The effects of volume versus pressure targeted non-invasive ventilation in amyotrophic lateral sclerosis

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A thesis submitted in partial fulfilment of the requirement of Manchester Metropolitan University for the award of Doctorate in Clinical Science.

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2025

Acknowledgments

Firstly, I would like to acknowledge the tremendous support from the research and development department at UHCW especially Claire Finnie for always going above and beyond.

I would like to thank Natalie, Absari and Catherine for their continued support during ventilation clinics and for always putting patients first.

Thanks to both Dr Siew-Wan Hee and Dr Peter Kimani, for their methodological and statistical guidance.

Thanks to Vicky and Trish, for their valuable advice and support especially during times of trouble.

I would like to thank Prof. Emma Hodson-Tole and Dr Virginia Hawkins for their invaluable support during the writing of this thesis. They have helped to improve my confidence with academic writing and provided me with a sense of empowerment for future work.

Dr Joanna Shakespeare and Dr Asad Ali have never doubted my ability to achieve. Knowing this, I have always approached challenges with determination knowing that they believe in me.

Finally, but not least, thank you to my wife Vicky and my children Seb and Florence for always being by my side.

Dedication

I would like to dedicate this thesis to all patients, families and caregivers who took part in this research study. Without you all it simply would not have been possible.

Declaration

Excepting any statements to the contrary, the contents of this thesis are the result of my own work. No aspect of this thesis has been copied from other sources or written by others, including people and artificial intelligence sources. Collaborators and contributors to this project have been acknowledged and their contributions stated. I understand that any evidence of plagiarism and/or the use of unacknowledged third-party content will be dealt with as a very serious matter and may lead to disqualification from the award or, or withdrawal of the degree. No materials presented in this thesis have been submitted, in part or in whole, to any other institution for any other qualification. This thesis does not exceed 80,000 words. No parts of this work have been submitted elsewhere for any other qualification.

Publications

Parkes, E. *et al.* (2024) ‘VOLUME VERSUS PRESSURE TARGETED NON-INVASIVE VENTILATION IN AMYOTROPHIC LATERAL SCLEROSIS (VOP ALS): study protocol for a randomised controlled trial’. Available at: https://doi.org/10.21203/rs.3.rs-4128978/v1.

Parkes, E., Shakespeare, J. and Ali, A. (2024) ‘S74 Improved NIV adherence with intelligent volume assured pressure support with automatic expiratory positive airway pressure (volume targeted) in amyotrophic lateral sclerosis (ALS)’. *Thorax*, 79(A5). Available at: https://doi.org/10.1136/thorax-2024-BTSabstracts.80

Abstract

Introduction

Few studies have compared adherence rates between different modes of non-invasive ventilation (NIV) for the treatment of chronic respiratory failure and sleep disordered breathing in patients with amyotrophic lateral sclerosis (ALS). Quality of life (QoL) in amyotrophic lateral sclerosis (ALS) is poor and significantly worse than patients living with cancer and indeed the general population. Previous studies have compared QoL outcomes between ALS patients using NIV and those receiving standard care (no NIV). Raised apnoea hypopnoea index (AHI) and nocturnal hypoventilation contribute towards reduced health reported quality of life (HRQoL) in ALS. The use of volume targeted NIV to treat sleep disordered breathing (SDB) is limited, reflecting clinical uncertainty about its role as an effective mode of NIV in ALS patients with diaphragmatic and bulbar muscle weakness. Therefore, a prospective pilot study with randomisation was conducted to explore adherence and HRQoL difference between volume targeted auto-adjusting EPAP and pressure targeted NIV in patients diagnosed with ALS.

Methods

Fifteen ALS patients were randomised to receive volume targeted auto-adjusting EPAP and pressure targeted NIV. Adherence data and HRQoL scores (revised amyotrophic lateral sclerosis functional rating score (ALSFRS-R), severe respiratory insufficiency (SRI) and modified hospital and anxiety score (mHADS)) were recorded at 14, 30, 60 and 90 days. All patients followed a standard ventilatory care pathway for ALS patients.

Results

Median adherence from 0 – 90 days for volume targeted auto-adjusting EPAP NIV was 7.1 hours per day (h/d) (0.28-9.0) and 3.93 h/d for pressure targeted NIV (0-7.3). Between group comparisons of adherence by time point showed median adherence for volume targeted auto-adjusting EPAP NIV to be statistically significantly higher than pressure targeted NIV at 30, 60 and 90 days (6.29h/d (0.1-8.55) vs 2.48h/d (0-7.3); 7.54h/d (2.43-9.08) vs 5.8h/d (0-7.3) and 9.05h/d (7.8-9.5) vs 6.22h/d (0-8.66), respectively). Seventy-nine patients would be required for each NIV mode to provide appropriate statistical power for a large-scale study. ALSFRS-R and SRI scores did not statistically significantly differ between volume targeted auto-adjusting EPAP and pressure targeted NIV across time points. At 90 days ALSFRS-R and SRI were higher in patients using volume targeted auto-adjusting EPAP NIV compared to those using pressure targeted NIV (29(13.5); 22.8(12.2), p=0.4483 and n=6 52.6(15.5); 46.5(12.3), p=0.4846, respectively). mHADS was lower in the volume targeted auto-adjusting EPAP NIV group compared to pressure targeted NIV at 90 (10.8(8.1); 13.3(6), p=0.5679, respectively).

Discussion

To our knowledge this is the only pilot study with randomisation comparing adherence and HRQoL between two NIV modes in ALS. Improved NIV adherence and higher ALSFRS-R, mHADS and SRI scores were observed in ALS patients using volume targeted auto-adjusting EPAP NIV compared to pressure targeted NIV. Our study provides evidence to support future clinical practice and recommends a large-scale study to fully explore the impact of volume targeted auto-adjusting EPAP NIV on adherence rates and HRQoL in ALS.

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List Abbreviations

ABG	Arterial Blood Gas
ACHD	Adult Congenital Heart Disease
ADL	Activities of Daily Living
AE	Adverse Event
AE-COPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AHI	Apnoea Hypopnea Index
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
AQoL-8D	Assessment of Quality of Life - 8 Dimensions
ARTP	Association for Respiratory Technology and Physiology
AV	Arteriovenous
BDI	Beck's Depression Inventory
BMI	Body Mass Index
CBG	Capillary Blood Gas
CO_2	Carbon Dioxide
COP	Clinical Operating Procedure
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPAP	Continuous Positive Airway Pressure
CRF	Chronic Respiratory Failure
CRQ	Chronic Respiratory Disease Questionnaire
CRRS	Clinical Results and Reporting System
C_{rs}	Compliance of the Respiratory System
EELV	End Expiratory Lung Volume
EMG	Electromyography
EPAP	Expiratory Positive Airway Pressure
EQ-5D	EuroQol- 5 Dimension
ESRD	End Stage Renal Disease
ET	Endotracheal Tube
FEV_1	Forced Expiratory Volume in the First One Second

FEV_1/FVC	Ratio of the Forced Expiratory Volume in the First One Second to the Forced Vital Capacity
FRC	Functional Residual Capacity
FTD	Frontotemporal Dementia
FVC	Forced Vital Capacity
FVL	Flow Volume Loop
GLI	Global Lung Initiative
h	Hours
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
HF	Heart Failure
HI	High Intensity
HMV	Home Mechanical Ventilation
HOT	Home Oxygen Therapy
HR	Heart Rate
HRQoL	Health-Related Quality of Life
HRR	Heart Rate Rises
iBR	Intelligent Backup Rate
IBW	Ideal Body Weight
IMV	Invasive Mechanical Ventilation
IPAP	Inspiratory Positive Airway Pressure
iPEEP	Intrinsic Positive End Expiratory Pressure
IQR	Interquartile Range
ISO	International Organization for Standardization
iVAPS-AE	Intelligent volume-assured pressure support with Automatic Expiratory Positive Airway Pressure
k	Constant
kg	Kilograms
kPa	Kilopascal
$L.min^{-1}$	Litre per minute
LFT	Liver Function Tests
LI	Low Intensity

LMN	Lower Motor Neurones
LTOT	Long Term Oxygen Therapy
LVR	Lung Volume Recruitment
MDT	Multidisciplinary Team
MEBS	Medical Equipment & Bioengineering Services
MI-E	Mechanical Insufflation-Exsufflation
MIP	Maximal Inspiratory Pressure
mL	Millilitre
mmHg	Millimetres of Mercury
MND	Motor Neurone Disease
MRF-28	Maugeri Foundation Respiratory Failure Questionnaire
MRI	Magnetic Resonance Imaging
MUAP	Motor Unit Action Potential Morphology
MV	Minute Ventilation
NCS	Nerve Conduction Study
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive Ventilation
NMD	Neuromuscular Disease
O_2	Oxygen
ODI	Oxygen Desaturation Index
OHS	Obesity Hypoventilation Syndrome
OSAS	Obstructive Sleep Apnoea Syndrome
$PaCO_2$	Partial Pressure of Carbon Dioxide
PaO_2	Partial Pressure of Oxygen
P_{aw}	Airway Pressure
PCF	Peak Cough Flow
Pdi	Transdiaphragmatic Pressures
PEEP	Positive End Expiratory Pressure
PEF	Peak Expiratory Flow
PEG	Percutaneous Endoscopic Gastrostomy
P_{el}	Respiratory System Elastic Recoil
pH	Potential of Hydrogen

PI_{O2}	Inspired Oxygen Partial Pressure
PRG	Percutaneous Radiological Gastrostomy
PS	Pressure Support
PSG	Polysomnography
PS_{max}	Maximum Pressure Support
PS_{min}	Minimum Pressure Support
$PtcCO_2$	Transcutaneous Carbon Dioxide
P_{tot}	Total Pressure
QIPS	Quality Improvement and Patient Safety
QoL	Quality of Life
R&D	Research and Development
R_{aw}	Airway Resistance
RCT	Randomised Controlled Trial
RCWD	Restrictive Chest Wall Disease
REM	Rapid Eye Movement
RIG	Radiologically Inserted Gastrostomy
RR	Respiratory Rate
R_{rs}	Resistance of the Respiratory System
SLT	Speech and Language Therapy
SAQLI	Sleep Apnoea Quality of Life Index
SB	Spontaneous Breathing
SDB	Sleep Disordered Breathing
SEM	Standard Error of the Mean
SF-36	36-Item Short Form Health Survey
SNIP	Sniff Nasal Inspiratory Pressure
SOP	Standard Operating Procedure
SpO_2	Peripheral Oxygen Saturation
SRI	Severe Respiratory Insufficiency
SSRI	Selective Serotonin Reuptake Inhibitors
ST	Spontaneous Timed
SVC	Slow Vital Capacity

T-90	Proportion of Cumulative Sleep Time with Oxygen Saturation Below 90% in Total Sleep Time
TI	Inspiratory Time
TI_{max}	Maximum Inspiratory Time
TI_{min}	Minimum Inspiratory Time
TMS	Transcranial Magnetic Stimulation
UHCW	University Hospitals Coventry and Warwickshire
UMN	Upper Motor Neurones
$\dot{V}$	Flow
$\dot{V}/\dot{Q}$	Ratio of Ventilation to perfusion
$\dot{V}_A$	Alveolar Ventilation
VC	Victal Capacity
$\dot{V}CO_2$	Total Body Carbon Dioxide Production
$\dot{V}_D$	Dead space
$\dot{V}_E$	Minute Ventilation
$\dot{V}O_2$	Total Body Oxygen Consumption
Vt	Tidal Volume
WEQAS	Wales External Quality Assessment Scheme
WOB	Work of Breathing
ΔV	Change in Volume
µL	Micro Litre

1 Respiratory Care and Non-Invasive Ventilation (NIV) in ALS: Background and Review of the Relevant Literature

1.1 ALS Clinical Phenotypes, Epidemiology and Pathophysiology

1.1.1 What is ALS?

Amyotrophic lateral sclerosis (ALS) is an idiopathic, progressive disease of the central and peripheral human motor systems. Originally described as a pure motor neurone disease by Jean-Martin Charcot in 1869 it is now recognised as a multisystem, heterogenetic, neurodegenerative disease (Charcot, 1869; Brain and Walton, 1969). It is one of a group of Motor Neurone Diseases (MNDs) that includes progressive muscular atrophy (PMA), progressive bulbar palsy (PBP), primary lateral sclerosis (PLS), and pseudobulbar palsy (Brain and Walton, 1969). These diseases are characterised by progressive destruction of the motor neurones located in the brain, spinal cord and peripheral nervous system that elicit muscle contraction. ALS involves the degeneration of the upper and lower motor neurones responsible for directing skeletal muscle contraction to perform the movements needed to walk, talk, breathe, and swallow (Charcot, 1869; Brain and Walton, 1969). Around 50% of patients with an ALS diagnosis will develop frontotemporal cognitive dysfunction (Lomen-Hoerth, Anderson and Miller, 2002) with a much smaller proportion of patients diagnosed with dementia of the frontotemporal type (Lomen-Hoerth, Anderson and Miller, 2002).

There is often a male predominance especially in limb ALS (Manjaly *et al.*, 2010) however female predominance is higher in bulbar onset disease (Palese *et al.*, 2019) (1.1.2 Clinical Phenotypes). Peak incidence occurs between the age of 60 and 75 years (Chio, 2004) and as disease onset is subtle and its progression insidious, most patients will survive between 2-5 years from the time of diagnosis (Chancellor *et al.*, 1993; Chio, 2004; Alonso *et al.*, 2009).

Progressive weakening of the diaphragm will eventually lead to the development of respiratory failure which is the most common cause of death in ALS (Wolf *et al.*, 2017).

Many patients will experience breathlessness, orthopnoea, early morning headaches and impaired cough strength (Shoesmith *et al.*, 2007) with the management of the disease focused on supportive, multidisciplinary and palliative care (Ng, Khan and Mathers, 2009).

1.1.2 Clinical Phenotypes

Clinical presentation of ALS is heterogeneous and there is no 'classic' set of signs or symptoms of the disease (Brown and Al-Chalabi, 2017; Brotman *et al.*, 2024). ALS phenotypes include spinal (limb) onset, bulbar onset, flair arm/leg variant, upper motor neuron predominant (UMNP), lower motor neuron predominant (LMNP), and ALS with frontotemporal dementia (ALS-FTD) (Quinn and Elman, 2020; Requardt *et al.*, 2021; Boostani *et al.*, 2023). Flail arm/leg variant, can be hard to differentiate from typical limb and bulbar onset ALS as diagnostic criteria are limited and often the primary diagnostic marker is the length of time the symptoms remain localised to patients distal limbs (Brotman *et al.*, 2024). Although the destruction of both UMN and LMN is synonymous with the disease, the number of which destroyed can dictate how a patient may present to clinic.

Patients with limb ALS will present with a combination of both UMN and LMN characteristics and those with bulbar ALS will present with mainly UMN signs (Kiernan *et al.*, 2011; Brotman *et al.*, 2024). Seventy percent of ALS patients present with limb onset ALS whereas only 25% of cases present with bulbar onset (Kiernan *et al.*, 2011). UMN damage results in reduced dexterity of the feet, hands, arms and legs, poor coordination, muscle spasticity and hyperreflexia. LMN features include muscle atrophy and fasciculations. Muscle weakness which is a hallmark feature of ALS is a result of both UMN and LMN involvement. The patients initial set of signs and/or symptoms can determine the pattern of disease progression and provide clinical prognostication (Brotman *et al.*, 2024).

Patients with limb onset ALS commonly present with asymmetric limb weakness including hands, shoulder girdle weakness (supraspinatus, infraspinatus, teres minor, and subscapularis) and foot drop. Dysarthria, dysphagia and sialorrhea are common in Bulbar onset ALS patients. These can lead to tongue muscle wasting and weakness, slow and distorted speech, copious amounts of salvia in the mouth and a weak cough

(Duffy, Peach and Strand, 2007). Dysphagia often leads to a reduced food intake and a poor nutritional status which in combination with muscle weakness causes increased fatigue and reduced exercise tolerance (Stambler, Charatan and Cedarbaum, 1998).

All ALS patients will eventually develop respiratory muscle weakness leading to the development of respiratory pump failure and sleep disordered breathing (SDB). Common signs and symptoms indicating respiratory impairment include dyspnoea at rest or during exertion, orthopnoea, morning headaches, nocturnal hypoventilation with associated daytime hypercapnia and weak cough (NICE, 2016). Progressive weakness of the respiratory muscles ultimately leads to respiratory failure which can often be complicated by pneumonia and is the most common cause of death in ALS (Wolf *et al.*, 2017) (Figure 1.1).

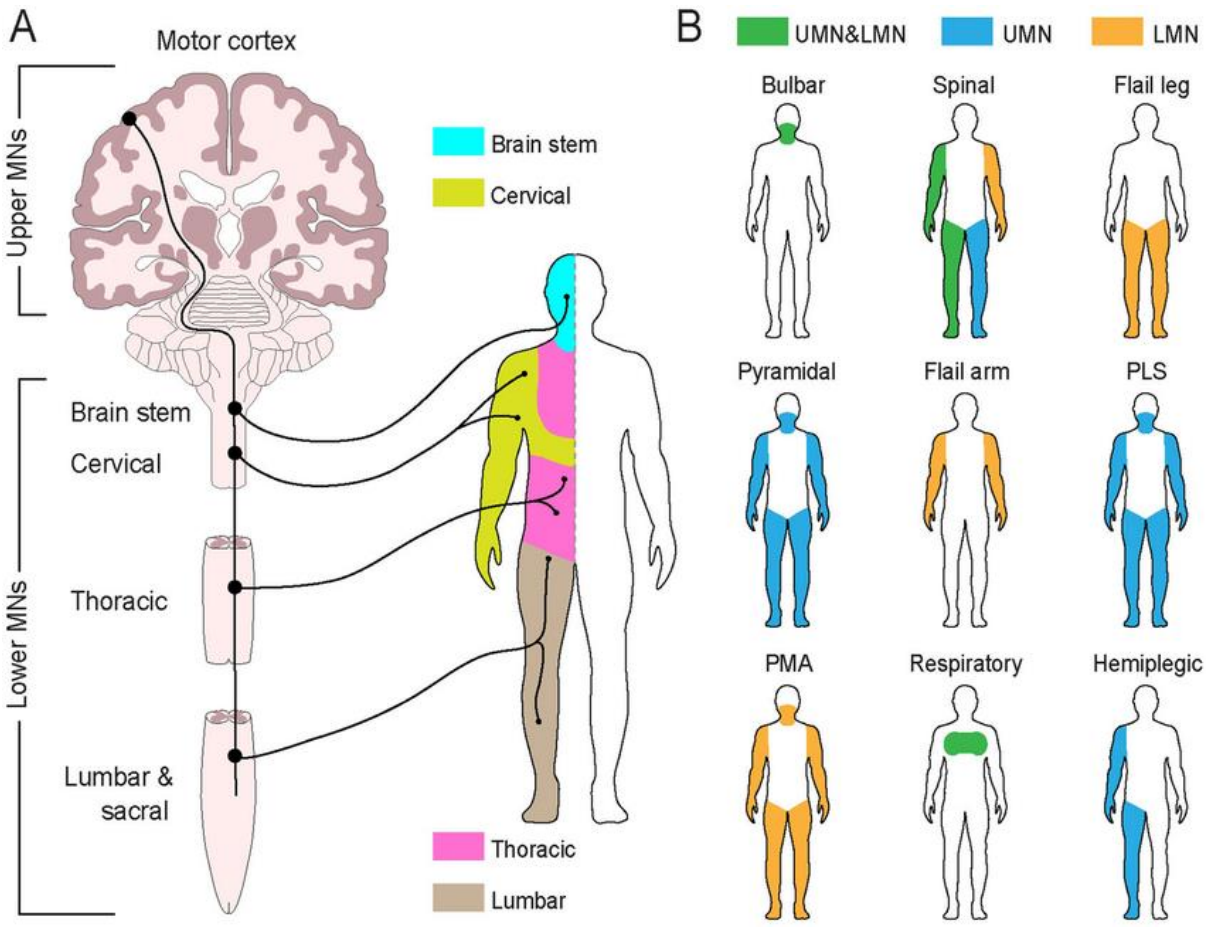

Figure 1.1. (A) ALS phenotypes and anatomical impact on normal motor function. Schematic representation of the human central nervous system with location of functional groups of motor neurons. UMN and LMN include brain stem or bulbar, cervical, thoracic, lumbar and sacral. Colour coded location of their innervation distribution along the body axis (left and right, respectively). (B) Colour coded

pattens of UMN and LMN involvement in ALS phenotypes. PLS is primary lateral sclerosis, PMA is progressive muscular atrophy. Taken from Ovsepian et al., 2024.

1.1.3 Epidemiology of ALS

Studies have reported a disease incidence and prevalence for ALS in England and Wales of 1.10 and between 4.02-4.91 per 100,000 population, respectively (Abhinav *et al.*, 2007; Gkiouleka *et al.*, 2019). There appears to be no clear geographical pattern of ALS incidence with rates varying between 0.6 and 2.4 per 100,000 (Cronin, Hardiman and Traynor, 2007). The use of diverse diagnostic criteria and study methodology may contribute towards the variation in incidence rates reported in studies. Furthermore, accurately identifying the date of disease onset and the time period between pathological changes and clinical presentation of the disease may also complicate epidemiological studies in ALS (Davenport *et al.*, 1996; Chio, 1999).

Interestingly, a group of studies using similar methodologies reported a more consistent incidence rate of approximately 2 per 100,000 (Traynor *et al.*, 1999; Piemonte and Valle d'Aosta Register, 2001; Logroscino *et al.*, 2005; Beghi *et al.*, 2007). The epidemiology of ALS still remains controversial, most studies agree that disease incidence peaks at an age between 75-79 in men and 70-74 in women, and then starts to decrease thereafter. However it is still unknown if this is due to a real decrease in incidence rates or due to an under diagnosis in the elderly population (Logroscino *et al.*, 2005).

A large population-based study performed in the United Kingdom utilised data from 3 million patients enrolled onto the General Practice Research Database. The study reported 830 new diagnoses of MND during 22,492,571 person-years of follow up between 1990 and 2005. Disease incidence was 3.9 for men and 2.9 for women per 100, 000. Incidence peaked for both sexes between 75 and 79 years of age. Men were at a 54% greater risk of developing MND compared to women with an overall life time risk of MND of 1 in 472 for women and 1 in 350 for men (Alonso *et al.*, 2009). A further population-based study performed within Greater London reported the age-specific and sex-specific disease prevalence of 4.02 per 100,000, higher in men than women at 5.13 and 3.01 per 100,000, respectively (Gkiouleka *et al.*, 2019).

1.1.4 Pathophysiology and ALS Associated Genetic Mutations

Over the past 30 years there have been significant scientific and medical advances in understanding the genetic associations with familial ALS as well as the functioning of the glutamate neurotransmitter system. This has provided a greater insight into the clinical heterogeneity of ALS, and that survival in ALS is dependent upon ALS phenotype, clinical presentation, early onset respiratory failure, rate of disease progression and nutritional status (Preux *et al.*, 1996; Chiò *et al.*, 2002; del Aguila *et al.*, 2003).

Between 5-10% of ALS diagnoses are familial with generally a Mendelian form of inheritance. Since 2009, there have been 13 genes and major effect loci identified as being associated with the development of ALS (Beleza-Meireles and Al-Chalabi, 2009; Maruyama *et al.*, 2010). Of the identified genes a typical clinical ALS phenotype occurs with a mutation in SOD1 (translates for copper/zinc ion-binding superoxide dismutase), TARDBP (also TDP-43; translates for TAR DNA binding protein), FUS (translates fusion in sarcoma), ANG (translates angiogenin, ribonuclease, RNase A family, 5), and OPTN (translates optineurin) (Rosen, 1993; Kabashi *et al.*, 2008). Mutations in these genes result in impairment of multifunctional proteins that are responsible for gene expression and regulation, including RNA splicing, transport, transcription and translation predominantly affecting glutamate signalling (Figure 1.2).

The pathological mechanisms of ALS are complex and multifactorial with interaction between both genetic and molecular cellular pathways (Figure 1.2) (Neusch, Bähr and Schneider-Gold, 2007; Vucic and Kiernan, 2009). The hallmarks of the disease are the degeneration of the pyramidal Betz cells in the motor cortex, lower motor nuclei of the brainstem and anterior horn cells located in the spinal cord. Once the motor neurones have been destroyed they are replaced by gliosis which leads to spinal cord atrophy and associated spinal muscles (Saberi *et al.*, 2015; Brown and Al-Chalabi, 2017).

There are many intracellular inclusions which have been associated which the degeneration of motor neurones. In a study examining 102 autopsy cases between 1962 and 2000, bunina bodies which are eosinophilic inclusions were identified as being unique to ALS (Piao *et al.*, 2003). Equally, the accumulation of the nuclear RNA/DNA binding protein responsible for the regulation of RNA processing, TAR DNA

43 (TDP-43), has been present in most cases of ALS and some cases of familial ALS (Brotman *et al.*, 2024). Various other notions for the development of ALS have been proposed including modification of gene expression rather than genetic code, increased oxidative stress, impaired RNA processing, excitotoxicity, neuroinflammation and mitochondrial dysfunction (Morgan and Orrell, 2016).

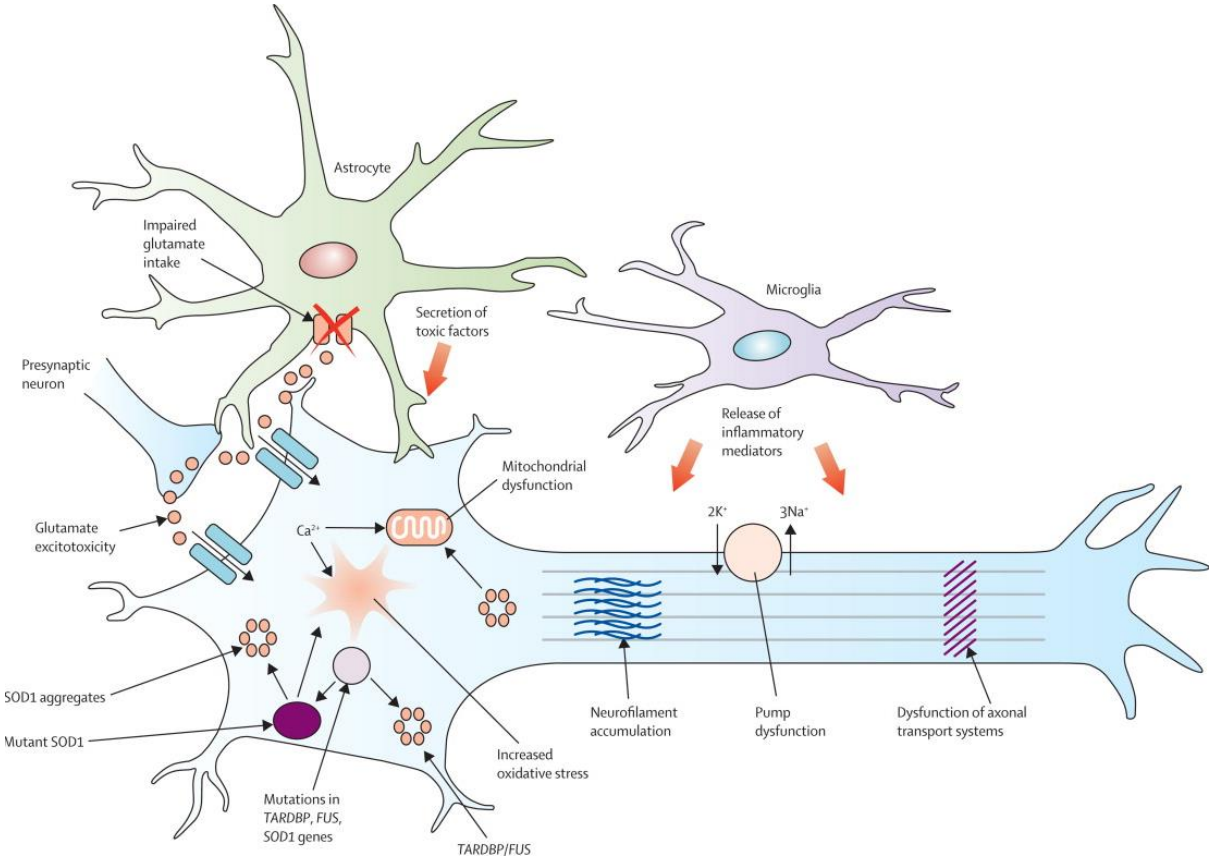

Figure 1.2. Cellular and molecular processes mediating neurodegeneration in ALS. SOD1 is Superoxide dismutase, FUS is heterogeneous nuclear ribonucleoprotein P2, TARDBP is transactive response DNA binding protein 43 kDa. Taken from Kiernan et al., 2011.

1.1.5 Prognosis

Survival can vary but is reported to be between 5 and 10 years for 4-30% of patients (Chancellor *et al.*, 1993; Stambler, Charatan and Cedarbaum, 1998) with 50% of patients not surviving beyond 10 years (Turner *et al.*, 2003). Factors influencing survival are bulbar predominate disease, early onset of respiratory muscle weakness, reduced forced vital capacity (FVC), higher Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score and older age at diagnosis being associated with a reduced survival (Piemonte and Valle d'Aosta Register, 2001;

Limousin *et al.*, 2010; Brotman *et al.*, 2024). Certain ALS phenotypes result in different survival times and therefore it is clinically important to differentiate MND phenotypes to ensure realistic prognostication (Preux *et al.*, 1996).

