted), predicted the presence of hypercapnoea with a specificity of 85% and sensitivity of 81%.

Invasive techniques of measuring respiratory muscle function gave a more accurate reflection of global inspiratory muscle strength as well as trans-diaphragmatic pressures. The passage of balloon tipped catheters into the mid oesophagus and stomach allowed the recording of oesophageal (P_{oes}) and gastric pressures (P_{gas}), reflecting pleural and intra-abdominal pressures respectively. The trans-diaphragmatic pressure measured during a maximal sniff ($S_n P_{di}$) is higher than the P_{di} recorded from a maximal static pressure, has a narrower normal range and is more reproducible (Polkey 1998). It is the most accurate and reproducible test available to assess global inspiratory muscle strength in clinical practice (Laroche 1988). But it is invasive and not practiced widely.

In addition, studies by Hart et al. (2003) and Landelli et al. (2001) showed that maximal inspiratory mouth pressures were greater than SNIP in patients with severe restrictive respiratory defect caused by neuro-muscular disease. Hence SNIP could underestimate inspiratory muscle strength in severe neuromuscular diseases. This challenges the view that SNIP is the most appropriate test to predict ventilatory failure.

1.22 Amyotrophic Lateral Sclerosis Functional Rating Score (ALSFERS)

The ALSFRS r score (Amyotrophic Lateral Sclerosis functional rating scale revised) and its progression rate have been investigated as survival predictors. The ALSFRS r score is a widely used clinical score for the functional status of a patient with MND. It is based on 12 clinical items, each of which is scored on a 0-4 points scale (appendix 2).

There is a correlation between ALSFRS r score at first visit and survival (Kimura 2006). The ALS CNTF treatment study) had revealed no significant difference between

groups with ALSFRS r score > 38 or < 38 (Stambler 1998). Kimura et al. (2006) measured the decline in ALSFRS r score (Δ FS) and found it to be a better prognostic indicator than the raw ALSFRS r score (Kimura 2006). The annual mortality rate of ALS patients with a slower initial rate of decline (Δ FS) was 6% as compared 48% amongst those with higher rate of decline (Traynor 2004).

A large retrospective study defined a new ratio of ALSFRS r score within 100 days as a predictor of survival in ALS patients (Kollewe 2008). The ratio of ALSFRS r score within 100 days is the difference of ALSFRS r score between two visits divided by days between these two visits. Patients with a ratio < 0.25 showed better survival (5-year survival 44%). Thus, ALSFRS r score can be a prognostic tool in predicting survival in MND patients.

The French multi-centre study confirmed that bulbar onset disease is associated with worse prognosis compared to limb onset disease (Clavelou 2013). There is no published literature looking at the role of the bulbar component of the ALSFRS r score in prognostication. There are 3 questions related to bulbar symptoms. Fattori et al, looked at the role of oropharyngoesophageal scintigraphy in assessment of swallowing in patients with MND. Patients in this study were subdivided into 3 subclasses: Class 1 (scores between 12 and 10), Class 2 (scores between 9 and 4) and Class 3 (scores between 3 and 0). The results indicated significantly worse swallowing tests for Class 2 versus Class 1. No significant difference was observed between Class 3 versus Class 2. No significant correlation was found between severity of dysphagia and duration of survival. However these observations indicate crucial neurogenic components which exhibit a typical deterioration when progressing from Class 1 to Class 2 of the BALSFRS r score (Fattori 2006).

1.23 Summary prognostic indicators of survival

Clavelou et al. (2013) performed a multicentre longitudinal cohort study to compare survival, progression of anthropometry, pulmonary capacity and functioning in ALS to identify the most relevant variables to adapt ALS management. They sub-divided the cohort into 3 ALS forms; upper limb onset form, lower limb onset form and bulbar onset group. Bulbar onset group had the shortest median survival time (1.9 years) compared to limb onset (2.85 years). This significant difference in survival remained when

correction for gastrostomy placement and NIV were made. The weight loss in bulbar onset was faster than the spinal onset for the first fifteen months and then fell in parallel. Patients with bulbar onset showed a significantly higher slope of decline of FVC loss during the first 6 months and then declined in parallel to the spinal forms. The rate of decrease in ALSFRS r score was similar between the three forms of ALS. The results of this study suggest that two variables, weight loss and FVC loss led to better discrimination during long-term follow-up.

1.24 A possible role for face mask measures of VC

Many patients with MND characterized by facial or bulbar muscle weakness cannot effectively seal their lips around a mouthpiece, especially during forced manoeuvres. In these patients, the conventional equipment with a tube or flanged type of mouthpiece is not adequate to evaluate respiratory muscle function. This may explain an unexpected outcome from the randomized controlled trial of NIV in people with MND (Bourke 2006). In this study people with maximum inspiratory pressures ($P_{i\ max}$) less than 60% of predicted, and bulbar features, had a better, untreated survival than patients with predominant limb involvement. Bulbar involvement usually carries a worse prognosis. Patients with moderate to severe bulbar involvement may have performed poorly on the tests of respiratory muscle assessment leading to an underestimation of their true respiratory muscle strength.

Bulbar ALS is associated with more upper motor neurone involvement and the presence of abnormalities of central activation of diaphragm (Arnulf 2000). This may also explain the lower mean values seen in tests to assess respiratory muscle weakness. Additionally, patients with bulbar dysfunction may find it difficult to distinguish choking from orthopnoea and hence this symptom might be misleading when deciding to initiate NIV. Lyall et al. (2001) hypothesized that patients with bulbar weakness may perform sub maximally in tests requiring mouthpiece and hence tests that do not rely on mouthpiece would have better power. However, in this cohort of patients (with significant bulbar involvement) all tests were poor predictors for hypercapnoea (Lyall 2001).

Chaudri et al. (2000) further confirmed the poor correlation between SNIP and hypercarbia. The likely contributory factors include upper airway collapse and disco-

ordinated contractions of the various upper airway muscles and the respiratory muscles (Garcia-Panchon 1994).

A face mask (mask) attached to a spirometer might be used to minimize air leakage in cases of bulbar MND. A study comparing a conventional mouthpiece with a mask for the measurement of spirometry in healthy subjects showed that with the mask FVC was 200 ml lower than with the mouthpiece (Wohlgemuth 2003). Whilst this difference was statistically significant, it would not be of any clinical significance in subjects with normal lung volumes. However, in MND with lower values of FVC a difference of 200 ml especially during follow up may have significant implications especially for predicting ventilatory failure. The same study recruited 252 additional healthy subjects to determine new prediction equations for facemask spirometry. Multiple regression analysis was performed to derive prediction equations for facemask spirometry. The prediction equations of both FVC and FEV1 were in line with those reported in literature. In this study the measurements obtained using the facemask were closely related to those obtained by the flanged mouthpiece. An acceptable low coefficient of variation (CV) for facemask FVC of 1.4% was found, showing that the facemask measurements have excellent reproducibility.

A case series of 27 patients showed that using a mask as an interface FVC could easily be measured in patients with severe bulbar symptoms (Khaliq 2009). Fourteen of these patients were unable to record FVC at all using a mouthpiece. The mean difference in FVC in those that could perform both (mask and mouthpiece) was 0.65 litres. In those that could not perform FVC with a mouthpiece, the mean FVC measured using a mask was 1.63 litres. The mean difference between the measures when both were available was clinically significant and could affect decision making regarding NIV. However, this case series selected patients with significant bulbar involvement who found performing FVC through a mouthpiece difficult. A formal study to further evaluate the role of face mask as an interface to measure lung functions and to identify if mouthpiece and face mask could be used interchangeably is justified.

1.25 Mode of dying with MND

The care of patients with MND has changed over the last 10 years with greater uptake of NIV and tube feeding (TF) (Anderson 2012). NIV has been shown to prolong life expectancy in those who use it (Bourke 2006). A proportion of patients become 24-hour ventilator dependent. In patients with minimal respiratory reserve, decompensation in respiratory function can trigger a rapid deterioration and with death often occurring within 24 hours (Neudert 2001). Forward planning in this group of patients would allow treatment strategies to be formulated in advance of the actual event occurring. This might help to avoid inappropriate resuscitation or admission in the acute setting especially if the patient preferred to die at home.

There have been no systematic surveys concerning the dying phase of MND patients. A retrospective survey in 2001 (Neudert 2001) was restricted to patients dying under the care of the specialist palliative care services but gives some data for comparison. The overwhelming majority of patients with MND die because of this disease rather than incidental co-morbidities. Respiratory failure frequently occurs in the terminal phase of disease progression. It can, on rare occasion, be the presenting feature. Respiratory complications account for most deaths with patients dying from hypoventilation with hypoxemia and hypercarbia often precipitated by respiratory infection, aspiration pneumonia or bronchial impaction with respiratory secretions (Heffernan 2006).

A retrospective review of 179 deaths at a MND centre over a 10-year period showed 45% died at home, in a hospice or in a nursing home (Chaudri 2003). Thirty-six percent of patients were admitted to hospital of whom 5% died in the intensive care unit (ICU). Continuing respiratory complications were responsible for most deaths in a prospective study of causes of death in 302 patients with a probable or definite diagnosis of MND, the most frequent cause of death was respiratory failure (77%) including ventilatory failure in 58% and pneumonia in 14% (Gill 2008).

This raises ethical issues and anxiety about how patients supported with NIV might die and whether the process of dying might be prolonged with increasing dependence on NIV. This further emphasises the importance of counselling patients and their carers to optimize treatment and pre-empt last minute decision making. The choice of

treatment should be broached in good time and patient's wishes documented. Some patients wish to draw up an advance directive which may allow terminal respiratory problems to be managed at home and avoid hospital admissions.

The ongoing management of progressive MND varies across the UK (Bourke 2002; O'Neill 2012). There is increasing evidence that early palliative care involvement provides a holistic assessment of patient and family within a multidisciplinary approach leading to increased length of survival and reduced hospital care (WHO 2002). However, the involvement and availability of palliative care across the UK and Europe varies reflecting the varying development of palliative care services especially with their involvement in non-malignant diseases. The European Association of Palliative Care (EAPC) have formed a task force to look at the role of palliative care within neurological diseases with the aim of improving care of people with neurological diseases as the disease progresses and end of life approaches. A common approach between neurology and palliative care is suggested leading to a more collaborative approach to care (Borasio 2013).

Chapter 2: AIMS

2.1 NICE recommends that a multi-disciplinary team coordinate and provide on-going management and treatment for patients with MND. A healthcare professional should perform a respiratory assessment soon after diagnosis. This would involve spirometry, sniff nasal inspiratory pressures or maximal mouth inspiratory pressures and pulse oximetry. It is recommended that such follow up is continued at 3 monthly intervals (with clinical discretion) to offer patients the opportunity of receiving NIV when they develop ventilatory failure.

In this thesis, I will explore the impact of such a structured follow up pathway on access to ventilatory support for people with MND. I will review whether it can lead to increased uptake of NIV.

2.2 NICE recommends considering NIV when FVC values fall below 50% predicted. Many patients with significant bulbar/facial weakness fail to achieve a seal using a standard mouthpiece (tube) and conventional spirometry may not reflect the patient's true respiratory reserve. Some investigators have used a mask applied to the face as an alternative interface for spirometry but this has not been formally validated in MND.

In this thesis, I will compare using a mask and a tube as the interface for spirometry in subjects with MND, recruited from a specialist clinic, to formally validate the interface and identify if it can be used interchangeably with a mouthpiece/tube.

2.3 Ventilatory failure is the most frequent cause of death in MND. Measuring pulmonary function as an indicator of respiratory muscle function may provide prognostic information. Whilst to date no single test has been shown to identify accurately when assisted ventilation will be needed (Miller et al, 1999), a more accurate measure of lung function

in this patient population may contribute towards the goal of instituting NIV at the appropriate time.

Through this thesis, I will aim to identify whether mask spirometry can predict time to ventilatory failure/ need for NIV than other measures currently used in clinical practice.

2.4 In a randomised controlled trial NIV has been shown to prolong survival in people with MND. Because of longer survival, complex, emotive issues including concerns about the possibility of prolongation of the process of dying may arise amongst patients, carers and colleagues. No systematic survey has looked at the terminal phase of care in patients with MND.

In this thesis, I will aim to identify if NIV and tube feeding lead to a prolongation of the process of dying. In addition, I aim to identify if advance care plans are in place and if this results in patients spending their terminal phase in the place of their choice. I aim to identify if ventilatory failure continues to remain the leading cause of death amongst this patient cohort.

Chapter 3 Study Design & Methods

This chapter describes the methods used for the 4 studies. Individual differences to the overall methods are included in the methods section of each study. This chapter describes the rationale for patient selection, the various methods for measuring respiratory muscle strength used in the study and details of other monitoring tools used as part of the monitoring process for patients with MND.

3.1 Overview

A review was done with the aim of assessing the prognostic markers in adults with MND, looking especially at respiratory assessment methods to accurately identify the onset of ventilatory failure. A comprehensive literature search was conducted with emphasis on non-invasive volitional tests used in the regular assessment of respiratory muscle strength in patients with MND. The literature search also looked at approaches that are effective (settings, intensity) and the outcomes that are affected. The literature search also covered the role of non-invasive ventilation in the management of patients with ventilatory failure in MND.

A literature search was conducted in the following sources:

- The Cochrane Neuromuscular Disease Group Specialised Register
- The Cochrane Central Register of Controlled Trials
- MEDLINE
- EMBASE
- CINAHLPlus

Clinical trials were sought, that aimed to identify the test best suited to identify the onset of respiratory muscle weakness and eventually hypercarbia in MND; or studies

that compared different non-invasive volitional tests in different settings or at different levels of intensity in patients with neuromuscular pathologies. In addition, studies of “other designs” (such as observational studies) were also selected with the acknowledgement that such studies could only be of limited contribution to the best evidence synthesis.

A case series of 27 patients, showed that using a facemask as an interface FVC could easily be measured in patients with severe bulbar symptoms (Khaliq 2009). This case series selected patients with significant bulbar involvement who found performing FVC through a mouthpiece difficult. A formal study to evaluate the role of facemask as an interface to measure lung function and to identify if mouthpiece and facemask could be used interchangeably was the basis for phase 1 of the study presented in this thesis. Phase 2 of the study was to identify if facemask spirometry can allow a rule based follow up protocol which will reduce the number of appointments without risking missed opportunities to offer appropriate treatment with NIV.

All aspects from literature search, protocol development, ethical approval from regional ethics committee and hospital research board to data collection and storage were performed by me with close support from the principal investigator Dr Ian Smith (Consultant Physician, Papworth Hospital Foundation Trust). Support and guidance from the hospital research department was invaluable in completing the documents for approval from the regional ethics committee (REC).

Pulmonary function tests along with respiratory muscle assessment including SNIP, MIP and MEP were conducted by the respiratory physiologists based at Papworth Hospital. Spirometry with tube and facemask were performed by me using the ATS/ERS guidance for test acceptance and end of test criteria. Supine FVC is another test of diaphragmatic weakness (Lechtzin 2002). ATS/ERS guidance suggests this test requires the patient to be in a supine position on an exam table that can be set in a completely horizontal position. It is not recommended that an actual bed is used as the softness may interfere with the ability to perform a maximal FVC manoeuvre. More over candidate patients may have limited mobility and may not be able to transfer to a bed without assistance. It could increase the chances of a candidate patient refusing to partake in the study if they didn't feel comfortable with the test especially in subjects

with significant bulbar involvement. MND patients can tire easily which can limit the number of times they can perform a spirometry effort. This could potentially prevent us from collecting accurate readings for the primary objective of this study. Hence a pragmatic decision was made not to collect supine FVC in our study patients.

Data collection documents with barcodes and software for data storage were prepared by the hospital research department. Data collection for the final 7 patients in phase 2 study was completed by another research fellow working in the department (respiratory support and sleep centre).

As per the protocols developed and approved by the REC all patients approached for enrolment in phase 1 and phase 2 of the study were to be provided with a patient information sheet in advance of their outpatient appointment. Informed consent was obtained from all participants entering the study. If any potential subject was not able to give a written consent due to disability produced by MND, the next of kin was asked to confirm verbal response and sign on the consent form. In the absence of a next of kin, a doctor employed at Papworth Hospital NHS Trust was asked to independently verify the verbal consent. The nature of the study, its purpose, the procedures involved, any potential risk and benefits involved and discomfort it may entail were explained to the subjects.

3.2 Impact of structured follow-up on ventilatory support for MND- a systematic review

3.2.1. Aims

To examine the impact of compliance with practice parameter recommendations in NICE to referral numbers to RSSC and uptake of NIV in East Anglia.

A retrospective review of the hospital database was undertaken to identify patients with MND referred for respiratory assessment from 1987 to 2010 in a regional respiratory support centre. Between 2001 and 2005, the MND Association helped to establish a care centre in Cambridge and closer working was established between the neurologists and the respiratory service. From 2006, the default position has been to

offer all patients seen in the care centre, newly diagnosed with MND, a respiratory assessment and 3 monthly follow-up appointments in a fashion subsequently detailed in the 2010 NICE guidance. Comparisons to national averages were made with regards to initial referrals, follow-up plans, NIV starters and percentage uptake of NIV from those referred.

3.3 The role of facemask spirometry in MND

3.3.1 Aim

The aim of this study was to determine whether the default interface for recording spirometry in people with MND should be a mask or a mouthpiece or whether both measures are required.

In a clinic population of patients with MND;

- To assess whether a mask or mouthpiece interface for spirometry (FEV₁ and FVC) produces a greater number of more accurate results. Since FVC is a maximal manoeuvre a numerically greater value is assumed to be more accurate.
- To assess accuracy of mask spirometry in subgroups according to the presence or absence of bulbar symptoms.
- To determine the number of patients in whom FVC is greater than 50% as measured by face mask and mouthpiece spirometry.
- To assess patient preference.
- To investigate whether values from face mask or mouthpiece spirometry correlate with measurements of arterial blood gases.

3.3.2 Outcomes

The primary outcome was whether spirometry with mouthpiece or face mask gives greater accuracy in a clinic population with MND.

Secondary Outcomes were;

- Patient preference
- Correlation with arterial blood gases.

3.3.3 Summary of Study Plan

This was a study in a clinic population with MND, comparing a face mask with a mouthpiece interface for spirometry. All participants had spirometric assessment using both interfaces, the order in which they were applied was randomised.

3.3.4 Study Population

The study group were patients with a new or existing diagnosis of MND made by a Consultant Neurologist, and referred to the respiratory sleep and support centre at Papworth Hospital NHS Foundation Trust. Patients were identified from clinics and those attending the hospital for assessment of their nocturnal ventilation.

Inclusion criteria:

Adult patients diagnosed with MND, confirmed by a Consultant neurologist, referred to the Respiratory Sleep and Support Centre and who were able and willing to give witnessed, informed consent to the study.