In a retrospective analysis of 625 ALS patients who attended a tertiary hospital clinic, features of bulbar ALS were reported in 21.6%, limb ALS in 23.68%, UMNP in 20.16%, LMNP in 33.12% and ALS-FTD in 1.44% of patients (Requardt *et al.*, 2021) Concomitant Chronic Obstructive Pulmonary Disease (COPD) was reported in 3.8% of patients and shown to have a negative impact on prognosis (Figure 1.3) (Requardt *et al.*, 2021; Ovsepian, O'Leary and Martinez, 2024).

Large ALS patient cohorts or registers consistently report a median survival for ALS limb patients of 2-3 and ALS bulbar patients of 3-5 years (Chancellor *et al.*, 1993; Chio, 2004; Alonso *et al.*, 2009). In a single centre retrospective analysis of a clinical cohort of ALS patients, a median survival of 48 months (IQR 32-121) from the onset of first symptoms was observed. There were significantly different survival times when patients were grouped by age at symptom onset, ALS phenotype, rate of disease progression accordingly to ALSFRS-R and presence of COPD (Figure 1.3) (Ovsepian, O'Leary and Martinez, 2024).

Rapid disease progression and reduced survival are observed in the A4V mutation of SOD1 and P525L mutation of FUS/TLS genes compared to a prolonged survival observed in patients with a lower expression of ephrin type-A receptor 4 (EPHA4) (Brown and Al-Chalabi, 2017; Tzeplaeff *et al.*, 2023). Although ALS is a heterogeneous disease, progression is usually linear with patients experiencing no remissions or exacerbations. Whilst there is significant variation in rate of disease progression between patients, the pattern of how ALS will progress and ultimately end is relatively predictable (Brotman *et al.*, 2024).

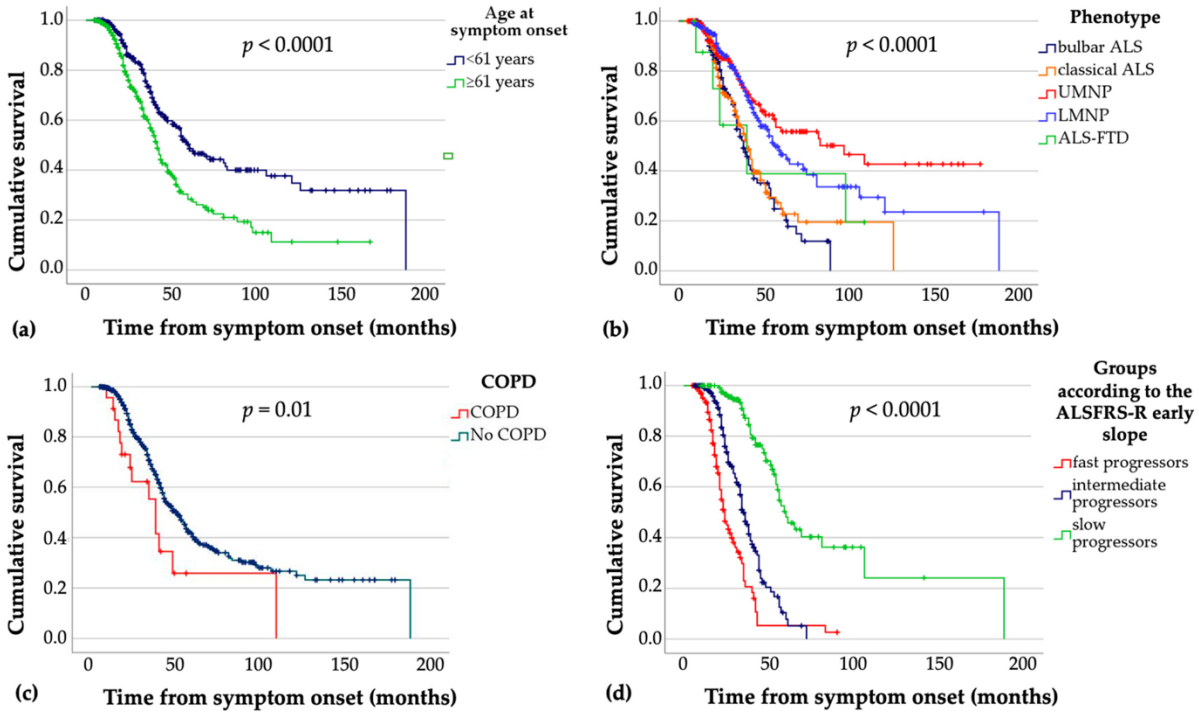

Figure 1.3. Kaplan–Meier survival curves of patients stratified by (a) age at symptom onset; (b) clinical phenotype; (c) concomitant COPD; (d) ALSFRS-R early slope. ALSFRS-R = revised ALS Functional Rating Scale; ALS-FTD = ALS with frontotemporal dementia; COPD = chronic obstructive pulmonary disease; LMNP = lower motor neuron predominant; UMNP = upper motor neuron predominant. Taken from Requardt et al., 2021.

1.2 ALS Diagnosis, Treatment and Clinical Management

1.2.1 Initial Diagnosis of ALS

The onset of ALS can be insidious and as such patients may disregard symptoms for weeks or even months (Dengler, 1999). The diagnostic process is complex and challenging which leads to delays, compromising disease treatment and enrolment onto clinical trials (Richards, Morren and Pioro, 2020). The average time from symptom onset to diagnosis ranges between 10–16 months with data from a UK based ALS population demonstrating a mean time from first symptoms to diagnosis of 12 months (Mitchell *et al.*, 2010; Turner *et al.*, 2010; Galvin *et al.*, 2017; Palese *et al.*, 2019). Several interventions to reduce the time taken to diagnose ALS have been reported, with one UK hospital implementing a fast-track neurology service for patients with suspected ALS/MND. Although the quality improvement study did not observe

any significant reduction in the overall time from symptom onset to diagnosis, there was a 51.9% reduction in the time taken from referral to diagnosis (104 vs 50 days) (Mitchell *et al.*, 2010).

Despite significant advances in clinical diagnostics over the past 50 years, the diagnosis of ALS remains one that is based on a combination of clinical history, physical examination, and neurophysiology investigations (Brotman *et al.*, 2024). Whilst, laboratory-based blood tests and radiological investigations, for example magnetic resonance imaging (MRI) are not exclusively diagnostic they are however required to rule out other conditions that would otherwise be treatable. Neuroimaging can be particularly useful in ruling out structural lesions that mimic ALS by producing a series of upper and lower motor neurone signs (Abe *et al.*, 1997).

1.2.2 Clinical Examination and Clinical Scoring Systems

Due to the variable forms of clinical presentation, limited set of diagnostic markers and similarity of clinical presentation with other forms of MND, there is no gold standard diagnostic test for ALS (Davenport *et al.*, 1996; Traynor *et al.*, 2000). As a result, a diagnosis of ALS is based mainly on identifying features of the disease including the combination of both UNM and LMN in the same body region with any evidence of disease progression to other body systems.

The clinical examination during the early phase of limb onset disease generally reveals atrophy of the muscles in the hand, forearms, shoulders, thigh and distal foot (Turner *et al.*, 2011; Simon, Lomen-Hoerth and Kiernan, 2014). Rarely patients present with muscle atrophy before the onset of muscle weakness (Vucic and Kiernan, 2007). Patients may have experienced fasciculations (involuntary muscle twitching) combined with cramps for months or years, but these are not normally presenting signs. Although muscle weakness and wasting are unsymmetrical in the early phase of the disease, the remaining limbs soon follow with most patients going on to develop bulbar impairment and respiratory symptoms, predominately breathlessness but also poor sleep, morning headaches and orthopnoea (Goetz, 2000).

Scoring systems have been proposed to help objectively diagnose ALS and its severity including the El Escorial criteria (Brooks, 1994) which uses a combination of clinical signs and symptoms exhibited by the loss of both UMN and LMN to provide a level of

diagnostic assurance. The El Escorial criteria has been used extensively, particularly in clinical trials, as patients can be enrolled according to their El Escorial score, with many clinical trial investigators using ‘probable’ or ‘definite’ scores as trial inclusion criteria. Despite its initial ability to classify ALS diagnoses, the scoring system lacked sufficient sensitivity especially in patients who received an early diagnosis of ALS and were receiving therapeutic intervention to good effect (Traynor *et al.*, 2000; Kiernan, 2003).

Clinical investigators became concerned that employing the El Escorial criteria to enrol patients into clinical trials would limit the number and type of ALS patients eligible (Kiernan, 2003). As a result, the El Escorial criteria was revised and subsequently includes results from neurophysiology testing, including electromyography (EMG), to help improve early diagnosis of the disease and overall sensitivity (Figure 1.4) (Ross *et al.*, 1998; Beghi *et al.*, 2002; Kiernan, 2003; Tiryaki and Horak, 2014).

Level of Certainty	Degree of Involvement
Suspected ALS	UMN signs only in one or more regions, or LMN signs only in one or more regions
Possible ALS	UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions without UMN signs rostral to the LMN signs
Probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Laboratory-supported probable ALS	UMN signs in one or more regions with LMN involvement by EMG in at least two regions
Definite ALS	UMN and LMN signs in three regions
Laboratory-supported familial ALS	UMN and LMN signs in one region and confirmatory genetic testing

Figure 1.4. Level of disease certainty according to degree of upper and lower motor neurone involvement using the revised El Escorial criteria. Taken from Tiryaki and Horak, 2014.

1.2.3 Neurophysiological Assessment

It is recommended that all patients with a suspected diagnosis of ALS, undergo neurophysiology investigations including nerve conduction studies (NCS), EMG and in some cases transcranial magnetic stimulation (TMS) (Winhammar *et al.*, 2005). EMG involves the temporary application of electrodes on the patient’s skin or in some

cases the use of a fine needle inserted into the muscle to record electrical muscle activity.

NCS, like EMG, uses electrodes applied to the patient's skin to measure nerve conduction time after being artificially stimulated. EMG remains an important diagnostic test and may identify LMN changes in muscle groups that show sub-clinical as well as clinically evident signs (Brooks *et al.*, 2000; Mills, 2011). It is particularly useful in identifying the loss of LMN and these can be correlated with clinical features of LMN disease (de Carvalho *et al.*, 2008). NCS are an essential part of the diagnostic process as they can exclude diseases which mimic the clinical presentation of ALS and directly contributes towards a diagnosis in approximately 90% of patients (Eisen and Swash, 2001; Gwathmey *et al.*, 2023).

Typical EMG findings are illustrated in Figure 1.5 and include acute denervation (defined as the presence of fibrillation potentials), positive sharp waves and chronic neurogenic changes, chronic denervation (defined as prolonged duration complex motor unit action potentials (MUAP)) and chronic reinnervation (defined as prolonged amplitude MUAPs) (Eisen and Swash, 2001; de Carvalho *et al.*, 2008; Naik, Selvan and Nguyen, 2016). A diagnosis of ALS is likely if EMG results indicate acute, acute on chronic or chronic denervation in a minimum of 3 spinal nerves including those of bulbar, cervical, thoracic or lumbosacral regions (Brotman *et al.*, 2024).

Of note, some EMG findings, specifically those of acute denervation can be present in clinically normal muscle (Eisen and Swash, 2001). NCS are predominately used to exclude other diseases which can mimic ALS, particularly demyelinating motor neuropathies (Eisen and Swash, 2001).

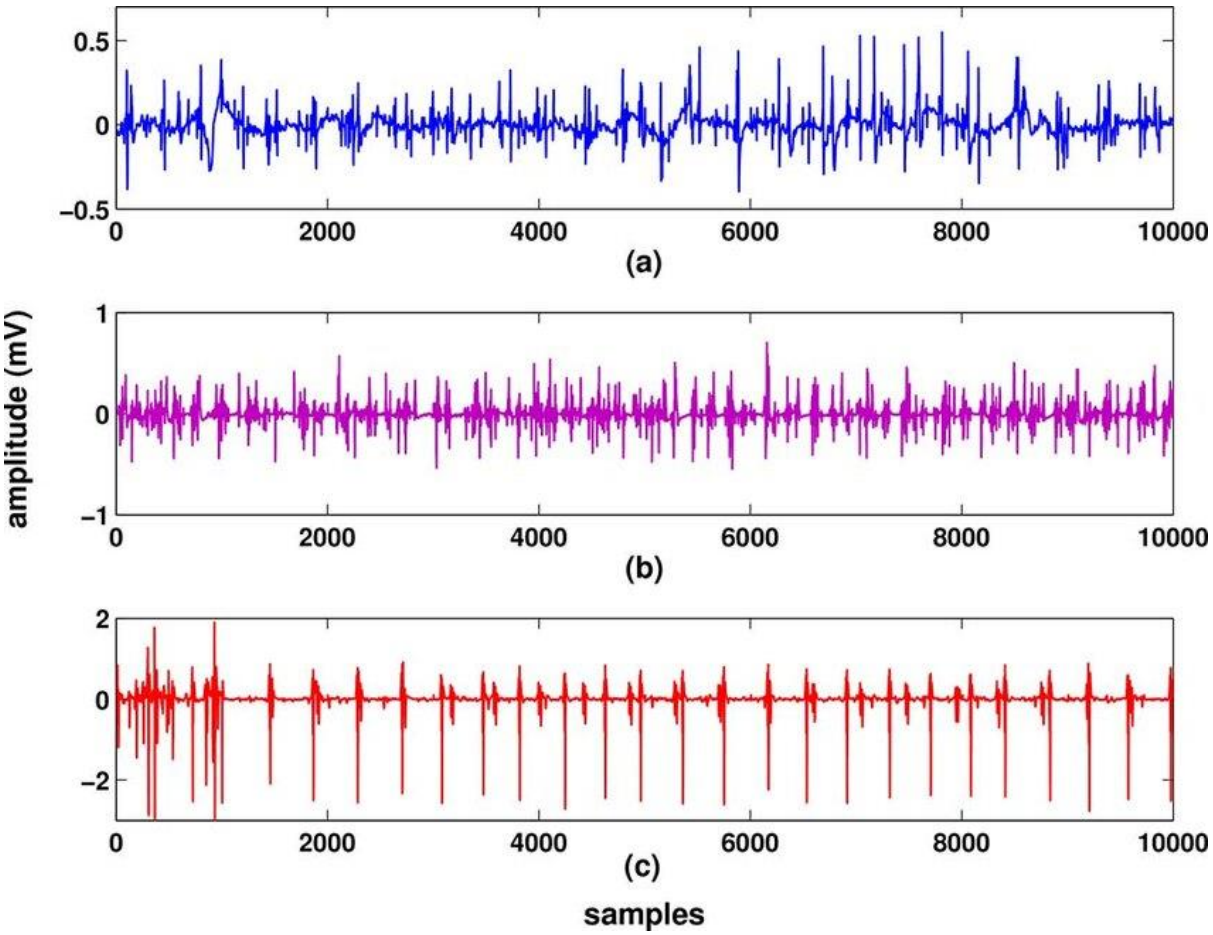

Figure 1.5. Classic EMG patterns for a healthy person (blue), myopathy (purple) and ALS (red). Taken from Naik et al., 2016.

1.3 ALS Patient Management with a Multidisciplinary Care Team

ALS is a clinically and diagnostically complex disease and a multidisciplinary team (MDT) approach to patient care is significantly important. In addition to neurology services, which are often the first which patients interact with whilst undergoing a diagnosis, respiratory, physiotherapy, speech and language therapy, occupational therapy, dietetics, social care, pharmacotherapy and psychotherapy are required to provide symptomatic support which remain the cornerstone of ALS care (Van den Berg *et al.*, 2005; NICE, 2006, 2016; Miller *et al.*, 2009; Boostani *et al.*, 2023; Tzeplaeff *et al.*, 2023). As the disease progresses the primary aim of MDT care is to reduce the overall burden of symptoms, improve health reported quality of life (HRQoL) and

survival (Berg *et al.*, 2005). Compared to patients who receive care from neurology clinics only, patients managed by an MDT have improved HRQoL which is often as a result of a more efficient use of resources both in and out of hospital, with improvement seen in some patients after only one MDT clinic visit (Berg *et al.*, 2005). A 45% reduction in the risk of death at 5 years has also been observed in those patients receiving MDT ALS care (Berg *et al.*, 2005).

1.3.1 First Line Pharmacological Treatments and Nutritional Care

Riluzole is the most common disease modifying drug prescribed to patients diagnosed with ALS. Riluzole is an artificial benzothiazole glutamine antagonist drug which at a dose of 50mg, limits the release of intracellular glutamate and yields neuroprotective properties, and has been shown to slow disease progression and improve survival in ALS (Hinchcliffe and Smith, 2017).

Two large randomised controlled trials (RCTs) reported a modest survival advantage of between 3-6 months in those ALS patients administering Riluzole (Bensimon, Lacomblez and Meininger, 1994; Lacomblez *et al.*, 1996; Miller *et al.*, 2007). These survival advantages were further improved in those patients receiving care from specialised centres employing MDT ALS clinics compared to other clinical settings. In addition, Riluzole provided most clinical benefit to those patients with moderate functional impairment (Traynor *et al.*, 1999; Bensimon *et al.*, 2002) and overall, the majority of evidence supports greater effects in patients with bulbar-onset disease (Bensimon, Lacomblez and Meininger, 1994; Lacomblez *et al.*, 1996; Bensimon *et al.*, 2002).

Riluzole is tolerated by most patients and as such is commonly prescribed to patients diagnosed with ALS. Riluzole has been found to disrupt normal hepatic function and increased levels of serum alanine aminotransferase of up to 3 times the normal levels have been reported in between 10-15% of ALS patients (Bensimon and Doble, 2004). Data from clinical trials have identified adverse events (AE) related to the development of asthenia and nausea, and as such should be considered side effects of the drug. There have been isolated reports of Riluzole induced neutropenia but these are rare but nevertheless should still be of concern for clinicians (Bensimon and Doble, 2004).

Dysphagia is initially manged by diet modification and is the main reason for weight loss and subsequent malnutrition in ALS. Speech and language therapists (SLT) should be involved to assess the patients ability to perform a safe swallow and manage factors which may prevent oral nutritional intake (NICE, 2016). Poor nutritional status may not be because of dysphagia alone with between 50-60% of patients demonstrating a hypermetabolic state which remains throughout the course of the disease and is influenced by sex, age and fat-free mass (Desport *et al.*, 2005; Andersen *et al.*, 2007; Bouteloup *et al.*, 2009; Funalot *et al.*, 2009). Weight loss is of particular importance as body mass index (BMI) is directly related to a poor prognosis (Funalot *et al.*, 2009) and as such effort should be made early on in the disease process to prevent weight loss by complimenting the patients current diet with calorie dense foods and nutritional drinks (NICE, 2006; Kasarskis *et al.*, 2009).

If weight loss continues despite attempts to maintain BMI with diet alone, insertion of a gastronomy is offered to patients. Gastronomy should be offered at an early stage of the disease and at regular intervals at follow up clinic appointments. Discussion around gastronomy should take into account the patients beliefs, ability to swallow safely, respiratory function, sleep symptoms, current BMI and previous weight loss (NICE, 2016). Several studies have assured the efficacy of the different approaches to gastronomy including percutaneous endoscopic gastronomy (PEG) and radiological inserted gastronomy (RIG) both used commonly in clinical practice (ProGas Study Group, 2015). Other approaches include Per-oral Image Guided Gastrostomy (PRG).

Insertion of a PEG is performed under sedation with the placement of the feeding tube made using endoscopic procedures compared to a RIG which is also performed under sedation but where the feeding tube is placed using radiological techniques. Consideration about the gastronomy procedure should be given to those patients with evidence of impaired respiratory function as it may be necessary to use NIV during the gastronomy insertion. This approach has been shown to be safe and effective and have no negative impact on mortality (Gaspar *et al.*, 2021) (Figure 1.6).

Patients who have either a PEG or RIG are likely to have a longer survival compared to those who opt against the procedure (Blondet *et al.*, 2010). A retrospective review of an interhospital ALS registry in Spain comprising 93 patients reported 38.8% of patients agreed to a PEG. BMI improved over a 6 month follow up period for patients

with a PEG (22.06 – 23.04; p=<0.01) but decreased in those without (24.59-23.87; p=>0.05). Patients with a PEG were observed to have a survival advantage compared to those with a PEG (PEG: 23 (15–35.5) months; NoPEG 11 (4.75–18.5) (López-Gómez *et al.*, 2021). The use of both NIV and gastronomy has been shown to improve survival in ALS which is also observed in those patients with bulbar-onset disease (Burkhardt *et al.*, 2017).

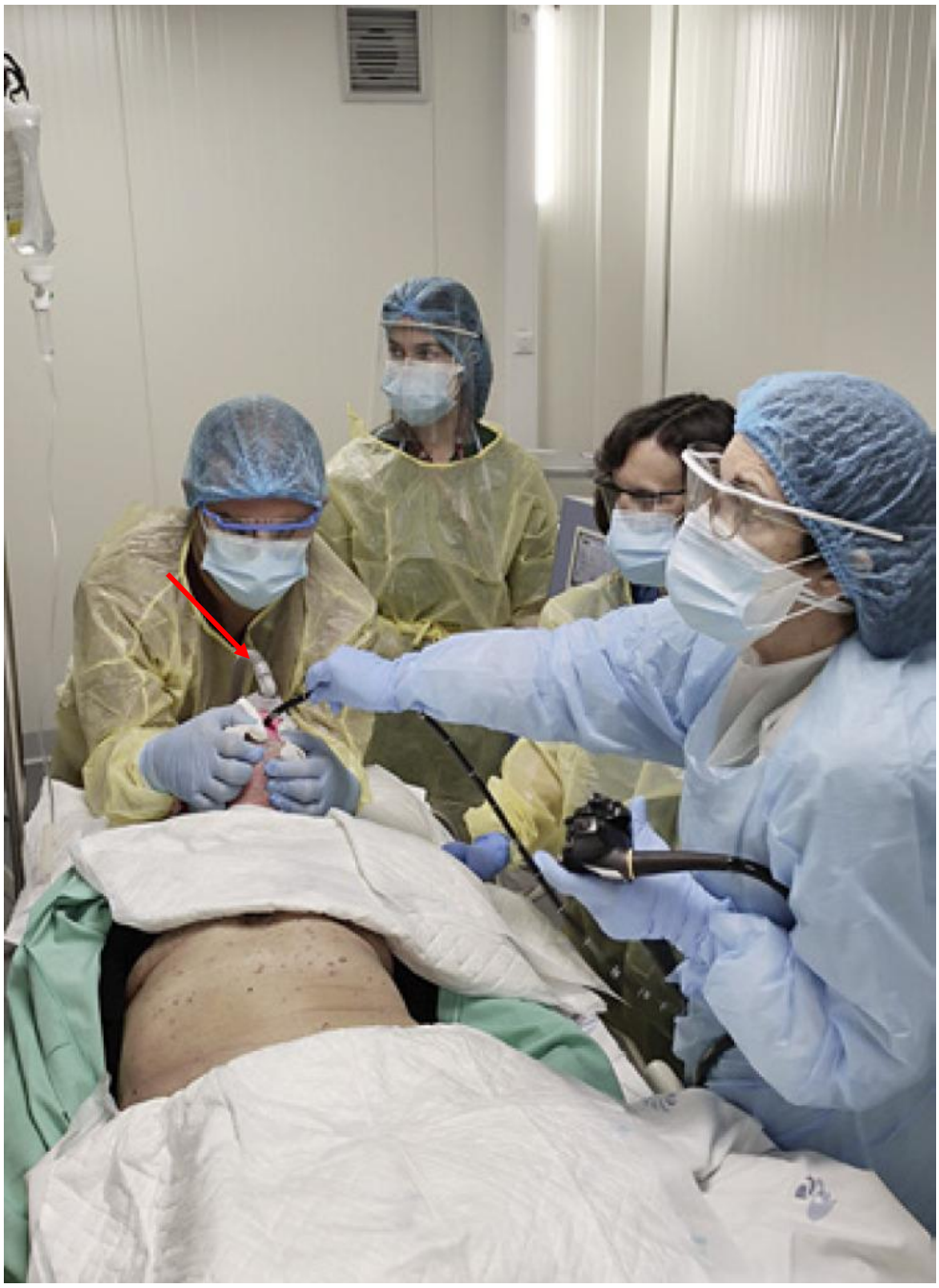

Figure 1.6. PEG placement in a patient with ALS and respiratory impairment using nasal NIV. Red arrow shows NIV interface and circuit. Taken from Gaspar et al., 2021.

1.3.2 Alleviation of Muscle Symptoms

Muscle symptoms are common in ALS and are treated pharmacologically. Symptoms include frequent and painful muscle cramps, spasticity, and stiffness (Kiernan *et al.*, 2011; NICE, 2016). Before drugs are prescribed and/or administered consideration should be given to how the medication will be delivered, either orally or via the patients gastronomy and the anticipated side effects of the medication as not to exacerbate any other symptoms associated with ALS (NICE, 2016).

First line medication for muscle cramps include quinine, if this is not tolerated due to side effects or if it is contraindicated, baclofen should be trialled (NICE, 2016). The results of a double-blind, placebo-controlled study demonstrated a significant reduction in the frequency and severity of muscle cramps using mexiletine (Weiss *et al.*, 2016). Baclofen, tizinadine, dantrolene and gabapentin should be considered to treat muscle stiffness and/or spasticity. If these drugs are not effective, tolerated or indeed contraindicated a referral to a specialist neuromuscular service for further assessment and treatment is recommended (NICE, 2016).

Muscle cramps, spasticity and pain combined with weakness, inevitability leads to a decline in functional status and the ability to carry out activities of daily living (ADL). To help maintain functional status and indeed independence, occupational therapy is important and can be used to identify useful assistive aids (crutches, orthoses and wheelchairs), removable neck or head rests, specialised/bespoke holding apparatus and pressure relieving mattresses to allow frequent body readjustment to reduce pain, risk of pressure sores and improve sleep quality (Borasio, Voltz and Miller, 2001).

1.3.3 Health Related Quality of Life and Mood Disorders in ALS

Mood disorders including anxiety and depression are commonly experienced in ALS. The causes for which are regarded as multifactorial, yet significantly reduce HRQoL, which in ALS is reported to be clinically worse than patients living with cancer and indeed the general population (Caballero-Eraso *et al.*, 2023). Understanding how ALS will change normal life, accepting the diagnosis, fear of dying, changes to perception of self, changes in physical, emotional and social relationships are factors which contribute towards anxiety, depression and reduced HRQoL (NICE, 2016; van Groenestijn *et al.*, 2016).

In a nested case control study of 1,752 patients diagnosed with ALS, there was a significantly higher risk of clinical depression compared to patients in the control group (odds ratio [OR] 1.7, 95% confidence interval [CI] 1.3–2.3). Interestingly, the risk was highest during the year preceding the ALS diagnosis (OR 3.5, 95% CI 2.1–5.6) (Roos *et al.*, 2016). The use of antidepressant drugs to treat depression was higher in the ALS group particularly in the year before and after diagnosis (OR 5.8, 95% CI 4.5–7.5; hazard ratio 16.1, 95% CI 11.5–22.6, respectively) (Roos *et al.*, 2016). Anxiety and depression in ALS are treated in a similar way to other disease and involves the use of antidepressant drugs including amitriptyline and selective serotonin reuptake inhibitors (SSRI) for example sertraline (Talati, Toledo and Akinyemi, 2022).

1.3.4 Chronic Respiratory Failure (CRF) and Sleep Disordered Breathing (SDB)

Finally, but of particular interest, ALS patients will eventually develop chronic respiratory failure (CRF) and SDB. Symptom onset significantly varies between patients with signs and symptoms including, dyspnoea, orthopnoea, disturbed and unrefreshing sleep, daytime sleepiness, morning headaches, increased respiratory rate (RR), weak cough, poor chest expansion and a paradoxical abdomen (inward rather than outward movement of the diaphragm during inspiration) (NICE, 2016).

Respiratory and sleep function tests are used to diagnose CRF and SDB in ALS and should be performed soon after diagnosis and every 3 months thereafter (NICE, 2016). Respiratory function tests include spirometry, measuring VC and FVC, sniff inspiratory nasal pressure (SNIP), measuring inspiratory muscle strength and arterial blood gas (ABG) analysis, including oxygen (PaO_2) and carbon dioxide ($PaCO_2$) (NICE, 2016; Sylvester *et al.*, 2020).

Sleep function tests include overnight pulse oximetry, transcutaneous carbon dioxide monitoring, cardio-respiratory polygraphy and in some hospitals but with limited use, polysomnography (PSG). Overnight pulse oximetry, measures oxygen (SpO2), heart rate (HR) with the addition of inspiratory nasal airflow, chest and abdomen effort when using cardio-respiratory polygraphy (NICE, 2016).

The use of home NIV to treat CRF and SDB (Arnulf *et al.*, 2000) and its ability to improve survival and HRQoL has been well reported (Bach, 1993; Pinto *et al.*, 1995;

Aboussouan *et al.*, 1997; Kleopa *et al.*, 1999; Bourke, Shaw and Gibson, 2001; Newsom-Davis *et al.*, 2001; Bourke *et al.*, 2006). A weak cough is problematic in ALS (Rafiq *et al.*, 2016) and is particularly concerning when a patients peak cough flow (PCF) measures <270L/min (Toussaint *et al.*, 2009).

The use of both NIV and a mechanical insufflator/exsufflator (MI-E) device has been shown to reduce airway and lung secretions by preventing or reducing significant atelectasis (collapsed parts of the lung due to reduced airflow and entry) (Lechtzin *et al.*, 2006; Rafiq *et al.*, 2016). The combined use of NIV and MI-E has been shown to reduce the frequency of annual respiratory related hospitalisations (20.14 ± 41.15 days per year to 1.43 ± 3.71) (Tzeng and Bach, 2000).

1.4 Respiratory Care and Non-Invasive Ventilation (NIV) in ALS

1.4.1 Diagnosis of Respiratory Impairment and SDB in ALS

The assessment and ongoing monitoring of respiratory function in ALS forms a vital part of MDT care (Berg *et al.*, 2005). This approach increases the opportunity to identify respiratory impairment soon after diagnosis or onset of first symptoms, resulting in the earlier use of NIV which can improve HRQoL by alleviating respiratory and sleep symptoms and prolong survival (Bourke *et al.*, 2006). American (Miller *et al.*, 2009), European (Andersen *et al.*, 2007) and British (NICE, 2016) guidelines both concur the timely first assessment of respiratory function in ALS and recommend on-going assessment, specifically every 3 months (NICE, 2016). The performance of spirometry, SNIP/maximal inspiratory pressure (MIP) and capillary/arterial blood gas analysis is recommended in ALS (NICE, 2016).

1.4.2 Respiratory Impairment

1.4.2.1 Respiratory Muscle Weakness

Muscle weakness in ALS impacts both inspiratory and expiratory muscles. During ALS progression most patients will develop CRF because of a weakening diaphragm and accessory respiratory muscles including sternocleidomastoid, scalenus, trapezius,

external intercostal, pectoralis, and paraspinal muscles (Dorst and Ludolph, 2019). CRF which is often complicated by acute respiratory disease, generally pneumonia is the main cause of death in ALS (Wolf *et al.*, 2017).

Diaphragmatic muscle weakness is caused by permanent and progressive destruction of the motor units located in the diaphragm muscle and the phrenic neurones located in the ventral horn at the cervical level of the spinal cord (Pinto *et al.*, 2009; Fogarty, Mantilla and Sieck, 2018). As the diaphragm continues to weaken, the accessory muscles play a more active role in breathing, with the development of hypoxia and hypercapnia, when the accessory muscles are unable to fully compensate for a primary weakened diaphragm (Li *et al.*, 2002; Xu *et al.*, 2011). In addition, bulbar muscle weakness, including the pharyngeal and laryngeal muscles, impairs effective function of the cough reflex and increases the risk of aspiration and associated lung infections (de Carvalho, Swash and Pinto, 2019).

Diaphragmatic muscle weakness is the most significant cause of CRF in ALS and was first described more than 20 years ago (Arnulf *et al.*, 2000). Dyspnoea is strongly correlated with diaphragmatic muscle weakness (Similowski *et al.*, 2000) and in some patients respiratory symptoms, mainly dyspnoea, occur sooner than others. Weakening of the diaphragm is first apparent during REM stages of sleep and as both expiratory and inspiratory muscles weaken, it extends to the remaining sleep stages (Arnulf *et al.*, 2000). Diaphragmatic muscle weakness strongly correlates with survival in ALS with a reported survival advantage of 402 days (median survival, 217 with muscle weakness vs 619 without muscle weakness days; p=0.015) (Arnulf *et al.*, 2000). Overall, respiratory muscle weakness, mainly that of the diaphragm, directly contributes towards the development of SDB and CRF in ALS.

1.4.2.2 Spirometry

Spirometry is the most common test to measure pulmonary function. Clinically, spirometry is indicated to identify the presence of lung disease and its severity, assess the impact of co-morbidities on respiratory function and to measure the effectiveness of an intervention for example, inhaled bronchodilator therapy (Sylvester *et al.*, 2020). It is a simple, volitional test which requires the patient to use a mouthpiece and perform breathing manoeuvres under instruction from a suitably qualified healthcare profession using an open circuit spirometer. Modern spirometers will use a

pneumotachograph device to measure volume which is calculated from measurements of flow using a bidirectional flow sensor.

The patient will be connected to the spirometer via the mouthpiece. Spirometry results are commonly reported using the FVC, forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), FEV_1/FVC and are interpreted mainly using standardised residuals (z-scores) but also percent of predicted alongside appropriate reference equations (Quanjer *et al.*, 2012a; Sylvester *et al.*, 2020). Graphical representation of the parameters measured during spirometry is available from most modern spirometry devices and is called a flow volume loop (FVL). A FVL can be used to visually interpret lung data and can be used to discern between common categories of respiratory function impairment including obstructive and restrictive lung disease.

Spirometry is recommended in ALS as it allows the measurement of both FVC and slow vital capacity (SVC) (NICE, 2016). ALS patients often present with a restrictive ventilatory pattern on spirometry with reduced lung volumes rather than airflows, as observed in other lung disease, commonly COPD (Laveneziana *et al.*, 2018) (Figure 1.7). An increased RR and low Vt are characteristic of ALS (Nicholson *et al.*, 2017) and spirometry can be used to objectify these clinical features of the disease.

FVC is of particular interest in ALS as it is a sensitive marker of disease progression and predictive of both nocturnal hypoventilation and survival (Fallat *et al.*, 1979; Magnus *et al.*, 2002). FVC can be used to track disease progression over time with a reported linear decline of approximately 3.5% per a month (Schiffman and Belsh, 1993). Although, a linear decline has been reported, there is significant interpatient variability and as such FVC decline should be assessed on an individual patient basis as what may be significant for patient may not be for another (Magnus *et al.*, 2002). FVC is not a strong predictor of hypercapnia, as gas exchange is relatively well preserved until FVC is severely reduced (Kaplan and Hollander, 1994).

The performance of quality assured spirometry is important to ensure the accurate technical and clinical interpretation of results and should be performed and reported in accordance with recognised guidelines (Sylvester *et al.*, 2020). Patients with bulbar dysfunction may find spirometry challenging to perform mainly due to problems with using either a tubular or flanged mouthpiece during a forced manoeuvre (Pinto and Carvalho, 2014). As SVC strongly correlates with FVC is can be used as an alternative

manoeuvre to FVC and has recently started to be used in clinical trials. SVC correlates with ALSFRS-S and is a predictor of disease progression, requirement for NIV and survival (Pinto and de Carvalho, 2017b, 2017a; Andrews *et al.*, 2018). Both SVC and FVC should be routinely performed in patients with ALS (NICE, 2016). An SVC or FVC of <50% patient predicted value or <80% patient predicted value plus signs and symptoms of respiratory impairment, mainly orthopnoea, respiratory impairment is present (NICE, 2016).

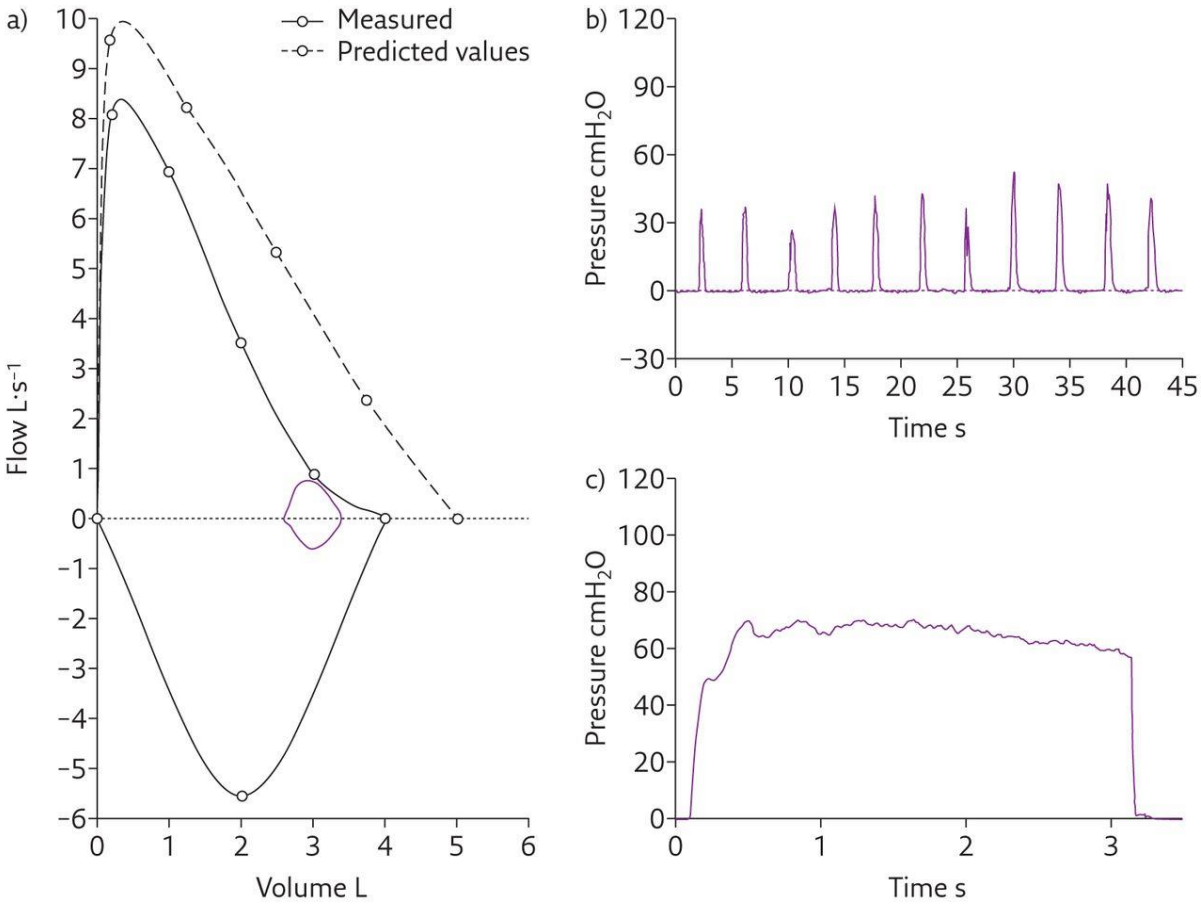

Figure 1.7. Maximal (outer black) and tidal (inner purple) FVLs at rest. The patients predicted FVL is shown as a dashed line. b) Resting SNIP traces c) Resting MIP traces. Taken from Laveneziana et al., 2018.

1.4.2.3 Sniff Nasal Inspiratory Pressure (SNIP) and Maximal Inspiratory Pressure (MIP)

SNIP and MIP are measures of maximal inspiratory muscle strength (Fitting, 2006; Caruso *et al.*, 2015; Sylvester *et al.*, 2020). Direct assessments of respiratory muscle strength including phrenic nerve stimulation and transdiaphragmatic pressure (Pdi) (Similowski *et al.*, 1989; Mills *et al.*, 1995), are complex and invasive tests which are not routinely used within clinical practice. Therefore indirect assessments, including MIP and SNIP are commonly used, and indeed in ALS patients, because they are simple, non-invasive and cost effective measures of inspiratory muscle strength (Sylvester *et al.*, 2020). Both tests require sufficient patient effort to produce clinically meaningful results, with patients breathing against a mouthpiece, as seen during MIP and using a nasal bung during SNIP.

SNIP is a common test performed to assess inspiratory muscle strength in ALS and is recommended by NICE (NICE, 2016). During a SNIP, the patient will be asked to place a nasal bung into the most patent nostril and perform a short, sharp sniff manoeuvre. The nasal bung is connected to a tube and pressure transducer which measures a pressure and records this on a visual display (Sylvester *et al.*, 2020). If performed by the same patient, SNIP generally records pressures higher than those of MIP (Miller, Moxham and Green, 1985). The pressure in the nostril, agrees with intrathoracic pressure and respiratory muscle strength, but special consideration should be made in patients with severe airflow obstruction as the pressure generated in the lungs does not transmit effectively to the nose and therefore results may be underestimated (Koulouris *et al.*, 1989; Héritier *et al.*, 1994).

Similar to the SVC and FVC the performance of SNIP and MIP should be quality assured and interpretation should be made using appropriate reference ranges (NICE, 2016; Sylvester *et al.*, 2020). If SNIP or MIP is <40cmH_2O or <65cmH_2O in men and <55cmH_2O in women plus signs and symptoms of respiratory impairment, mainly orthopnoea, respiratory impairment is probable. (NICE, 2016). Serial performance of SNIP and MIP can be used to monitor inspiratory muscle strength over time with a decrease of >10cmH_2O over 3 months is suggestive of respiratory muscle strength decline (NICE, 2016).

SNIP compared to FVC, better predicts mortality or the need for tracheostomy within 1 year (Capozzo *et al.*, 2015). Furthermore, there is a linear relationship between SNIP

and nocturnal desaturation and lower SNIP values are associated with the development of hypercapnia in ALS (Chaudri *et al.*, 2000; Carratù *et al.*, 2011). The performance of SNIP and MIP can be challenging in ALS especially those with significant bulbar dysfunction and therefore the most clinically effective methodology for assessment of inspiratory muscle strength may indeed be the one which patients can perform comfortably achieving technically sound results (Pinto and de Carvalho, 2018).

1.4.2.4 Measurements of Arterial Blood Gases (ABG)

Measurements of arterial blood gases can be made either by arterial or capillary sampling. An arterial blood gas (ABG) is the gold standard sampling method to assess for the requirement of long-term oxygen therapy (LTOT) and involves inserting a needle into the radial artery (Hardinge *et al.*, 2015; NICE, 2019). Although marked as the gold standard it is not commonly used to sample respiratory blood gases in ALS, mainly due to its invasive nature and discomfort experienced by some patients (Sylvester *et al.*, 2020). As an alternative, arterialised blood sampling from the earlobe, is a common, less invasive and accurate method to determine pH, $PaCO_2$ and PaO_2 (Pitkin, Roberts and Wedzicha, 1994; Fajac *et al.*, 1998; Eaton, Rudkin and Garrett, 2001).

A capillary blood gas (CBG) sample contains both arterial and venous blood and the arteriovenous (AV) difference in theory determines the agreement between arterial and capillary blood sampling. The AV difference is greater for PaO_2 compared to pH and $PaCO_2$ and should be considered when making clinical decisions, for example the prescription of LTOT (Sylvester *et al.*, 2020). A CBG involves heating up the earlobe with a vasoactive agent, normally in the form of a cream. After 15 minutes the cream is removed and the earlobe punctured with a lancet of <3mm approximately 3mm from the edge of the earlobe (Sylvester *et al.*, 2020). A blood sample of (90–150 µL) is taken and processed immediately to obtain measurements of pH, $PaCO_2$ and PaO_2. A medical gauze is used to ensure any bleeding stops.

Hypercapnia, defined by a $PaCO_2$ >6.0kPa (NICE, 2016), can vary across the clinical spectrum of ALS and should be measured soon after diagnosis or onset of first symptoms and every 3 months thereafter (NICE, 2016). The early detection of CRF in ALS is important as to provide a timely assessment and initiation of NIV. However nocturnal hypercapnia may be a more significant marker rather than a ‘one off’

measurement in an outpatient clinic and as such the use of nocturnal capnography may be preferred but not available in all hospitals. Nevertheless, NICE recommend that ALS patients with a $PaCO_2$ >6.0kPa or ≤6.0kPa with signs and symptoms of respiratory impairment are referred for specialist assessment for NIV. Measurements of $PaCO_2$ are an important part of the diagnosis and management of CRF in ALS.

1.4.3 Sleep Disordered Breathing (SDB)

Normal sleep places a strain on the capacity-drive relationship of the respiratory system and the time tension index of the diaphragm muscle which can be further exacerbated in ALS (Gould *et al.*, 1988). In healthy individuals, RR, Vt and pharyngeal muscle tone decrease (Douglas *et al.*, 1982; Wiegand, Zwillich and White, 1989; Kubin, Davies and Pack, 1998). During REM sleep diaphragmatic muscle tone is well preserved with almost complete loss of intercostal muscle activity and therefore adequate diaphragmatic muscle strength is crucial to allow sufficient nocturnal ventilation (Kubin, Davies and Pack, 1998). In ALS, the combined effects of a weak diaphragm, reduced pharyngeal muscle strength and supine position result in SDB including nocturnal hypoventilation (Arnulf *et al.*, 2000).

Even in the early stages of ALS, respiratory function during sleep is adversely impacted even though respiratory and bulbar muscle weakness may not be significant enough to cause daytime symptoms of breathlessness. Nevertheless, as ventilation in ALS is further compromised during sleep, it is often the case that respiratory dysfunction in the sleeping state occurs sooner than signs and symptoms of daytime hypercapnic respiratory failure (Ward *et al.*, 2005).

Continuous nocturnal monitoring is of importance in ALS particularly in patients who have sleep related respiratory symptoms and includes overnight pulse oximetry, nocturnal transcutaneous capnography, cardio-respiratory polygraphy and polysomnography (de Carvalho *et al.*, 2009; Storre *et al.*, 2011; Hardinge *et al.*, 2015). SDB has been reported in between 17-76% of patients diagnosed with ALS (Gaig and Iranzo, 2012).

1.4.3.1 Overnight Pulse Oximetry

Overnight pulse oximetry is a simple, practical, non-invasive test which measures percutaneous oxygen saturation (SpO_2) and heart rate (HR) overnight. It employs the use of a pulse oximeter which attaches to the patient's index finger and connected to

a watch like device which is placed on the patient's wrist. It is clinically useful as it measures SpO_2 and HR during a physiologically stressful state, when the patient is, mostly, supine and sleeping (de Carvalho, Swash and Pinto, 2019).

The pattern of the SpO_2 can be particularly useful in determining the presence of REM related hypoventilation (Figure 1.8) which is observed in 60% of patients with an associated rise in transcutaneous CO_2 ($PtcCO_2$) of >10mmHg beyond baseline levels (Boentert *et al.*, 2015). An SpO_2 pattern indicative of nocturnal hypoventilation is a predictor of survival in ALS and in some ALS phenotypes, mainly those with predominant UMN involvement and preserved muscle strength, can be suggestive of a central respiratory drive impairment (de Carvalho *et al.*, 2009).

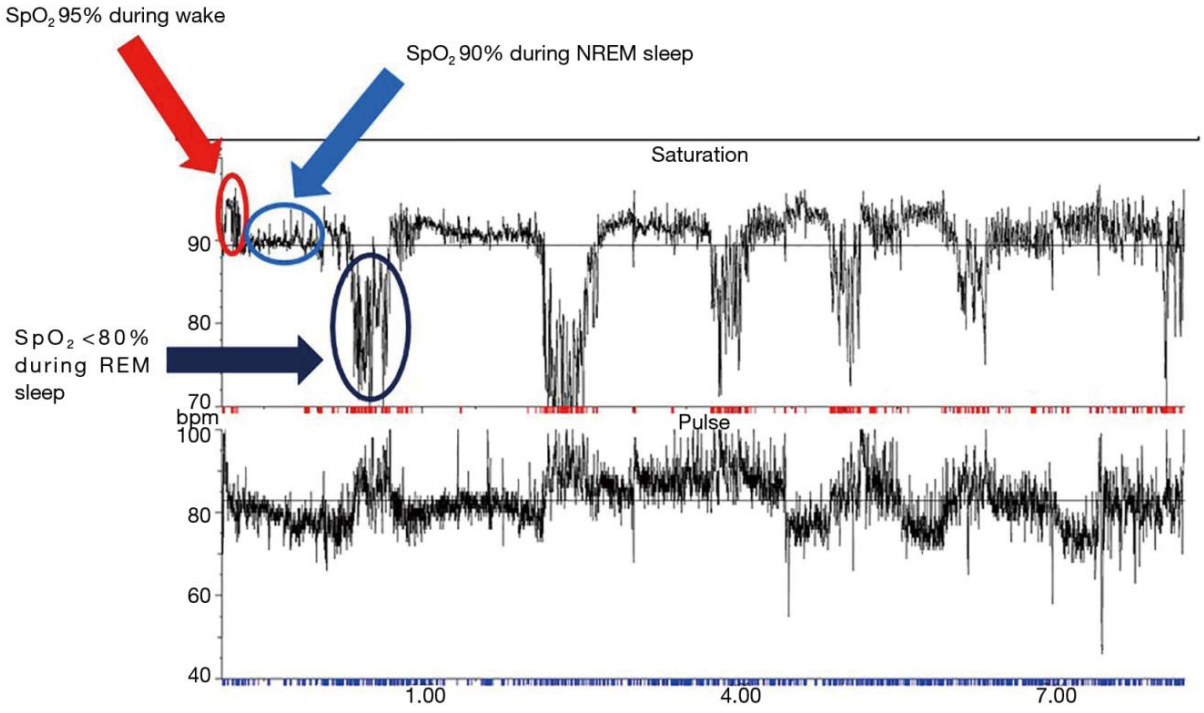

Figure 1.8. Overnight pulse oximetry traces of a patient with MND and SDB. The patient hypoventilates during assumed non-REM sleep and further hypoventilates during assumed REM sleep (red arrow is awake; light blue arrow is non-REM sleep and dark blue arrow is REM sleep). Taken from D'Cruz et al., 2018.

The AHI is a diagnostic marker of OSAS (AASM, 2023) and correlates with the oxygen desaturation index (ODI), a parameter which is obtained during overnight pulse oximetry (Sharma *et al.*, 2024).

1.4.3.2 Cardio-respiratory Polygraphy

In addition to SpO2 and HR, cardio-respiratory polygraphy, measures nasal flow, respiratory effort using chest and abdomen impedance belts and sleep position (Nuredini *et al.*, 2024) (Figure 1.9). Cardio-respiratory polygraphy is a non-invasive and clinically useful test to perform in ALS with the utility of measuring AHI which is significantly higher in REM and associated with nocturnal hypoxia (Ferguson *et al.*, 1996). The AHI in ALS has been reported to decrease with disease progression. In patients with an ALS diagnosis of <1 year, AHI was 23.4±14.6 events/hour, decreasing to 18.1±13.9 events/hour at 1–2 years, and to 15.8±15.2 events/hour in those diagnosed with ALS for > 2 years and is likely linked to progression of diaphragmatic muscle weakness (Santos *et al.*, 2003).

Obstructive apnoeas are less common in ALS compared to other sleep conditions including OSAS. The prevalence of OSAS in ALS is variably reported in the literature (Gay *et al.*, 1991; Kimura *et al.*, 1999) and although the presence of apnoeas were not associated with nocturnal hypoventilation, patients with an obstructive AHI ≥5 per an hour had a shorter time to tracheostomy or death (Quaranta *et al.*, 2017). Bulbar impairment plays a significant role in the aetiology of OSAS in ALS but is again variably reported within clinical cohorts of ALS patients. Whilst some studies report no association between bulbar impairment and OSAS, other studies report a link between the two and suggest that bulbar impairment combined with predominantly supine sleeping position due to global muscle weakness can induce collapse of the upper airways (Kimura *et al.*, 1999).

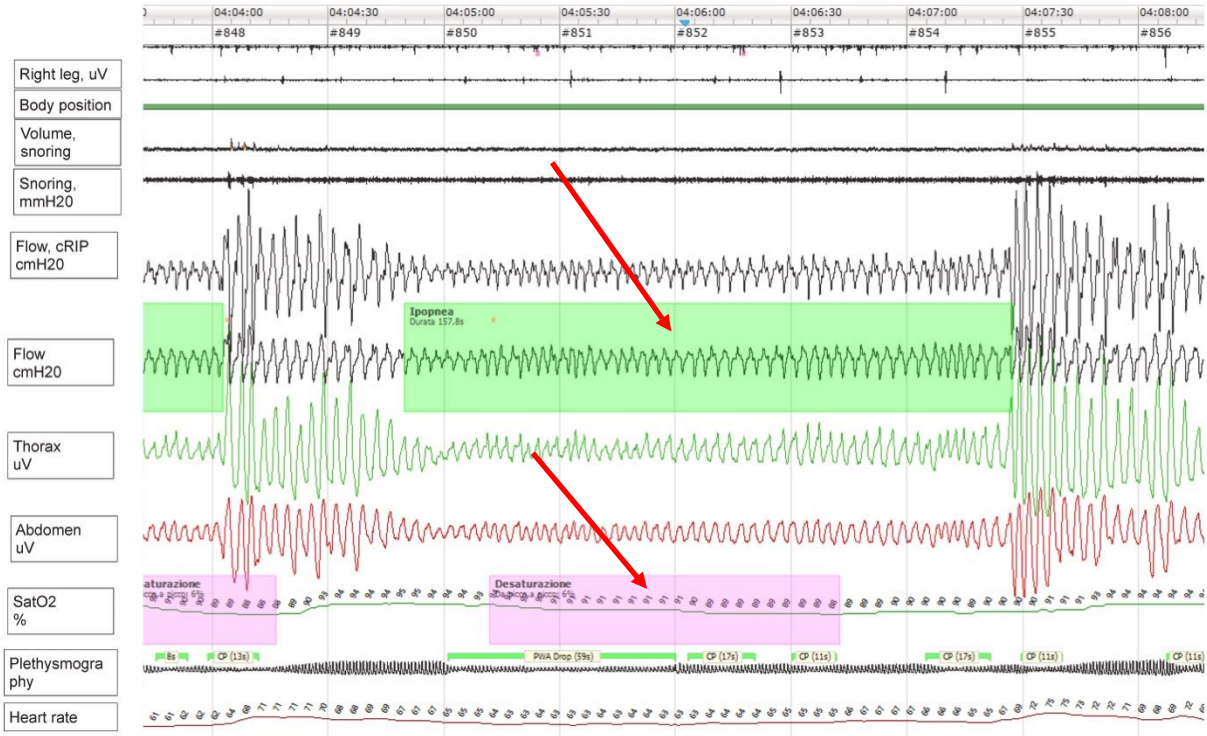

Figure 1.9. Cardio-respiratory polygraphy performed by a patient diagnosed with ALS. The green highlighted section is an hypopnea. The pink highlighted section is an oxygen desaturation ≥ 3% (marked using red arrows). Taken from (Nuredini *et al.*, 2024).

1.4.3.3 Transcutaneous Capnography

Transcutaneous capnography is a modern diagnostic test used to assess for presence of nocturnal hypoventilation and is strongly recommended in ALS (Ogna *et al.*, 2016; Boentert *et al.*, 2018). Measurements of $PtcCO_2$ are obtained by attaching a probe to the patient's skin, usually forearm or earlobe during sleep and strongly correlate with measurements of $PaCO_2$ obtained from ABG (Storre *et al.*, 2011). In a similar way to using the SpO_2 trace from overnight pulse oximetry, the pattern of the $PtcCO_2$ trace can be used to identify nocturnal periods of hypoventilation and associated hypercapnia. A mean $PtcCO_2$ >5.33kPa for >10% of the total sleep study is suggestive of impaired ventilation (Ogna *et al.*, 2016). Similar to overnight pulse oximetry, $PtcCO_2$, is a more sensitive rather than specific diagnostic test and is unable to identify the cause of nocturnal hypoventilation/hypercapnia, for example because of ALS, OHS or COPD (Storre *et al.*, 2011).

1.4.3.4 Polysomnography (PSG)

PSG has been extensively investigated in ALS (Zhang *et al.*, 2023). Reduced duration of REM sleep particularly in the presence of significant diaphragmatic muscle weakness has been reported in ALS (Ferguson *et al.*, 1996) with an interesting hypothesis that this is a protective mechanism against REM related hypoventilation (Arnulf *et al.*, 2000). Interestingly however, in ALS patients with less severe respiratory muscle weakness, hypoventilation is commonly observed in both REM and non-REM sleep and is reported to be associated with a reduced central respiratory drive (de Carvalho *et al.*, 2009). Studies involving the performance of PSG in ALS have reported increased sleep latency, decrease efficiency and fragmented sleep architecture (Lo Coco and La Bella, 2012). ALS patients generally report poor sleep quality which correlates with the stage of disease progression. Poor sleep quality is associated with a reduced ALSFRS-R score and depression in ALS (Lo Coco and La Bella, 2012; Goudarzi *et al.*, 2023).

1.5 Home Mechanical Ventilation (HMV) for Long-term Respiratory Care

Two decades have nearly passed since the Eurovent study (Lloyd-Owen *et al.*, 2005) reported a variable and increasing prevalence of home mechanical ventilation (HMV) in Europe. In 2016 a systemic review which included the results from a series of observational studies from USA, Canada and Europe, albeit with those studies investigating COPD being excluded (MacIntyre *et al.*, 2016) continued to report significant heterogeneity in the systems, processes and clinical practices employed to deliver HMV services. Both studies performed a decade apart continued to report an ever increasing number of patients receiving HMV, the clinical evidence base for which has improved but is still limited, with the indications for commencing non-invasive, rather than invasive, ventilation (Lloyd-Owen *et al.*, 2005; MacIntyre *et al.*, 2016; Simonds, 2016).

The prevalence of HMV per 100,000 population in the UK was 4.1 per 100,000 population (Lloyd-Owen *et al.*, 2005) with 13% of HMV patients using invasive ventilation via tracheostomy. In a similar study, prevalence of HMV in Australia was 9.9 and 12 per 100,000 in New Zealand with a significantly lower proportion of patients

using invasive ventilation at home (3.1%) (Garner *et al.*, 2013). Although HMV has been historically used to treat CRF and SDB in patients diagnosed with neuromuscular conditions, there has been a substantial increase in the number of patients with COPD and hypoventilation syndrome (OHS) using HMV (Janssens *et al.*, 2003).