Exclusion criteria:

- Ventilator dependent patients (24-hour dependence)
- Patients with tracheostomy.
- A second neurological condition which could affect spirometric values.
- Contraindications for spirometry testing as per “ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING”;
 - Recent Myocardial Infarction (1 month)
 - Recent stroke, eye surgery, thoracic/abdominal surgery
 - Haemoptysis
 - Known thoracic, aortic or cerebral aneurysm
 - Recent pneumothorax

- Uncontrolled hypertension
- Pulmonary embolism

3.3.5 Study Details

Informed consent was obtained from all participants. Consecutive patients with a definite or probable (El Escorial criteria) diagnosis of MND referred for respiratory assessment or under regular follow up in a specialist respiratory support clinic were invited to participate in the study.

A detailed history including duration of illness, progression of symptoms, Epworth sleepiness scale scores (ESS) and a smoking history were taken. A focused clinical examination was undertaken and included measurement of weight, height, neurological examination of the motor system and detailed respiratory system examination. All patients performed spirometry using a tube/ flanged mouth piece measuring FEV₁, FVC, maximal inspiratory pressures, maximal expiratory pressures and sniff nasal inspiratory pressure. In addition, a spirometry measuring FEV₁ and FVC using a face mask attached to the spirometer was performed. Other investigations which include arterial blood gases and chest X-ray were performed as per hospital's current guidelines.

3.3.6 Statistical Analysis:

The statistical analysis has been devised and supported by Dr Linda D. Sharples (*MRC Biostatistics Unit, Robinson Way, Cambridge*), the Statistics Division of the Research and Development Department at Papworth Hospital. She kindly talked me through the plan to ensure my understanding of the techniques used.

Within patient standard deviation is no more than 5% for healthy individuals. In patients with MND within patient standard deviation may be larger, perhaps 10%. Thus, using the methods of Jones et al. (1996) with 80% power and a 95% confidence interval on the difference, I required 44 patients with both mouthpiece and face mask measurements of lung function to demonstrate a significant difference between the 2 interfaces. In a pilot study, only 15 of 26 patients (58%) tested could provide spirometry using both a face mask and a mouthpiece. However, these subjects were selected as those who struggled with mouthpiece spirometry. Thus, I needed to recruit

approximately 60 patients to be confident that 44 will be able to provide both measurements. Results from patients who can only use one of the 2 modes of measurement will also be reported.

For FEV₁ and FVC the methods of Bland & Altman (1986) for assessment of agreement between 2 measurements of the same variable were used to compare the mask and mouthpiece. The difference between the measurements was plotted against the mean. The mean difference, the standard deviation of the mean difference and the correlation between difference and mean of the measurements were estimated. These methods also considered the order in which the modes of measurement were applied. I have presented the proportion of patients for whom each measurement could be completed and the proportion in whom FVC is greater than 50% as measured by face mask and mouthpiece spirometry. Since FVC is a maximal manoeuvre the measurement that is biggest was assumed to be more accurate. The association between accuracy (as described above) and the presence or absence of bulbar symptoms will also be assessed. Patient preference was assessed by asking each patient which method they preferred, this analysis was stratified according to the order in which the tests were completed.

Correlation between face mask or mouthpiece spirometry and measurements of arterial blood gases were estimated. The ability of spirometry to predict blood gases were assessed and the predictive value of face mask and mouthpiece measurements were compared by investigating measures of model fit.

3.3.7 Ethical Approval

Ethical approval for the study was granted by the regional research ethics committee (Cambridgeshire 3 Research Ethics Committee, REC reference number 10/H0306/9).

3.4 Facemask spirometry as a prognostic tool in MND

3.4.1 Aim

The main aim of this study was to determine whether FVC measured with facemask spirometry on referral for respiratory assessment and serially thereafter can accurately predict time to non-invasive ventilation or death in MND.

There were a series of secondary aims

- Was the difference in FVC recorded between mask and tube spirometry in study 1 reproducible in a second cohort of patients with MND?
- Was facemask spirometry a better predictor of time to ventilatory failure/need for NIV and/or death than tube spirometry?
- Were these predictions influenced by bulbar function at the time of the measurement?
- Was facemask spirometry a better predictor of time to ventilatory failure/need for NIV and/or death than other measures of respiratory function or general performance status including SNIP, $P_{i_{max}}$, $P_{e_{max}}$ and ALSFRS?

3.4.2 Outcomes

Primary Outcome

The primary outcome in this prospective cohort study is time from initial assessment at Papworth hospital to the composite endpoint of ventilatory failure or NIV and/ or death, whichever occurs first. Ventilatory failure is defined as arterial blood PCO_2 greater than 6kPa, self-ventilating in room air. Since the interval from developing ventilatory failure to death in untreated patients has been shown on average to be short we have treated these time points as equivalent (Bourke 2006).

Subgroup analyses

To assess accuracy of spirometry measures in predicting outcomes in bulbar and non-bulbar MND subjects.

3.4.3 Trial Design and participants

Ethical approval for the study was granted by the regional research ethics committee (Hertfordshire Research Ethics Committee, REC reference number 11/EE/0232).

This was a prospective, cohort study in a clinic population of MND confirmed by a neurologist, measuring spirometry using a facemask at baseline and on serial follow up visits. All participants had spirometric assessment along with other routine investigations performed as part of their follow up plans. The default follow up interval during surveillance for ventilatory failure was 3 months in keeping with NICE guidance. We aimed to record predictive measurements for 5 visits, which included the initial visit on day of enrolment to the study and 4 further follow up visits. The duration of study follow up was planned to be a maximum of approximately one year. The clinical team were blinded to results of mask spirometry and so treatment and follow up interval decisions were made independent of these results.

Some patients with severe symptoms had more frequent follow up and the reason for these visits (clinician determined at previous visit or patient request due to poor functioning/symptoms) was recorded. If patients developed respiratory failure during the study, they were provided with NIV as per hospital protocol ($PCO_2 > 6$ KPa, orthopnoea, overnight hypoventilation). Once a patient was initiated on domiciliary NIV, no further data were collected for the study.

Recruitment Strategy

All patients diagnosed with MND, newly referred or under regular follow up at the RSSC were screened for inclusion in the study.

Informed Consent:

Informed consent was obtained from all participants entering the study. If any potential subject was not able to give written consent because of a lack of dexterity due to disability produced by MND, the next of kin was asked to confirm their verbal response and sign on the consent form. In the absence of a next of kin, a doctor employed at Papworth Hospital NHS Trust but not involved in the study was asked to independently verify the verbal consent. The nature of the study, its purpose, procedures involved, any potential risk and benefits involved and discomfort it may entail were explained to the subjects.

3.4.4 Statistical Analysis

The statistical analysis for the study was completed by Dr Neil H. Spencer (Reader in Applied Statistics, Director of Statistical Services and Consultancy Unit, Hertfordshire Business School, University of Hertfordshire)

Analyses for the primary outcome were based on 'time to event' models, with the time origin (time=0) corresponding to the measurements taken at the first visit to Papworth Hospital following diagnosis of MND.

Statistical analyses were planned to be in two phases.

The first analysis examined the data for FVC recorded at the baseline assessment at Papworth. Exploratory analyses were based on Kaplan-Meier survival estimates for time to the primary outcome (the composite endpoint of ventilatory failure or non-invasive ventilation or death).

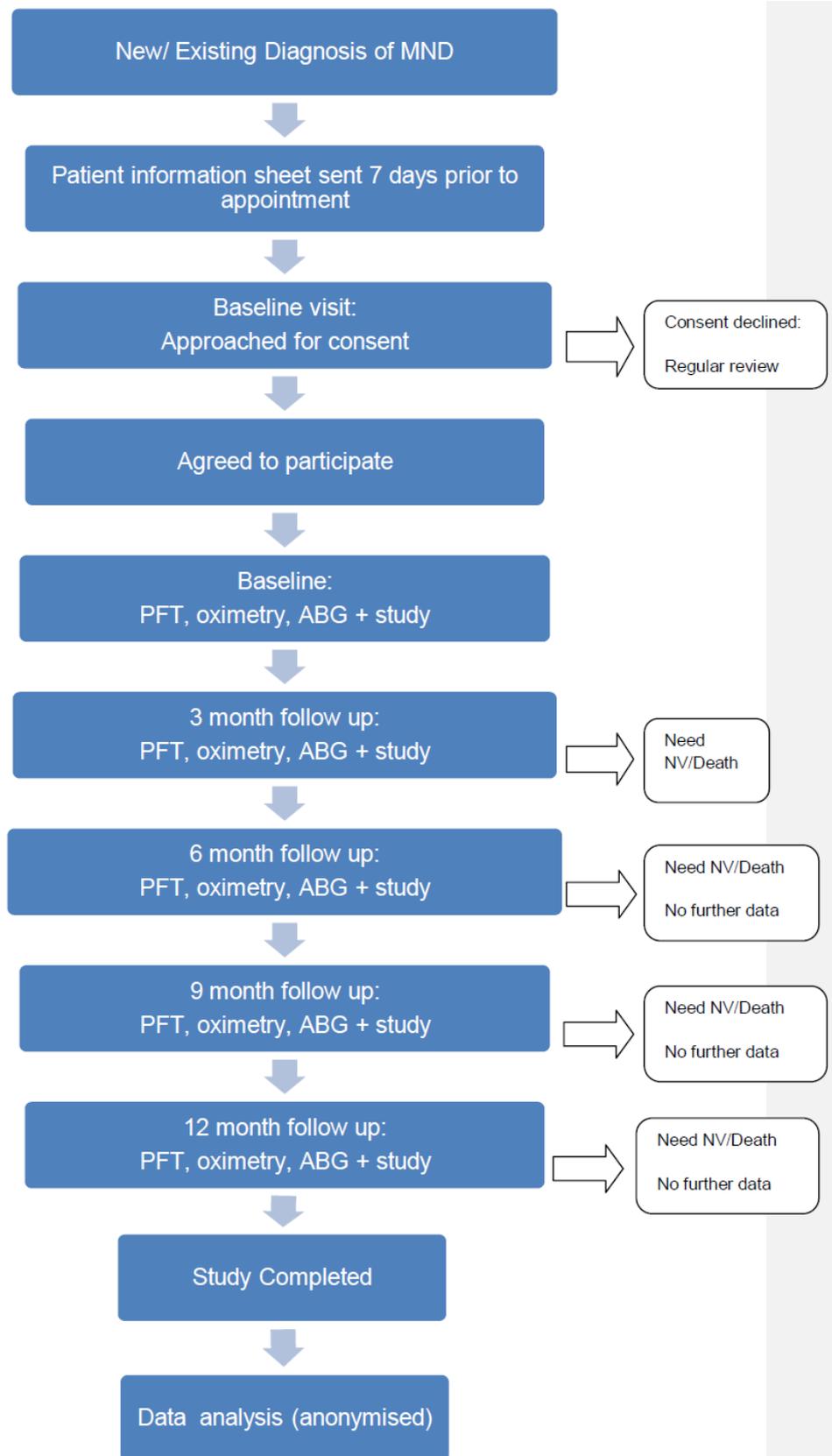
Subjects were divided into two groups using the cut-off values of >75% predicted VC or < 75% predicted. This cut-off was based on a large cohort study (1034 patients) with a diagnosis of MND where the association of FVC with tracheostomy free survival was investigated (Czaplinski 2006). In this study patients with baseline FVC < 75% progressed more rapidly, with a median survival of 2.91 years compared with 4.08 years for patients with baseline FVC > 75%. From the methodology of the study it is not clear how patients with an FVC that was exactly 75% would be categorised. In my data, this did not arise and so we were able to follow the previous paper's precedent.

The second analysis considered the joint analysis of serial measurements of predictors (including FVC) and the primary outcome. Comparisons were made between mask and tube spirometry results as predictors of the time to the primary endpoint on baseline and on serial measurements. The same analyses were made for the other measures of pulmonary function and the ALSFRS score.

3.4.5 Study Update

Early in the study there was concern that more subjects than anticipated would achieve the primary outcome early in the trial with fewer than expected surveillance visits for analysis. A minor amendment was submitted to the REC to allow an extension in the recruitment target. As the study progressed the early concern was not realised and we therefore closed enrolment of patients into the study with a total population of 67 subjects.

Figure 3.1 Flow chart



3.5 A survey of deaths in MND in the era of non-invasive ventilation

A prospective survey was performed of all patients with probable or definite MND in the East of England region, identified by a network of clinicians, who died from October 2010 to December 2011. A structured questionnaire was distributed to involved clinicians, community practitioners and MND association care co-ordinators. They completed questionnaires for patients dying under their care, where necessary with input of family members. The questions focused on the use of non-invasive ventilation and tube feeding, advance care directives, the place of death, the palliative care administered in the terminal phase and cause of death. Where incomplete details were supplied, a further structured telephone interview with the general practitioner or carer who was present at the moment of death or in the 24 hours preceding the death was undertaken.

The results were compared with retrospective data published in 2001 of 50 patients who died from Amyotrophic Lateral Sclerosis (ALS). This group was comprised of patients who had been reviewed periodically by the Wisdom Hospice, Rochester, UK (Neudert 2001). The data were obtained from the patients' hospital charts, which included carer's accounts as well as medical information recorded by nurses and doctors.

Figure 3.2: Questionnaire sent to carers, GP or district nurses involved in care of patient
Questionnaire sent to carers for Prospective Survey of MND Deaths in East Anglia

/ Female? D.O.B _____

Local hospital

Place of death?

Own home Relatives home

Hospice Nursing home

Residential home Hospital

Other (please specify)

Advance Care Plan in place? Y/N

If yes was it used to inform decision making? Y/N

Did the place of death match Advance Care Plan?
 Y/N

Had the patient been prescribed ventilatory support (e.g. Nippy)?
 Y/N

If no, please proceed to Q 9

ventilatory support delivered via

For people who had been prescribed ventilatory support how dependent had they been on the ventilator?

Never really used at home A few hours in the day or night

All night but not in the day All night and day time top up

Virtually / actually 24-hour user

For people who had been prescribed ventilatory support, when was it last used?

Patient died using ventilator A few hours before death

24 hours before death More than 24 hours before death

Had the patient been prescribed oxygen therapy?

No In the last 24 hours of life

In the last week of life More than 1 week

Did the patient have a: PEG tube? (Please circle as applicable). If no feeding tube go to Q13

For people with a feeding tube, had feeding been instituted?

No Supplements to oral intake

Majority / all of feeding requirements

For people with a feeding tube was the feed suspended prior to death?

No In the last 24 hours of life

In the last week of life for more than 1 week

How long was the dying process?

Sudden death Less than 24hours

24 to 48 hours more than 48 hours

Was the patient prescribed any of the following?

Just in case box IM/IV bolus medication

A syringe pump?

If prescribed, was this done in advance of the dying process being recognised?

Y/N

17) What was the certified cause of death?

Please add any other observations or comments

Please return results to:

Dr Ian Smith

ian.smith@papworth.nhs.uk

3.6 Pulmonary function tests

Routine spirometric assessment was performed by a respiratory physiologist in the RSSC. The FVC was obtained as the best of at least three manoeuvres performed seated and using a rotary turbine spirometer (*Micromedical, Kent, UK*) with a standard flanged mouthpiece (*PK Morgan, Rainham, Kent, UK*) and according to national guidelines (BTS 1994). Nasal clips were applied to prevent nasal air leak and strong verbal encouragement was provided during each manoeuvre to ensure maximal effort. An adequate test required a minimum of three acceptable FVC manoeuvres. Acceptable repeatability is achieved when the difference between the largest and the next largest FVC is ≤ 0.150 L (Hankinson 1991). In patients with MND, the "within patient standard deviation" whilst performing spirometry was assumed to be 10% (Polkey 1995). The maximum value obtained is compared with values predicted from age, sex and height (Standardization of lung function tests 1993). Where the subject was unable to stand, height from previous documentation or arm span was used to estimate height.

3.7 Measurement of respiratory muscle strength

Routine respiratory muscle strength assessment was performed by a respiratory physiologist in the ward based at the RSSC, Papworth Hospital NHS Foundation Trust.

3.7.1 Sniff nasal inspiratory pressure (SNIP)

A sniff is a short, sharp voluntary inspiratory manoeuvre performed through one or both nostrils. It involves contraction of the diaphragm and other inspiratory muscles. The pressure measured through a securely fitting bung occluding one nostril during maximal sniffs performed through the contralateral nostril is the SNIP. This non-invasive test of global inspiratory muscle strength has been shown to closely resemble the sniff oesophageal pressure (Héritier 1994). In normal subjects the pressure measured in the oesophagus during a sniff is closely related to that in the mouth, nasopharynx and nose. Thus, in both normal subjects and patients with inspiratory muscle weakness the SNIP provides a reasonable estimate of inspiratory muscle strength. In patients with COPD the SNIP, unlike the MIP, underestimates strength;

this is expected because the sniff is a short manoeuvre and the transmission of the pressure response from the oesophagus to mouth and nose is dampened in COPD (Polkey 1995). Lyall et al. (2001) identified that maximal sniff oesophageal (sniff P_{oes}) had greater discriminatory power to predict respiratory failure in patients without bulbar involvement compared to SNIP. However, in the clinic setting non-invasive SNIP was considered to have the best discriminatory power to predict hypercarbia compared to VC, MIP and MEP. Miller and co-workers showed that normal subjects generated greater trans diaphragmatic pressure (P_{di}) during maximal sniffs than during maximal static inspiratory efforts, probably because the manoeuvre achieved rapid, fully coordinated recruitment of the inspiratory muscles (Miller 1985). Normal values for the SNIP have been established in one study of 160 subjects (men >70 cm H₂O, women >60 cm H₂O) (Uldry 1995). A multicentre study (n=243 healthy subjects) to identify reference values for SNIP in healthy subjects in Brazil identified a predictive equation to determine a mean lower limit of normal. This study further confirmed the findings of Uldry et al. (1995) where the mean lower limit of normal was 69.2 cm H₂O in males and 61.9 cm H₂O in females. This study also showed that age had a negative influence on SNIP and should be included in determining reference values. The independent variables of weight, height and BMI did not correlate with SNIP (Saldhana de Araujo 2012).

In a study of 71 healthy subjects maximal SNIP value was obtained in 7+/- 3.7 attempts and 7.4 +/- 3.7 attempts respectively in the first and second week. This study observed that SNIP results were reproducible from session to session and not subject to learning effects (Terzi 2010). In contrast Lofaso et al. (2006) reported higher values in sniffs 11-20 as compared to the first 10 suggesting a warming up or learning effect. According to ATS/ERS statement regarding respiratory muscle testing regarding the SNIP test, most subjects achieve a plateau of pressure values within 5–10 attempts (ATS/ERS statement, 2002). Hence in my study SNIP was measured during 10 maximal sniff attempts. In the current studies the SNIP was measured in an occluded nostril during a maximal sniff performed via the contra-lateral nostril. The plug was made of soft foam hand-fastened around the tip of a catheter (internal diameter, 1 mm; length, 100 cm). The catheter was connected to a hand-held pressure meter displaying peak pressure (P_{max} Mouth Pressure Monitor; *P. K. Morgan, Rainham-Gillingham,*

Kent, UK). SNIP was measured during 10 maximal sniffs performed from FRC, each separated by 30 seconds with visual feedback. All manoeuvres were recorded and the highest pressure was accepted. After a rest period, the bung was placed in the opposite nostril and the process repeated to ensure that the maximum value was obtained. In addition, predicted SNIP values were also calculated (Uldry 1995).