These shifting trends of HMV observed across Europe, Canada and the USA, can mainly be attributed towards the reduction in respiratory related hospital admissions of up to 2 years in COPD and 5 years in non-COPD patients. In addition the move towards using cheaper pressure mode NIV devices has improved the overall cost effectiveness of HMV for healthcare providers (Janssens *et al.*, 2003; Simonds, 2016). In the UK, data shows approximately 40% of HMV patients have a diagnosis of neuromuscular disease (NMD), 30% disease(s) of the lung or airways and 30% restrictive chest wall disease (RCWD).

1.5.1 Invasive mechanical ventilation (IMV)

Invasive mechanical ventilation (IMV) involves insertion of an endotracheal (ET) tube or tracheostomy tube connected to a humidified circuit attached to a ventilator. IMV is generally applied within a critical care setting in sedated or unconscious patients to maintain life in clinically acute, life-threatening situations including a compromised airway, impaired ventilation or hypoxaemic respiratory failure (Hickey, Sankari and Giwa, 2024).

IMV can deliver both pressure and volume mode ventilation and is considered a closed system and single compartment lung model as the use of either a ET or tracheostomy tube overcomes turbulent airflow and resistance caused by the upper airway (Rabec *et al.*, 2011; Hickey, Sankari and Giwa, 2024). IMV delivers positive pressure breaths to the patient and relies on the resistance and compliance of the respiratory system. IMV breaths are either triggered by the patient during spontaneous breathing or by the ventilator if the patient is unable to trigger independently (Hickey, Sankari and Giwa, 2024). During spontaneous breathing the inspiratory muscles contract causing a negative pleural pressure and lung expansion is the result of a subsequent increase in transpulmonary pressure. During ventilator controlled breaths, IMV uses positive pressure to drive gas into the airways and lungs, creating a positive pressure system (Hickey, Sankari and Giwa, 2024).

1.5.2 Non-Invasive Ventilation (NIV)

NIV involves using a patient interface (mask) connected to a ventilator via a tube (Ackrivo *et al.*, 2021) (Figure 1.10). It can be delivered in both acute and chronic settings but requires strict patient selection, monitoring and optimisation to ensure positive outcomes and maintain patient safety (Davidson *et al.*, 2016; Messer *et al.*, 2024). The purpose of NIV is like that of IMV, to ensure adequate pulmonary gas exchange, by maintaining sufficient levels of PaO_2 and $PaCO_2$ in arterial blood and reduce the work of breathing (WOB) by unloading the respiratory muscles (Kallet and Diaz, 2009).

NIV devices can deliver positive end expiratory pressure (PEEP) which permits recruitment of additional alveolar units, and the overall power output required from the inspiratory muscles to overcome intrinsic PEEP is reduced (Banner, Kirby and MacIntyre, 1991; Kacmarek *et al.*, 1995). NIV can also provide non-respiratory support and has several effects on cardiac function. It can reduce venous return and thus can support patients diagnosed with heart failure (HF) or fluid overload (Kallet and Diaz, 2009). However, if delivered inappropriately, NIV can have negative consequences on cardiac output (Marini, Culver and Butler, 1981; Lemaire *et al.*, 1988).

Figure 1.10. A patient using NIV with a single limb circuit with intentional leak and a nasal interface (marked using red arrows). Taken from Ackrivo et al., 2021a.

During NIV delivery, assuming there is no significant increase in dead space ($\dot{V}_D$), minute ventilation ($\dot{V}_E$) is increased because of increasing tidal volume (Vt) either during ventilator or patient triggered breaths (MacIntyre, 2019). The resultant effect is a substantial increase in alveolar ventilation ($\dot{V}_A$) providing increased O_2 and CO_2 in alveolar gas (more O_2 is delivered, and more CO_2 is removed). The relationship between $\dot{V}_A$ and partial pressures in alveolar gas is complex but is mathematically represented using the following formulas, where PIO_2 is inspired oxygen, $\dot{V}O_2$ is total body oxygen consumption, $\dot{V}CO_2$ is total body CO_2 production, and k is a constant: (Comroe *et al.*, 1963).

$PaO_2 = PIO_2 - (\dot{V}O_2/ \dot{V}_A) \times k$

$PaCO_2 = (\dot{V}CO_2/ \dot{V}_A) \times k$

The effects of ventilation and perfusion ($\dot{V}/\dot{Q}$) are different for both CO_2 and O_2. CO_2 is highly soluble in blood and there is a linear relationship between PCO_2 and CO_2 content in pulmonary venous blood (West and Wagner, 1998). PO_2 is poorly soluble in plasma and haemoglobin (Hb) is fully O_2 saturated at a pressure of >9.33–10.66kPa. Consequently, total PCO_2 is a flow-weighted average of all perfused alveolar units which received inspired gas and, in contrast PO_2 which is not a flow-weighted average depends on regional $\dot{V}/\dot{Q}$ matching (MacIntyre, 2019). In clinical practice the application of NIV will increase systemic O2 levels which tend to plateau with increases in $\dot{V}_E$ and $\dot{V}_A$, consideration should be given to Hb levels and $\dot{V}/\dot{Q}$ matching which can influence the effectiveness of NIV. As $\dot{V}_E$ and $\dot{V}_A$ increase with the use of NIV, systemic CO_2 will fall, as there is less dependence on $\dot{V}/\dot{Q}$ (Comroe *et al.*, 1963; MacIntyre, 2019) (Figure 1.11).

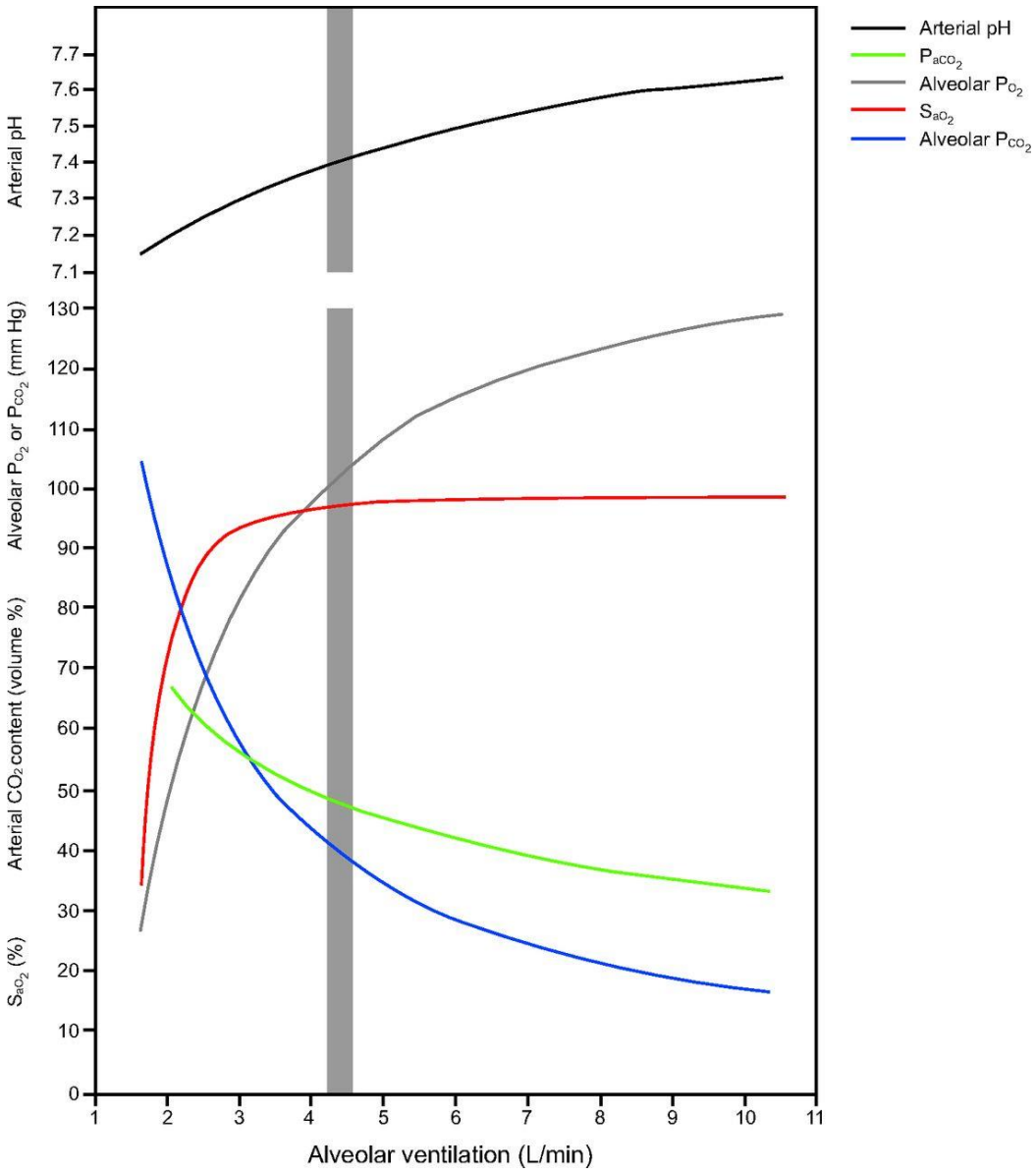

Figure 1.11. The relationship of $\dot{V}_A$ to alveolar PO_2 and PCO_2 and SaO_2 and $PaCO_2$. Oxygen consumption is 250 mL/min and CO_2 production is 200 mL/min. The shaded area represents a normal $\dot{V}_A$. Taken from Comroe et al., 1963; MacIntyre, 2019.

NIV can reduce the patients WOB by unloading the muscles involved in respiration and can be achieved in two ways; 1) reduce the total number of breaths that require the patient to volitionally trigger the ventilator and 2) for a given Vt and during ventilator assisted breaths, the total respiratory muscle load is lower and therefore the total muscle power output required is reduced. The simplified equation for mechanical muscle motion can be used to illustrate these physiological effects of NIV on respiratory muscle function, where for a given flow ($\dot{V}$) and change in volume (ΔV), P_{tot}

is the total pressure required to overcome respiratory system elastic recoil (P_{el}) and airway resistance (R_{aw}). C_{rs} is compliance of the respiratory system and R_{rs} is resistance of the respiratory system (Marini and Crooke, 1993; Duiverman *et al.*, 2017; MacIntyre, 2019) (Figure 1.12).

$P_{tot} = P_{el} + R_{rs}$

$P_{tot} = (\Delta V / C_{rs}) + R_{aw} \times \dot{V})$

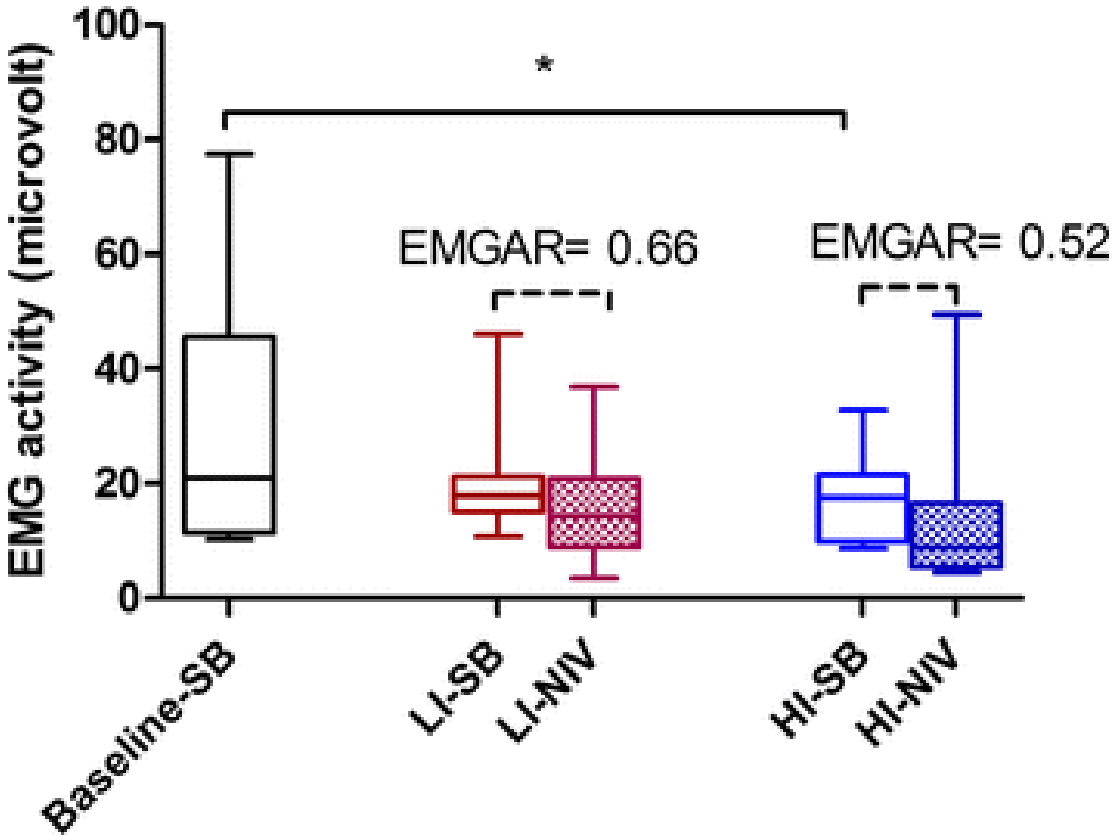

Figure 1.12. Total EMG activity of the intercostal and diaphragm muscles during spontaneous breathing (SB) and under NIV. LI is low intensity, and HI is high intensity NIV. An EMGAR of 0.66 is a 1.5-fold reduction in EMG activity using LI and an EMGAR of 0.52 is a 1.9-fold reduction in EMG activity using HI compared to SB. *=p<0.01. Taken from Duiverman et al., 2017.

1.5.3 Clinical Effects of NIV in Disease

1.5.3.1 COPD

Patients with end-stage COPD are at a high risk of developing CRF characterised by debilitating symptoms, reduced HRQoL and increased morbidity and mortality (Budweiser *et al.*, 2007). CRF in COPD can be treated with both home NIV and home oxygen therapy (HOT) (Kotanen, Brander and Kreivi, 2022). In 2017 an RCT was performed to investigate the beneficial effects of both home NIV and HOT on readmission rates and mortality in hypercapnic COPD patients after an acute exacerbation (AE-COPD) requiring admission to hospital (Murphy *et al.*, 2017). The trial reported COPD patients discharged from hospital following an AE-COPD, received significant reductions in hospital readmission and death within 12 months when using non-home NIV and HOT (Murphy *et al.*, 2017) (Figure 1.13).

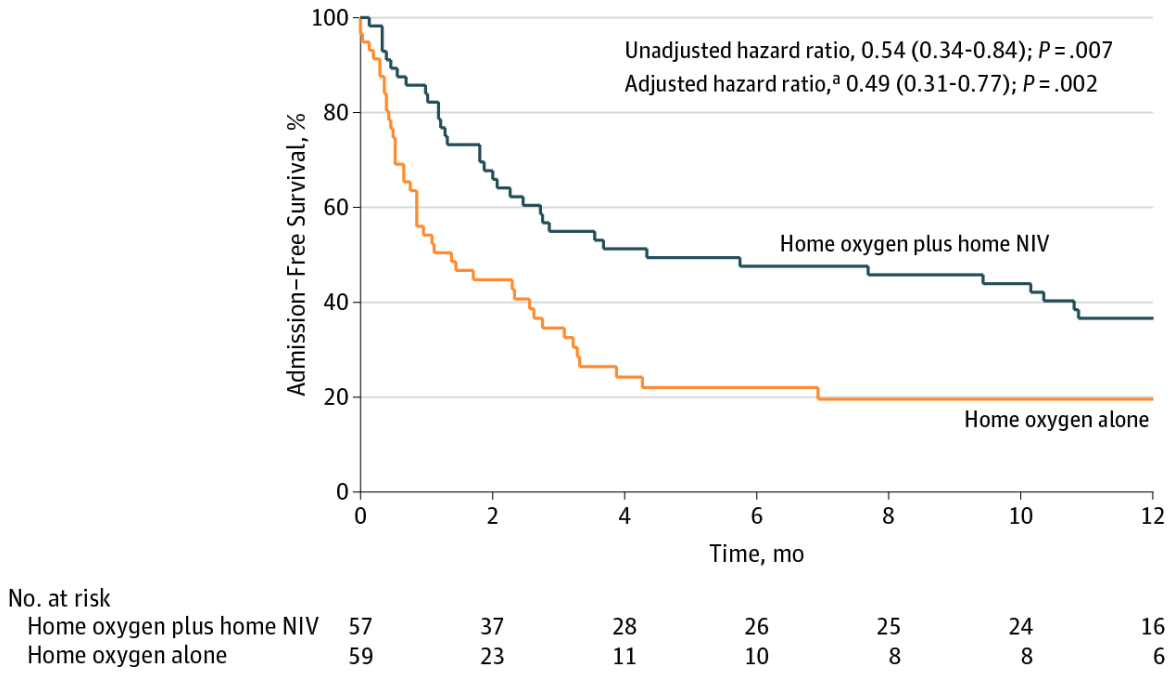

Figure 1.13. Kaplan–Meier survival curves of time to readmission or death from randomisation to the end of trial follow up at 1 year. (a) adjusted for number of COPD readmissions with previous year, prior use of HOT, age and BMI. Taken from (Murphy *et al.*, 2017).

1.5.3.2 OHS

There has been significant growth in the use of home NIV to treat obesity related respiratory failure, particularly OHS, where patients demonstrate a BMI >30 kg/m^2 and daytime hypercapnia. Studies have identified certain phenotypes of OHS including those with significant nocturnal desaturation, hypercapnia and progressively worsening hypoventilation in rapid eye movement (REM) stage sleep (Pépin *et al.*, 2016).

A recent RCT has investigated the use of an 'intelligent' mode of NIV which utilises both volume and pressure modes to deliver a 'hybrid' type of ventilation in OHS (Patout *et al.*, 2020). Patients diagnosed with OHS from multi hospitals were randomised to either receive pressure targeted NIV or volume targeted auto-adjusting EPAP with a primary trial endpoint of sleep quality at 2 months. Pressure targeted NIV and volume targeted auto-adjusting EPAP adherence were similar at 6.2 hours per a night with a non-significant mean reduction of $PaCO_2$ (pressure targeted mode, -0.87 kPa 95% CI: -1.12 to -0.46; volume targeted auto-adjusting EPAP, -0.87 kPa 95% CI: -1.14 to -0.50, p=0.984). The trial concluded that pressure targeted mode and volume targeted auto-adjusting EPAP had similar effects on sleep quality and nocturnal ventilation in patients with OHS (Patout *et al.*, 2020).

1.5.3.3 ALS

Historically, invasive home ventilation via tracheostomy has been used to ventilate patients diagnosed with ALS (Moss *et al.*, 1993). A pioneering study, performed more than 25 years ago, investigated the outcomes of 20 ALS patients allocated either home NIV or palliative care (Pinto *et al.*, 1995). The results of the study showed that patients receiving home NIV demonstrated a significantly longer all cause survival and survival from improving nocturnal gas exchange (p = 0.006 and p = 0.0004, respectively) (Pinto *et al.*, 1995).

To date there has been only one RCT performed to investigate the clinical benefit of home NIV in ALS (Bourke *et al.*, 2006). A total of 92 patients diagnosed with ALS were randomised to either the home NIV or control group. Results from the study demonstrated a significant survival advantage of 219 days (range, 75–1,382 days) for patients using home NIV compared to 171 days (range, 1–878 days) for the control group. Interestingly, the greatest survival advantages were observed in those patients with mild bulbar dysfunction (Bourke *et al.*, 2006).

Optimising the use of NIV is of particular importance to ensure patients receive maximum clinical benefit. Attention to factors which can influence the number of hours patients will use NIV should be considered and these include NIV mode, settings, interface, place of initiation and airway secretions (O'Brien *et al.*, 2019). Pressure and volume are the two main types of NIV mode however the optimum methodology remains unclear. In addition, evidence is required regarding the effectiveness of more modern modes of NIV including those which can automatically adjust settings to meet patient specific ventilatory requirements.

1.5.4 NIV Modes

Although clinically valuable information is provided by respiratory blood gas analysis and sleep studies, a detailed understanding of NIV mode, triggering modality, circuit type, pressurisation slope and interface type are required as they will have physiological consequences on patient-ventilator synchrony and the overall effectiveness of NIV.

When NIV was first introduced there were a limited number of available ventilators all with very few adjustable settings. There are now more than 30 brands offering a wider range of ventilators and adjustable settings (Gonzalez-Bermejo *et al.*, 2006). Unlike other medical devices, ventilators are not required to comply with such stringent medical regulations and as such manufactures are free to give different names to the same type of ventilator or even create new names for ventilators which carry only minor iterations to previous models. This contributes to the wide-ranging and often confusing terminology used to describe NIV modes.

NIV in theory could be provided using the same ventilators and modes as IMV however in reality it is delivered using either volume or pressure modes. More recently, 'intelligent' modes of NIV have been developed which utilise both volume and pressure modes to deliver a 'hybrid' type of NIV (Windisch *et al.*, 2005).

NIV is widely used as a first-line clinical strategy to improve $\dot{V}_A$ for treatment of chronic hypercapnic respiratory failure (Nam *et al.*, 2020; Park and Suh, 2020). An NIV device is connected to a circuit which consists of a tube and interface which is attached to the patient. NIV devices can commonly deliver both pressure or volume mode ventilation, each demonstrating advantages and disadvantages within clinical practice and

therefore the preferred choice of NIV mode should be aligned with individual patient requirements (Nam *et al.*, 2020). Pressure mode NIV is able to compensate for unintentional interface leak and limit high airway pressures where in contrast volume mode NIV is able to deliver accurate Vt (Nam *et al.*, 2020).

NIV devices have proprietary algorithms which are used to estimate Vt, RR and leak compensation and each NIV device can utilise different circuit configurations, including vented (has intentional leak) and non-vented (has no intentional leak) (Park and Suh, 2020). When applying NIV, healthcare professionals should consider the status of the patient's clinical condition and as well the prognosis of the primary disease. The patients daily functional status, expected duration of NIV use to achieve effective ventilation, social support and financial impact should also be considered before commencing NIV (Park and Suh, 2020).

1.5.4.1 Volume Mode

In this mode the ventilator is programmed to deliver a fixed target tidal volume when triggered by the patient. The ventilator will provide a pressure which is required to achieve this volume based on a range set by a clinician, despite the patient's own contribution towards ventilation. Airway pressure (P_{aw}) is not constant and is a result of the interaction between the patients spontaneous breathing efforts, the compliance and resistance of the respiratory system and the ventilator settings (Figure 1.14). Any additional inspiratory attempts will not lead to any changes, increases or decreases in flow or volume, but instead a decrease in P_{aw} (Schettino *et al.*, 2003).

Each patient's breath will be delivered within the same flow-time profile and the volume will be determined using the area under the flow-time curve, meaning that the main advantage of employing volume mode NIV is the ability to deliver a strict volume, independent of the resistance and compliance of the patient's respiratory system. The main disadvantage of volume mode NIV is the inherent nature of the modality, in that, the delivery of a fixed volume will not allow the patients varying ventilatory requirements to be taken into consideration.

Another disadvantage is the inability to compensate for interface leaks which are a common side effect of the therapy. When the patients interface leaks, there will be no compensatory increase in flow and the overall pressure generated will be lower and as such the delivered volume will be proportionally smaller (Windisch *et al.*, 2005).

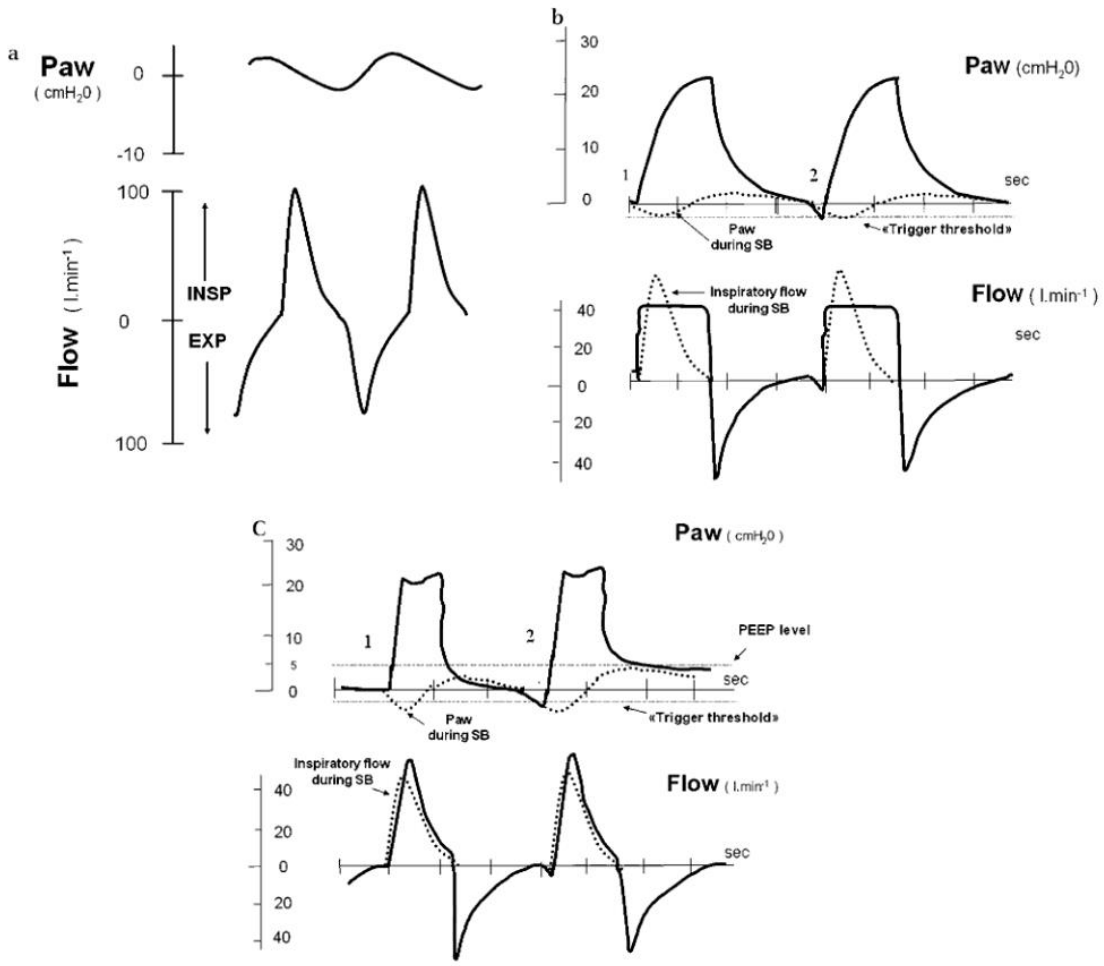

Figure 1.14. Airflow and interface pressure during (a) spontaneous breathing, (b) volume mode NIV and (c) pressure mode NIV. 1 is controlled cycle; 2 is assisted (supported) cycle. In (b) and (c) the dashed lines represent SB traces from (a). Taken from Rabec et al., 2011.

1.5.4.2 Pressure Mode

In this mode the ventilator is programmed to deliver a fixed positive pressure when triggered by the patient. To ensure a constant P_{aw} over a given time, airflow is adjusted by the ventilator. The ventilator will constantly monitor the flow rate and P_{aw} to determine the airflow adjustments which are required to maintain a 'square wave' pressure (Figure 1.14).

When the ventilator is triggered by the patient the initial increase in airflow at the start of inspiration is rapid as there is a large difference between the circuit and target pressures (Rabec *et al.*, 2011). As the pressure gradient narrows over the duration of

inspiration, airflow decreases until circuit and target pressure are equal and inspiratory airflow finishes, preparing for expiration.

A disadvantage of pressure mode NIV is the inability to ensure a set volume, because the volume delivered is dependent on the interaction between the compliance and resistance of the respiratory system, the patient's inspiratory effort and the target inspiratory pressure (Rabec *et al.*, 2011). In contrast to volume mode, pressure mode NIV can compensate for interface leaks (Storre *et al.*, 2006). The main differences between pressure and volume NIV are listed in Figure 1.15.

	Volume-targeted	Pressure-targeted
Pressure curve pattern		
Flow curve pattern		
Type of ventilatory assistance delivered	Fixed volume in spite of changing resistance (R) and compliance (C)	Fixed pressure. Tidal volume may vary with changes in C and R
Controlled variable	Maintains a constant inspiratory preset flow	Maintains a constant inspiratory preset pressure
Breath-to-breath adjustments	Not possible: ventilator delivers a fixed assistance	Possible: flow and volume can be varied in a breath-to-breath basis
Possibility to guarantee a fixed delivered tidal volume	Yes (if no leaks)	No
Peak airway pressure	Not limited*	Limited (useful in patients at risk of barotrauma or gastric distension
Leak compensation	Poor, leaks may significantly reduce delivered volume and induce hypoventilation	Good for mild to moderate leaks

Figure 1.15. Comparison between volume and pressure mode NIV. R=resistance of respiratory system. C=compliance of the respiratory system. *except if maximal pressure limit is reached. Taken from Taken from Rabec et al., 2011.