3.7.2 Maximal inspiratory mouth pressure ($P_{i_{max}}$)

Maximal inspiratory mouth pressures are another technique used for non-invasive evaluation of respiratory muscle function. The $P_{i_{max}}$ reflects the strength of the diaphragm and other inspiratory muscles. Portable inexpensive mouth pressure meters allow immediate measurement of the $P_{i_{max}}$ (and expiratory pressures) at the bedside or in the clinic. A $P_{i_{max}}$ (>80 cm H₂O) is of value in excluding clinically important inspiratory muscle weakness (ATS/ERS statement 2002). The predicted normal range for maximal respiratory pressures in Caucasian adults and children are based on a study of 370 normal Caucasian adults and children (Wilson 1984). This study revealed that values for $P_{i_{max}}$ and $P_{e_{max}}$ were generally higher in men than women. These differences were significant ($p < 0.001$), for $P_{i_{max}}$ the female value was 69% of the male value and for $P_{e_{max}}$ it was 60%. There was no significant difference between the age of the groups. In young girls both the $P_{i_{max}}$ and $P_{e_{max}}$ were 83% of the boy's value. This study also revealed maximal respiratory mouth pressures were related to age in men but to height in women. An earlier study had shown a higher reference range although in this study subjects were pushed to extremes such that some suffered nose bleeds and conjunctival haemorrhage (Ringqvist 1966). Seventy-one healthy medical students were asked to perform the test (mouth inspiratory pressures) over 2 sessions separated by a week. The maximal value for $P_{i_{max}}$ was obtained in 4.5 +/- 1.7 trials on the first session compared to 3.4 +/- 1.9 for second session. This result indicates that a warming up effect or a learning effect is necessary to achieve the maximal values during the tests.

For the current studies the $P_{i_{max}}$ was measured using a standard flanged mouthpiece connected to a hand-held pressure meter computing average pressure sustained over 1 s (*Mouth Pressure Meter; P. K. Morgan*). The subjects were studied seated with their nose occluded with a nose clip. The subjects were instructed to seal their lips firmly

around the mouthpiece, exhale slowly and completely (that is to residual volume) before pulling in breath hard, as if they were trying to suck up thick fluid. The subjects were asked to maintain inspiratory pressure for at least 1.5 seconds and the largest negative pressure sustained for 1 second was recorded. Visual or verbal feedback and encouragement was provided during and after each manoeuvre. The goal was for the variability among measurements to be less than 10 cm H₂O.

3.7.3 Maximal expiratory mouth pressure (*P_{emax}*)

The P_{emax} reflects the strength of the abdominal muscles and other expiratory muscles. However, it can be difficult to ensure that the subject is making a truly maximal effort. While normal subjects can potentially activate peripheral and respiratory muscles fully during voluntary efforts, one cannot always do it reliably and naïve subjects have greater difficulty than practiced individuals (Wilson 1984). Therefore, it is hard to know whether low mouth pressures truly represent reduced respiratory muscle strength or merely reduced neural activation. P_{emax} was measured using the same device used for measuring P_{imax} . The manoeuvre was performed from a maximal inspiration that is total lung capacity (TLC). The subject was asked to inspire to TLC, the valve on the handheld pressure metre was then closed by the operator and the subject was encouraged to expire maximally against the occlusion for at least 1.5 second. A semi rigid flanged mouthpiece was used and the best effort from at least 3 attempts was recorded. The goal was for the variability among measurements to be less than 10 cm H₂O. Absolute values were obtained and compared with predicted values. The published literature (Wilson SH et al, 1984) has shown that men produce higher values than women as mentioned above. Based on the ATS/ERS statement, more data on MEP values, especially female, with a flanged mouthpiece, are needed. P_{emax} like P_{imax} has a learning effect and is hence less reproducible, compared to SNIP (Terzi 2010).

3.7.4 Spirometry for research protocol

The FVC declines with time in patients with MND and is an indicator of disease progression (Czaplinski 2006). An FVC of <50% predicted is recommended by some authors as an indication for non-invasive ventilation. Both the baseline FVC, that is at

first assessment, and the rate of decline in FVC, are predictive of survival except in patients with bulbar involvement. Many patients with facial or bulbar muscle weakness cannot effectively seal their lips around a mouthpiece, especially during forced manoeuvres. This might be one of the reasons that spirometry does not predict time to ventilatory failure. In these cases, the conventional equipment with a tube or flanged type of mouthpiece is not adequate to evaluate respiratory muscle function. A facemask might provide more accurate values than a mouthpiece in people with MND with bulbar involvement. Since the true value of FVC is maximal, it should not be possible for a different technique to overestimate it so long as the equipment is correctly calibrated. A previous study has assessed the validity of face mask spirometry in normal subjects (Wohlgemuth 2003). Values obtained using a face mask were around 200 mls less than with a conventional mouthpiece showing that in the absence of a leak a face mask is disadvantageous or gives a lower value than conventional measures via a mouth piece.

Subjects enrolled into the current studies were asked to perform spirometry using the face mask and tube mouthpiece or flanged type of mouthpiece in a randomised order for comparison of values. A Laerdal child's face mask number 4 was used as the face mask interface for the study (Fig 3.3). The plastic mouthpiece tubing of a peak flow meter was used for connection of the facemask to the instruments for measurement of spirometry. FVC and FEV₁ were measured using a Micro plus hand held spirometer (*Micro Medical, Chatham, Kent*) (Fig 3.4). The spirometer was calibrated daily using a 1 litre syringe. The spirometer with the mask was held and pressed against the subject's face by the investigator while the conventional mouthpiece device was held by the subject. Test order randomisation was based on computer generated random numbers, stored in sealed envelopes. At least three measurements were performed with each technique and two readings within 10% of the largest value were deemed acceptable. In patients with MND, the "within patient standard deviation" whilst performing spirometry, was assumed to be 10% for power calculations (Polkey 1995).



Figure 3.3: Laerdal child's face mask number 4

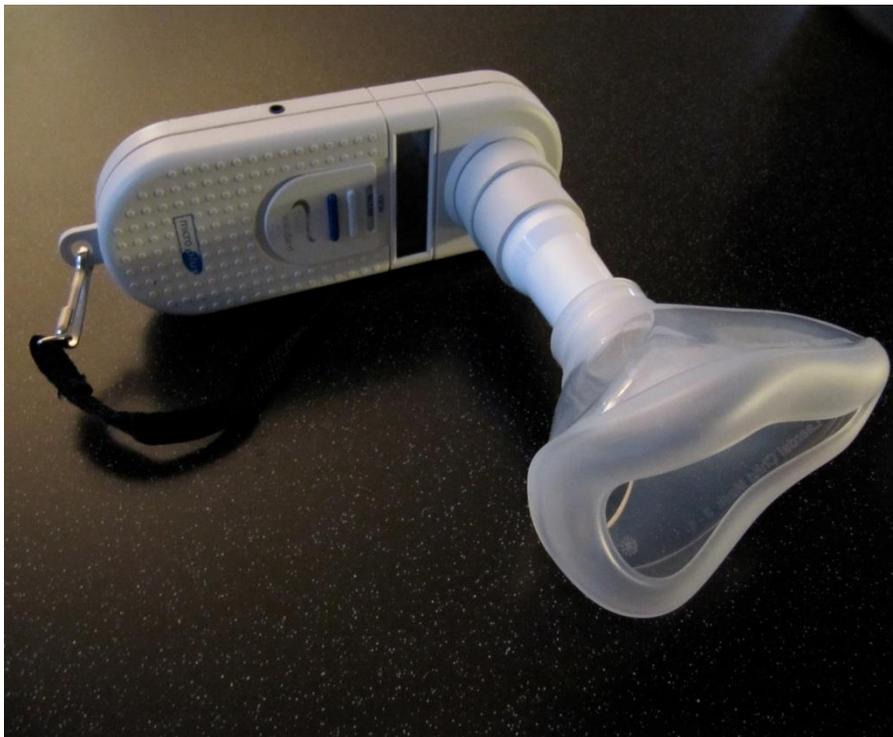


Figure 3.4: A Laerdal child's face mask number 4 was used as the face mask interface

All equipment was cleaned with chlorclean before and after use by the subject.

3.7.5 Arterial Blood Gas analysis

Arterial blood gases (ABG's) were measured in blood samples taken from the radial artery using pre-heparinised syringes. Patients were at rest for a minimum of 20 minutes before the radial puncture. ABGs were measured either on air or additional oxygen depending on the subject's usual therapy. Patients were assessed on the same oxygen flow rate on each visit to allow comparison between measured values. In subjects, reluctant to have an arterial puncture, capillary blood gas (CBG) samples were used for data collection. For capillary samples a rubefacient was applied to either ear lobe and after about three minutes a stab about 1–2 mm deep was made with the point of a size 11 scalpel in the fleshy part of the ear lobe. We collected the blood in a heparinised capillary tube held horizontally against the puncture site. The ABG and CBG samples were analysed in an automated blood gas analyser (*GEM Premier 3000, Instrumentation laboratory, Lexington, USA*) whose accuracy has been validated (Steinfeldt-Visscher 2006). No correction for body temperature was performed (assumed to be 37° C).

A metanalysis of 29 studies has shown sampling capillary blood from the fingertip or earlobe (preferably) accurately reflects arterial PCO₂ and pH over a wide range of values. Sampling blood, too, from earlobe (but never the fingertip) may be appropriate as a replacement for arterial PO₂ (Zavorsky 2007).

3.7.6 Overnight Oximetry

Pulse oximetry (*3900 Datex-Ohmeda, Hatfield, UK*) was recorded overnight in the patients' own home typically between 2300 and 0700 hrs. Finger probes were used. Pulse oximetry reports an estimate of arterial oxygen saturation (SpO₂) which accurately reflects the true arterial oxygen saturation (SaO₂) and by inference reflects the partial pressure of oxygen in the blood (PaO₂) when the value of SaO₂ is >70% (Jubran 1999). The oximeter used updates its output trend every 3 seconds however the recording system samples the output at 16 Hertz and records one value per second which is the lowest value during that one second period. These data were downloaded and stored centrally on the RSSC on a single computer server and analysed using an automated system (*Download 2000, Stowood Scientific instruments, Oxford, UK*).

Values of less than 60% for SpO₂ were treated as artefact. Calculated values for the period monitored include a 4% desaturation index (number of desaturations of 4% or over per hour), mean heart rate, mean and minimum SpO₂ values.

3.7.7 Amyotrophic Lateral Sclerosis Functional Rating Score (ALSFRS r score)

To quantify bulbar involvement, we used the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS r score), a validated rating instrument for monitoring the progression of disability in patients with MND. The components of the scale group into four domains that encompass gross motor tasks, fine motor tasks, bulbar functions and respiratory function. It is a score from 0 to 48 and consists of 12 questions, each rated from 0 to 4. The first 3 questions are related to bulbar functions and a total score of 12 for these questions indicates no bulbar symptoms. Decreasing values on these 3 questions (b ALSFRS r score) indicate progressively greater bulbar symptoms. Heart of England NHS Trust, Birmingham Fattori et al. (2006), showed clinically significant swallowing difficulty in patients when the b ALSFRS r score was less than 9. In our study, we proposed *a priori* that a score of less than 9 defines the subgroup with important bulbar symptoms.

3.7.8 Data acquisition, storage and analysis

The data from pulmonary function tests of respiratory muscle strength, overnight oximetry, arterial blood gases and ALSFRS r score was recorded on a data sheet which was ultimately stored in an anonymised manner on an excel spreadsheet on a personal computer situated in the research office at the RSSC. Access to the computer and the data was password protected to ensure safety of data. The statistical analyses performed are outlined in the relevant chapters.

Chapter 4: RESULTS

The results section is divided into 4 main sections:

Section 4.1: Impact of structured follow up pathways on access to ventilatory support for people with MND

Section 4.2: The role of facemask spirometry in MND

Section 4.3: Face mask Spirometry as a prognostic tool indicator in MND

Section 4.4: A survey of deaths of people with MND in the era of non-invasive ventilation

Section 4.1: Impact of structured follow up on ventilatory support for MND

4.1.1 Summary

NICE recommend that a multi-disciplinary team coordinate and provide on-going management and treatment for patients with MND. It is recommended that such follow up is continued at 3 monthly intervals (with clinical discretion) to offer patients the opportunity of receiving NIV when they develop ventilatory failure. The aims of the review were to examine the impact of compliance with practice parameter recommendations in NICE to referral numbers to RSSC and uptake of NIV in East Anglia. A retrospective review of the hospital database was undertaken to identify patients with MND referred for respiratory assessment from 1987 to 2010 in a regional respiratory support centre.

4.1.2 Population

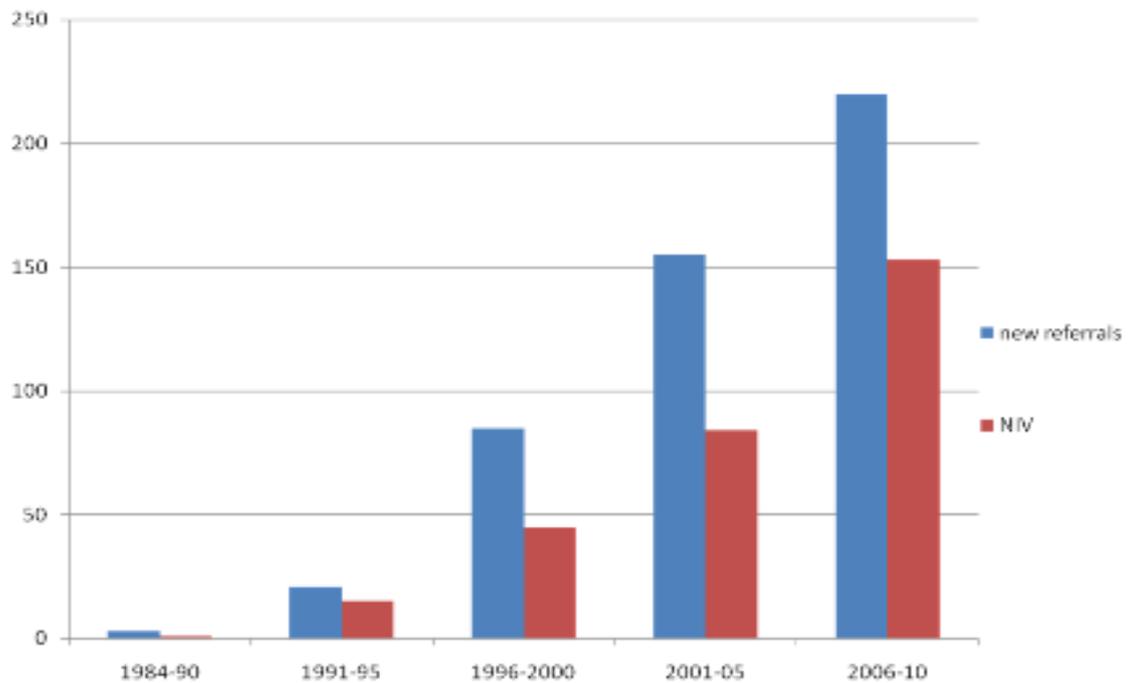
The numbers of new referrals and people starting NIV are shown below in the figure 4.1.

1984-2000: Mean annual referrals were 7 with 4 new NIV starters per year (57%).

2001-2005: Closer working between neurologists in the care centre and respiratory unit established. Mean annual referrals increased to 31 with 17 new NIV starters per year (55%).

2006-2010: Default referrals and 3 monthly follow-ups established. Mean annual referral numbers grew to 44 with 31 NIV starters per year (70%).

Fig 4.1: Referral pattern to regional respiratory support centre in 5 year periods for respiratory assessment with uptake of NIV.



Taking an annual incidence of 2.8 per 100000, we estimated 70 new cases of MND per year in the catchment population. Therefore 60% of patients were being referred and 70% of these were starting NIV. The national average had been reported at 35% of patients with MND being referred for consideration of NIV (O'Neill 2012).

Section 4.2. The role of facemask spirometry in MND

4.2.1 Summary

The objective of this study was to determine whether the default interface for recording spirometry in people with MND should be a mask or a mouthpiece or whether both measures are required. My specific aims of this study were to assess whether a mask or mouthpiece interface for spirometry (FEV₁ and FVC) produces a greater number of more accurate results. Since FVC was a maximal manoeuvre a numerically greater value is assumed to be more accurate. To assess accuracy of mask spirometry in subgroups according to the presence or absence of bulbar symptoms.

4.2.2 Population

I screened 73 consecutive subjects for potential enrolment. Thirteen were excluded for the following reasons; 4 declined consent, 5 were on continuous NIV, 1 had developed dementia, 1 had a mini tracheostomy tube in situ, 1 had recurrent pneumothoraces and 1 had undergone recent cataract surgery. Among the recruited 60 subjects there were 36 (60%) men, the mean age was 64.7 (SD 10.5) years, mean BMI 26.7 (SD 5.5) kg/m². Thirty-three (55%) were never-smokers and 27 were current smokers or ex-smokers. The median (inter-quartile range) for time between diagnosis of MND and test completion was 558 (728) days. The mean b ALSFRS r score was 7.8 (3.3) and 30/60 (50%) subjects had a score of < 9. Seventeen (28%) subjects had been issued NIV with 14 reporting regular nocturnal use. Thirty-four (57%) subjects had been prescribed riluzole.

4.2.3 Spirometry

Results were available for all 60 patients using the mask and 54 patients using the tube (McNemar $p < 0.001$). From the total of 60 subjects, 51 (85%) managed SNIP measurements and 45 (75%) inspiratory and expiratory mouth pressure measurements.

Table 4.1 shows the mean FVC measured by mask and tube in the study population. Table 4.2 shows the comparative information regarding FVC between tube and mask in subjects with varying degrees of bulbar involvement and shows greater accuracy of mask, compared to tube spirometry, with worsening bulbar scores.

Inspection of the Bland Altman plot comparing tube and mask FVC (fig 4.2) shows more points above $y=0$ (mask value greater) than below. The mask gave the higher reading in 36 cases, was equal to the tube in 1 and lower in 17. The mask gave significantly greater values for FVC than the tube, the mean difference was 0.19 litres (95%CI 0.07, 0.31; $p=0.0024$). On linear regression, the difference between the FVC measurements of tube and mask decreased as the mean FVC increased, with the two measurements coinciding at about 3.3 litres (difference in FVC = $-0.56 + 0.17 \times \text{average in FVC}$). Both the intercept and slope were significantly different from zero suggesting that the relative accuracy of the two methods varies with the value of the FVC measurement.

The scatter plot (Fig 4.3) shows FVC results for the mask against those for the tube, with a 45° line of agreement super-imposed. The mask gave higher measurements of FVC for patients with low FVC values but slightly lower values for patients with higher FVC values. A linear regression was fitted to predict mask results from tube results. The resulting regression equation was:

$$\text{Mask} = 0.61 + 0.80 \text{ Tube } (R^2 = 90\%)$$

The intercept was significantly greater than zero, confirming that the estimated mask records higher FVC for low values, and the slope was significantly less than one, so that estimated mask measurements are lower for values of FVC above approximately 3 litres.

4.2.4 Effect of bulbar disease (subgroup analysis)

All 30 subjects with bulbar ALSFRS r score ≥ 9 could record both mask and tube FVC measurements. Six of the 30 subjects with b-ALSFRS r score < 9 could not perform tube measurements, but all 30 had a result using the mask (McNemar $p < 0.0001$). Five

patients with preserved bulbar function and 4 patients with B ALSFRS r score < 9 (86%) were unable to record SNIP.

For patients with both FVC measurements the mask was higher or equal in 21/24 (88%) of cases with bulbar disease and 15/30 (50%) with non-bulbar disease (Fisher's exact test 0.004). Figure 4.4 shows the difference between measurements plotted against the average, split by whether the patients have bulbar disease (bulbar ALSFRS r score < 9, right) or not (bulbar ALSFRS-r score \geq 9, left). Patients with bulbar disease had higher mean FVC measurements with the mask but the non-bulbar group did not. The mean difference between mask and tube FVC measurements was 0.32 litres (95%CI 0.15, 0.49), $p=0.001$ in the bulbar group and 0.09 litres (95%CI -0.08, 0.25) in the non-bulbar group, $p=0.283$.

Table 4.1: Descriptive data: Mean and standard deviation of FVC

	FVC mask	FVC tube only	P
No of cases	60	54*	
Mean (litres)	2.24 [▫]	2.13*	0.0024
Standard Deviation (litres)	1.10	1.30	
Minimum (litres)	0.58	0.37	
Maximum (litres)	4.84	5.20	

*Six patients had measurements of FVC equal to zero using the tube. These have been coded as missing. [▫] Mean FVC of 60 patients * Mean FVC of 54 patients

Table 4.2: Comparative data based on Bulbar ALSFRS r score

B ALSFRS r	N		FVC mask	FVC tube	P value
12	8	Mean (Litres)	3.43	3.54	0.414
		Standard Deviation	1.37	1.57	
≥ 9	30	Mean (Litres)	2.69	2.60	0.283
		Standard Deviation	1.16	1.34	
< 9	30	Mean (Litres)	1.88	1.56	<0.001
		Standard Deviation	0.87	1.01	

Table 4.2 gives comparative information regarding FVC between tube and mask in subjects with varying degrees of bulbar involvement and shows greater accuracy of

mask, compared to tube spirometry, with worsening bulbar scores. The difference in FVC between facemask and tube interface is statistically significant in patients with moderate to severe bulbar involvement. This difference could affect decision making regarding referral for initiation of NIV suggesting a more accurate measure of lung function in this patient population may contribute towards the goal of instituting NIV at the appropriate time.

Fig 4.2: Bland Altman plot of FVC measurements using mask and tube in litres

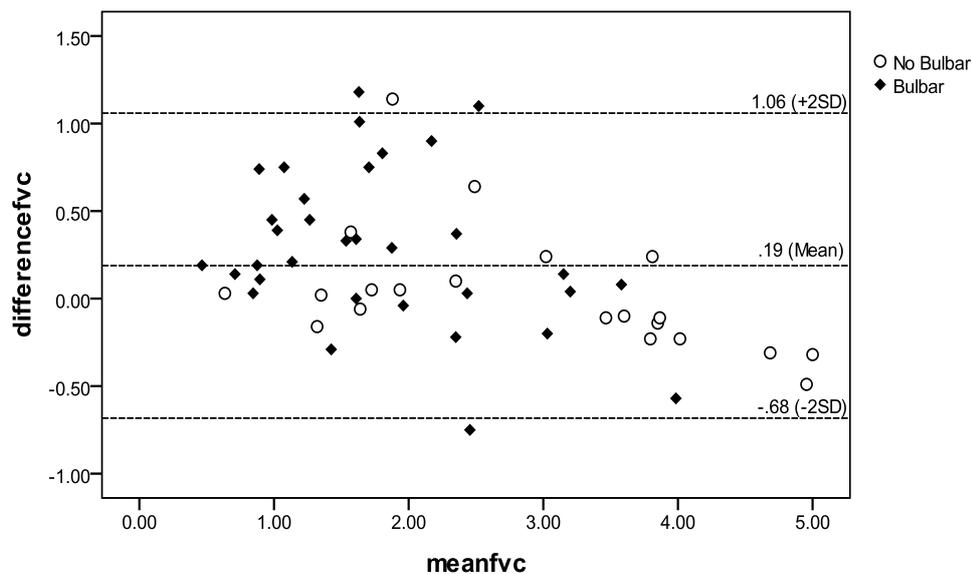


Figure 4.2. Bland Altman plot showing mask readings were higher in 36 cases, equal to the tube in 1 and lower in 17. The overall mean difference was 0.19 litres (95%CI 0.07, 0.31; p=0.0024) in favour of the mask. In five subjects the difference was greater than 1 litre.

Fig 4.3: Scatter plot of spirometry results for mask against tube (litres)

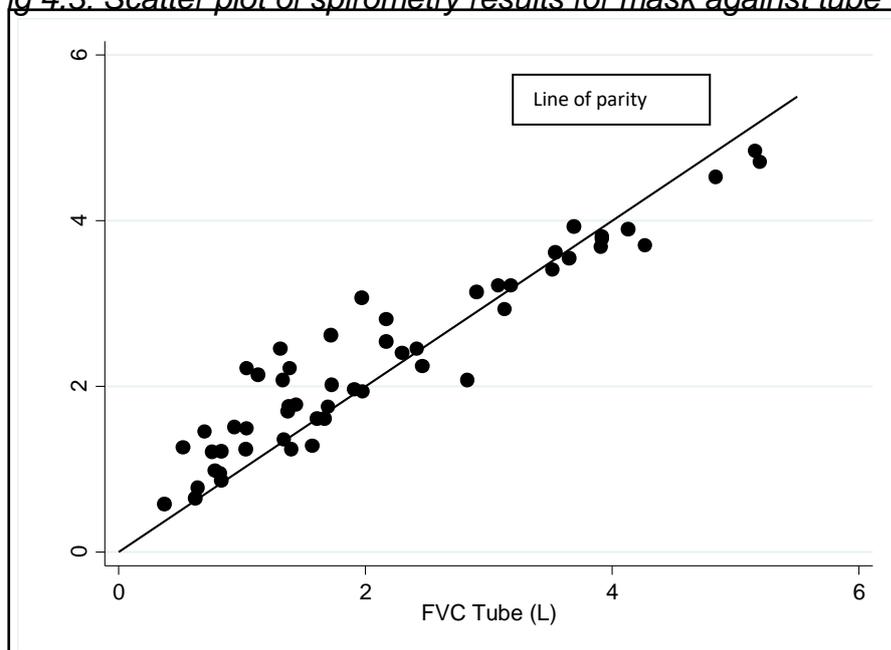


Figure 4.3: Linear regression fitted to predict mask results from tube results gives: $\text{Mask} = 0.61 + 0.80 \text{ Tube}$ ($R^2 = 90\%$). The intercept is > 0 and slope < 1 , i.e. estimated mask FVC is higher for low values and lower for high values (above approximately 3 litres).

Fig 4.4: Bland Altman plot comparing bulbar with non-bulbar measurements of FVC using mask and tube

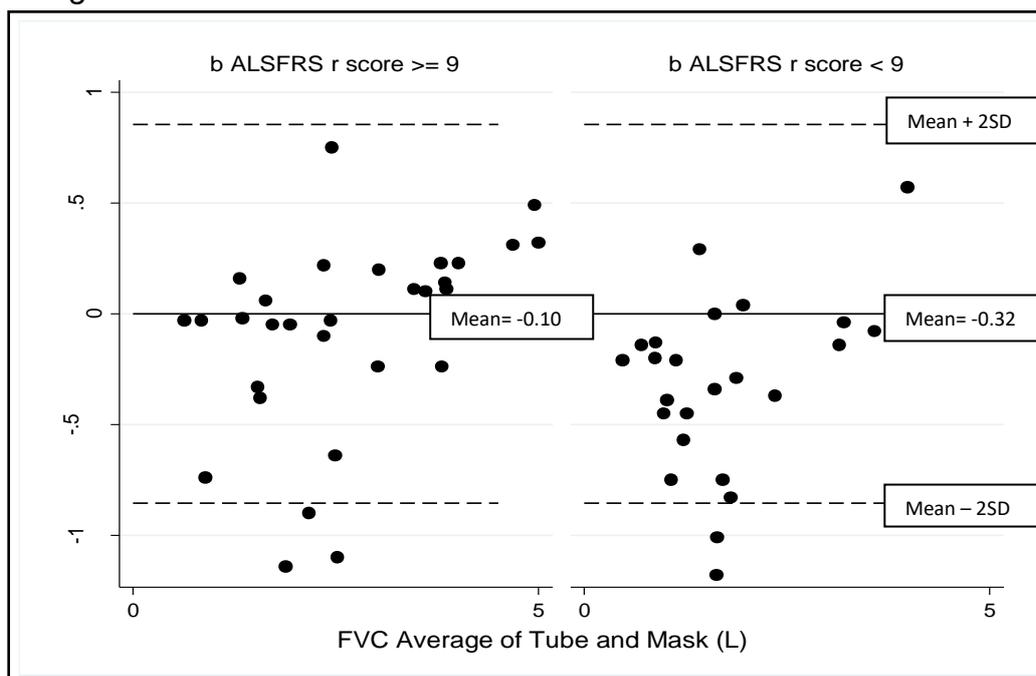


Figure 4.4: For patients with both FVC measurements the mask value was higher or equal in 21/24 (88%) of cases with bulbar disease and 15/30 (50%) with non-bulbar disease (Fisher's exact test 0.004).

In summary, in this study the mask gives higher values than the tube when FVC is less than 3 litres (bulbar and non-bulbar) and for all patients with moderate to severe bulbar involvement regardless of the value of FVC. All 60 patients could perform FVC using a mask, whilst only 54 (90%) managed with the tube. Six patients, who produced a mean FVC of 1.45 (0.68) litres with the mask, could not record anything with tube spirometry. However, at higher forced expiratory volumes, tube spirometry tended to produce higher values. The potential under reading of FVC at higher volumes means

that mask cannot completely replace tube as an interface for measuring spirometry in patients with MND.

Section 4.3 Facemask spirometry as a prognostic indicator in MND

4.3.1 Summary/ Overview of aims

The main objective of this study was to determine whether FVC measured with facemask spirometry on referral for respiratory assessment and serially thereafter can accurately predict time to non-invasive ventilation or death in MND. There were a series of secondary objectives

- To identify if the difference in FVC recorded between mask and tube spirometry in phase 1 was reproducible in a second cohort of patients with MND.
- We wanted to identify if facemask spirometry was a better predictor of time to ventilatory failure/need for NIV and/or death than tube spirometry.
- Were these predictions influenced by bulbar function at the time of the measurement.
- Was facemask spirometry a better predictor of time to ventilatory failure/need for NIV and/or death than other measures of respiratory function or general performance status including SNIP, P_{imax} , P_{emax} and ALSFRS.

4.3.2 Population

I screened 78 consecutive subjects with a new or existing diagnosis of MND not using NIV and without a tracheostomy for potential enrolment. Eleven were excluded for the following reasons; 4 declined consent, 7 were identified to have ventilatory failure on day of enrolment. Thus, a total of 67 subjects were enrolled for the study. Three of these subjects had been recruited to phase 1 study (role of facemask spirometry in MND). One subject needed NIV before his next, planned, follow-up visit and hence did not have at least 2 measurements. As per protocol, the subject was therefore not included for analysis. Thus 66 patients were included in the final analyses. The mean age of the cohort was 64.9 (SD 12.15) years with a mean BMI of 27.1 (SD 5.91) kg/m². There were 40 (60.6%) men and 26 women (39.4%). The time interval from symptom onset to diagnosis was 17.1 (SD 14.88) months. The mean interval between diagnosis

and entry to this study was 22.8 months (SD 17.28). The mean ALSFRS r score at time of enrolment was 31.8 (SD 8.46) along with a bulbar ALSFRS r score of 9.1 (SD 2.77).

Of the 66 patients included, 17 died between follow up appointments, 21 developed ventilatory failure and were treated with NIV, 24 completed the study period without reaching the primary endpoint and 4 were lost to follow-up. Hence 38 patients reached the primary endpoint of NIV/death in this cohort of patients (of whom 36 had complete data). None of the patients who had recorded ventilatory failure declined NIV.

All subjects were able to perform mask spirometry at baseline. Six subjects were unable to perform spirometry with tube interface at baseline and another failed on their follow up visits prior to reaching the end point of ventilatory failure or death. All 7 of these subjects had a BALSFRS r score of ≤ 6 . Four of these subjects were unable to perform spirometry with tube interface on their final assessment before reaching the end point of ventilatory failure or death while 2 subjects were unable to perform tube FVC for 2 or more follow up visits. One subject was unable to perform spirometry with the facemask interface during follow up visits but was also unable to perform tube spirometry, SNIP or MIP. Four of the subjects unable to perform tube spirometry were unable to complete SNIP, MIP or MEP manouevres. Of the 7 subjects unable to perform tube spirometry, 1 was unable to perform mask FVC as well but of the remaining 5 subjects the mask FVC was less than 50% predicted in all cases. These data highlight the limitation of only using an oral tube as an interface for measuring serial FVC as it cannot be obtained in the later stages of the disease in about 30% of cases with moderate to severe bulbar involvement.

Table 4.3 Time to primary endpoint for baseline measurement of vital capacity using either a mask or tube employing a cut off value of 75% of predicted.

		Time to primary endpoint (days)	SD
FVC < 75% pred	Facemask n = 20	156	95.1
	Tube n= 21	156.5	96.4
FVC > 75% pred	Facemask n = 16	199.8	114.3
	Tube n = 12	221.3	117

The mean time to primary outcome event for subjects with Facemask VC >75% predicted was 43.8 days longer than for those subjects with VC less than 75%. However, this difference was not significant (unpaired t test; $t = 1.255$ and $p = 0.218$). The mean time to primary outcome event for subjects with Tube VC >75% predicted was 64.8 days longer than for those subjects with VC less than 75%. This difference was not significant either ($t = 1.1.718$ and $p = 0.958$).

This result does not reflect the outcomes that might be expected from previous studies although these recorded VC at diagnosis while the current subjects were at different stages of disease progression. The outcome was examined in other ways. Whether either tube or mask FVC < 75% is associated with the chance of having an event in the first year, was explored using Chi square analysis.

Table 4.3.1 For mask

	VC <75	VC > 75
Event	21	16
No event	9	15

Chi square = 2.16 p = non-significant

Table 4.3.2 For tube

	VC <75	VC > 75
Event	21	13
No event	11	11

Chi square= 0.75, p=non-significant

It is possible that the cut off 75% predicted was not appropriate for the mask which gives higher values on average than the tube in an MND population. The data were re-examined to see if there was a difference in the mean predicted VC for those who did and did not meet the primary endpoint of either death or starting NIV.

For Facemask, subjects not meeting the primary endpoint (n= 24) had a mean VC predicted of 80.6 % while for those with an event (death or NIV, n= 37) it was 70.4 %. Using unpaired t tests these were not significantly different though there may be a trend (p = 0.084). For Tube spirometry, subjects with no event (n = 22) had a mean VC predicted of 73.9% while for those who had an event (n= 34) it was 63.4% and this difference was not significant (p= 0.116)

The mean duration from the point of enrolment into the study, to the primary endpoint did not reach statistical significance. This might be because the follow up of one year was too short and excluding subjects who reached the 1 year cut off reduced the explanatory power of differences in the data. Re-examining the data based on end

point becoming initiation of NIV, death or reaching the endpoint of 1 year increases the power of the statistics by increasing the population while not directly addressing the primary question of the study. The data on this basis are presented in table 4.4. As in the previous study (Czaplinski 2006), patients with a VC <75% predicted met the criteria for this hybrid endpoint sooner than those with VC >75% predicted. The Kaplan Meier plot is shown in Figure 4.5 for this hybrid end-point where all patients enrolled in the study have been included in the analysis. The mean times to hybrid endpoint are shown in table 4.4.