1.5.4.3 Volume targeted NIV with auto-adjusting EPAP

Volume targeted NIV with auto-adjusting EPAP is an advanced volume targeted mode of NIV with the ability to automatically adjust all NIV settings within a programmed

range to support in real time the patients ventilatory requirements (ResMed, 2016). It is designed to take into consideration the patient's anatomical $\dot{V}_D$ and target the patient's $\dot{V}_A$ to provide effective ventilation. Volume targeted NIV with auto-adjusting EPAP monitors breath by breath RR and $\dot{V}_A$, comparing this data to target values and then adjusts automatically to meet patient requirements (Jaye *et al.*, 2009; ResMed, 2016) (Figure 1.16).

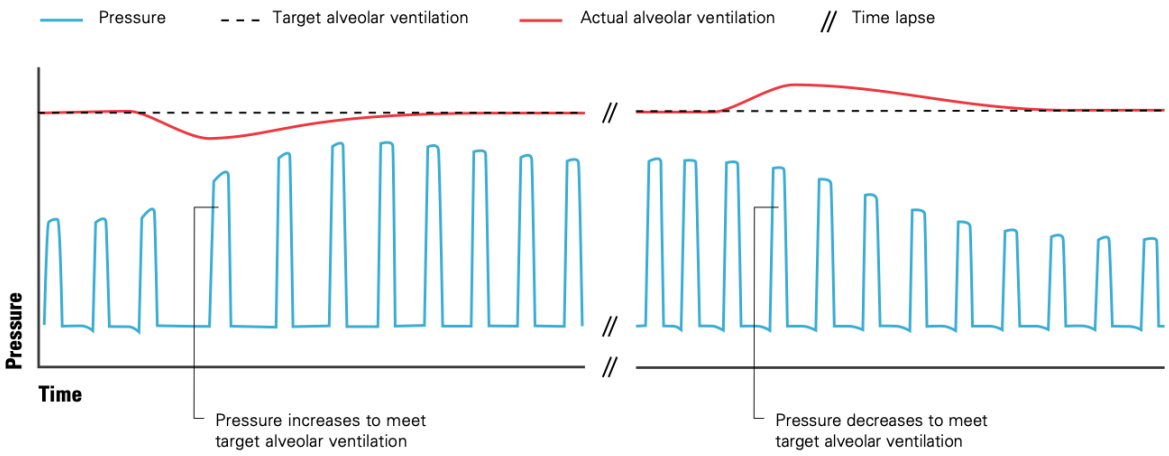

Figure 1.16. Pressure response over time using volume targeted NIV. Taken from ResMed, 2016.

When commencing volume targeted NIV with auto-adjusting EPAP a minimum and maximum inspiratory and expiratory positive airway pressure (IPAP; EPAP) will be set allowing the ventilator to deliver a target $\dot{V}_A$ by providing a variable IPAP and EPAP within a predetermined range. The patient's height is used to calculate a target Vt to guarantee a set $\dot{V}_A$. The anatomical $\dot{V}_D$ ($\dot{V}_A$ = minute ventilation (MV) minus anatomical $\dot{V}_D$ ventilation) is calculated using the patients height (Hart, Orzalesi and Cook, 1963). All other NIV settings will be programmed as per standard pressure or volume mode NIV and the intelligent backup rate (iBR) mode will be turned onto automatic.

Volume targeted ventilators in auto-adjusting mode can also automatically adjust EPAP and iBR settings in response to upper airway obstruction and/or failed spontaneous breaths. iBR adjusts between two determined thresholds, the patients target BR and the patients background frequency (which is two-thirds of the patients target BR) (ResMed, 2016). This provides the patient with the maximum opportunity to spontaneously trigger the ventilator. When the patient fails to produce a spontaneous breath, the iBR will activate and adjust from the background frequency

to the target rate within 4-5 breaths. The iBR is reset once the ventilator detects the recommencement of the patients spontaneous breathing (Figure 1.17) (ResMed, 2016).

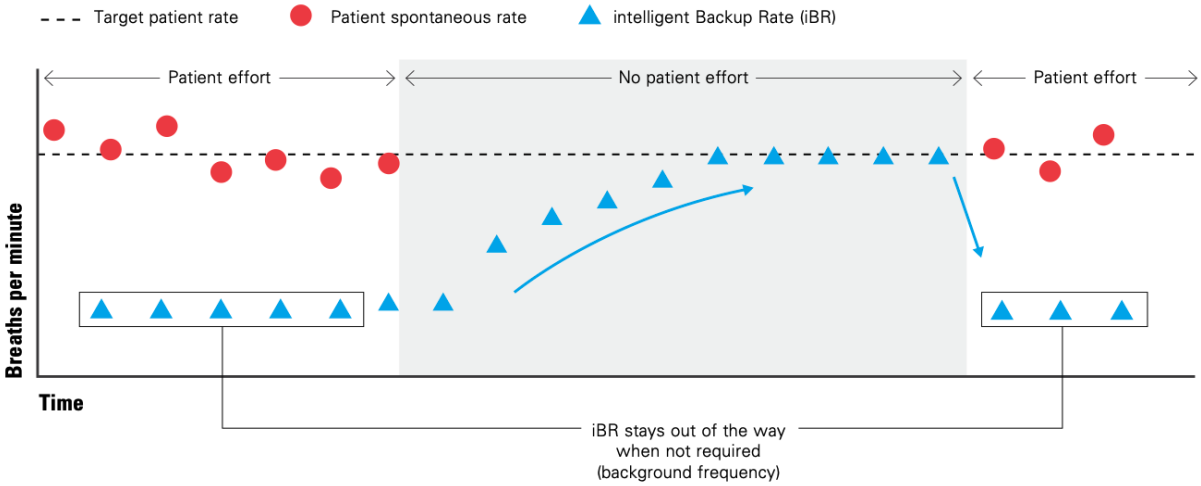

Figure 1.17. Breaths per a minute overtime using iBR. Taken from ResMed, 2016.

1.5.5 NIV settings

1.5.5.1 Inspiratory Positive Airway Pressure (IPAP)

IPAP is the pressure that is delivered and maintained in the patient's interface during the ventilator preset inspiratory time (Ti). IPAP is the total pressure of the EPAP and pressure support (PS) (Figure 1.18). Ventilators used to deliver IMV will often require the setting of an EPAP and PS compared to ventilators used within the patients home requiring the setting of an IPAP and EPAP (Arnal *et al.*, 2019; Hickey, Sankari and Giwa, 2024). The IPAP will need to be adjusted to reduce the patients daytime hypercapnia and therefore any increase in IPAP will increase Vt and should result in a decrease in $PaCO_2$ (Dorst, Behrendt and Ludolph, 2019). IPAP is also used to resolve nocturnal hypoventilation. The IPAP is set using clinical data from respiratory blood gas analysis, sleep studies and the severity of patient symptoms.

1.5.5.2 Expiratory Positive Airway Pressure (EPAP)

EPAP is the pressure delivered and maintained in the patient's interface during the ventilators expiratory time (Figure 1.18). It is common clinical practice to set a minimum EPAP of $4cmH_2O$ to ensure sufficient washout of CO_2 and maintain a

minimum level of upper airway patency. The EPAP is adjusted to overcome upper airway obstruction seen commonly in OSAS (Zhang and si, 2012) but also in ALS patients with bulbar disease (Georges *et al.*, 2016). In COPD the EPAP can be adjusted to offset iPEEP and improve trigger efficacy by reducing the effort required to trigger the ventilator to cycle into expiration (Brochard, 2002). The EPAP can also be adjusted to improve compliance of the respiratory system and decrease the possibility of atelectasis improving oxygenation (Arnal *et al.*, 2019). In some 'hybrid' NIV modes, an AE can be set where the EPAP will move between a range predetermined by the clinician.

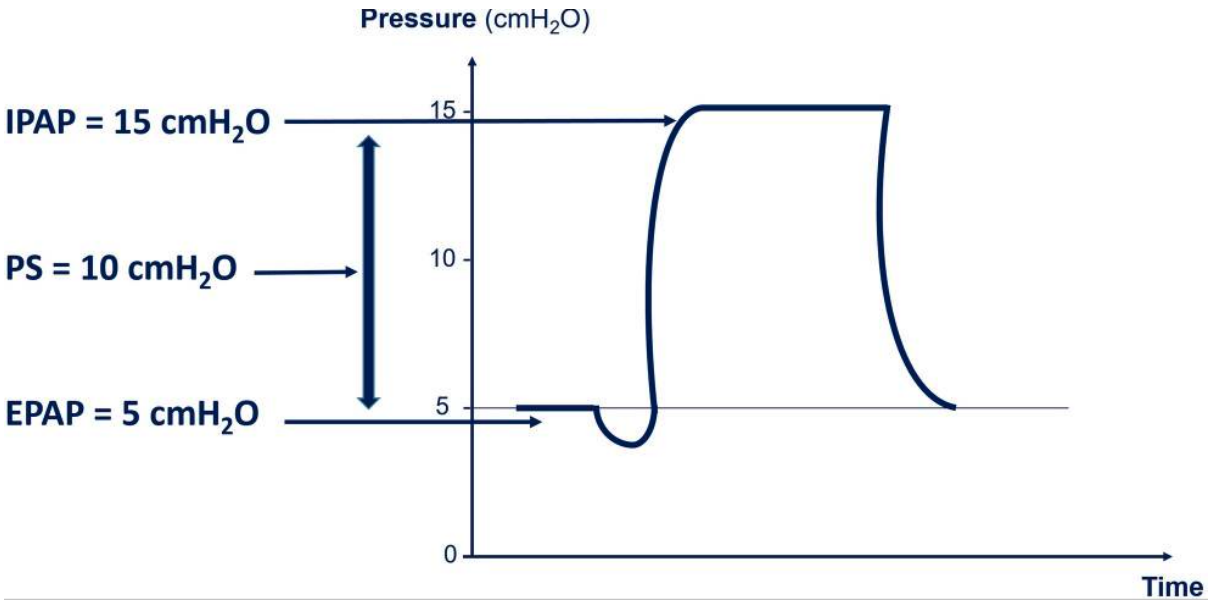

Figure 1.18. Schematic representation of IPAP, EPAP and PS. Taken from Arnal et al., 2019.

1.5.5.3 Backup Rate (BR)

A BR instructs the ventilator to deliver a set number of breaths per a minute if the patient fails to trigger a breath within a set period of time (Vignaux *et al.*, 2009; Carlucci *et al.*, 2013) (Figure 1.19). The BR is commonly set 2-4 breaths below the patients

spontaneous RR as not to cause ventilator-patient asynchrony or breathing discomfort (Arnal *et al.*, 2019).

Special attention must be made to ensure that the BR is low enough as not to interfere with the patients spontaneous breathing but high enough to ensure effective ventilation in the absence of patient triggered breaths (Contal *et al.*, 2013). In some patients, including those with cystic fibrosis (Fauroux *et al.*, 2004), there may be clinical benefit to set the BR marginally higher than the spontaneous rate as to reduce muscular work and allow the ventilator to trigger the majority of breaths (Arnal, 2021).

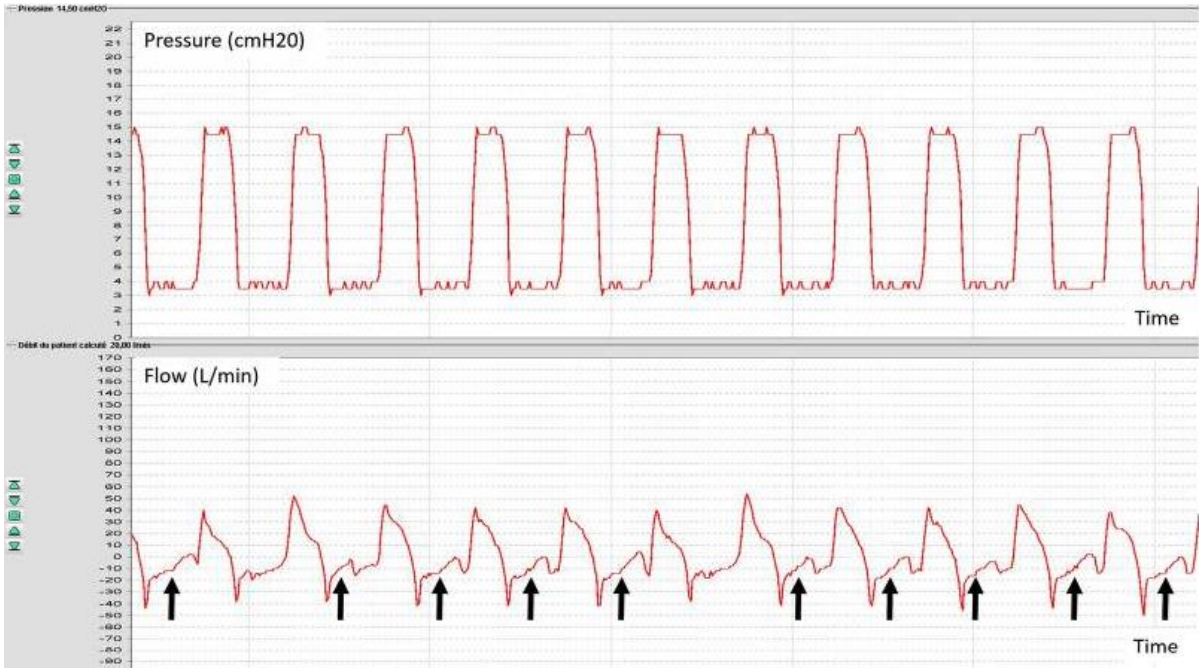

Figure 1.19. An example of a patient receiving NIV. The patient is demonstrating patient-ventilator asynchrony with frequent failed spontaneous breaths (black arrows) and the ventilator delivering backup breaths shortly afterwards according to the pre-set BR. Taken from Arnal et al., 2019.

1.5.5.4 Inspiratory and Expiratory Trigger

The inspiratory trigger level will determine how easy it will be for the patient to trigger a breath. If the inspiratory trigger level is low the patient will need to generate a low inspiratory flow rate to trigger the ventilator (Arnal, 2021). If the inspiratory trigger is inappropriately set it will increase the risk of auto triggering leading to failed breaths and patient-ventilator asynchrony (Sassoon, 2011; Arnal *et al.*, 2019). When setting the inspiratory trigger consideration needs to be given to the difference in the patient's

respiratory effort when awake and when asleep and how this may influence the inspiratory trigger (Figure 1.20).

The expiratory trigger which is also referred to as ‘cycling’ instructs the ventilator when to stop IPAP and transition to EPAP and is calculated as a percentage of the patients peak inspiratory flow (Figure 1.20) (Arnal *et al.*, 2019). The expiratory trigger is particularly important to ensure a high level of patient-ventilator synchrony and patient comfort. The expiratory trigger is disease specific relative to changes in respiratory mechanics (Thille *et al.*, 2006).

In obstructive lung disease, for example COPD, a high expiratory trigger is required to cycle from inspiration to expiration sooner, allowing a longer expiratory time and overcome iPEEP (Tassaux *et al.*, 2005). In contrast, restrictive lung diseases, including ALS, require a low expiratory trigger to allow a complete inspiration and ‘normalise’ Ti. The expiratory trigger can also influence Ti and as a result Vt (Arnal *et al.*, 2019). A high expiratory trigger can cause a short Ti and low Vt and the opposite for a low expiratory trigger.

Most modern NIV devices allow for both the inspiratory and expiratory trigger to be set either as low, medium, high or on a numerical scale which are defined by certain percentages of peak inspiratory flow (Arnal *et al.*, 2019).

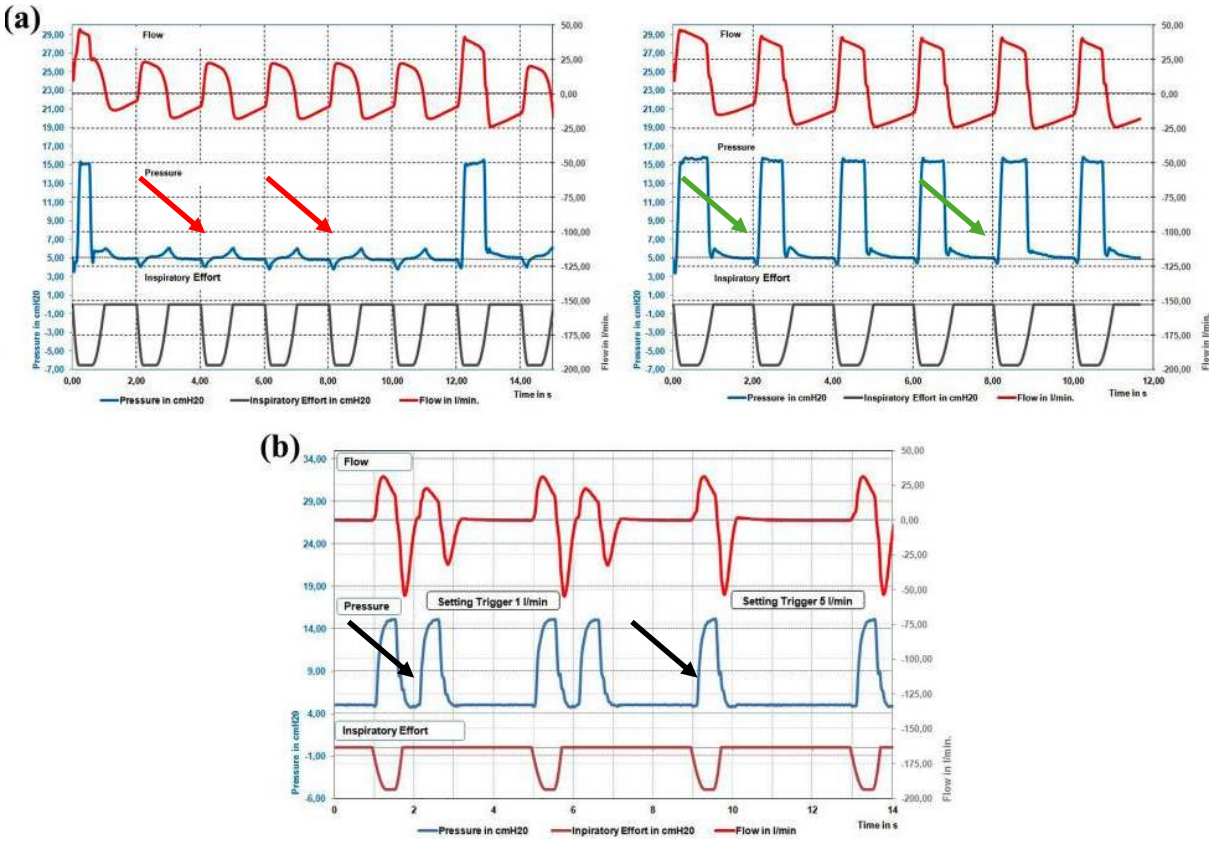

Figure 1.20. Ventilator recorded flow, pressure and inspiratory effort are plotted over time. An example of a patient receiving NIV. The patient is demonstrating ineffective triggering; (a) the inspiratory trigger level is set too low (left; marked with red arrows) and is increased to improve patient-ventilator synchrony (right; marked with green arrows); (b) the inspiratory trigger is set to high resulting in the patient auto triggering the ventilator (marked with black arrows). Taken from Arnal et al., 2019.

1.5.5.5 Rise Time

The rise time is the time the ventilator requires to increase P_{aw} from EPAP to IPAP. The rise time is commonly set to reflect the patients spontaneous inspiratory flow rate and is often disease dependant. Patients with obstructive lung disease often require a low rise time to instigate a greater expiratory time with a prolonged rise time often required in restrictive lung disease to unload the respiratory muscles (Bonmarchand *et al.*, 1999). The rise time is included in the Ti and therefore if an inappropriately high rise time is selected, the ventilator will have a shorter time at the actual IPAP resulting in a lower than desired Vt and an increased work of breathing for the patient

(Bonmarchand *et al.*, 1996, 1999). Patients with a high RR require a low rise time and the opposite for a low RR.

1.5.5.6 Minimum and Maximum Inspiratory Time

The minimum Ti will ensure a minimum time of IPAP and guarantees that a patient will receive inspiration for a set time (Arnal *et al.*, 2019). For those patients with obstructive lung disease, for example COPD, it is commonly set to a short time to allow a longer expiratory time and the opposite for those patients with restrictive lung disease to prolong inspiration and increase Vt (Arnal *et al.*, 2019). When the Ti of the ventilator equals the patients neural time (patients intrinsic Ti) ventilator-patient asynchrony is likely to be abolished. The minimum inspiratory time is recommended to be set below the patients spontaneous inspiratory time (Arnal *et al.*, 2019).

The maximal Ti will limit the time the patient can be in inspiration. In pressure mode NIV, the end of inspiration and the cycle into expiration is determined by the expiratory trigger level and allows a variable breath by breath inspiratory time according to the patient's inspiratory effort and lung mechanics (Arnal *et al.*, 2019).

Air leak from the patient's interface can mimic inspiratory flow and therefore the patient may not be able to actively trigger the expiratory trigger resulting in delayed cycling. The maximal Ti will ensure that in the presence of unintentional leak, the patient and ventilator are able to cycle from inspiration to expiration (Arnal *et al.*, 2019). The maximum Ti is ordinarily set 0.2 seconds longer than the Ti but can be longer depending on the patient's lung mechanics and disease profile. If the maximum inspiratory time is inappropriately short, each patients spontaneous breath will have the same 'fixed' Ti leading to patient discomfort (Calderini *et al.*, 1999).

1.5.6 NIV Circuits

Ventilators used to deliver IMV generally use a double limb circuit with an integrated expiratory valve. This allows inspiratory and expiratory gases to be separated so that the rebreathing of CO_2 does not occur. In comparison NIV devices commonly use a single limb circuit with an expiratory valve incorporated into the interface to allow the washout of CO_2. The leak from the interface is calibrated by the ventilator as to differentiate between intentional and unintentional air leak (Rabec *et al.*, 2009) and a mandatory minimum EPAP of 4cmH_2O is required to ensure the effective washout of

CO_2 and reduced the risk of CO_2 rebreathing (Lofaso *et al.*, 1995). The expiratory valve for intentional leak can be positioned either at the ventilator or patient end of the circuit, however it is best practice to position this within the patient interface to achieve the greatest washout of CO_2 (Figure 1.21) (Schettino *et al.*, 2003).

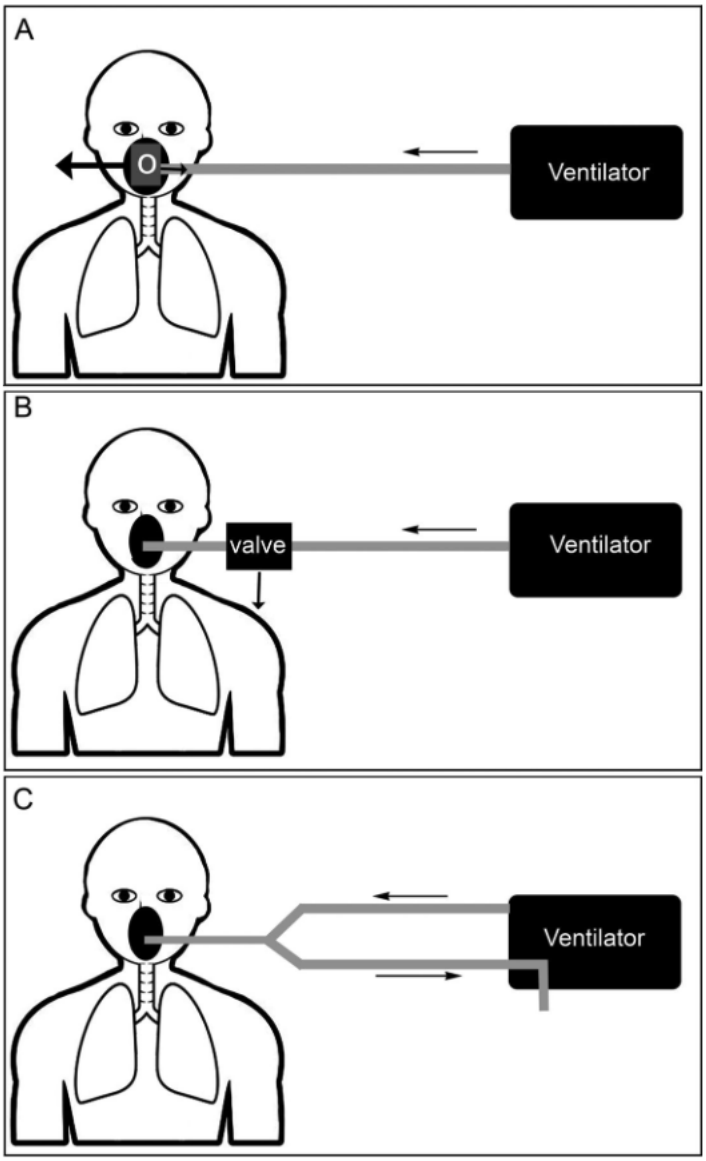

Figure 1.21. Types of NIV circuits with (a) a single limb circuit with an interface expiratory valve (vented interface) (b) a single limb circuit with a tube expiratory valve (non-vented interface) and (c) double limb (closed) circuit with inspiratory and expiratory limbs. Taken from BaHammam et al., 2018.

1.5.7 Patient Interface

Much consideration is required to ensure that the most appropriate NIV interface is selected as to avoid patient discomfort and/or in some circumstances NIV withdrawal and failure (Elliott, 2004). The time of NIV application, the number of hours NIV is required to be used, timing of NIV use, during the day, night or both and other disease characteristics all need to be considered to increase the likelihood of NIV success and positive patient outcomes (Antonelli *et al.*, 2001). Furthermore, the type of NIV interface must be considered including how it will adhere to the patients face and neck and how it can be attached to the fixing system (headgear) (Cammarota, Simonte and De Robertis, 2022).

Types of NIV interfaces include, nasal, full face, hybrid, nasal pillows, total face interface and helmet (Figure 1.22). NIV interfaces will either be vented or non-vented depending on which type of NIV circuit is being applied. All NIV interfaces will attach to the patient using a headgear and attach to the ventilator using a tube fixing. Over the past decade medical device manufactures have developed NIV interfaces with a range of various technologies and materials, largely aimed at improving patient comfort, reducing skin breakdown and air leak (Vaschetto *et al.*, 2014).

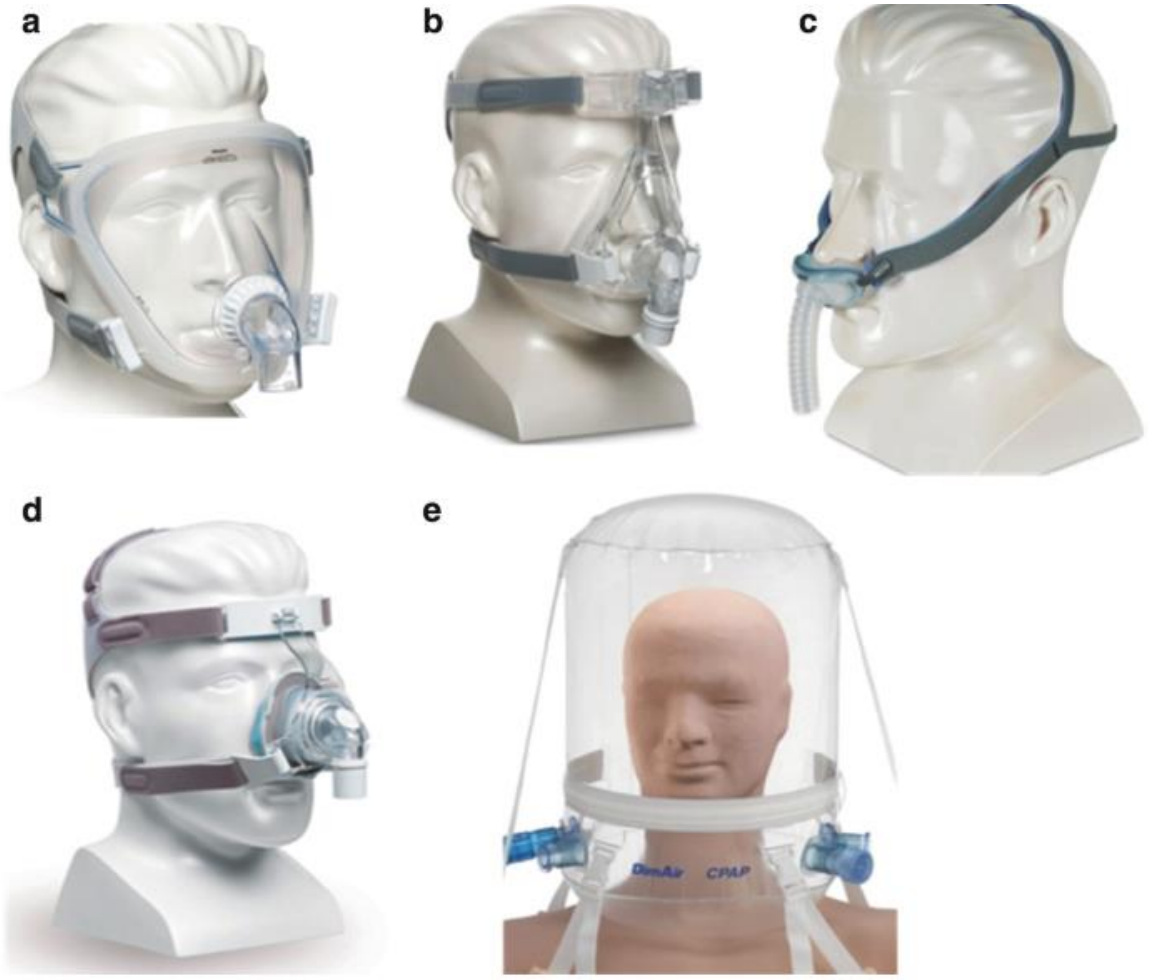

Figure 1.22. Types of NIV interface (a) shield (b) full face (c) nasal pillows (d) nasal and (e) helmet. Taken from Iglesias et al., 2022.