Figure 4.5: The survival curves for subjects with VC< and VC> 75% predicted

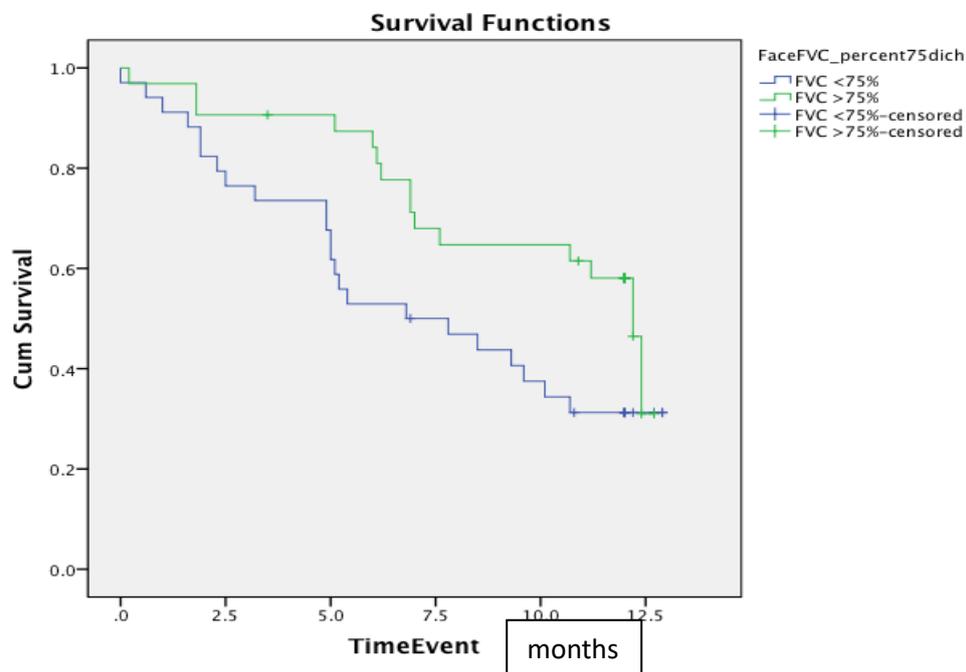


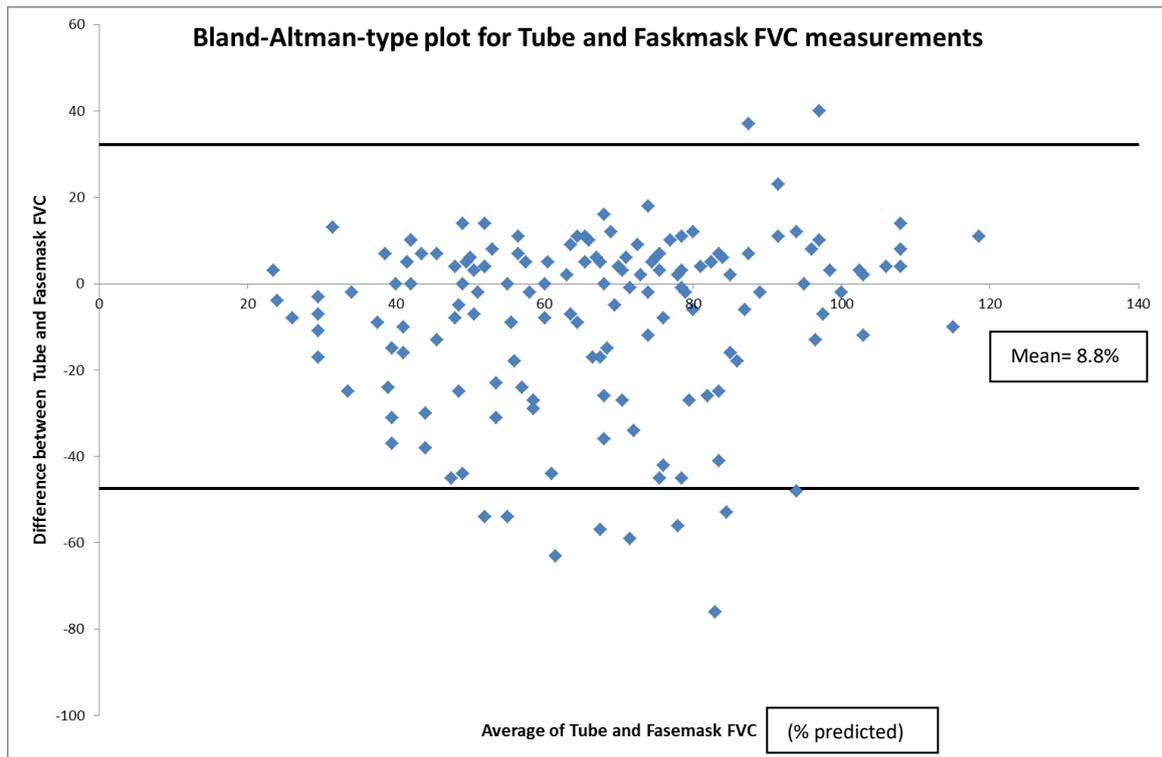
Table 4.4: Comparing time to hybrid endpoint based on baseline measurements of facemask and tube FVC above and below the cut-off point of 75% predicted.

		Time to hybrid endpoint (days)	SD
FVC < 75% pred	Facemask n = 34	227.1	137.4
	Tube n= 36	234.1	129.5
FVC > 75% pred	Facemask n = 32	297.9	116.4
	Tube n = 25	302.2	79.3

4.3.3 Comparison of mask and tube spirometry in current cohort

Over all the results including those from follow up visits, the values for the mask FVC were 8.8% higher than they were for the tube interface. This difference was statistically significant ($p < 0.001$, 95% CI 4.41, 13.24) which supports the findings from phase 1 of study. Inspection of the Bland Altman type plot shows more points below $y=0$ (mask greater than tube) than above it. It should be noted that most patients contributed more than one point on the plot.

Figure 4.6: Bland Altman type plot for tube and facemask measurements



4.3.4 Comparison of facemask and tube spirometry at baseline and time to primary end point by 75% cut off.

Although times to the primary endpoint were not identical for subjects grouped by mask FVC and by tube FVC the differences were not significant (Table 4.3). The survival curves for the mask and tube FVC for > 75% predicted and < 75% predicted are shown respectively in figures 4.7 and 4.8.

Figure 4.7: Kaplan Meier plots of reaching the primary outcome using tube or facemask for subjects with baseline FVC < 75% predicted

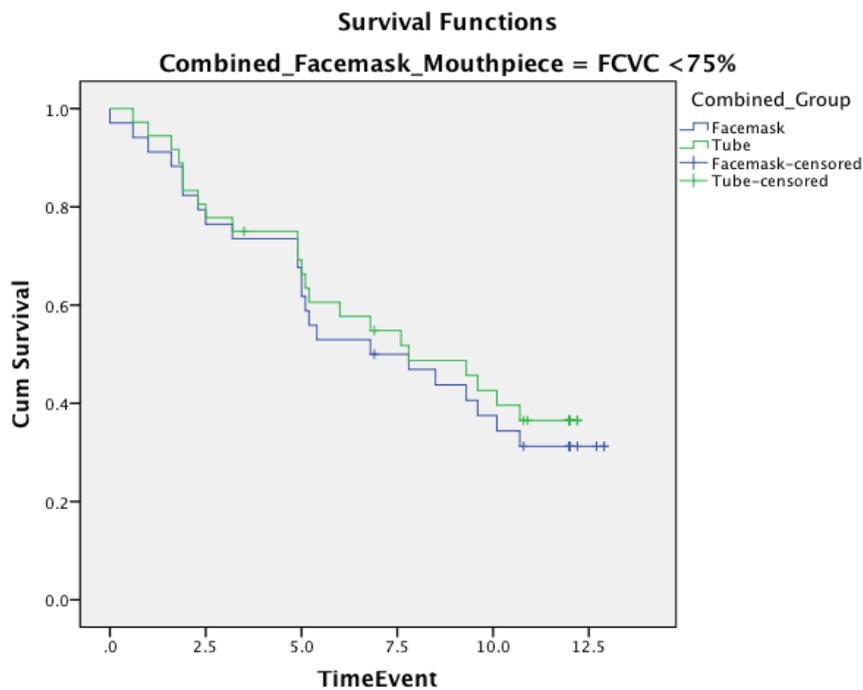
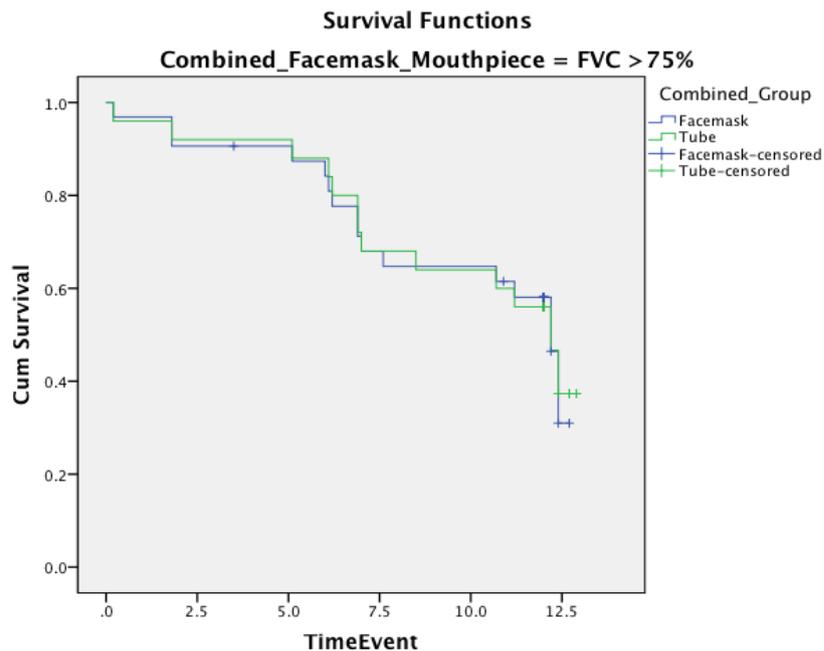


Figure 4.8: Kaplan Meier plots of reaching primary endpoint using tube or facemask for subjects with baseline FVC > 75% predicted



4.3.5 Impact of bulbar dysfunction

Seventeen subjects were identified as having moderate to severe bulbar involvement at time of inclusion into study (bALSFRS r score ≤ 9). There was a non-significant difference in time to the primary outcome between patients with bulbar and non-bulbar MND with survival times respectively of 7.38 (CI 5.27 and 9.49) and 9.00 (CI 7.81 and 10.19) months ($p=0.318$).

Neither Tube nor Facemask FVC percentage value at first measurement have a significant relationship with the logarithm of the number of days to endpoint using the 5% level of significance ($p = 0.079$ and $p = 0.166$ respectively).

SNIP and MIP at first measurement did have a significant relationship with the logarithm of the number of days to endpoint using the 5% level of significance although neither have R^2 values that suggest that the prediction is anything other than very weak. SNIP has an adjusted R^2 value of 0.154 and for each additional SNIP point, the days until endpoint increase by 2.02% ($p = 0.005$, 95% CI (0.644%, 3.417%)). MIP has an adjusted R^2 value of 0.091 and for each additional MIP point, the days until endpoint increase by 1.22% [$p = 0.026$, 95% CI (0.151%, 2.293%)].

This study does not have the power to give precise predictions of the number of days to endpoint. Confidence intervals given in the table are approximate 95% intervals for the days to endpoint using the 25th percentile, median and 75th percentile of the variable used in the modelling. MEP at first measurement does not have a significant relationship with the logarithm of number of days to endpoint ($p=0.183$), nor do ALSFRS r score ($p=0.440$) or bALSFRS r score ($p=0.969$) at first measurement.

4.3.6 Relationship between days to end point and potential predictors across measures made at first assessment and subsequent follow up visits

All of Facemask FVC percentages predicted, Tube FVC percentage predicted, SNIP, MIP, MEP and ALSFRS_r have significant relationships with days to endpoint at the 5% level of significance but bALSFRS_r did not when serial measures are analysed. Measurements, which are at the primary outcome point are excluded from the analysis. This is because the measurements taken are likely to have influenced in part any decision to start ventilation and the need for NIV would have been reached prior to that point in time. However, as can be seen in the table (Table 4.5), none of them give predictions that have much accuracy. The confidence intervals given in the table are approximate 95% intervals for the days to endpoint using the 25th percentile, median and 75th percentile of the variable used in the modelling. Thus if a subject had a VC measured at the 25th centile using a tube interface we would predict with 95% certainty that they would reach an endpoint of death or NIV at between 84 and 147

days. If they recorded a VC using the same interface that was at the 75% centile we anticipate this (with 95% certainty) to occur between 165 and 286 days.

All the intervals were wide reflecting this lack of accuracy. The accompanying graphs show the same relationship with the solid line being the prediction and the dotted lines indicating the boundaries of the 95% confidence interval. The horizontal axes go from zero to just beyond the maximum value in the dataset for the relevant variable (Figures 4.9-4.15).

Table 4.5: Relationship between days to end point and potential predictors over all measurements (Facemask FVC percentages predicted, Tube FVC percentage predicted)

Variable	p-value	Approximate 95% interval for time to end point at 25th centile for variable	Approximate 95% interval for time to end point at median for variable	Approximate 95% interval for time to end point at 75th centile for variable
Tube FVC	< 0.001	(84, 147)	(116, 198)	(165, 286)
Facemask FVC	< 0.001	(79, 136)	(119, 193)	(160, 262)
SNIP	< 0.001	(85, 140)	(128, 203)	(196, 350)
MIP	< 0.001	(84, 150)	(128, 216)	(185, 334)
MEP	< 0.001	(84, 158)	(107, 189)	(186, 352)
ALSFRS _r	< 0.001	(75, 133)	(107, 183)	(174, 304)
BALSFRS _r	0.106	(110, 180)	(130, 202)	(138, 253)