Several studies have investigated the advantages and disadvantages of NIV interfaces evaluating both effectiveness and tolerability (Figure 1.23) (Navalesi *et al.*, 2000; Khatib *et al.*, 2021). Poor NIV tolerance is predominantly associated with those patients using nasal interfaces due to significant leak through the patients mouth during sleep (Leone *et al.*, 2020). This results in ineffective triggering and poor patient-ventilator synchrony due to dryness of the oronasal orifice (Nava and Hill, 2009). In some patient groups, where increased airway secretions, frequent cough or claustrophobia impedes NIV use, a nasal interface may be appropriate (Hess, 2013).

Types	Advantages	Disadvantages
Nasal mask	•Less claustrophobic	•High incidence of leaks
	•Easy to cough or expectorate	•Eye irritation
	•Easy to speak	•Higher resistance
	•Less risk of aspiration	•Nasal irritation or damage
Nasal prongs	•Less claustrophobic	•High incidence of leaks
	•Easy to cough or expectorate	•Nasal irritation
	•Easy to speak	
	•Option for a rotating strategy	
Mouth pieces	•Less claustrophobic	•High incidence of leaks
	•Little dead space	•Less effective for ARF
	•Option for a rotating strategy	
Oro-nasal mask	Good for ARF	•More claustrophobic
		•Possible air-leaks
		•Eye irritation
Total face mask	•Adequate for prominent facial anatomy	•More claustrophobic
	•No pressure on nasal bridge	•Difficult to speak
	•Low air-leaks	
Helmet	•Adequate for prominent facial anatomy	•Can be claustrophobic
	•Low air-leaks	•Noise
	•Easy to speak	•High gas flow required
	•No pressure on nasal bridge	•Discomfort of axillae with armpit braces

Figure 1.23. Advantages and disadvantages of different NIV interfaces. ARF is acute respiratory failure. Taken from Cammarota et al., 2022. Data for comparison taken from Auriant et al., 2011; Ferrer et al., 2003; Maggiore et al., 2014.

Air leaks are a significant negative consequence of an inappropriately fitting interface, headgear and/or fixing mechanism (Elliott, 2004). Over time the headgear generally made from a neoprene material will become slack and cause both small and large interface leak leading to ineffective ventilatory support. Modern ventilators especially those using pressure mode NIV will compensate with higher peak inspiratory flow rates of between 120–180 $L \cdot min^{-1}$ (Elliott, 2004) however volume mode NIV has a limited ability to compensate for leak which can reduce Vt of >50% (Smith and Shneerson, 1996).

Over tightening of the headgear can lead to patient discomfort and creasing of the interface seal resulting in air leak (Brill, 2014). One approach to overcome mouth air leak is to employ a chin strap. This is a simple device which fits underneath the patients chin and over and around the patient's head preventing the patients mouth form opening especially during sleep. Chin straps however are in the vast majority of patients ineffective and in some further add to a sense of claustrophobia (Elliott, 2004).

Finally, care should be taken to reduce pressure sores especially those located on the patient's nasal bridge as if left untreated can not only result in NIV withdrawal but also an infection risk. To reduce the risk of pressure sores a range of interventions have been proposed including a rotation of different NIV interfaces including those that relieve pressure on the nose, barrier tapes, additional cushioning and reusable pads position between the interface and seal and the patients nose (Nava and Hill, 2009).

1.5.8 Remote Monitoring

European Respiratory Society reports published in 2016 have estimated a prevalence of 6.6 per 100,000 of ventilator dependent patients within the countries of Europe (Lloyd-Owen *et al.*, 2005). This vast number of complex patients which is ever increasing places a huge strain on the delivery of quality healthcare from both the primary and secondary providers. In addition due to the lack of healthcare provision and resources which are largely insufficient to adequately provide care for these patients with multifactorial health conditions, emphasis is often placed on care to be provided by the patients family or non-professional care providers (van den Biggelaar, Hazenberg and Duiverman, 2023); this particularly relevant in patients with ALS.

There have been significant investments in the provision of health information technology as healthcare providers aim to deliver safe, effective and patient centred care (Black *et al.*, 2011). The health information technology industry is projected to be worth $230 billion by 2030 introducing new healthcare technology products for hospital and home, including remote monitoring platforms and modem enabled ventilators (Cresswell, Blandford and Sheikh, 2017).

As a result tele-monitoring systems have become more readily accessible and therefore more healthcare providers are implementing them within clinical practice. Tele-monitoring has been shown to contribute towards increasing outpatient capacity

as well as admission avoidance programmes (van den Biggelaar, Hazenberg and Duiverman, 2023). The use of health information technology, including remote monitoring of home NIV is aligned with the NHS long term plan which underpins the integration of healthcare technology across NHS services (NHS, 2019).

Remote monitoring is only possible when using ventilators with in-built modems which allow data to be sent to a secure web-based platform via 4G networks. Remote monitoring of data can vary according to device type and manufacture but generally includes adherence, estimated apnoea-hypopnoea index (AHI), interface leak and ventilator machine functionality.

Changes to a patients ventilation prescription including IPAP, EPAP and BR can be made remotely without the need to provide a face to face outpatient appointment with some platforms offering breath-by-breath flow and pressure curves (Gonzalez-Bermejo *et al.*, 2019; van den Biggelaar, Hazenberg and Duiverman, 2023). Remote monitoring platforms allows a variety of clinical reports to be created with the data that has been sent from the patient's ventilator. Data can be presented using a variety of graphs (Figure 1.24). Common report types include standard diagnostic report, detailed diagnostic report, compliance (Figure 1.25) and therapy reports.

Figure 1.24. Examples of the most common types of graphs used in a NIV remote monitoring report reports. These examples show Usage, Leak, Events and SpO2. Taken from (ResMed Ltd, Bella Vista, Australia).

Usage

04/22/2015 - 05/19/2015

Usage days	**26/28 days (93%)**
>=4 hours	**26 days (93%)**
<4 hours	**0 days (0%)**
Usage hours	240 hours 38 minutes
Average usage (total days)	**8 hours 36 minutes**
Average usage (days used)	9 hours 15 minutes
Median usage (days used)	9 hours 25 minutes

AirSense™ 10 AutoSet™ for Her

Serial number	00102499960
Mode	AutoSet
Minimum pressure	4 cmH2O
Maximum pressure	10 cmH2O
EPR	Fulltime
EPR level	3

Therapy

Pressure - cmH2O	Median:	**6.8**	95th percentile:	**7.1**	Maximum:	**7.5**
Leaks - L/min	Median:	**21.1**	95th percentile:	**23.6**	Maximum:	**24.3**
Events per hour	AI:	**6.1**	HI:	**0.4**	AHI:	**6.1**
Apnea Index	Central:	**4.6**	Obstructive:	**1.3**	Unknown:	**1.0**
RERA Index						**5.0**
Cheyne–Stokes respiration (average duration per night)						**20 minutes (9%)**

SpO_2 - %	Time spent SpO_2 < 88%:			**18 min**
	Median:	**92**	95th %:	**97**

Usage - hours

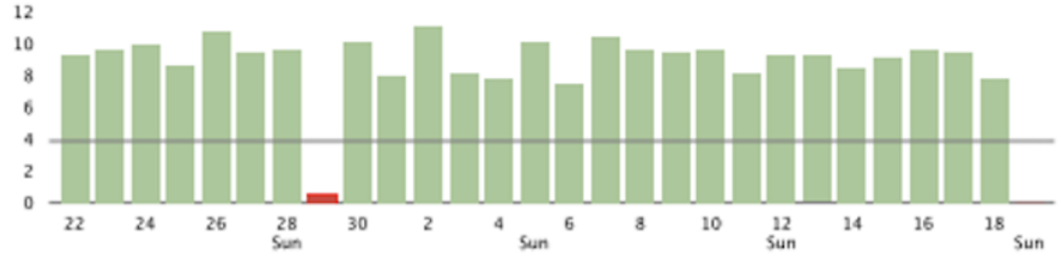

Figure 1.25. Example of a Compliance Report. This is a fictional patient. Taken from (ResMed Ltd, Bella Vista, Australia).

The long-term benefits of remote monitoring particularly patients using CPAP to treat OSAS is unclear however there is evidence to support improved adherence during the initial period of commencing treatment (Hwang *et al.*, 2018; Aardoom *et al.*, 2020). Furthermore, studies have shown that patients with long-term conditions feel empowered when using remote monitoring as they are encouraged to self-manage aspects of their own care resulting in reduced costs to deliver these services (Juarros Martínez *et al.*, 2023).

The data obtained from the remote monitoring of home NIV is clinically useful and can support clinicians to make decisions regarding optimisation of ventilation leading to improved patient perceptions of treatment and adherence (Mansell *et al.*, 2018, 2020). For those home NIV services which cover large geographical areas or those services in more rural areas, remote monitoring can be used to review and prioritise home visits and ensure that outpatient appointment capacity is utilised effectively (van den Biggelaar, Hazenberg and Duiverman, 2023). Furthermore, clinicians have reported that the use of remote monitoring allows for a more efficient clinical workflow from which the time saved can be used to focus care on more clinically complex home NIV patients (Mansell *et al.*, 2018, 2020).

Remote monitoring does present certain challenges, particularly the need for more robust evidence to support its clinical and cost effectiveness but also the modernisation of information technology systems within some healthcare providers. Interestingly, some remote monitoring platforms use inbuilt alerts to identify certain patient groups, for examples those patients who have a low adherence or high leak. If these alerts are not patient specific or frequent enough, then the remote monitoring platform can itself become inefficient (Garuti *et al.*, 2013; van den Biggelaar, Hazenberg and Duiverman, 2023).

Careful and sensitive patient education regarding remote monitoring is required as not to lure patients into a false sense of clinical security and delay seeking medical help if they become unwell. Regarding data protection and clinical governance some clinicians have raised concerns regarding the invasion of a patient's medical privacy however this has not been reported by patients (Mansell *et al.*, 2018, 2020; Muñoz-Bonet *et al.*, 2020).

1.5.9 Place of NIV Initiation

Historically, home NIV has been initiated during an elective inpatient admission on a respiratory ward however with an increasing incidence and prevalence of home NIV for patients diagnosed with COPD, MND and OHS, the number and availability of acute hospital beds are not sufficient and as such alternative models of care to safely and effectively initiate home NIV have been developed (Kampelmacher, 2023). Currently, practices for commencing home NIV can vary widely between countries, regions and hospitals and are largely dictated by local healthcare systems, healthcare funding and historical clinical practices. Considerations relating to the feasibility, safety, funding and clinical effectiveness are important as to ensure the right patient receives the right care at the right time (Kampelmacher, 2023). Both outpatient and home initiation of NIV pose different challenges but have been deemed safe, clinically effective, feasible and cost effective and therefore hospital services should consider which method is best for patients, family and caregivers (Figure 1.26) (Murphy *et al.*, 2019; Duiverman *et al.*, 2020).

Advantages	**Outpatient Initiation**	**Home Initiation**
Feasible in all disease groups: NMD, RLD, COPD, OHS	+++	+++
Fewer hospital beds needed	+++	+++
Reduced waiting time to NIV initiation	+++	+++
Potential for fewer acute admissions	+++	+++
Similar acceptance as inpatient initiation	+++	+++
Adverse effects similar to inpatient setup	+++	+++
Effectiveness equal to inpatient initiation	+++	+++
Adequate therapeutic compliance	+++	+++
Potential for cost savings	++	+++
Reduced infection risk	++	+++
Adequate resources and availability of experienced and involved caregivers for personal needs	+	+++
Familiar and supportive environment for patients	+	+++
Possibility to fulfil family or job obligations	+	+++
Patient convenience	++	+++
Patient preference	++	+++
Disadvantages	Outpatient Initiation	Home Initiation
Unsuitable for patients with unstable medical conditions, severe comorbidities, complex care needs, lack of motivation, cognitive impairment, anxiety of living far from hospital, etc.	++	+++
Implementation depends on local geography, infrastructure, and health system features	+	+++
Potential for complications, which may be difficult to manage	+	+++
Potential for higher healthcare utilization (phone calls, unscheduled hospital stays, outpatient clinic visits, and emergency home visits)	++	+++
Staff needs extensive knowledge and experience with initiation of NIV	++	+++
Need for change in staffing model	+	+++
Technical problems with (tele-)monitoring	+	+++
Investment in equipment needed	+	+++
Logistical challenges in arranging for delivery of equipment and training	+	+++
Potential for increased caregiver burden	+	+++

Figure 1.26. Advantages and disadvantages of outpatient and home initiation of home NIV. Applicability of each item is presented as follows: + = hardly applicable, ++ = somewhat applicable and +++ = very applicable. NMD is neuromuscular disease, RLD is restrictive lung disease. Taken from Kampelmacher, 2023.

1.6 Clinical Benefits of NIV in ALS

1.6.1.1 Survival

Over the past 20 years there have been considerable improvements in the treatment and therapy options for patients diagnosed with ALS, with a greater emphasis on improving survival (Berg *et al.*, 2005; Millul *et al.*, 2005; Simmons, 2005; Orrell, 2010). Any survival benefit cannot be achieved from one treatment or therapy alone and as such care should be enhanced through the MDT (Berg *et al.*, 2005). The use of NIV to treat CRF and SDB in ALS has been extensively reported in the literature with early reports suggesting a mean survival of 4.4 +/- 3.9 yr (range = 1 month to 26.5 yr) using NIV (Bach, 1993).

One RCT investigated survival between patients using NIV and those who received palliative care reporting a significantly longer survival time for patients using NIV ($p < 0.006$) (Pinto *et al.*, 1995). A significant difference in survival time was observed in a clinical cohort study of 122 patients, where patients were randomised to one of three groups; Group 1 were adherent with NIV, Group 2 were not adherent with NIV and Group 3 declined NIV. Group 1 demonstrated the most significant survival advantage with a median survival of 14.2 months compared to a median survival of 7 months in Group 2 and 4.6 months in Group 3 (Kleopa *et al.*, 1999). NIV has been reported to reduce mortality in ALS of up to 26% and 37% for patients with limb-onset disease (Ackrivo *et al.*, 2021).

In a prospective study using a historical group of patients as a control, overnight pulse oximetry and an ODI >15/hr to diagnosis SDB, NIV provided a noteworthy survival benefit (Pinto *et al.*, 2003). The only RCT with survival as its primary outcome included 92 patients diagnosed with ALS randomised to either receive NIV or standard care (no NIV). Median survival in the NIV group was 219 days (range, 75–1,382 days) and 171 days (range, 1–878 days) in the control group. The study reported that a 7 month survival advantage was observed in those patients using NIV (Bourke *et al.*, 2006). Of important note the survival advantage was seen predominantly in patients with less severe bulbar disease; however, a more recent study has reported conflicting results.

In a retrospective analysis of a clinical cohort of 30 ALS patients, no significant difference in survival time was reported between bulbar onset and limb onset ALS (p

=0.877) (Ristell *et al.*, 2019). Furthermore, no significant difference was observed in the time from ALS diagnosis to the time of NIV initiation (211 vs 402 days; p =0.077) and although, this difference was not statistically significant, clinically, it may suggest bulbar onset patients experience a greater number of days with a preserved functional status (Ristell *et al.*, 2019).

Adding to the evidence supporting the use of NIV in bulbar-onset disease, a median tracheostomy free survival time of 28 months was reported in a large clinical cohort of 928 ALS patients who received NIV compared to 15 months in those who did not (Univariate Cox regression HR=0.61 (0.51 to 0.73), p<0.001). In the same study, NIV was reported to provide a whole group survival benefit of 13 months with a significantly longer survival in patients with bulbar dysfunction (Univariate HR=0.50 (0.36 to 0.70), multivariate HR=0.59 (0.41 to 0.83)) (Berlowitz *et al.*, 2016).

Further studies have tried to ascertain the survival benefit of NIV for ALS patients with bulbar disease. In a prospective study of 140 ALS patients from a clinical cohort, patients using NIV demonstrated a longer survival time compared to those who declined NIV (median 18.50 months, 95% CI 12.62–24.38 months; 3.00 months, 95% CI 0.82–5.18 months, respectively; p<0.001). Interestingly, when patients were sub-grouped by ALS phenotype, patients with bulbar dysfunction survived longer compared to those with less severe or no bulbar impairment (13.00 months 95% CI 9.49–16.50 months; 3.00 months 95% CI 0.85–5.15 months, respectively, p<0.001) (Sancho *et al.*, 2018). When adjusted for NIV failure, the severity of bulbar disease was directly related to NIV adherence (hazard ratio (HR) 0.5, 95% CI 0.92–0.97; p=0.001) (Sancho *et al.*, 2018).

1.6.1.2 HRQoL

Patients with ALS have a reduced HRQoL which is routinely assessed using psychometric, disease specific and treatment specific instruments, including the mHADS, ALSFRS-R and the Severe Respiratory Insufficiency Questionnaire (SRI) (Windisch *et al.*, 2003; Gibbons *et al.*, 2011; Ghosh *et al.*, 2012; Walterspacher *et al.*, 2016; Moore, Young and Hughes, 2018; Russo *et al.*, 2021; Caballero-Eraso *et al.*, 2023).

Studies have reported strong correlations between reduced HRQoL and respiratory muscle strength with SNIP demonstrating to be the single most significant independent predictor of HRQoL in ALS. Of important note, weak correlations between HRQoL and PSG parameters have been identified, suggesting that reduced HRQoL is driven by the negative physiological impact of nocturnal hypoventilation rather than poor quality sleep as a result of an increased frequency of apnoeas and hypopneas (Bourke, Shaw and Gibson, 2001).

The ALSFRS-R is a measure of functional status in ALS and is a recommended measure to assess HRQoL in ALS (Leigh *et al.*, 2004). In its original format, the ALSFRS, limb and bulbar domains were disproportionately scored compared to respiratory and dysfunction domains and as such was revised. In its most recent format, the ALSFRS-R can provide a clear and concise clinical assessment of respiratory, bulbar and motor function (Dams *et al.*, 2013). In a post-hoc analysis of data from the Breathe-MND 1 trial, a reduction in the ALSFRS-R was observed after 2 months of using NIV and has demonstrated its ability to measure the effectiveness of NIV on functional status in ALS (median [IQR] 13.9 [9.4 to 28.4]%) (Aiyappan, 2017).

The Hospital Anxiety and Depression Scale (HADS) is a simple, evidence based, psychometric instrument to measure anxiety and depression (Zigmond and Snaith, 1983; Crawford *et al.*, 2001; Bjelland *et al.*, 2002). The HADS did not include somatic symptoms and therefore it has been used with ALS patients in both clinical practice and clinical trials (Abrahams *et al.*, 1997; Goldstein, Atkins and Leigh, 2002; Goldstein *et al.*, 2006; Wicks *et al.*, 2007). However, the HADS had never undergone specific validation within a clinical cohort of ALS patients and as such some questions including “I feel as though I am slowed down”, raised questions about its appropriateness in ALS.

Subsequent Rasch analysis has developed a modified version of HADS which is suitable for use in ALS clinical care and clinical trials (Gibbons *et al.*, 2011). The Beck Depression Inventory - II (BDI) is an alternative tool for identifying the presence of and quantifying the significance of depression in ALS (Beck *et al.*, 1996). In a study investigating the characteristics of a large ALS clinical cohort of 159 patients, depression was identified in 30% and 25% when somatic items were removed from

the BDI. The study also reported that a low ALSFRS-R score was associated with a higher BDI (Körner *et al.*, 2015).

The SRI is a treatment specific instrument used to assess the effectiveness of NIV with its use in ALS validated against the 36-Item Short Form Health Survey (SF-36) (0.21<r<0.79) (Windisch *et al.*, 2003). The SRI has been reported to be a predictor of mortality across a range of diseases including neuromuscular respiratory failure. The SRI-Physical Functioning (HR 0.97, 95% CI: 0.94–1.00), SRI-Psychological Well-Being (HR 0.97, 95% CI: 0.95–0.99) and SRI-Social Functioning (HR 0.97, 95% CI: 0.94–0.99) were observed to be significant risk factors for mortality in patients receiving both invasive and non-invasive ventilation (Markussen *et al.*, 2019). The study's authors confirmed SRI as a predictor of mortality and recommended its use within clinical practice as part of a regular follow up plan for patients using NIV (Markussen *et al.*, 2019).

Overall, there appears to be limited evidence to inform clinicians on how HRQoL, measured using a range of psychometric, disease specific and treatment specific instruments, influence NIV adherence in ALS. One recent study which observed 72 patients diagnosed with ALS reported that respiratory (ALSFRS-R respiratory sub score, p=0.03) status was a significant predictor of how long it would take to achieve NIV adherence and concluded that the presence of cognitive impairment and absence of respiratory symptoms were negative predictors of NIV adherence (Russo *et al.*, 2021).

1.6.1.3 NIV Adherence in ALS

Modifiable and non-modifiable factors can influence NIV adherence in ALS. Modifiable factors can include NIV mode, settings, circuit, patient interface, place of initiation, caregiver involvement and management of symptoms including airway secretions. Non-modifiable factors include marital status, household income and level of education (Jackson *et al.*, 2021). Achieving NIV adherence in ALS is of important significant as it is associated with improved survival and HRQoL.

NIV adherence has been defined by using historic data from patients using CPAP to treat OSAS. Early studies demonstrated a clinical benefit from using CPAP for a minimum of 4 hours and 7.5 hours, to improve daytime sleepiness and functional

status, respectively (Weaver *et al.*, 2007). These thresholds, particularly 4 hours, have been used in both clinical trials and are used commonly in clinical practice to determine NIV adherence (Gruis *et al.*, 2005; Coco *et al.*, 2006; Kim *et al.*, 2011; Mansell *et al.*, 2018; Vitacca *et al.*, 2020; Rudnicki *et al.*, 2021).

It is widely reported that using NIV ≥4 hours per a night is an acceptable NIV adherence. However, this may underestimate the adherence required to improve survival, HRQoL or both. An NIV adherence of 9.3 hours per a night has been associated with a survival advantage (Bourke *et al.*, 2006) and therefore the general applicability of ≥4 hours per a night across all ALS phenotypes may not necessarily be appropriate and in some cases may not result in any clinical benefit.

Generally, NIV adherence is inconsistently reported across studies in ALS cohorts, and this may indeed be because of the natural heterogeneity of the disease itself. Studies have reported NIV adherence rates of between 33 and 90% (Kleopa *et al.*, 1999; Gruis *et al.*, 2005; Coco *et al.*, 2006; Czudaj, Suchi and Schönhofer, 2009; Ristell *et al.*, 2019; Vitacca *et al.*, 2020; Rudnicki *et al.*, 2021; Russo *et al.*, 2021).

The time taken for ALS patients to demonstrate NIV adherence ranges from 7.8 to 58 days and the number of hours per a night NIV is used ranges from 6.5 and 12.3 hours per a night. In a post-hoc analysis of a multicentre pilot study of nutrition and NIV, total % of patients who demonstrated NIV adherence using pressure mode was 52.3% at 28 days increasing to 57.8% at 84 days and 74% at 224 days. This study demonstrated not only that many ALS patients are able to use NIV but that adherence improves over time (Jackson *et al.*, 2021).

Previous studies reporting NIV adherence rates have included the use of both pressure and volume modes, and currently no one NIV mode has been proven to be superior in terms of ventilation effectiveness (Sancho *et al.*, 2014). In a retrospective analysis of 271 ALS patients from a single centre reported an adherence of 67% and 6.6 hours per a night for pressure mode and 70% and 6.5 hours per a night for volume mode NIV (Nicholson *et al.*, 2017).

In a smaller retrospective observational study of 144 ALS patients, adherence was recorded at 1, 3 and 6 months. For pressure mode NIV adherence at each time point was 8.66±2.37, 10.56±4.31 and 13.53±5.80 and 9.41±3.42, 9.49±3.20 and 11.36±5.53

for volume mode NIV (Sancho *et al.*, 2014). Interestingly, this suggests that a greater NIV adherence can be achieved than reported in previous studies (Bourke *et al.*, 2006) and agrees with studies which have observed an improvement in NIV adherence over time (Jackson *et al.*, 2021).

Other clinical factors which can influence NIV adherence need to be considered before commencing NIV in ALS. Previously it has been reported that patients with a low FVC at NIV initiation tended to achieve lower adherence however a more recent study of 88 who were stratified using an FVC using < or > 80% patient predicted value demonstrated no significant differences in NIV adherence (Vitacca *et al.*, 2020; Jackson *et al.*, 2021). Two prospective studies have reported the negative impact of airway secretions on NIV adherence (Volanti *et al.*, 2011; Vandenberghe *et al.*, 2013) observing greater NIV adherence in those patients without airway secretions (odds ratio 11.5, 95% CI 1.3-98.4). The use, therefore, of cough augmentation using MI-E in combination with NIV has been showed to improve NIV adherence. Similar adherence rates have been reported between ALS with and without bulbar impairment (Parkes *et al.*, 2019).

The effect of where NIV is initiated in ALS has been briefly reported and demonstrated no significant difference in adherence rates between day case and overnight inpatient setups at 1 or 3 months (76% versus 80%, p=0.733 and 68% versus 76%, p=0.529, respectively) (Bertella *et al.*, 2017). The type of patient interface is important as previous studies have reported poor interface fit and discomfort to be associated with poor NIV adherence (Volanti *et al.*, 2011; Martínez *et al.*, 2015).

Remote monitoring of NIV in ALS has demonstrated a 55% reduction in total costs to deliver healthcare however the impact of remote monitoring systems on survival and ventilation effectiveness has not been fully investigated. One longitudinal study has demonstrated a marginal increase in NIV adherence from NIV initiation and follow up visit with the use of remote monitoring (Lopes de Almeida *et al.*, 2012; Mansell *et al.*, 2018). The involvement of caregivers has been shown to influence the success of NIV. Determination, perseverance, sense of hope and engaging with treatment were associated with improved NIV adherence whereas feelings of hopelessness of caregivers resulted in poor NIV adherence (Ando *et al.*, 2014).

Optimising NIV adherence in ALS and understanding the clinical factors which can influence NIV effectiveness is of great importance. Current guidelines either make no or limited reference to many of the clinical considerations described and although there is a substantial amount of evidence to support clinical care many studies are observational and overall there is a lack of RCT's. Further, due to the heterogeneity of ALS and ethical consideration regarding research trails, the lack of high-quality evidence may remain for some time. It remains unclear which NIV mode, and settings are optimal to achieve maximum benefit from NIV and improve survival and HRQoL in ALS.

1.7 Aims and Objectives

NIV mode and settings in ALS differ from those required in other disease, for example, COPD and OHS. NIV pressures in ALS are reported to range from an IPAP 10-18 cmH_2O and an EPAP 4-6 cmH_2O (Ward *et al.*, 2015; Nicholson *et al.*, 2017; Ristell *et al.*, 2019) with data from my NIV service demonstrating an IPAP 10-22 cmH_2O and EPAP 4-8 cmH_2O (Parkes *et al.*, 2019; Ristell *et al.*, 2019).

The aim of this study was to explore the impact of using volume targeted auto-adjusting EPAP on NIV adherence and HRQoL in ALS patients treated with home NIV. We predict that volume targeted auto-adjusting EPAP could improve adherence and HRQoL in ALS due to the following reasons:

1. *Greater relief for SOB*

ALS patients commonly develop a rapid, shallow breathing pattern. Volume mode NIV has been shown to result in significantly less rapid shallow breathing compared to pressure targeted NIV and therefore may consequently relieve shortness of breath to a greater extent (Nicholson *et al.*, 2017). Volume targeted auto-adjusting EPAP NIV could demonstrate similar results.

2. *Increased ability to trigger ventilator*

Respiratory muscle weakness in ALS may lead to ineffective ventilator triggering. Volume targeted auto-adjusting EPAP has an iBR which provides maximum opportunity for the patient to spontaneously trigger the ventilator (Crescimanno, Marrone and Vianello, 2011).

3. *More adaptive control to limit obstructive events*

ALS patients with bulbar dysfunction may experience an increased frequency of either partial or complete collapse of the upper airway during sleep. These episodes can vary in frequency and duration. Volume targeted auto-adjusting EPAP NIV can adjust automatically to ensure that all obstructive episodes are effectively controlled, compared to pressure targeted NIV that may not be able to fully prevent all obstructive episodes because of its fixed pressure limitations (Gay *et al.*, 1991; Kimura *et al.*, 1999; Boentert, 2020).

4. *More adaptive to varying RR and effort during sleep*

RR and effort are variable during sleep and therefore the use of volume targeted auto-adjusting EPAP NIV, which can track a patient's breathing and automatically adjust NIV settings, will ensure appropriate optimisation to meet the patient's ventilation requirements. Pressure targeted NIV is unable to adjust automatically (Ambrogio *et al.*, 2008).

5. *Adaptive to changes in muscle tone during sleep*

Respiratory muscle weakness is more pronounced during REM and greater ventilatory support is therefore required in ALS patients during these sleep periods. The automatic adjustment ability of volume targeted auto-adjusting EPAP NIV ensures maintenance of an appropriate Vt which reduces the likelihood of sleep fragmentation caused by large fluctuations in volume. Pressure targeted NIV delivers a fixed pressure, which may not be appropriate for all the stages of sleep: if this pressure has to be set higher to increase VT during REM, this may be excessive for light sleep leading to fragmented and poor quality sleep (Gay *et al.*, 1991; Ferguson *et al.*, 1996).

6. *Reduced number of hospital visits*

Current best clinical practice is to change pressure targeted NIV settings in response to changes in FVC, SNIP, nocturnal SpO_2 and $PaCO_2$, which is likely to require a hospital visit. The automatic adjustment of volume targeted auto-adjusting EPAP NIV could reduce the number of hospital visits and tests required and improve patient experience.

7. *Decreased interface leak*

Interface leakage is less likely to be problematic using volume targeted auto-adjusting EPAP NIV and patient comfort is likely to improve.

8. *Adaptive over time better suits rapid disease progression*

The rate of progression of ALS varies greatly between patients and the flexibility provided by the auto-adjustment of volume targeted auto-adjusting EPAP NIV is likely to improve effectiveness, tolerability and adherence despite unpredictable disease progression (Nicholson *et al.*, 2017).

1.7.1 Primary Aim of Study

The primary aim of the study was to explore the differences in NIV adherence between pressure targeted and volume targeted auto-adjusting EPAP NIV modes in patients diagnosed with respiratory failure due to ALS.

1.7.2 Secondary Aim of Study

The secondary aim of the study was to explore the differences in HRQOL between pressure targeted and volume targeted auto-adjusting EPAP NIV modes in patients diagnosed with respiratory failure due to ALS.

2 Methods

Methods is based on Parkes *et al.,* 2024.

2.1 Ethics

Ethical approval for this study was granted by the Health Research Authority (HRA) and Health and Care Research Wales (HRCW) (REC Reference 21/NW/0326; IRAS Project ID 293304) and Manchester Metropolitan University EthOS (53907). Study sponsorship was provided by University Hospitals Coventry and Warwickshire NHS Trust (R&D Reference EP545921).

2.2 Protocol Registration

Within six weeks of recruiting the first research participant this research trial was registered on ClinicalTrials.gov (Identifier NCT05328492).

2.3 Recruitment

All patients who had been diagnosed with ALS either at a specialist neurology clinic or an MND MDT (as part of the patient's standard care pathway), were considered for recruitment.

Patients were approached with details of the study after the diagnosis of respiratory impairment and discussions around the use of NIV had been completed by a Respiratory Healthcare Professional (Consultant Physician or Consultant Clinical Scientist) with a specialist interest in ALS. The study was explained to the patient, relatives, and their caregivers both verbally in clinic and using a patient information sheet. Patients were contacted no earlier than 24 hours after providing the patient information sheet to enquire if they would like to participate and arrange, if appropriate, for consent to be provided. Written patient consent was obtained prior to the commencement of NIV.

2.4 Inclusion Criteria

Patients included in the study had to conform to the following criteria:

- Be either male or female
- Be aged between 18-90 years old
- Have respiratory impairment related to ALS according to criteria set out in NICE NG42 which is based upon one or more of the following clinical criteria
    - Daytime $PaCO_2$ >6.0kPa (using either ABG or CBG)
    - FVC or VC obtained from the performance of Spirometry of ≤50% of predicted value or ≤80% of predicted value plus any signs or symptoms of respiratory impairment.
    - SNIP ≤40 cmH_2O or ≤65 cmH_2O for men or ≤55 cmH_2O for women plus any signs and symptoms of respiratory impairment or repeated regular tests show a rate of decrease in SNIP of ≥10 cmH_2O over 3 months.
    - Evidence of SDB (suspected REM related hypoventilation) on overnight pulse oximetry.

2.5 Exclusion Criteria

All patients were assessed for contraindications to NIV therapy according to our hospitals clinical operating procedure (COP) '*The initiation of domiciliary non-invasive ventilation for patients with chronic hypercapnic respiratory failure (CHRF)'*. Contraindicated patients were those who did not fulfil criteria according to our COP.

This COP was approved by the hospitals Respiratory Medicine Quality Improvement and Patient Safety (QIPS) Committee.

2.5.1 Clinical Status

Any patients who were acutely unwell as assessed by the lead investigator were urgently reviewed by a specialist Consultant Physician and were unable to enrol onto the study.

2.5.2 Comorbidities

Any patients who had significant co-morbidities, as assessed by the lead investigator were reviewed by a specialist Consultant Physician. Patients were excluded from participating if, it was deemed that there were significant co-morbidities which would likely impact on the use of NIV.

2.5.3 Neuro-disability

Patients who demonstrated an inability to remove interface independently (with no waking night caregiver) or cognitive/behavioural limitation affecting ability to use NIV safely were excluded from the study.

2.6 General Considerations

This study followed a standard care pathway for patients diagnosed with ALS requiring NIV as set out by the Respiratory Medicine and Respiratory and Sleep Sciences Departments at UHCW NHS Trust.

Consideration was required to exclude those patients who were unlikely to survive longer than the duration of the study. Enrolling those patients with a likely survival time less than 90 days may be considered unethical. The prediction of survival in ALS, however is very difficult due to the unpredictability of disease progression that is observed. This includes variability in the time between diagnosis and onset of respiratory muscle weakness, the stage of disease at which disease modifying drugs (such as Riluzole) are commenced, the time of onset of impaired cough strength and development of respiratory failure. Consequently, it was not possible to predict which patients were not expected to survive 90 days (duration of study) from the start of treatment and this was not, therefore, applied as an exclusion criterion.

2.7 NIV Modes

This is an exploratory study with randomisation and patients were randomly assigned to either pressure targeted or volume targeted auto-adjusting EPAP NIV using permuted block randomisation to ensure an equal number of patients in each study group. In addition, to ensure an equal number of each ALS phenotype (bulbar and limb) was included in each group, stratified block randomisation was used.

Randomisation was undertaken by an independent person using a sealed envelope protocol in conjunction with the hospital's R&D department.

Participants were randomised into either:

Group 1 - Pressure targeted NIV (ST)

Pressure targeted NIV is recognised as a standard mode of NIV and is used at our hospital.

or

Group 2 - Volume targeted auto-adjusting EPAP NIV (iVAPS-AE)

Volume targeted auto-adjusting EPAP NIV is the new mode of NIV under investigation.

Participants were blinded to which group they had been allocated however to ensure the NIV was setup accurately and safely the healthcare professional was not blinded.

Pressure targeted NIV was delivered using a ResMed Lumis 100 VPAP ST-A device in ST mode (ResMed Ltd, Bella Vista, Australia). Volume targeted auto-adjusting EPAP NIV was delivered using a ResMed Lumis 150 VPAP ST-A device in iVAPS-AE mode (ResMed Ltd, Bella Vista, Australia). Both NIV modes employed a heated single limb leak circuit with either a full face or hybrid interface depending upon patient comfort and preference (Figure 2.1).

Target Vt were based on 8 ml/kg of patient's ideal body weight (IBW) using the NIV (Resmed Lumis 100 and 150) devices in-built algorithm calculation for volume targeted auto-adjusting EPAP and a manual calculation for pressure targeted.

The same range of NIV device, *'Lumis'*, was used to ensure there was consistency of NIV algorithms to limit the potential effect this may have on any observed differences in outcome variables. Remote monitoring was enabled for both groups using ResMed AirView (ResMed Ltd, Bella Vista, Australia).

2.7.1 Pressure Targeted NIV

Patients assigned to pressure targeted, had an IPAP, EPAP and BR selected in combination with Ti_{min}, Ti_{max} and rise time which were based on patient specific requirements.

Patients started with an IPAP of 8 cmH_2O, EPAP of 4 cmH_2O and BR of 12. NIV settings were adjusted for the following: target Vt at 8 ml/kg of IBW, patient comfort, and efficient breathing patterns. During the patient's clinic appointment, TI_{min}, TI_{max} and rise time were adjusted according to patient comfort and level of patient-ventilator asynchrony.

For optimisation of pressure targeted, IPAP, EPAP and BR were changed according to ABG, patient symptoms or at the patients request to improve therapy comfort.

IBW in pressure targeted was calculated using the following formulae:

Males, 50 + 2.3[height (inches) − 60]

Females, 45.5 + 2.3[height (inches) − 60] (Ekkernkamp *et al.*, 2014).

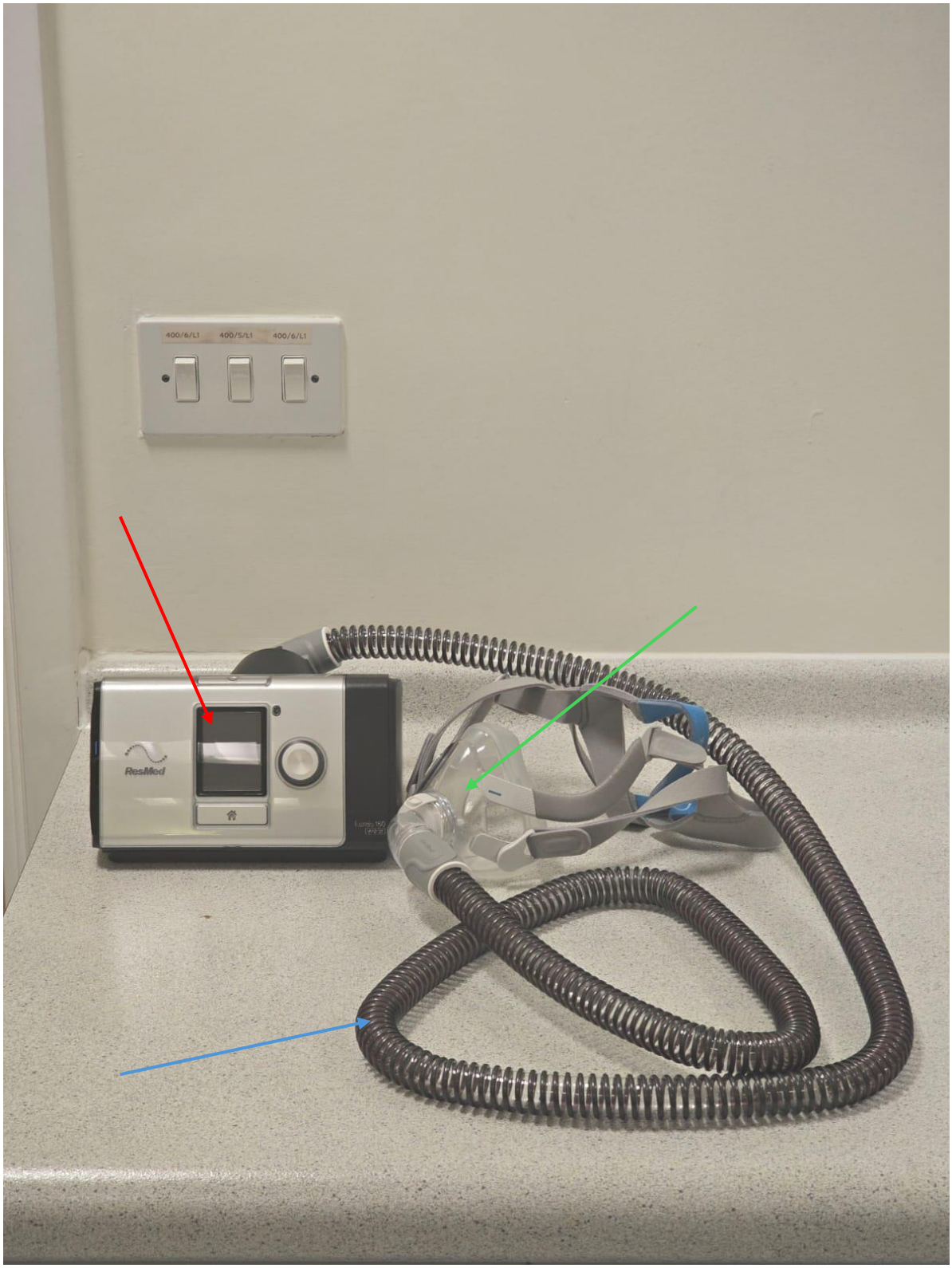

Figure 2.1. ResMed Lumis™ 150 VPAP pressure targeted-A device (red arrow), ClimateLineAir™ 10 (blue arrow) and AirFit™ F20 (green arrow) (ResMed Ltd, Bella Vista, Australia).

2.7.2 Volume targeted NIV with auto-adjusting EPAP

Patients assigned to volume targeted started with a PS_{min} of 2 cmH_2O, PS_{max} of 10 cmH_2O, $EPAP_{min}$ of 4 cmH_2O, $EPAP_{max}$ of 8 cmH_2O and a target rate of 16 (or the patient's spontaneous rate, which is most likely to be disproportionally raised due to hospital environment). These settings provided an equivalent IPAP range of 10-18 cmH_2O and EPAP range of 4-8 cmH_2O. The patients height was used to calculate target Vt using the devices in-built algorithms. During the patient's clinic appointment, TI_{min}, TI_{max} and rise time were adjusted according to patient comfort and level of patient-ventilator asynchrony.

For optimisation of volume targeted auto-adjusting EPAP, target Vt was increased (to between 8-10ml/kg) according to ABG or patient symptoms. PS and EPAP range were only increased if the target Vt is met and further optimisation is required beyond 10ml/kg.

Optimisation of either pressure targeted or volume targeted auto-adjusting EPAP was discussed with the home NIV MDT if required. In both modes settings were based on providing the patient with the best level of therapy comfort to facilitate NIV adherence.

2.8 Data Collection

Visits emphasised in **bold** were part of the standard care for patients with ALS attending the respiratory clinic.

Visit 1 (0-7 days) - Patients were asked to perform FVC, SNIP, nocturnal SpO_2 and blood gas sampling *(CBG/ABG). Patients were asked to complete ALSFRS-R, SRI and mHADS. Patients were commenced onto NIV in accordance with local protocol in the outpatient clinic.

***CBG was the main method for sampling arterial blood. If after all reasonable attempts, it was not possible to obtain an accurate CBG the patient was asked if they consent to perform an ABG. This is part of the standard care ventilatory pathway.**

Day 3 - Telephone call with remote monitoring to review NIV adherence, AHI and interface leak. Patient education on the use of NIV including maintenance of interface and changing consumables would be provided as well as clinical problem solving if appropriate. No measurements were taken at this timepoint.

Visit 2 (14 days +/- 2 days), 3 (30 days +/- 2 days), 4 (60 days +/- 2 days), **5 (90 days +/- 2 days)** - Patients were asked to perform FVC, SNIP, nocturnal SpO_2 and blood gas sampling. Patients were asked to complete ALSFRS-R, SRI and mHADS. Adherence, AHI, and interface leak data from the NIV device was analysed via ResMed AirView (ResMed Ltd, Bella Vista, Australia).

This study followed a standard care pathway and therefore visits 3 and 4 were additional visits. All visits were face to face unless the patient had significant mobility issues and were unable to attend the hospital. As part of the standard care pathway a home visit was arranged for these patients to ensure they had fair and equal access to the appropriate respiratory care.

If a patient was unable to tolerate the NIV mode they were allocated, they were offered to trial the alternative NIV mode, if clinically appropriate (Parkes *et al.*, 2024).

2.9 NIV Circuit

2.9.1 Interface

All commercially available interfaces were offered to deliver both NIV modes and these included full face, nasal and hybrid interface designs (Figure 1.22; 2.1) Patients had access to all three interface types and chose the most comfortable option.

Interface issues, especially leak, were addressed through patient coaching and education, visual demonstrations and ensuring the correct interface was chosen to meet patient specific needs. Interface leak was measured subjectively by the patient and objectively by using the NIV device. A recognised interface leak threshold of >24L/min was used to signify that corrective action was required. Clinical staff were able to download interface leak data from the NIV device. Patients were able to identify interface leak using a 'smiley face' feedback mechanism on the front of the NIV machine after each use. A 'red smiley face' advised the patient that their leak overnight was excessive whereas a 'green smiley face' advised the patient that their overnight interface fit was good.

If patients developed areas of discomfort caused by pressure on the skin and soft tissues from their interface, the standard clinical care pathway was followed including education/training on interface fit, cleaning and changing the interface for an alternative type.

2.9.2 Humidification

Patients who complained of oral or nasal dryness were assessed for a humidified NIV circuit. Special considerations were made to those patients who had evidence of sialorrhea as not to worsen the secretion burden and if clinically appropriate these patients were discussed at the weekly NIV MDT. Both NIV devices used the same *HumidAir* (ResMed Ltd, Bella Vista, Australia) external humidifier which connected to the side of the NIV device and filled with sterile water to between the minimum and maximum mark. The humidity was set to off or at a setting between 1 and 8, where 1 was the lowest humidity setting and 8 was the highest humidity setting. Patients were advised to increase the humidity of the NIV circuit to improve oral and nasal dryness and to decrease the humidity of the NIV circuit if there was moisture in the NIV interface.

2.10 ALS Details

Details relating to the patient's ALS diagnosis were taken from the patient's neurology consultation clinic letter and/or the regional MND MDT outcome proforma. Both these documents were accessed from the hospital's Clinical Results and Reporting System (CRRS). Any patient specific details regarding the patients ALS diagnosis were discussed with the patients Neurology Consultant.

2.10.1 Comorbidities and Medications

The patient's comorbidities and medications were reviewed using either the patient's neurology or respiratory consultation clinic letter, regional MND MDT outcome proforma or respiratory physiology report. Comorbidities which were known to cause or contribute towards the development of CRF were discussed with the Lead Consultant Physician for Sleep and Ventilation. Disease modifying medications including Riluzole were recorded from the patient's neurology consultation clinic letter and medications which were known to depress intrinsic respiratory drive were discussed with Lead Consultant Physician for Sleep and Ventilation.

2.11 Respiratory and Sleep Investigations

Before each investigation was performed, information regarding any benefits and risks were explained to the patient. Testing did not proceed without appropriate voluntary verbal patient consent. All investigations were performed in accordance with local standard operating procedures (SOP). All SOP's had been reviewed and agreed by the hospital's Respiratory Medicine QIPS committee.

2.11.1 Spirometry

Spirometry was performed in accordance to local SOP based on Association of Respiratory Technology and Physiology (ARTP) quality standards (Sylvester *et al.*, 2020) and performed by ARTP accredited Healthcare Scientists using a prevent® flow sensor and CPFS/D USB spirometer (Medical Graphics, UK). The spirometer was calibrated and maintained in accordance with manufacture guidelines and ARTP

quality standards. FVC, FEV_1, PEF, FEV_1/FVC were calculated from measurements of flow using a bidirectional prevent® flow sensor.

Patients were asked to insert a flange mouthpiece with bite grip. Once the patient was connected to the spirometer, they were instructed to breathe tidally to establish an accurate baseline at functional residual capacity (FRC). Once comfortable the patient was then instructed to take a maximal inspiration and then immediately exhale *'as hard and as fast as possible'* until the end of expiration is achieved, or the patient self terminates the test. The patient is then instructed to complete a maximal inspiratory manoeuvre (Sylvester *et al.*, 2020).

Each spirometry manoeuvre was quality assessed against ARTP acceptability and reproducibility criteria to obtain quality assured diagnostic spirometry results. The highest vales for each parameter were taken from three technically acceptable tests and if three technically acceptable/reproducible results were not obtained reasons for this should be documented on the spirometry report (Sylvester *et al.*, 2020).

The Global Lung Initiative (GLI) reference equations were used for all patients. Spirometry was interpreted using ARTP quality standards and NICE NG42 (Quanjer *et al.*, 2012b). A spirometry report was completed and uploaded onto the patient's electronic records.

2.11.2 SNIP

SNIP was performed in accordance with local SOP based on ARTP quality standards (Sylvester *et al.*, 2020) and performed by ARTP accredited Healthcare Scientists using a MicroRPM Respiratory Pressure Meter (MicroMedical, UK). SNIP was interpreted using ARTP quality standards and NICE NG42 (NICE, 2016; Sylvester *et al.*, 2020). The MicroRPM Respiratory Pressure Meter was verified by the hospital's Medical Equipment & Bioengineering Services (MEBS) and maintained in accordance with manufacture guidelines and ARTP quality standards.

SNIP was measured using a nasal bung attached to a pressure catheter connected to a pressure transducer within the MicroRPM Respiratory Pressure Meter. When the patient was seated comfortably, the nasal bung was placed firmly in the patient's most patent nostril. The patient was then instructed to make a sharp, short maximal sniff

through the unoccluded nostril from a position of end expiratory lung volume (EELV). The peak pressure for each sniff was measured for each sniff attempt (Sylvester *et al.*, 2020).

2.11.3 Arterial and Capillary Blood Gas Sampling

CBG was the primary method of blood gas sampling however in the event of a CBG being unobtainable, the patient was asked if they would consent to an ABG being performed as occurs in routine clinical practice. ABG was performed by inserting a needle syringe into the patient's radial artery at a 35 to 45 degree angle to obtain a sample of arterialised blood. CBG was performed using a safety needle lancet to make a 3mm stab in the patient's inferolateral pinna. The arterialised blood was collected in a capillary tube for no more than 30 seconds.

Both ABG and CBG were performed in accordance with local SOP and by an appropriately trained healthcare professional. ABG were performed using BD Eclipse™ Needle 21 G x 1" & 3ml Luer-Lok™ Syringe (Becton, Dickinson and Company, UK) and CBG were performed using *safe*CLINITUBES (Radiometer, UK). Respiratory blood gas samples obtained by both methods were analysed immediately using a Radiometer ABL90 FLEX blood gas analyser (Radiometer, UK) and discarded as per standard clinical care. The blood gas analyser was calibrated in accordance with manufacture instruction including a 1-point every 1-2 hours and a 2-point every 4-6 hours.

The blood gas analyser was included in an independent, external quality assurance programme called Wales External Quality Assessment Scheme (WEQAS) which operates to United Kingdom Accredited Services (UKAS) and International Organisation for Standardisation (ISO) standards 4301 for proficiency testing and calibration. The blood gas analyser was maintained by the hospital's MEBS.

ABG and CBG were interpreted by an appropriately trained and registered healthcare professional in accordance with NICE and ARTP guidelines (NICE, 2016; Sylvester *et al.*, 2020).

2.11.4 Overnight Pulse Oximetry

Patients performed a one-night pulse oximetry study. The overnight pulse oximetry was reported by a suitably qualified member of the team in accordance with NICE and the American Academy of Sleep Medicine (AASM) version 3 guidelines (NICE, 2016; AASM, 2023). Parameters reported included SpO_2, HR, ODI, % of study time SpO_2 was <90% (T-90) and heart rate rises (HRR). An abnormal ODI threshold was ≥5 desaturations per an hour.

The overnight pulse oximeters were maintained in accordance with the manufactures guidelines and serviced by the hospital Trusts MEBS team.

2.12 HRQoL

Patients were asked to complete three validated questionnaires to enable HRQoL to be assessed.

2.12.1 Severe Respiratory Insufficiency (SRI)

Patients were asked to complete the SRI based on health and wellbeing over the previous 2 weeks.

Each question of the questionnaire was scored on a 5 point scale from -2 to +2 which measured either a positive or negative response with written comments from ‘strongly disagree’ to ‘strongly agree’. Each aspect was then converted to a score between 0 and 100 using a well-established scoring system (Ghosh *et al.*, 2012).

Patients completed a paper copy of the SRI which was then inputted into an electronic form on a Microsoft Excel Spreadsheet. If any questions were omitted or not completely answered the questionnaire was not accepted as not to negatively influence the results.

2.12.2 mHADS

Patients were asked to complete the mHADS which consists of 14 questions within two sub domains of anxiety and depression. Each question was scored between 0-3

with total scores for depression and anxiety between 0-21. In accordance with appropriate evidence, D8 *'I feel as though I am slowed down'* and A6 *"I feel restless as if I have to be on the move"* were omitted on a reasonable assumption that these questions would be confounded by the natural physical impairment of ALS (Abrahams *et al.*, 1997; Goldstein *et al.*, 2006; Gibbons *et al.*, 2011).

Patients completed a paper copy of the mHADS which was then inputted electronically onto a Microsoft Excel spreadsheet. If any question from each domain was omitted or not answered completely the total score for this domain would not be reported.

The mHADS was interpreted using the methodology detailed below (Gibbons *et al.*, 2011) –

Possible Depression	-	Scores 5-7
Probable Depression	-	Scores ≥ 8
Possible Anxiety	-	Scores 7-8
Probable Anxiety	-	Scores ≥ 9

2.12.3 ALSFRS-R

Patients completed a paper copy of the ALSFRS-R which was then inputted electronically onto a Microsoft Excel spreadsheet. If any question was omitted or not answered completely a total ALSFRS-R score could not be obtained. The ALSFRS-R was interpreted using an online scoring platform (Cedarbaum *et al.*, 1999).

2.13 NIV Parameters

NIV parameters were downloaded remotely from ResMed AirView (ResMed Ltd, Bella Vista, Australia).

Vt was automatically calculated using a manufacturer and device specific algorithm from measured flow and pressure profiles (Ackrivo *et al.*, 2021). Vt was reported in millilitres (mL). The median tidal volume was downloaded at each patient visit.

The patient's reported RR was displayed as the median of the previous five breathing cycles. The NIV device directly measured the timing and duration of each respiratory cycle. RR was reported in breathes per minute. The median RR was calculated at each patient visit.

The patient's AHI was calculated as the total number of apnoea's and hypopnoea's divided by the total sleep study time. The AHI was reported as events per hour (events/hr). The AHI was automatically calculated using a manufacturer and device specific algorithm from measured flow and pressure profiles. The median AHI was calculated at each patient visit. The AHI was reported as mild (5-15 events/hour), moderate (15-30 events/hr), or severe (> 30 events/hr) (AASM, 2023).

Interface leak was calculated automatically using the total intended leak minus the total volume of unintended interface leak. An abnormal patient interface leak was reported as >24 $L \cdot min^{-1}$ for >20% of the total leak trace (Teschler *et al.*, 1999; Rabec *et al.*, 2009). The interface leak was calculated using a manufacturer and device specific algorithm from measured flow and pressure profiles. The median interface leak was calculated at each patient visit.

Adherence was automatically recorded by the ventilator in hours and is the sum of the nightly hours divided by the number of nights within a set period. NIV adherence was measured from day 0 to day 90 and reported as continuous data by way of number of hours per a night. Each patient will have up to 90 adherence data points. Measurements of NIV adherence were made at each study timepoint and consisted of the 14 days leading up to the timepoint, for example, NIV adherence at 30 days was adherence from day 16 to day 30.

2.14 Statistical Methods

2.14.1 Power and Sample Size

A sample size of 40 participants was initially identified following discussion with a Statistician recommend by the hospital.

Sample size consideration was dictated by the following -

1) the average number of ALS patient's setup onto NIV per a year at our hospital (n=20)

and

2) that this study formed part of an academic programme with a fixed term data collection/recruitment period of 2 years.

The first patient participant was recruited in March 2022, with an average recruitment rate of 1 patient per month. We anticipated that we would not reach the expected 40 patients (an expected recruitment rate prior to COVID-19 pandemic).

However, the recruitment period was shortened to 18 months following the COVID-19 pandemic and after further consultation with the hospital's Statistician patient recruitment was reduced to 15 and the study was amended to follow an exploratory methodology. We expected the recruitment rate of 1 patient per a month to continue allowing up to 15 patients recruited by October 2023. We therefore expected to have a total recruitment of 15 patients with 7/8 patients in each NIV group.

2.14.2 Missing Data

Any data that had been missed or unable to be collected was reported. Only data which was queried and validated was entered for statistical analyses. Data was checked by another member of the research team to ensure that all aspects of the data had been equally represented.

2.14.3 Statistical Analyses

Specific statistical testing is reported in the related analysis sections 3.3.1 and 4.3.1.

3 Results: Improved NIV adherence may occur in people living with ALS using volume targeted NIV

3.1 Introduction

NIV is commonly used to manage sleep and breathing symptoms associated with progressive respiratory muscle weakness in ALS with an ambition to improve survival and HRQoL, whilst delaying time to mechanical ventilation (tracheostomy) or death (Kleopa *et al.*, 1999). Data from the EuroVent study (Lloyd-Owen *et al.*, 2005) demonstrated an estimated home NIV prevalence of 6.6 per 100,000 in Europe with noticeable differences in NIV provision for both tracheostomy and non-tracheostomy ventilated ALS patients. However, in patients who demonstrate sufficient NIV adherence, studies have reported an increased median survival by 205 days with improved and maintained HRQoL (Bourke, Shaw and Gibson, 2001; Bourke *et al.*, 2003, 2006). This data suggests a consequential and clinically meaningful therapeutic response suggesting NIV should not only be considered a palliative care intervention.