Figure 4.9: Prediction of Tube FVC to days to end point

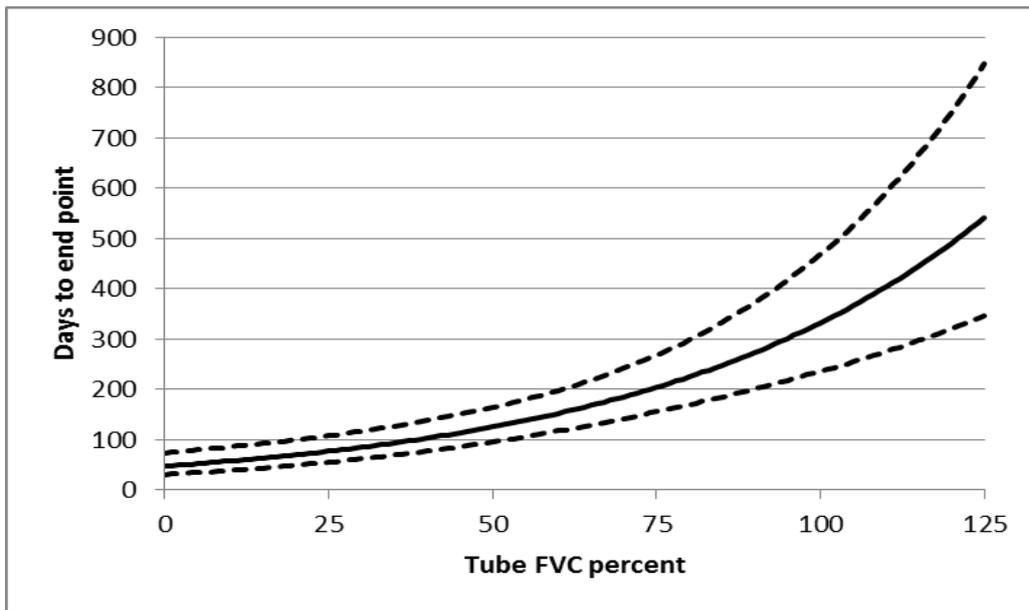


Figure 4.10: Prediction of Facemask FVC to days to end point

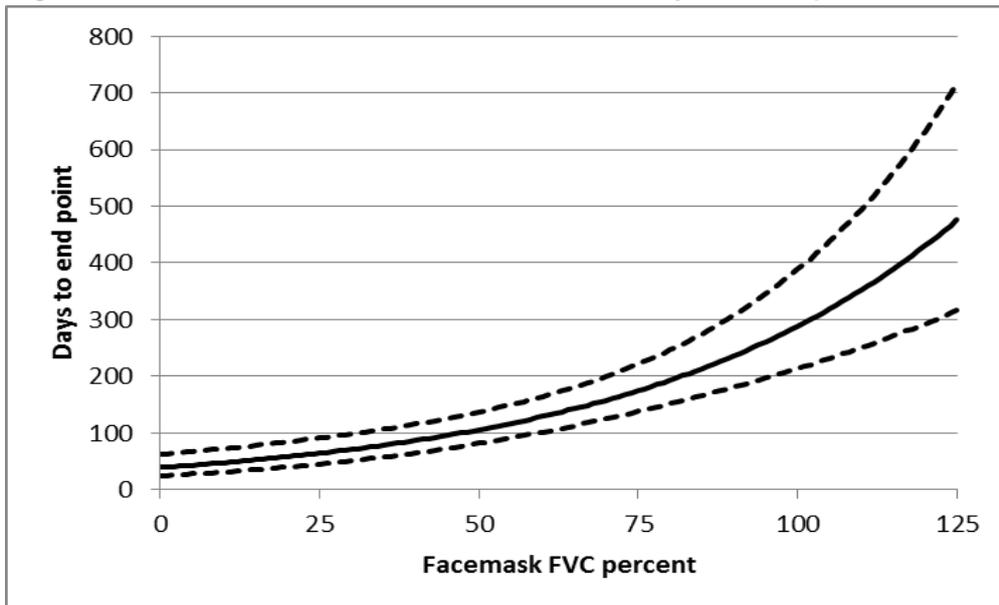


Figure 4.11: Prediction of SNIP to days to end point

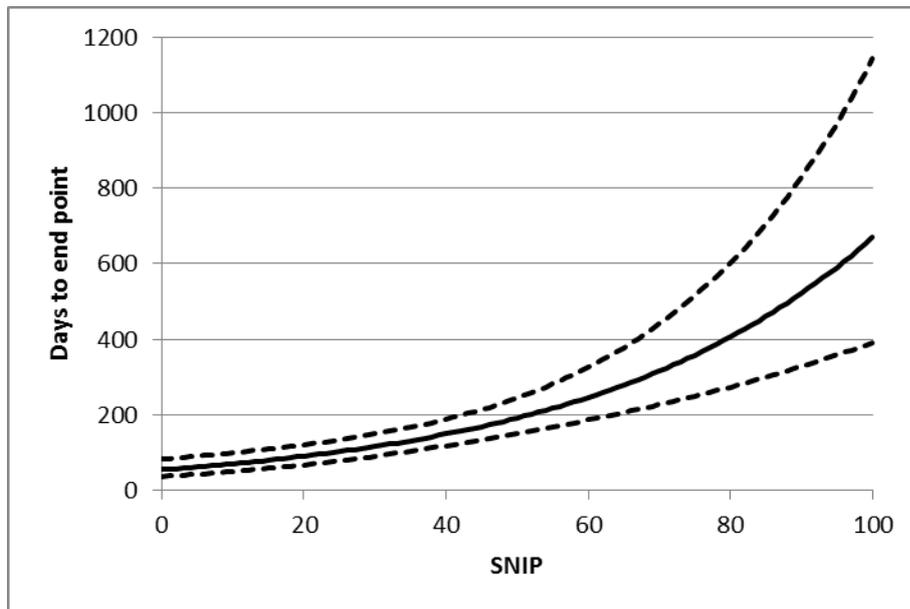


Figure 4.12: Prediction of MIP to days to end point

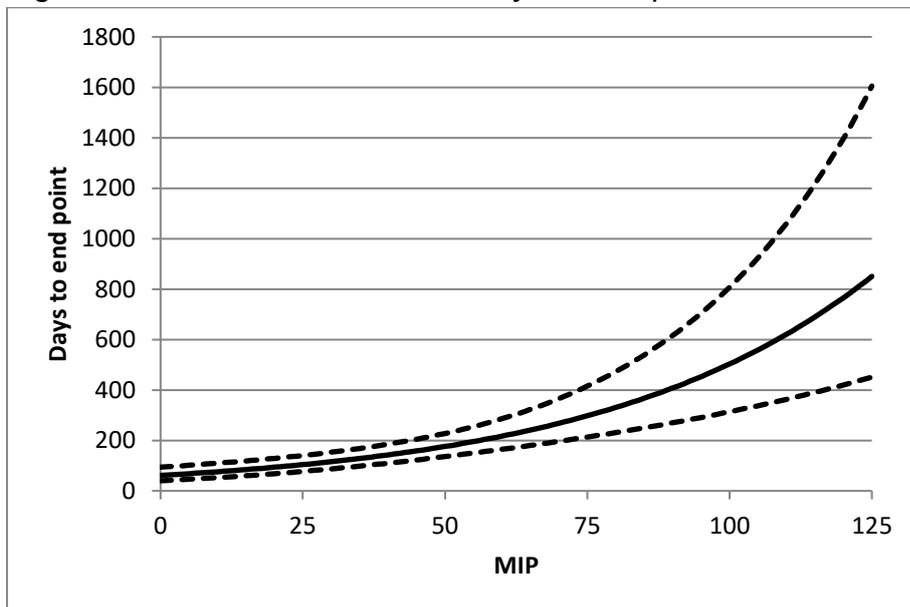


Figure 4.13: Prediction of MEP to days to end point

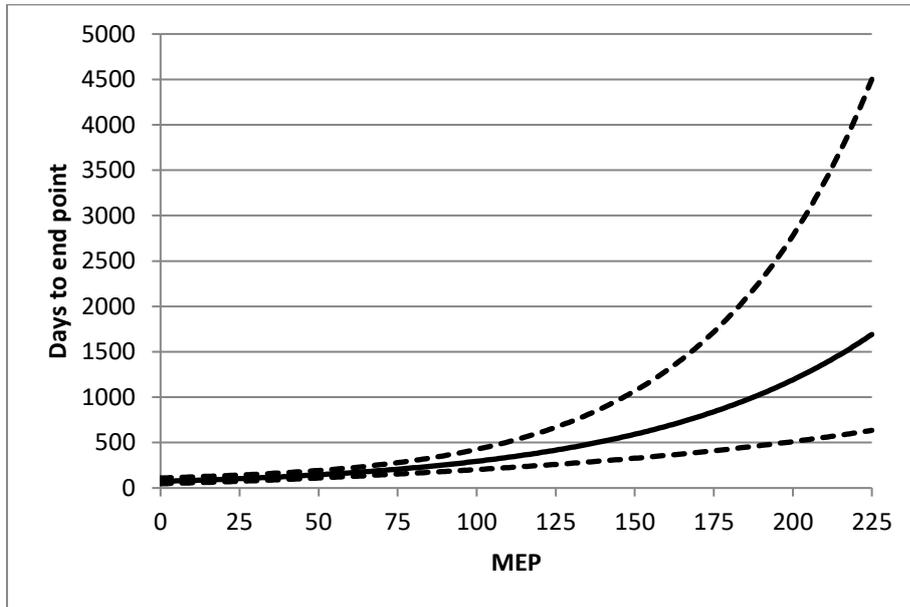


Figure 4.14: Prediction of ALSFRS r score to days to end point

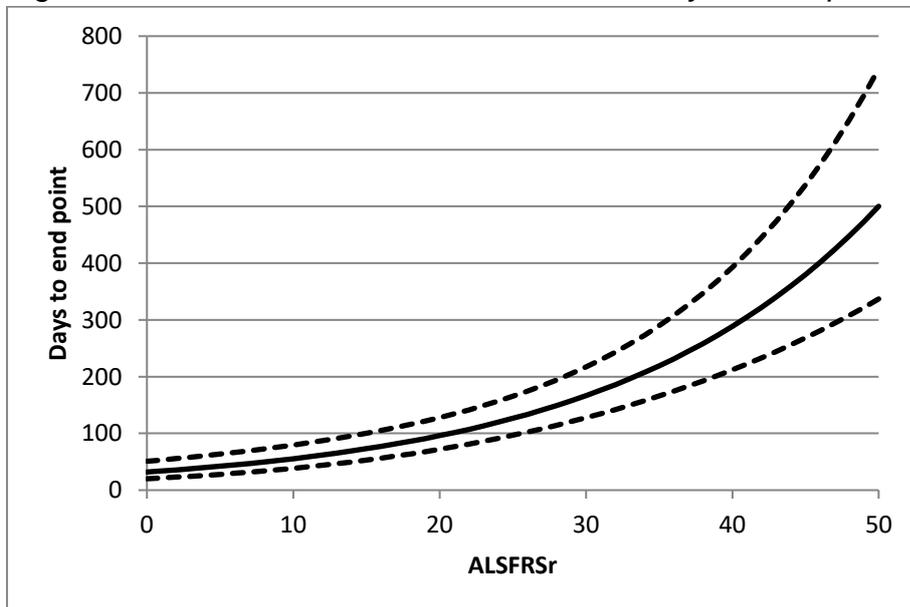
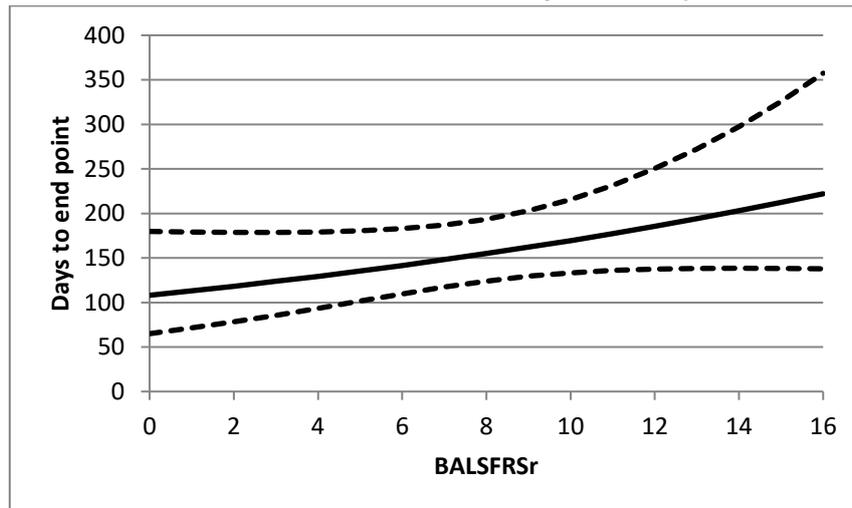


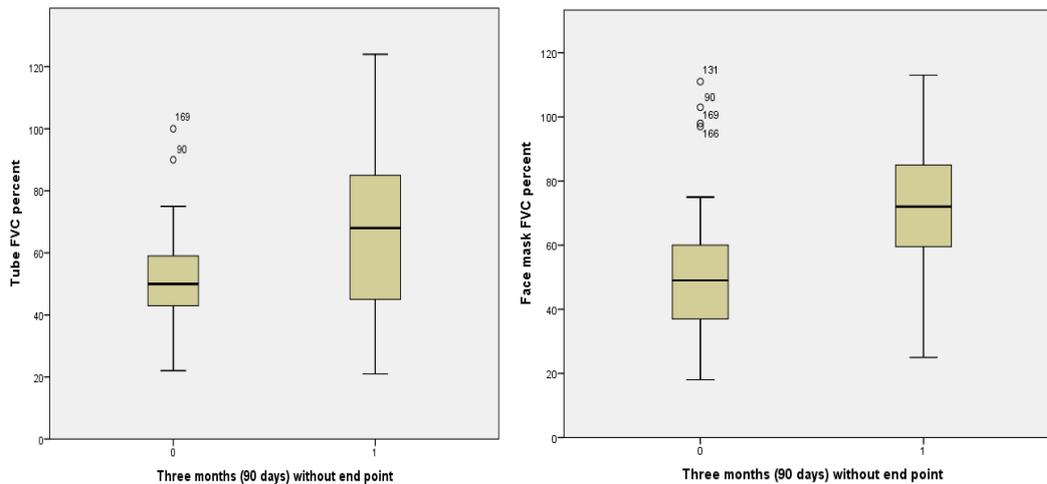
Figure 4.15: Prediction of B ALSFRS r score to days to end point



4.3.7 Can the measures tell us whether a patient will have reached an end within 3 months?

I undertook logistic regression with the outcome variable being whether an endpoint is reached within three months of each measurement. The following box plots (Figure 4.16) show the relationship between this outcome and the tube FVC % predicted and facemask FVC % predicted. The FVC % predicted is higher for those for whom an endpoint is not reached in the next 3 months than for those for whom an endpoint is reached.

Figure 4.16: Box plots showing relationship of reaching end point within 3 months of each measurement



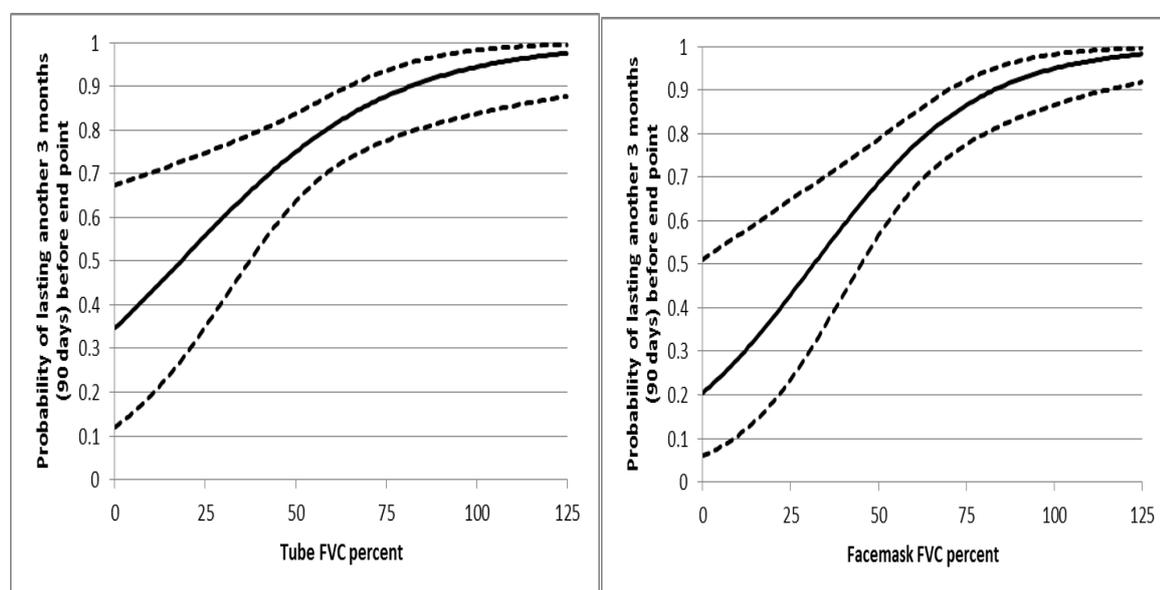
Serial measurements of FVC are therefore predictive if only weakly of ventilatory failure or death in MND patients. When FVC% predicted values fall below a cut-off value for either tube or facemask of around 70% predicted there is a higher likelihood of reaching endpoint of ventilatory failure or death within 3 months. Any patient therefore approaching this level should be carefully assessed for symptoms and signs of ventilatory failure. Patients in whom serial measures of FVC% predicted remain above this cut-off are unlikely to develop hypercapnia and it may be that they could be followed up at an interval greater than 3 months.

4.3.8 Modelling Trajectories

A prediction of whether a patient will have reached an endpoint (death or NIV) within 3 months can be modelled to consider the trajectory of serial measurements. We can construct two models, one for the tube FVC% predicted and one for the facemask FVC% predicted that gives the trajectory of the measurements over time until an endpoint is reached.

In this modelling exercise, tube FVC% predicted is statistically significant in predicting whether an endpoint is reached in the next 3 months ($p= 0.003$). Similarly, facemask FVC% predicted is statistically significant in predicting whether an endpoint is reached in the next 3 months ($p=0.001$). The models are shown graphically in fig 4.17.

Figure 4.17: Modelling trajectories comparing Tube and Facemask FVC% predicted on whether an end point will be reached in 3 months (dotted lines showing 95% confidence interval)



In summary, in the present prospective observational study, we have shown that FVC measured at baseline identified MND patients with early respiratory dysfunction, being a prognostic indicator of NIV or death during follow-up. At the chosen cut point of FVC of 75% there is a statistically significant difference in time to a hybrid endpoint of NIV, death or survival at 1 year. Patients with FVC <75% met the endpoint at “7.7 months” and those with an FVC >75% meeting it at “9.9 months”. There was no statistically significant difference in survival / time to NIV identified between using tube and face mask as the interface when measuring FVC.

Section 4.4 A survey of deaths of people with MND in the era of non-invasive ventilation

From October 2010 to December 2011, 70 deaths were recorded. The mean (SD) age was 67.8 (11.3) years and there were 38 (54.3%) males. Assisted ventilation had been prescribed to 40 (38 NIV & 2 tracheostomy ventilated). Fifteen patients were entirely dependent on NIV. Tube feeding (TF) had been initiated in 44 patients and 36 patients were completely dependent on TF for all caloric and nutritional intake. NIV and TF were discontinued before death in 26 and 14 patients respectively.

It was felt from the start of the dying process that 45% in the NIV group and 38% in the non NIV group died within 24 hours while 40% and 34.5% in NIV and non NIV respectively were thought to be 'dying' for more than 48 hours before death occurred. Palliative care support during the terminal decline prior to death was provided to 45 (65%) patients. Forty three percent of patients were prescribed morphine and/or benzodiazepines in the terminal phase. Advance care plans had been documented in 29 (41%) patients. For those patients, the advance care plan informed decision making in 22 (76%) and matched patient plans in 18 (62%). Thirty-six patients (51.4%) died in an acute hospital, 20 (28.6%) and 11 (15.7%) died at home and hospice respectively.

The commonest certified cause of death was MND (24/70) followed closely by pneumonia (21/70). Respiratory failure was reported in 5 (7.1%). No patient had a post mortem.

Table 4.6: Place of Death

	Frequency	Percent
own home	20	28.5
hospice	11	15.7
residential home	1	1.5
relatives home	1	1.5
hospital	36	51.4
community hospital	1	1.5
Total	70	100.0

Table 4.7: Ventilatory support provided

	Frequency	Percent		
Not known	2	2.8		
Yes	40	57.1	NIV	38
			Tracheostomy	2
No	28	40		
Total	70	100.0		

Table 4.8: Dependence on ventilatory support

	Frequency	Percent
Not provided	30	42.8
Never really used	10	14.2
all night	4	5.7
few hours during day & night	3	4.2
all night with daytime top up	6	8.5
Dependent	17	24.2
Total	70	100.0

Table 4.9: Time from stopping NIV until death

	Frequency	Percent
Not provided	30	42.8
Not stopped	14	20
Few hours	12	17.1
24 hours	3	4.2
more than 24 hours	11	15.7
Total	70	100.0

Table 4.10: Feeding Tube

	Frequency	Percent
Not provided	26	37.1
PEG	32	45.7
RIG	11	15.7
NGT	1	1.4
Total	70	100.0

Table 4.11: FT suspended prior to death

	Frequency	Percent
Not known	4	9.1
not suspended	25	56.8
less than 24 hours before death	9	20.5
less than 7 days before death	5	11.4
greater than 7 days	1	2.3
Total	44	100.0

Table 4.12: Duration of dying process

	Frequency	Percent
Not known	2	2.9
Sudden	16	22.9
Less than 24 hours	13	18.6
24-48 hours	12	17.1
greater than 48 hours	27	38.6
Total	70	100.0

Table 4.13: Cause of Death

Death certificate	Numbers
Pneumonia/chest infections	21
MND	24
Respiratory Failure	5
Swine flu	1
Cardiac	2
Sepsis	1
Pancreatitis	1
Suicide	1
Not known	14

The Wisdom Hospice (WH) cohort had a similar proportion of men and the mean age at death was 66 years. None of the patients had assisted ventilation and only 7 (14%) had TF. The process of dying was 24 hours or less for 24 (48%) patients. They did not record a category of greater than 48 hours but did record a time of death greater than 72 hours in 17 (35%). The commonest recorded cause of death was respiratory failure (96%). Around half (52%) of the patients died at home and 82% of patients received opioids and benzodiazepines during the terminal phase of their illness (Neudert 2001).

Chapter 5: Discussion

Subjects with MND and nocturnal hypoventilation can now be effectively treated with nocturnal ventilatory support. It has so far proven difficult to identify relevant symptoms or a daytime index of pulmonary function which may alert the physician to the presence and severity of ventilatory failure. The appropriate institution of ventilatory support may prevent the development of further respiratory compromise which may ultimately lead to untimely death in this population.

This thesis presents a detailed analysis that compliance with practice parameter recommendations in NICE, serial measurements of respiratory muscle strength and advance planning are important parameters to undertake timely treatment of respiratory failure and ensuring patients spending the terminal phase of their illness in the place of their choice.

5.1 Impact of structured follow-up pathways on access to ventilatory support for people with MND

Assuming an annual incidence of 2.8 per 100000, I estimated 70 new cases of MND per year in our catchment population. My results of the retrospective clinic referral database, demonstrated only 60% of potential patients were being referred and 70% of these were starting NIV. The national average had been reported at 35% of patients with MND being referred for consideration of NIV. This figure included patients from Cambridge, which had a much higher contribution of referrals to the regional respiratory support centre than the average, which would have influenced the national figures (O'Neill 2012). Of those referred 73% were successfully initiated on NIV but this would still mean only 9% of the prevalent population with MND were started on NIV compared to 42% in East Anglia.

The higher referral rates and NIV starters observed in my analysis was likely due to an early implementation of the care pathway which was later published in the NICE guidance of 2010. Implementation of the guidance could have a similar impact across the UK showing an improvement on the position in year 2000, when only around 3% of patients were being offered NIV and only 35% were referred.

One possible result of increased referrals would be a decreased proportion being offered or accepting NIV and wasted healthcare resources. However, this was not our experience. The practice parameter from the American Academy of Neurology, 2009 and NICE guidance, 2010 recommended the need to discuss respiratory function monitoring soon after diagnosis as well as symptoms and signs of respiratory impairment, what to expect, use of investigations and available interventions including NIV. The care pathway established in Cambridge resulted in early referral and thereafter respiratory function monitoring being carried out every 3 months or earlier if there were increasing symptoms.

A multi-disciplinary team of respiratory physician, respiratory specialist nurse, respiratory physiotherapist, respiratory physiologist and speech and language therapist reviewed and supported the patient at each visit. The investigations carried out included measurement of overnight oximetry, respiratory function tests including FVC, SNIP and MIP and ABG's. At each visit, detailed discussions about the impact of NIV, the ensuing risks and benefits were carried out. These discussions provided reassurance and support to patients and their families and were likely to decrease anxiety about NIV. As patients were closely involved in decision making about instigating NIV, along with close monitoring of compliance, this may have been greater at RSSC.

5.2 The Role of Facemask Spirometry in Motor Neurone Disease (MND)

In this study, the mask spirometry produced higher values than the tube when FVC was less than 3 litres (bulbar and non-bulbar) and for all patients with moderate to severe bulbar involvement regardless of the value of FVC. On the scatter plot (fig 4.3) the difference between the FVC measurements of tube and mask decreased as the mean FVC increased, such that correlation was higher for measurements of tube FVC above approximately 3 litres. All 60 patients could perform FVC using a mask, whilst 90% managed with the tube. Six patients, who produced a mean FVC of 1.45 (0.68) litres with the mask, could not produce any result with tube spirometry. However, at higher forced expiratory volumes, tube spirometry tended to produce higher values. This study showed that using a facemask for screening purposes was a valid and easy

method to measure respiratory function in MND. Comparison between the conventional tube mouthpiece with the facemask connection to the instrument (handheld spirometer) showed that they cannot be used interchangeably.

5.3. Face mask Spirometry as a prognostic tool indicator in Motor Neurone Disease (MND)

Ventilatory failure was the most frequent cause of death in MND. Measuring pulmonary function as an indicator of diaphragmatic function provided prognostic information but raised doubts about the likely time to developing ventilatory failure and consequently mandated frequent surveillance visits for these patients. Whilst it is possible that no single test would predict accurately when assisted ventilation would be needed (Miller, 1999), a more accurate measure of lung function in this patient population may contribute towards the goal of instituting NIV at the appropriate time. Further studies to identify whether mask spirometry had better predictive power for time to ventilatory failure and the need for NIV were justified by these results.

Results of my prospective observational study, has shown that FVC measured at baseline, identified MND patients with early respiratory dysfunction, as a prognostic indicator of NIV or death during follow-up. At the chosen cut point of FVC (75% of predicted) there was a significant difference in time to a hybrid endpoint of NIV, death or survival at 1 year. Patients with FVC <75% reached the endpoint >2 months earlier than those with an FVC >75%. There was no difference in survival / time to NIV between patients using tube and face mask when measuring FVC.

For all subjects, the FVC by facemask measurement was higher than that for tube measurements. This predicted difference was 8.8% and was statistically significant ($p < 0.001$). This further confirmed the findings of chapter 4, which showed that the mask produced higher values than tube when FVC is less than 3 litres (bulbar and non-bulbar) and for all patients with moderate to severe bulbar involvement regardless of the value of FVC. As most patients were contributing more than one point on the Bland Altman plot (fig 4.6), we must interpret it with caution. For this reason, the analysis to find out if FVC less than 3 litres was associated with higher values using a facemask interface, was not repeated for the present study.

Population based studies have previously shown that bulbar onset disease is associated with a worse prognosis than spinal onset in MND (Chio 2009; Del Aguila 2003). Results from a population based study suggested that the site of onset did not influence the risk of early death, defined as within 12 months (Wolf 2014). Another multicentre longitudinal cohort study, based on follow up over 30 months, revealed a significant difference of survival between limb onset and bulbar onset group even when gastrostomy placement and NIV were considered as events (Clavelou 2013). My results suggest a trend towards better prognosis for subjects with spinal onset of disease in keeping with previously published data, but the study was not powered to look at this aspect of prognosis. The present study also did not record the site of onset of disease but classified subjects as moderate to severe bulbar (bulbar onset) based on bALSFRS r score during assessment at entry.

Neither tube nor facemask FVC (% predicted value at first measurement) were found to have a significant relationship with the time to the end points. While SNIP and MIP (at first measurement) had a weak but significant relationship with time to NIV or death. Previous studies have looked at threshold SNIP pressures at baseline to identify risk of NIV or death in MND patients (Capozzo 2014; Morgan RK 2005). Lyall et al. (2001), looked at the predictive power of SNIP to identify the presence of hypercapnoea. Other assessment tools such as MEP, ALSFRS r score and BALSFRS r score did not predict prognosis at first measurement in our cohort.

In the present study, each test of respiratory muscle strength was analysed individually with simple regression analysis. Serial measurements of tube FVC % predicted, facemask FVC % predicted, SNIP, MIP, MEP and ALSFRS r score demonstrated as variables, some predictive power to detect the primary or composite endpoint of ventilatory failure, need for NIV or death. However, none of them gave predictions with much accuracy as the confidence intervals used in the modelling were wide, reflecting this lack of accuracy.

The present study whilst comparing the role of tube and facemask spirometry, also aimed to identify the variable that should be monitored regularly to support and adapt management of MND. None of the variables performed particularly well, which shows

that the progression of weakness and the risk of death in MND do not appear to be related in a linear way with any measure of respiratory muscle strength.

Previous studies have shown similar findings of poor sensitivity and specificity in predicting the onset of ventilatory failure in MND (Lyll 2001, Miller 1999). Whilst several studies have looked at the role of various respiratory muscle strength measures at the impact on survival, very few have prospectively assessed the progression rate of such measures.

Clavelou et al (2013) suggested the decrease in slow VC was similar in bulbar and limb onset MND and along with weight loss led to a better discrimination between MND patients at inclusion and during long-term follow up. In the present study, I have plotted serial measurements of tube and facemask FVC % predicted against time before a composite endpoint.

In a logistic regression analysis patients with higher FVC % predicted, took longer before reaching the defined composite endpoint. My results demonstrated that serial measurements of tube or facemask FVC correlated with progression to respiratory failure or death. Moreover, in the later stages of the disease, the facemask FVC could still be performed by 98% of patients. My results established that tube FVC % less than 50% and face mask FVC % less than 58% were associated with a likelihood of developing respiratory failure or death within 3 months.

Prior studies attempting to predict deterioration in respiratory muscle strength have reported that FVC % predicted may be difficult to test accurately in the later stages of the disease due to decreasing facial muscle strength, lack of coordination and difficulty in performing repeated maximal voluntary efforts, irrespective of mask or tube. Similar observations were identified regarding SNIP, MIP and MEP.

My cohort did show that using a face mask as an interface in performing FVC was a reliable surrogate of respiratory muscle strength in MND and could be performed in the presence of advanced disease, giving prognostic information even at the point of developing ventilatory failure or death. My observations may therefore have distinct implications in choice of serial measurements affecting clinical practice for patient management in MND.

An unexpected finding from this study was the number of people who died between study visits, before they had developed evidence of ventilatory failure. Most were certified simply as having died from MND with no information of the mode of death. Some patients were very likely to have died of pneumonia due to aspiration in the context of bulbar dysfunction. A proportion of patients may have died from asphyxiation in the context of inspissated respiratory secretions with poor cough mechanics.

Other causes of death such as pulmonary embolism cannot be excluded in the absence of post mortem examinations. These deaths would not be as closely related to worsening diaphragm function and the risk of ventilatory insufficiency and therefore may not be predicted by changes in FVC. This may explain why none of the respiratory muscle tests that we performed had a close relationship to time to the primary endpoint.

Whatever the cause of death, it poses the question as to whether the 3-month surveillance window was appropriate. Partly in response to this result, further data were collected in the respiratory support centre (Thaivalappil 2014) auditing all deaths in a year to see whether the unselected clinic population showed similar results. In their audit 17% died without being offered NIV compared to our study where 17 of 66 (26%) died without being offered NIV, in the duration of the study. Others remained at risk of this outcome at the end of the study as they were still alive and not on NIV. A larger prospective study of unselected patients is required to review the utility of the 3 month follow up interval in the care of people living with MND.

In conclusion, this study has reinforced that FVC whether measured by tube or mask is a reliable surrogate of respiratory muscle strength in MND. With either interface, spirometry on first assessment of FVC > 75% is correlated with longer survival. Although mask spirometry showed higher values, which we can assume were more accurate, this technique did not show a stronger relationship with the composite endpoint than conventional tube spirometry. Serial measurements give extra information and an increasing proportion of patients were only able to perform spirometry with the mask as the follow up interval progressed. It is likely that people with FVC > 75% predicted at any point in the disease course could be followed up at

an interval longer than 3 months but this will need validation in another cohort before changes to practice are recommended. O'Neill et al (2012) in their survey identified that regular assessment of respiratory symptoms and function is associated with increased use of elective NIV and in patients with good bulbar function, improved survival. The importance of this is further augmented by Aboussouan et al (2001) who identified improved tolerance to NIV in patients with higher FVC and MEP.

5.4. A survey of deaths of people with MND in the era of non-invasive ventilation

My data showed that there was no trend to a prolonged death in patients with MND using NIV and TF. The anxiety amongst physicians that there would be a large cohort of patients who were ventilator dependent having a prolonged and distressing death was not borne out by our data. Of those patients using NIV the majority (26/40) elected to discontinue NIV in the hours or days before death. Some patients who were dependent on NIV may wish for it to be stopped because they could no longer tolerate it or due to deterioration in their quality of life. Some would have made written statements as advance directives for withdrawal. Previous literature suggests that while patients on assisted ventilation wanted to issue a directive in advance about circumstances in which they would wish to stop ventilation, few had the opportunity to do so (Moss 1996). Our experience was that all concerned (patient, family and doctors) found withdrawal of ventilation challenging. Whitehead et al (2011), explored end of life decision making with patients and with bereaved carers in Preston, UK and identified a need for shared decision making with more information provided to patients and their carers. Gannon et al (2005), noted a high level of distress for staff and change in their behaviour in a hospice setting where they considered accepting patients with MND for withdrawal of NIV. There is very little evidence discussing the practical, ethical and clinical aspects of withdrawal of NIV in MND. There is some published evidence on the withdrawal of ventilation for conscious patients with prolonged assisted ventilation (Oppenheim 2010).

A study aiming to explore the doctor's perspective especially with issues relating to withdrawal of NIV at the request of a patient with MND, identified considerable challenges faced by palliative care doctors (Faull 2014). Key issues identified included practical, ethical and emotional challenges. The survey identified the huge time and

planning burden involved in the process and the difficulties of communication with patients especially in terms of timing, sensitivity and in the absence of any prior discussions or planning. There was the added ethical issue of appropriateness of withdrawal and the need for the intentions to be clear to all. Many respondents were clearly concerned that while NIV withdrawal was not euthanasia, the process could be identified as causing the death and thus potentially open to external criticism. The fact that withdrawal of treatment is allowing death to occur, rather than causing the death may not be fully appreciated by all involved, even within the healthcare team. These issues can result in emotional challenges especially managing the emotions of others and conflict resolution (Faull 2014). Thus, clarity about advance wishes to understand in what circumstances would patients no longer want to continue with NIV is a sensitive but extremely important component of multi-disciplinary care for MND patients.

The European Association of Palliative Care Taskforce in collaboration with the European Academy of Neurology undertook a review of the literature to establish an evidence based consensus for palliative and end of life care for patients with progressive neurological disorders and their families (Oliver, 2016). The development of a fully evidence based guideline was not feasible as there was little strong evidence in the literature. Whilst early palliative care in cancer is associated with increasing length of survival, there is limited evidence to suggest that this is the case in MND (Bakitas 2009). A specialised palliative care team had been shown to improve family satisfaction and symptom management (Zimmermann C, 2008). The lack of evidence does not necessarily reflect the actual strength and usefulness of this intervention but merely the absence of robust published literature.

Advance care plans remained patchy with only 41% of patients having written documentation in this series. The recent NICE 2016 guidance further identified the lack of evidence on providing information to patients and family using NIV in relation to end of life care. It also suggested discussion regarding withdrawal of care should be initiated either before or as NIV is started. Further discussion should be instigated if the patient or family request or if there has been further clinical deterioration in the patient. In my study, advance care plans informed decision making in 76% and matched patient plans in 62% of those who made them. In the real clinical practice, the advance care plan decisions need to be discussed with the patient and their family

in early with clarity and gain agreement in the MDT about the rationale for NIV withdrawal. The European Association of Palliative Care Taskforce recommended an early involvement of a MDT team consisting of a palliative care physician, nurse and social worker or psychologist in the care of an MND patient. This allows an open approach and clear discussion of the setting of goals and options of therapy and management. Early advance care planning is strongly recommended, especially when impaired communication and cognitive impairment is possible as part of disease progression as seen in MND (Bede P, 2011). There is limited evidence of the effectiveness of this multi-disciplinary approach but in Ireland it was found that MND patients had a better prognosis with a median survival of 7.5 months longer than patients seen in primary care or within a general neurology clinic (Traynor 2003).

Our survey has shown that almost half of the patients who died at home or in a hospice were provided support in the form of opioids and benzodiazepines in the terminal phase. The recognition of the final stages of dying over the last few days of life can be useful in allowing the focus to be clarified towards a palliative care approach. There is evidence to suggest that regular review of patient care helps identify the final stages of life and encourages the incorporation of appropriate multidisciplinary management of the patient and their family including the management of symptoms, provision of medications, psycho-social support of the patient and their family and consideration of spiritual issues (Verbeek 2008). This survey was still a very superficial exploration of this area of practice and further research into the terminal phase of decline and the psychological challenges faced is warranted.

The cause of death in the WH cohort was respiratory failure in 96% of the cases. With the introduction of NIV this reduced in a subsequent study to 31% (Chaudri 2003). Our data revealed a further reduction in respiratory failure as a cause of death to 7%. The commonest reported cause of death in our cohort was MND.

We know that a proportion of patients withdrew NIV and TF prior to their death and so probably some did die of respiratory failure. It comes down to semantics as to how such a death should be recorded. The quality of death certificates were poor with little detail on the immediate causes of death. This is another potential area of study. The doctors certifying the deaths in the current series may have considered that since the

respiratory failure could have been treated this was not the cause of death, rather it was MND, which caused the patient to discontinue NIV that caused death.

In comparison to the WH cohort, the use of NIV and TF had increased in my cohort. The number of patients dying at home and hospice remained about the same over the last decade. My data revealed that almost half the patients were still admitted as an acute admission to hospital. The recognition of the deterioration in the disease process near to the end of life is essential in enabling provision of appropriate care and support for patients and family. This survey had identified that some of the challenges of end of life care can be addressed by the development of guidance on integration of palliative care in the care of patients with progressive MND can encourage open discussion about the dying process especially with regards to wishes to restrict treatment and interventions (Oliver 2016). Education, careful planning of care and targeted MDT discussions are each important component of any MND service in developing a clear and precise pathway to patients living with MND and planning proactively for the approach of the end of their end of life.

Chapter 6: Conclusions

My retrospective review of services in East Anglia has identified the impact of a structured pathway for referrals and consequent uptake of NIV. It has shown higher referral rates and a greater proportion of NIV starters as compared to the national average, with 60% of people with MND being referred and 70% of these starting NIV.

In my study, a mask interface for spirometry gave higher values than tube (when FVC was less than 3 litres; bulbar and non-bulbar) and for all patients with moderate to severe bulbar involvement, irrespective of the value of FVC. My study demonstrated that tube and mask connections to the spirometer cannot be used interchangeably in people with MND.

An accurate measure of respiratory muscle weakness may contribute towards the goal of instituting NIV at the appropriate time. My study did not find any significant additional benefit from using a facemask as an interface compared to a tube for the measurement of FVC towards the goal of instituting NIV at the most appropriate time or predicting death.

My study has shown that serial FVC (% predicted) can be used as a prognostic tool to appropriately identify patients at risk of ventilatory failure. The study failed to identify any superiority of other measures for respiratory muscle weakness routinely used in clinical practice such as SNIP, MIP and MEP over spirometry as a surveillance tool.

However, my results show that facemask spirometry was the most likely measure of respiratory muscle strength to be successfully performed at the later stages of the disease. The role of ALSFRS r score was also reviewed and did not predict the onset of respiratory failure.

My study has demonstrated that the rate of decline of serial FVC measures has some ability to predict the likely onset of ventilatory failure irrespective of non-bulbar or bulbar involvement within a specified time frame, once the trigger value for tube % FVC and facemask % FVC have been crossed. My study results established that tube FVC % less than 50% and face mask FVC % less than 58% is associated with a likelihood of developing respiratory failure or death within 3 months.

From modelling both tube and mask FVC percent were statistically significant in predicting whether an endpoint is reached in the next three months. It is likely that people with FVC > 75% predicted at any point in the disease course could be followed up at an interval longer than 3 months.

My findings have implications for clinical practice and suggest the present NICE guidance for follow up and assessment of patients with MND could reasonably be altered to ensure more frequent and appropriate reviews once tube FVC percent predicted drops below 50% and if facemask interface is used, the FVC percent predicted is below 58%.

My prospective survey has confirmed that the dying process is not prolonged for patients who have used NIV at home. Many patients discontinue NIV prior to their terminal event. Many patients died at home or in a hospice and were provided with adequate support and planning for end of life to ensure as peaceful a death as possible. The quality of death certificates is poor with little detail on the immediate causes of death.

The data in this thesis have highlighted the role of a structured referral pathway for respiratory assessment early in the disease process along with clinical vigilance, serial measurements of vital capacity and advance planning for managing end stage respiratory problems in MND patients.

Areas for future study

Accurate prediction of survival in people with MND would be of great use to clinicians and to the person with MND, their families and carers. Accurate predictions of survival would enable professionals to create and deliver more effective management and care plans and provide services when most appropriate for example specialist palliative care. The tests of respiratory muscle weakness with the greatest discriminatory power to predict hypercapnia are required to determine their role in the management of MND patients especially in those with severe bulbar abnormality.

Appendix 1

List of Publications & Abstracts:

Banerjee SK, Davies MG, Sharples L, Smith IE. The role of facemask spirometry in motor neuron disease. *Thorax* 2013; 68(4): 385-6.

Banerjee SK, Smith IE, Davies MG, Chadwick R. Role of facemask spirometry in motor neurone disease (MND). *European Respiratory Journal* Sep 2011; 38(55): p2136

Banerjee SK, Davies MG, Smith IE. Impact of structured referral and follow up pathways on access to ventilatory support for people with motor neurone disease (MND). *Thorax* 2011; 66: A178.

Banerjee SK, Davies MG, Smith IE. Motor neurone disease (MND); a survey of deaths in the era of non-invasive ventilation. *Thorax* 2011; 66: A178.

RESEARCH LETTER

The role of facemask spirometry in motor neuron disease

Respiratory failure is the most frequent cause of death in people with motor neuron disease (MND). Vital capacity and maximal inspiratory and expiratory mouth

pressures are the methods most commonly used to assess respiratory muscle impairment. Forced vital capacity (FVC) at diagnosis, and the rate of decline, are predictors of survival. An FVC of <50% predicted is proposed by the National Institute of Clinical Excellence (NICE, UK) as an indication of the need for evaluation for non-invasive ventilation.¹

For many patients with MND who have facial or bulbar muscle weakness,

standard spirometry with a mouthpiece or tube is inaccurate due to mouth leaks as they are unable to effectively seal their lips around the tube/mouthpiece. Sniff nasal inspiratory pressure (SNIP), and maximal inspiratory mouth pressure (PiMax) may be preferable, but are less widely available and not always successful.² Mask spirometry has been used but not validated in MND² and in healthy volunteers, tube spirometry gives greater

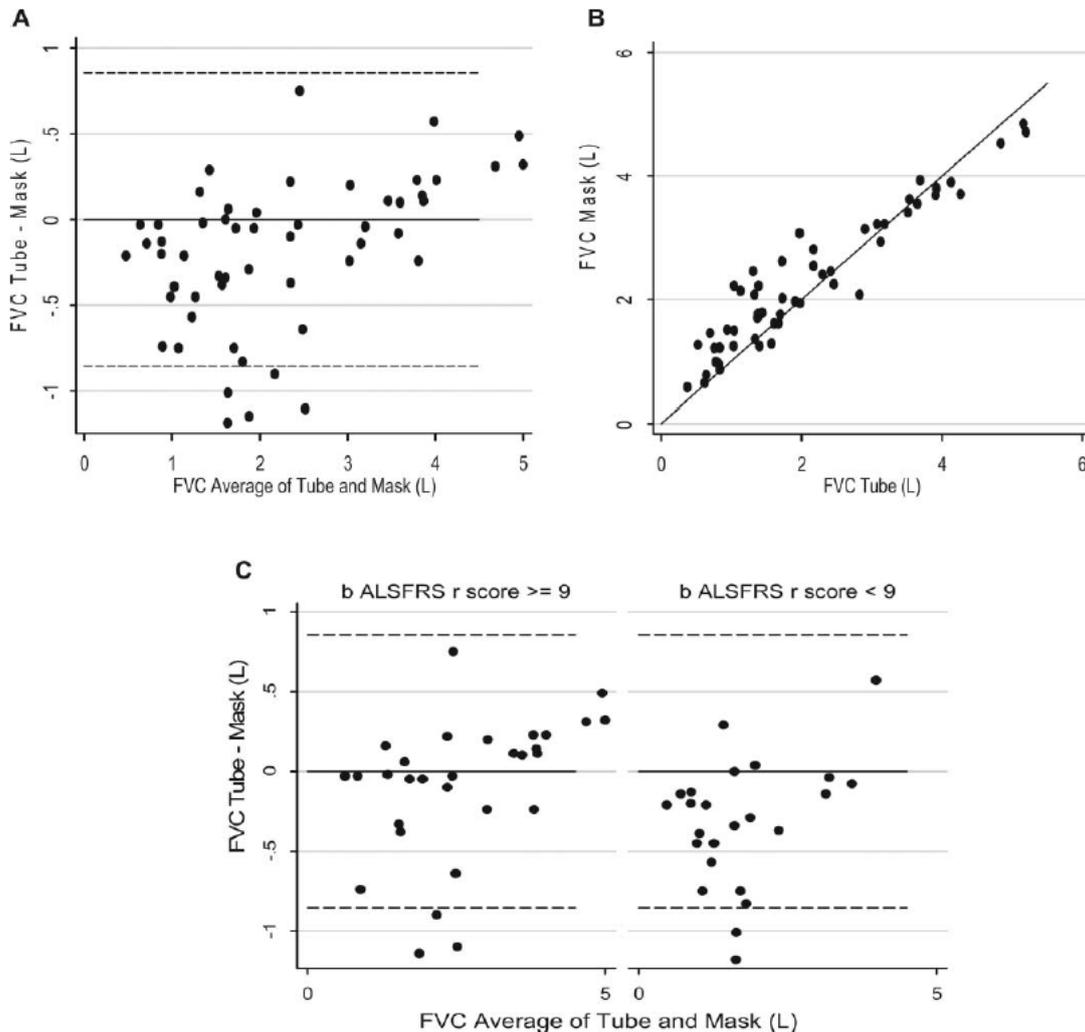


Figure 1 (A) Bland-Altman plot showing that mask readings were higher in 36 cases, equal to the tube in one and lower in 17. The mask gave significantly greater values for FVC than the tube, the mean difference was 0.19 l (95% CI 0.07 to 0.31; $p=0.0024$, paired Student *t* test). In five subjects, the difference was >1 l (B) Linear regression fitted to predict mask results from tube results gives: Mask (litres) = $0.61 + 0.80$ Tube (litres) ($R^2=90\%$). The equivalence line (intercept) is >0 and slope <1, that is estimated mask FVC is higher for low values and lower for high values (above approximately 3 l). (C) For patients with both FVC measurements, the mask value was higher or equal in 21/24 (88%) of cases with bulbar disease, and 15/30 (50%) with non-bulbar disease (Fisher's exact test 0.004).

PostScript

values than a mask.³ We compared mask and tube interfaces for spirometry in subjects with MND.

Consecutive patients were approached in our MND clinic. Exclusions included continuous ventilator dependence, tracheostomy and standard contraindications for spirometry. Bulbar involvement was quantified using the first three questions of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (b ALSFRS r score) and a score <9/12 defined important bulbar symptoms. FVC was measured with a calibrated hand-held spirometer via a tube or a face mask (Leardal, child No.4) in randomised order. PiMax and SNIP were also recorded by trained technicians (methodology explained in greater detail in on-line supplement).

Of 73 subjects approached, four declined consent, nine were excluded and 60, (36 men), mean age 64.7 (SD 10.5) years, were recruited. The mean b ALSFRS r score was 7.8 (SD 3.3) and half the subjects scored <9. The mask was preferred by 44 subjects. McNemar's test was used to compare the number of patients who were able to provide spirometry results with each interface. Successful measurement was achieved for mask spirometry in all 60, tube spirometry 54 (McNemar $p < 0.001$), SNIP 51 and PiMax just 45 subjects. Compared with tube spirometry, the mask gave significantly greater values in those who managed both techniques (figure 1A). The difference was most marked at low volumes (figure 1B), and in people with bulbar symptoms (figure 1C). The six patients who could not record anything with tube spirometry were measured to have a mean FVC of 1.45 (SD 0.68) litres with the mask.

Respiratory muscle strength is a key prognostic factor in MND, and survival is

measured in weeks when patients develop ventilatory failure.⁴ NICE guidelines recommend follow-up every 3 months, but a balance is needed between frequent disruptive clinic visits, and the risk of missing the opportunity to start NIV which may improve survival and quality of life.⁴ It is possible that if the measured FVC is artefactually low, patients may be started prematurely on NIV. In Duchenne's Muscular Dystrophy this was shown to be associated with an adverse outcome.⁵ There are no data for MND, but it would seem to be at least a waste of a resource, and could negatively impact the patient's quality of life. In this study, regression models (figure 1B) showed that predicted mask spirometry measurements of FVC are higher for FVC <3 L, and in patients with moderate to severe bulbar involvement. Mask spirometry was achieved by more subjects than tube spirometry, SNIP or PiMax. Further studies to identify whether mask spirometry has better predictive power for time to ventilatory failure and need for NIV are justified.

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► Additional material is published online only. To view this file please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2012-201804>).

All authors had full access to all the data in the study, and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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sequences for mask and tube spirometry. We are grateful to all subjects who took part in this study.

Contributors SB, MD and IS designed the study and obtained ethical approval. LS completed the statistical analysis and generated the figures. SB, MD and IS co-wrote the manuscript. All authors approved the final version.

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Competing interests None.

Patient Consent Obtained.

Ethics approval The study was conducted with approval of the Cambridgeshire III Research Ethics Committee (REC ref. no: 10/H0306/9).

Provenance and peer review Not commissioned; externally peer reviewed.

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- 3 Wohlgenuth M, Van der Kooi E, Hendriks J, *et al*. Face mask spirometry and respiratory pressures in normal subjects. *Eur Respir J* 2003;**22**:1001–6.
- 4 Bourke S, Tomlinson M, Williams T, *et al*. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis. A randomised controlled trial. *Lancet Neurol* 2006;**5**:140–7.
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Poster sessions

Results Mean age was 50.6 (21.3). 44% male. 53% used NIV at night. All were naïve to NIV during exercise. NIV increased cycle time by 146 s (105%). All stated they would be prepared to repeat this type of exercise (Abstract P269 table 1).

Conclusion NIV is well tolerated, feasible and significantly increases exercise capacity in patients hospitalised with an acute exacerbation of respiratory disease.

P270 MOTOR NEURONE DISEASE (MND): A SURVEY OF DEATHS IN THE ERA OF NON-INVASIVE VENTILATION

doi:10.1136/thoraxjnl-2011-201054c.270

S K Banerjee, M G Davies, I E Smith. *Papworth Hospital NHS Foundation Trust, Papworth Everard, UK*

Background The care of patients with MND has changed radically with greater uptake of non-invasive ventilation (NIV) and tube feeding (TF). Community colleagues in our region have expressed anxiety about how such supported patients might die and in particular whether the process of dying might be prolonged. We sought to investigate these concerns.

Methods A structured questionnaire was distributed to involved clinicians, community practitioners and MND care co-ordinators. They completed questionnaires for patients dying under their care, where necessary/appropriate with the input of family members. The data are compared with an historical, retrospective series (n=50) reported by the Wisdom Hospice (WH).¹

Results From October 2010 to June 2011, 51 deaths were recorded (mean age 67 years, 29 men). Thirty deaths were in an acute hospital, 15 at home, six in a hospice or community hospital. 16 patients had advance care plans (ACP) of whom 10 died in their "preferred place". Assisted ventilation had been prescribed to 30 and tube feeding to 37 patients. NIV and TF were discontinued before death in 13 and five patients respectively. For 22 patients the process of dying was sudden or <24 h in duration. NIV was not associated with a prolonged process of dying. The commonest certified cause of death was an unqualified "MND", with pneumonia reported in seven cases. No patient had a post mortem examination. The WH cohort had a similar proportion of men and the mean age at death was 66 years. None of the patients had assisted ventilation and only seven had tube feeding. The process of dying was 24 h or less for 24 patients. The commonest recorded cause of death was respiratory failure (22 individuals).

Conclusion These preliminary results show that there is no trend to prolonged deaths in patients with MND using NIV and TF. Several patients have elected to discontinue NIV. ACP's in our region remain patchy and require further attention. The quality of death certification is poor with little detail on the mechanism of death.

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P271 IMPACT OF STRUCTURED REFERRAL AND FOLLOW-UP PATHWAYS ON ACCESS TO VENTILATORY SUPPORT FOR PEOPLE WITH MOTOR NEURONE DISEASE (MND)

doi:10.1136/thoraxjnl-2011-201054c.271

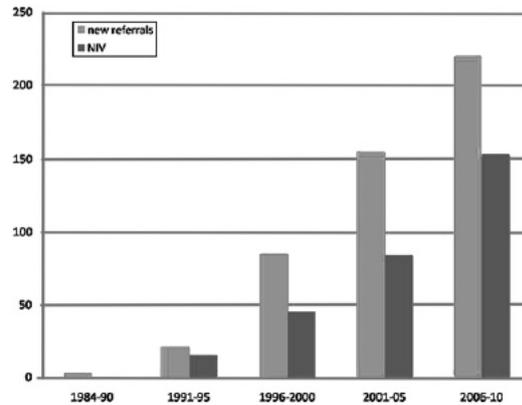
S K Banerjee, M G Davies, I E Smith. *Papworth Hospital NHS Foundation Trust, Papworth Everard, UK*

Introduction Attitudes to surveillance for and treatment of ventilatory failure among people with MND have changed over several years. In the UK this culminated in the publication in July 2010 of National Institute of Clinical Excellence (NICE) guidance designed to increase access to non-invasive ventilation (NIV). The services

offered in our respiratory unit have evolved on the basis of published evidence in advance of formal guidelines. We examined the impact of compliance with practice parameter recommendations in NICE to our referral numbers and uptake of NIV in East Anglia.

Methods A retrospective review of number of referrals and new NIV starters from 1984 to 2010 in a regional respiratory support unit. Between 2001 and 2005 the MND Association helped to establish a care centre in Cambridge and closer working was established with the respiratory service. From 2006 the default position was to offer all patients newly diagnosed with MND a respiratory assessment and structured 3 monthly follow-up appointments in a fashion subsequently detailed in the NICE guidance.

Results The numbers of new referrals and people starting NIV are shown in Abstract P271 figure 1. Between 1984 and 2000 there was slow growth but the mean annual values were just seven referrals and four new NIV starters (57%). With closer working between neurologists in the care centre and the respiratory unit between 2001 and 2005 mean referral numbers increased to 31 with 17 new NIV starters (55%) per year. With default referral and 3 monthly reviews the number referred grew to 44 with around 31 NIV starters per year (70%).



Abstract P271 Figure 1

Conclusion With an estimated population of 2.5 million in East Anglia, and an annual incidence of 2.8 per 100 000 we estimate 70 new cases of MND per year. Around 60% of patients are therefore being referred and 70% of these are starting NIV. Implementing the NICE guidance could have a similar impact across the UK, a great improvement on the position in 2000 when only around 3% of patients were being offered NIV.¹

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P272 A 7 YEAR RETROSPECTIVE EVALUATION OF INITIATION OF LONG TERM NON-INVASIVE VENTILATORY SUPPORT FOR MOTOR NEURONE DISEASE

doi:10.1136/thoraxjnl-2011-201054c.272

J Palmer, P Hughes. *Plymouth Hospitals NHS Trust, Plymouth, UK*

In 2010 NICE (1) published its guideline for the use of non-invasive ventilation in the management of motor neurone disease (MND). We have offered long-term non-invasive ventilation (NIV) in this

Appendix 2: Amyotrophic Lateral Sclerosis Functional Rating Score (revised)

Amyotrophic Lateral Sclerosis Functional Rating Score (ALSFRS r score)

SPEECH

4. Normal speech
3. Detectable speech disturbance
2. intelligible with repeating
1. speech combined with non-vocal communication
0. loss of useful speech

SALIVATION

4. Normal
3. slight but definite excess of saliva in mouth, may have night time drooling
2. moderately excessive saliva
1. marked excess of saliva with some drooling
0. marked drooling, requires constant tissue

SWALLOWING

4. Normal eating habits
3. early eating problems, occasional choking
2. dietary consistency changes
1. needs supplemental tube feedings
0. NPO (exclusively parental or enteral feedings)

HANDWRITING

4. Normal
3. slow or sloppy, all words legible
2. not all words legible
1. able to grip pen, unable to write
0. unable to grip pen

CUTTING FOOD AND HANDLING UTENSILS

(patients without gastrostomy)

4. Normal
3. somewhat slow and clumsy, needs no help
2. can cut most foods, slow of clumsy, some help needed
1. foods cut by someone else, can still feed slowly
0. needs to be fed

CUTTING FOOD AND HANDLING UTENSILS

(patients with gastrostomy)

4. Normal
3. clumsy, able to perform all manipulations
2. some help needed
1. provides minimal assistance to caregiver
0. unable to perform any aspect of task

DRESSING AND HYGIENE

4. Normal
3. independent self care with of decreased efficiency
2. intermittent assistance or substitute methods
1. needs attendant for self care
0. total dependence

TURNING IN BED AND ADJUSTING BED CLOTHES

4. Normal
3. somewhat slow or clumsy, needs no help
2. can turn alone or adjust sheets with great difficulty
1. can initiate, cannot turn or adjust sheets
0. helpless

WALKING

4. Normal
3. early ambulation difficulties
2. walks with assistance
1. non-ambulatory functional movement only
0. no purposeful leg movement

CLIMBING STAIRS

4. Normal
3. slow
2. mild unsteadiness or fatigue
1. needs assistance
0. cannot do

DYSPNOEA

4. None
3. occurs when walking
2. occurs with one more more: eating, bathing, dressing
1. occurs at rest, either sitting or lying
0. significant difficulty, considering mechanical support

ORTHOPNOEA

4. None
3. some difficulty sleeping, d/t shortness of breath, does not routinely use >2 pillows
2. needs extra pillows to sleep (>2)
1. can only sleep sitting up
0. unable to sleep

RESPIRATORY INSUFFICIENCY

4. None
3. intermittent use of BiPAP
2. continuous use of BiPAP at night
1. continuous use of BiPAP day and night
0. invasive mechanical ventilation by intubation/trach

Appendix 3:

Data Sheet for Face mask Spirometry studies

Study ID _____

Patient initials _____

Date of consent / entry _____

1st (Baseline) Visit

Demographic data:

Age _____

Sex _____

Date of 1st symptoms _____

Date of diagnosis _____

Duration from symptoms to diagnosis _____

ALSFRS r score at symptom onset _____

B ALSFRS r score at symptom onset _____

ALSFRS r score at diagnosis _____

B ALSFRS r score at diagnosis _____

ALSFRS r ratio between 1st symptom and diagnosis _____

ALSFRS r score at induction _____

B ALSFRS r score at induction _____

ALSFRS r score ratio between first visit and last visit _____

Known respiratory illness _____

Riluzole ? _____

Study ID _____

1st Visit

Height _____ Weight _____ BMI _____

Spirometry

PFT

Tube FEV1 _____

Tube FVC _____

MIP _____

MEP _____

SNIP _____

Face mask

FEV1 _____

FVC _____

Arterial Blood Gases

pH _____

PCO2 _____

PO2 _____

HCO3 _____

Overnight Oximetry

Mean SpO2 _____

Min SpO2 _____

DI _____

Mean CO2 _____

Data Sheet for Face mask Spirometry studies

Study ID _____

2nd Visit (at 3 months)

Weight _____ BMI _____

ALSFERS r score at visit _____

B ALSFERS r score at visit _____

ALSFERS r score ratio between first visit and last visit _____

Spirometry

PFT

Tube FEV1 _____

Tube FVC _____

MIP _____

MEP _____

SNIP _____

Face mask

FEV1 _____

FVC _____

Arterial Blood Gases

pH _____

PCO2 _____

PO2 _____

HCO3 _____

Overnight Oximetry

Mean SpO2 _____

Min SpO2 _____

DI _____

Data Sheet for Face mask Spirometry studies

Study ID _____

3rd Visit (at 6 months)

Weight _____ BMI _____

ALSFRS r score at visit _____

B ALSFRS r score at visit _____

ALSFRS r score ratio between first visit and last visit _____

Spirometry

PFT

Tube FEV1 _____

Tube FVC _____

MIP _____

MEP _____

SNIP _____

Face mask

FEV1 _____

FVC _____

Arterial Blood Gases

pH _____

PCO2 _____

PO2 _____

HCO3 _____

Overnight Oximetry

Mean SpO2 _____

Min SpO2 _____

DI _____

Data Sheet for Face mask Spirometry studies

Study ID _____

4th Visit (at 9 months)

Weight _____ BMI _____

ALSFRS r score at visit _____

B ALSFRS r score at visit _____

ALSFRS r score ratio between first visit and last visit _____

Spirometry

PFT

Tube FEV1 _____

Tube FVC _____

MIP _____

MEP _____

SNIP _____

Face mask

FEV1 _____

FVC _____

Arterial Blood Gases

pH _____

PCO2 _____

PO2 _____

HCO3 _____

Overnight Oximetry

Mean SpO2 _____

Min SpO2 _____

DI _____

Data Sheet for Face mask Spirometry studies

Study ID _____

Visit 5 (at 12 months)

Weight _____ BMI _____

ALSFRS r score at visit _____

B ALSFRS r score at visit _____

ALSFRS r score ratio between first visit and last visit _____

Spirometry

PFT

Tube FEV1 _____

Tube FVC _____

MIP _____

MEP _____

SNIP _____

Face mask

FEV1 _____

FVC _____

Arterial Blood Gases

pH _____

PCO2 _____

PO2 _____

HCO3 _____

Overnight Oximetry

Mean SpO2 _____

Min SpO2 _____

DI _____

Data Sheet for Face mask Spirometry studies

Study ID _____

Primary Endpoints

Date Initiated NIV _____

Time to NIV from visit 1 _____

Time to NIV from diagnosis _____

Date of tracheostomy _____

Time to tracheostomy from visit 1 _____

Date of death _____

Time to death from visit 1 _____

Cause of death _____

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