Previous studies have demonstrated marked improvements in survival and HRQoL with the use of NIV for ≥4 hours per day (h/d) (Ackrivo *et al.*, 2021). However, approximately 30% of patients demonstrate non-adherence to this level of use, with data suggesting adherence is even lower in bulbar ALS patients (Kleopa *et al.*, 1999; Gruis *et al.*, 2005; Bourke *et al.*, 2006).

The VITALITY-ALS study of 195 patients reported mixed adherence rates with 78.5% of patients using NIV for ≥2 h/24 h, 71.3% for ≥4 h/24 h, and 11.8% for ≥22 h/24 h (Rudnicki *et al.*, 2021). In a review of the Pooled Resource Open Access ALS Clinical Trials database of 604 patients, only 33.9% of patients reported using NIV (Thakore *et al.*, 2019). Other studies have reported adherence rates ranging between 33, 67 and 90% (Kleopa *et al.*, 1999; Gruis *et al.*, 2005; Coco *et al.*, 2006; Czudaj, Suchi and Schönhofer, 2009; Ristell *et al.*, 2019; Thakore *et al.*, 2019; Vitacca *et al.*, 2020; Rudnicki *et al.*, 2021; Russo *et al.*, 2021).

Median NIV adherence reported in hours per night ranges between 6.5 and 12.3 (Nicholson *et al.*, 2017; Sancho *et al.*, 2018). However, many of the studies reporting

NIV adherence have done so with the use of standard pressure targeted NIV, commonly spontaneous/timed mode (Pinto *et al.*, 1995; Bourke *et al.*, 2003, 2006; Gruis *et al.*, 2006). Alternatively, volume targeted NIV, specifically volume assured pressure support, has been investigated in broader neuromuscular disease cohorts (Jaye *et al.*, 2009; Crescimanno, Marrone and Vianello, 2011; Annane, Orlikowski and Chevret, 2014).

Volume targeted auto-adjusting EPAP (ResMed Ltd, Bella Vista, Australia) is an enhanced version of NIV. It differs from standard volume targeted NIV as, being more technologically advanced, it can automatically adjust a greater number of parameters including EPAP and iBR. Pressure targeted NIV, with its fixed pressure limitations, is unlikely to effectively preclude all obstructive sleep events frequently experienced by patients with predominantly bulbar disease. Therefore, it may be unable to ensure an appropriate airway pressure is maintained across all sleep stages. In contrast, volume targeted auto-adjusting EPAP NIV has the potential to reduce the likelihood of sleep fragmentation caused by large fluctuations in volume and/or pressure and thus improve sleep quality (Gay *et al.*, 1991; Ferguson *et al.*, 1996; Kimura *et al.*, 1999; Ambrogio *et al.*, 2008; Boentert *et al.*, 2015; Boentert, 2020).

Although pressure targeted NIV is commonly used in ALS, neither pressure targeted nor volume targeted auto-adjusting EPAP NIV have been shown to be superior in terms of adherence. Of three studies, all including patients with NMD, two reported no significant differences between pressure targeted and volume targeted NIV with the third reporting improved adherence with volume targeted NIV (Jaye *et al.*, 2009; Crescimanno, Marrone and Vianello, 2011; Kelly *et al.*, 2014).

3.2 Aims and Objectives

3.2.1 Primary Aim of Study

The primary outcome was NIV adherence measured from day 0 to day 90, reported as a continuous variable. Each patient had up to 90 adherence data points. Measurements of NIV adherence were made at each study timepoint and consisted of the 14 days leading up to the timepoint, for example, NIV adherence at 30 days was adherence from day 16 to day 30.

The primary aim of this study was to explore the differences in NIV adherence between pressure targeted and volume targeted auto-adjusting EPAP NIV.

3.2.2 Secondary Aim of Study

Secondary outcomes were AHI, interface leak and respiratory blood gas parameters measured at each study timepoint (0, 14, 30, 60 and 90 days)

The secondary aim of the study was to explore differences in AHI, interface leak and respiratory blood gas parameters between pressure targeted and volume targeted auto-adjusting EPAP NIV.

3.2.3 Tertiary Aim of the Study

Tertiary outcome was an effect and sample size using a power of 0.8 and alpha of 0.05.

The tertiary aim of the study was to calculate an effect and sample size to be used to adequately power future large scale, multicentre studies with a primary outcome of NIV adherence.

3.3 Methods

Methods are described in Chapter 2. Here I present details specific to the data analysis required to address the aims outlined above (See section 3.2).

Optimisation of either NIV mode for clinically complex patients, including those with multiple co-morbidities or care needs, were discussed at the home NIV MDT. In both modes, settings were adjusted with the primary goal to provide the patient with the best level of therapy and comfort to facilitate adherence. Once allocated to either pressure targeted or volume targeted group, patients followed a standard ventilatory care pathway for patients diagnosed with ALS requiring NIV, as set out by both the Respiratory Medicine and Respiratory and Sleep Sciences Department at UHCW NHS Trust.

All visits were face to face unless the patient had significant mobility issues and was unable to attend the hospital. For these patients a home visit was arranged to ensure accessibility to the appropriate respiratory care.

All commercially available NIV interfaces were available to deliver both modes including full face, nasal and hybrid interface designs (Figure 1.22; 2.1). Interface issues, especially leak, were addressed through patient coaching and education, visual demonstrations and ensuring the correct interface was chosen to meet patient specific needs.

3.3.1 Statistical Analyses

Statistical analyses were performed using STATA version 11.0 (Statacorp, California, USA). Statistical analyses are mostly descriptive using count and percentage for categorical data, mean with standard deviation and median with $25^{th}/75^{th}$ percentiles for continuous data. NIV adherence trends over time were visually examined using, boxplots, violin plots and time series charts. Linear and non-linear regression lines were applied to adherence over time plots for both groups to assess which model best fit these data. R^2 values for each model are reported.

Continuous data were assessed for normality using the Shapiro–Wilk test. Where appropriate, parametric, or nonparametric testing was performed for between-group comparisons, using unpaired t-testing or the Mann–Whitney U test for continuous

variables. Patients were sub-grouped into adherent and non-adherent groups using visual inspection of adherence data over time plots. A two-tailed level of significance less than 0.05 was chosen for all analyses. An effect and sample size using a power of 0.8 and an alpha of 0.05 was calculated using G*Power version 3.1.9.7 (Faul *et al.*, 2009).

3.4 Results

3.4.1 Study Population

3.4.1.1 Whole Study Population Characteristics

Patient demographics are shown in Table 3.1. In total 24 patients were commenced onto NIV at the Department of Respiratory and Sleep Sciences, UHCW NHS Trust, between March 2021 and October 2023. Of these 24 patients, 15 patients consented and enrolled onto the pilot study. A CONSORT flow diagram reporting enrolment, NIV mode allocation, follow-up and analysis of data is shown in figure 3.1.

Table 3.1 Patient demographics

Characteristic	**Patient number**	**Value**
Median ages [years] (IQR)	15	71 (65-77)
Male (%)	15	60
Mean weight [kg] (SD)	12	63.93 (19.15)
Mean height (cm) (SD)	12	168 (10.83)
Mean BMI [kg/m^2] (SD)	12	22.3 (5.15)
Median smoking history [pk/years] (IQR)	14	0 (0-20)

Table entries are median (IQR), mean (SD) or count (%).

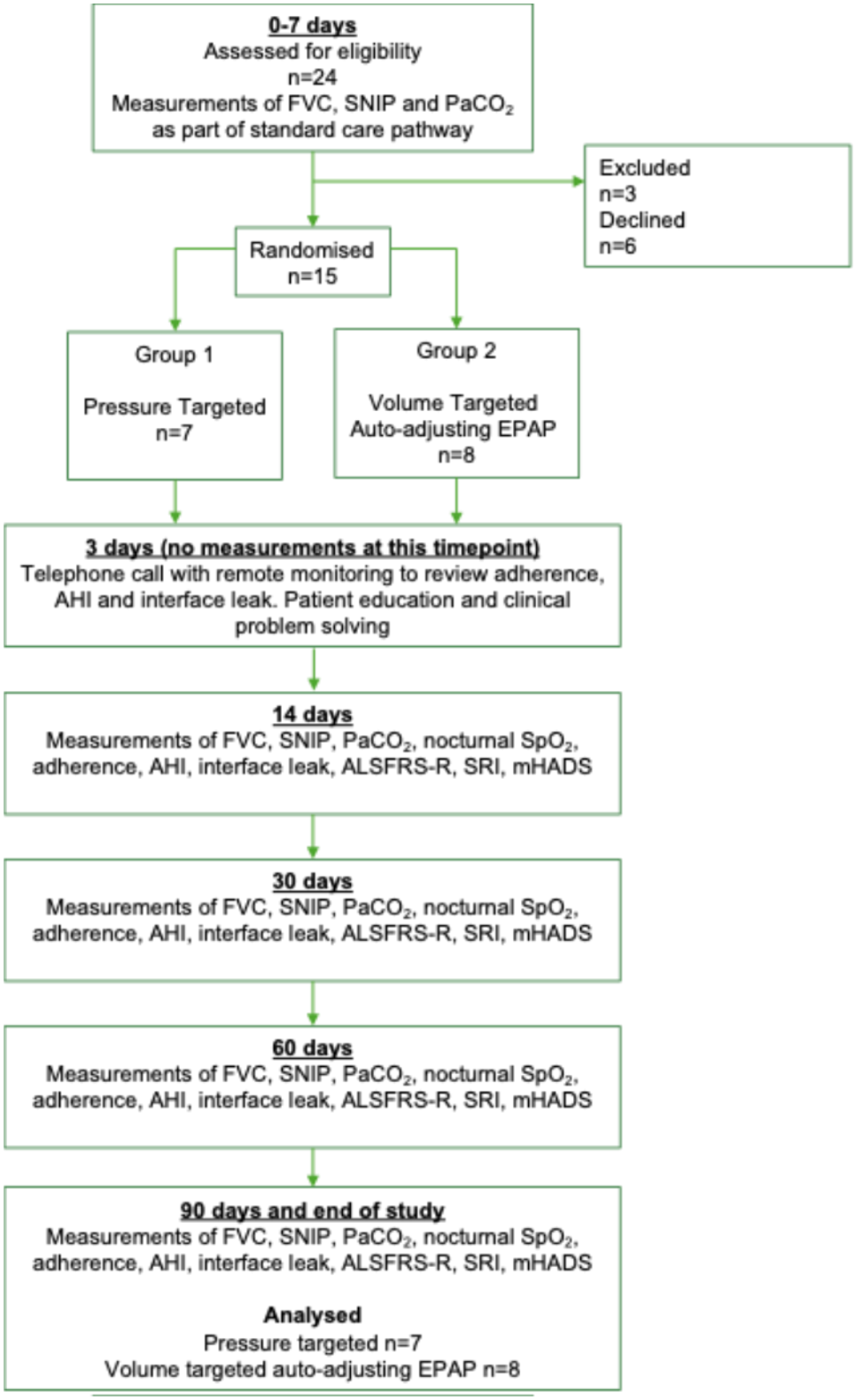

Figure 3.1. CONSORT flow diagram reporting enrolment, NIV mode allocation, follow-up and analysis of data.

ALS characteristics are shown in Table 3.2. Limb weakness was the predominant ALS phenotype with most patients prescribed Riluzole. Bulbar impairment was observed in more than two thirds of patients.

Table 3.2 ALS characteristics

Characteristic	**Patient number = 15**
Limb predominant ALS	9 (60)
Riluzole	12 (80)
PEG	4 (27)
Bulbar impairment	11 (73)

Table entries are count (%); PEG is percutaneous endoscopic gastroscopy.

Respiratory and sleep function data are shown in Table 3.3. A total of 8 patients were able to perform spirometry but only 2 patients were able to achieve quality assured technically acceptable results. In total 7 patients were unable to perform spirometry, 6 due to the severity of bulbar impairment. Overall, spirometry, overnight pulse oximetry, respiratory muscle function and blood gas analysis data suggest the presence of respiratory impairment and/or chronic hypercapnic respiratory failure; this was expected as a pre-requisite to commencing NIV.

Table 1.3 Characteristics of respiratory and sleep function

Characteristic	Patient number	Value
Mean FEV1 [SR] (SD)	8	-2.08 (1.44)
Median FVC [SR] (IQR)	8	-2.11 (-3.65 - -1.87)
Mean FEV1/FVC [SR] (SD)	8	0.61 (2.30)
Mean PEF [SR] (SD)	8	-2.46 (2.30)
Median ODI [events/hour] (IQR)	13	4.64 (2.04 – 7.33)
Median nocturnal SpO_2 [%] (IQR)	13	94 (92 – 95)
% of sleep with nocturnal SpO_2 <90%	13	3.25 (0.1 – 4)
Mean HRR [rises/hour] (SD)	11	15.15 (10.7)
Mean HR [bpm] (SD)	13	76 (16)
% nocturnal hypoventilation	13	62
Mean SNIP [cmH_20] (SD)	13	32 (11)
Mean pH (SD)	15	7.44 (0.03)
Median $PaCO_2$ (kPa) (IQR)	15	6.00 (5.44 – 6.32)
Mean PaO_2 [kPa] (SD)	15	10.13 (1.18)
Mean Bicarbonate [mmol/L] (SD)	15	30.56 (2.29)
Mean SaO_2 (%)	14	95 (2)

Table entries are median (range), mean (SD) or count (%); n=number of patients.

HRQoL characteristics are shown in Table 3.4. Generally, patients demonstrated a high severity of disease including respiratory function with a low ALSFRS-R, evidenced with a mean score of 29 out of a maximum score of 48 points. Patients demonstrated borderline depression with a normal anxiety score using mHADS. Overall, HRQoL was low with an SRI-SS of <50%.

Table 3.2. HRQoL characteristics

Characteristic	Patient number = 15
Mean ALSFRS-R (SD)	29 (14)
Median mHADS Anxiety (IQR)	5 (6 – 13)
Mean mHADS Depression (SD)	6 (4)
Mean SRI-SS (SD)	48 (19)

Table entries are median (range) or mean (SD); n=number of patients. SS is summary score.

3.4.1.2 Patient Characteristics within each NIV Group

Patient demographics within each NIV group are shown in Table 3.5. A total of 7 patients were commenced onto pressure targeted with the remaining 8 patients commenced onto volume targeted auto-adjusting EPAP.

Table 3.3. Patient demographics of volume targeted auto-adjusting EPAP and pressure targeted groups

Characteristic	Volume targeted auto-adjusting EPAP (n=8)	Pressure targeted (n=7)	p value
Median ages in years (IQR)	70 (65 – 77)	71 (65 – 77)	1.00
Male	6 (75)	3 (43)	0.31
Mean weight [kg] (SD)	60.8 (15.5)	67.2 (23.3)	0.58
Mean height [cm] (SD)	168.8 (11.1)	167.7 (11.6)	0.85
Mean BMI [kg/m^2] (SD)	21.2 (5.2)	23.4 (5.4)	0.47

Table entries are median (range), mean (SD) or count (%); n=number of patients. * indicates variables that were significant with $p < 0.05$.

ALS characteristics within each NIV group are shown in Table 3.6. There were a greater number of patients with limb predominant ALS in the volume targeted auto-adjusting EPAP group with a greater number of patients demonstrating bulbar muscle weakness in the pressure targeted group.

Table 3.4. ALS characteristics of volume targeted auto-adjusting EPAP and pressure targeted groups

Characteristic	Volume targeted auto-adjusting EPAP (n=8)	Pressure targeted (n=7)	p value
Limb predominant ALS	7 (88)	2 (29)	0.04*
Riluzole	7 (88)	5 (71)	0.56
PEG	2 (25)	2 (29)	1.00
Bulbar impairment	4 (50)	7 (100)	0.07

Table entries are count (%); n=number of patients. * indicates variables that were significant with a p value <0.05 (chi square).

Respiratory and sleep function characteristics within each NIV group are shown in Table 3.7. There were no statistically significant differences in any of these measures between volume targeted auto-adjusting EPAP and pressure targeted. However, patients assigned to pressure targeted had a much-reduced FVC compared to those patients using volume targeted auto-adjusting EPAP. In total 7 patients were unable to perform spirometry predominately due to bulbar dysfunction. A total of 8 patients performed spirometry with 6 patients able to produce quality assured results. Both groups had comparable sleep function as assessed using overnight pulse oximetry, although patients using pressure targeted demonstrated a higher ODI. Respiratory gas analysis was unremarkable between the two groups with comparable daytime hypercapnia, however patients in the volume targeted auto-adjusting EPAP group demonstrated a marginally higher bicarbonate.

Table 3.5. Respiratory and sleep function characteristics of volume targeted auto-adjusting EPAP and pressure targeted groups

Characteristic	Volume targeted auto-adjusting EPAP (n=8)	n	Pressure targeted (n=7)	n	p value
Mean FEV1 [SR] (SD)	-1.92 (1.36)	6	-2.61 (2.16)	2	0.58
Median FVC [SR] (IQR)	-2.11 (-3.52 - -1.85)	6	-3.06 (-4.26 - /)	2	1.00
Mean FEV1/FVC [SR] (SD)	0.87 (2.26)	6	-0.155 (3.11)	2	0.62
Mean PEF [SR] (SD)	-2.39 (1.71)	6	-2.63 (2.51)	2	0.87
Median ODI [events/hour] (IQR)	4.64 (0.50-5.00)	8	4.71 (2.03-5.61)	7	0.62
Median nocturnal SpO2 [%] (IQR)	92 (90-94)	7	95 (94-95)	6	0.51
Mean HRR [rises/hour] (SD)	11.45 (9.20)	6	19.60 (11.63)	5	0.22
Mean HR [bpm] (SD)	81 (18)	7	69 (10)	6	0.17
Nocturnal hypoventilation	4 (50)	7	4 (57)	6	1.00
Mean SNIP [cmH_2O] (SD)	32 (13)	7	32 (9)	6	0.98
Mean pH (SD)	7.45 (0.34)	8	7.43 (0.01)	7	0.16
Median $PaCO_2$ [kPa] (IQR)	6.04 (5.43-6.38)	8	6.00 (5.50-6.30)	7	1.00
Mean PaO_2 [kPa] (SD)	10.0 (1.59)	8	10.2 (0.47)	7	0.71
Mean Bicarbonate [mmol/L] (SD)	31.28 (2.41)	8	29.72 (1.98)	7	0.19
Mean SaO_2 [%] (SD)	95 (2)	7	96 (1)	7	0.39

Table entries are median (range), mean (SD) or count (%); n=number of patients.

HRQoL measures within each NIV group are shown in Table 3.8. HRQoL was comparable between group with no statistically significant differences, however patients assigned to pressure targeted demonstrated an overall lower SRI score.

Table 3.6. HRQoL characteristics of volume targeted auto-adjusting EPAP and pressure targeted groups

Characteristic	Volume targeted auto-adjusting EPAP (n=8)	Pressure targeted (n=7)	p value
Mean ALSFRS-R (SD)	27 (12)	31 (16)	0.54
Median mHADS Anxiety (IQR)	7 (5-14)	5 (3-10)	0.28
Mean mHADS Depression (SD)	5 (4)	7 (3)	0.34
Mean SRI-SS (SD)	55 (21)	40 (14)	0.13

Table entries are median (range) or mean (SD); n=number of patients. * indicates variables that were significant with a p value <0.05.

3.4.1.3 Primary Outcome

A non-parametric equality of medians test (Mann Whitney U) for each time point was performed to assess differences in adherence between NIV modes. Median adherence across the entirety of the assessment period (0 – 90 days) for volume targeted auto-adjusting EPAP was 7.1 hours per day (h/d) (IQR 0.28-9.0) and 3.93 h/d for pressure targeted (IQR 0-7.3). Between group comparisons of adherence by time point incorporating the 14 day period building up to the stated timepoint are shown in Table 3.9. After the initial 14 days, median adherence in the volume targeted auto-adjusting EPAP group was statistically significantly higher than the pressure targeted group (p = <0.001) (Figure 3.1).

Table 3.7 Adherence (h/d) of both NIV groups by timepoints

	Group		
Timepoint (days)	**Volume targeted auto-adjusting EPAP (n=8)**	**Pressure targeted (n=7)**	**p value**
14	1.32 (0 - 2.4)	0.84 (0 - 6.46)	0.325
30	6.29 (0.1 - 8.55)	2.48 (0 - 7.3)	<0.001*
60	7.54 (2.43 - 9.08)	5.8 (0 - 7.3)	<0.001*
90	9.05 (7.8 - 9.5)	6.22 (0 - 8.66)	<0.001*

Table entries are median (range); n=number of patients. * indicates variables that were significant with a p value <0.05 (nonparametric equality-of-medians test).

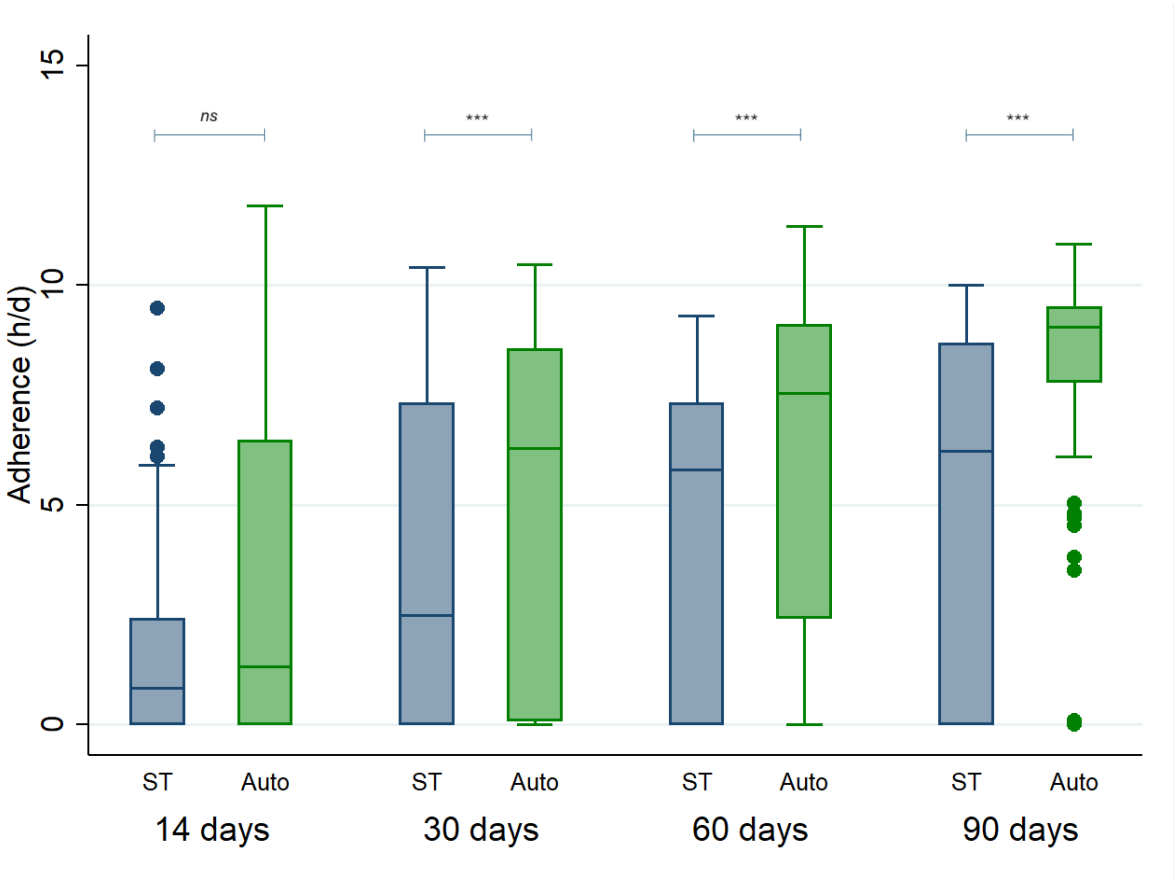

Figure 3.2. Box-plot of adherence by timepoints for both NIV groups. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset. Data points denoted as circles are outliers. ns=p value >0.05. P value ≤0.05 is designated with one (*) asterisk, ≤0.01 two (**) asterisk, ≤0.001 three (***) asterisk and ≤0.0001 four (****) asterisks. h/d=hours per a day.

Violin plots were used to visualise the distribution of adherence for both groups over 90 days (Figure 3.2) and at each timepoint (Figure 3.3). The violin plots show the distribution of adherence within each NIV mode, with the median adherence for pressure targeted lower than for volume targeted auto-adjusting EPAP (white dot, Figure 3.2). Although both volume targeted and pressure targeted demonstrate a bimodal distribution shape, volume targeted auto-adjusting EPAP demonstrates the widest distribution of data points towards the top of the violin indicating adherence is highly concentrated above the median.

In contrast the widest distribution of data points is towards the bottom of the violin for pressure targeted the shape of the distribution indicating the adherence of pressure targeted patients are highly concentrated below the median. Using visual inspection, the violin plot suggests a higher probability for patients using volume targeted auto-adjusting EPAP to achieve adherence of >7.0 h/d, compared to pressure targeted where there is a higher probability that patients will achieve an adherence of <4.0 h/d (red line, Figure 3.2). Overall, data demonstrates volume targeted auto-adjusting EPAP led to a greater adherence than pressure targeted, a greater number of patients with volume targeted auto-adjusting EPAP use NIV for >4h/d and adherent patients use volume targeted auto-adjusting EPAP for longer compared to pressure targeted (Figure 3.2).

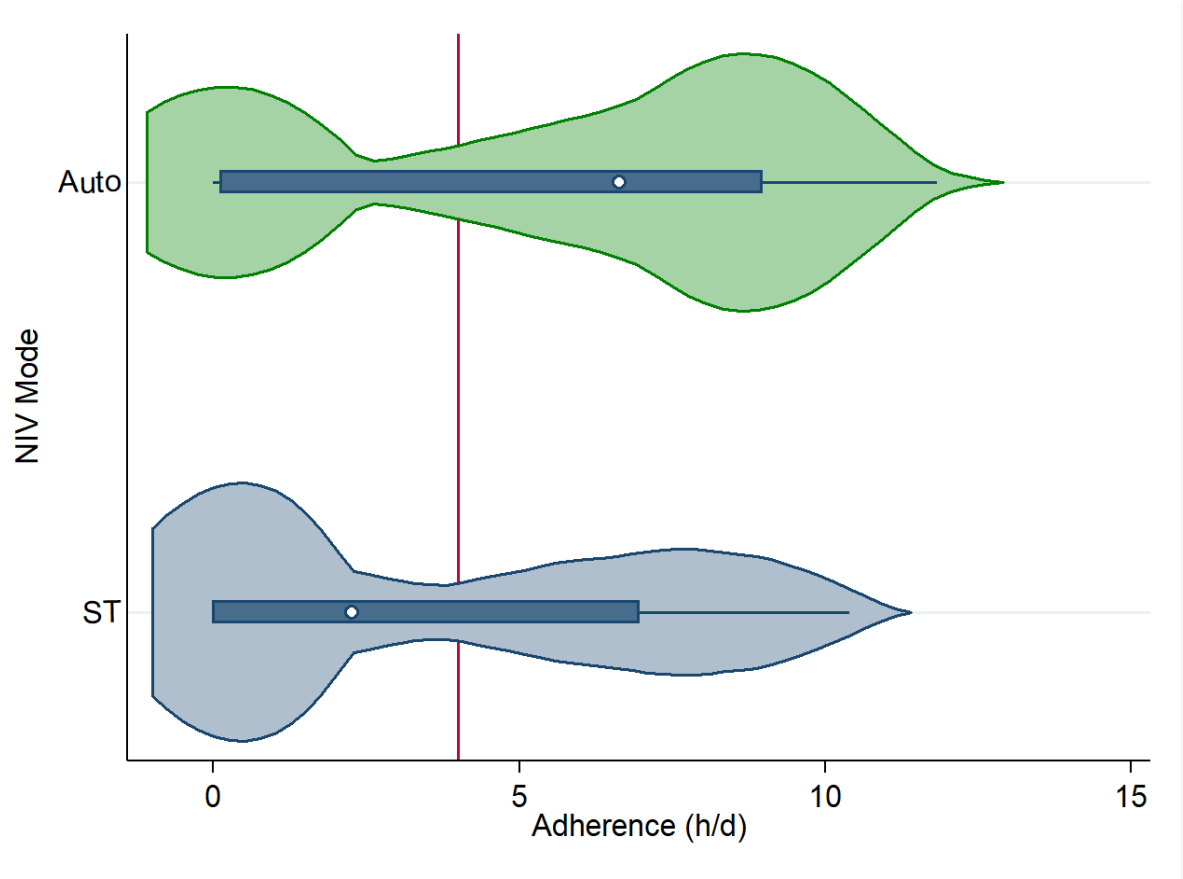

Figure 3.3. Violin plot of NIV adherence by NIV group over 90 days. Red line indicates adherence of 4h/d. White dot=median h/d. h/d=hours per a day. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP.

Violin plots showing the distribution of adherence for both NIV groups at each timepoint are shown in Figure 3.3. At 14 days both NIV groups demonstrate a unimodal distribution with data highly concentrated around the median. At 30 days volume targeted demonstrates a bimodal distribution of adherence data with a high concentration of data above the median value compared to pressure targeted which continues to demonstrate a unimodal distribution. At 60 days both NIV groups demonstrate a bimodal distribution of data albeit with high concentrations of data around the median. At 90 days pressure targeted continues to demonstrate a bimodal distribution however volume targeted auto-adjusting EPAP now demonstrates a unimodal distribution with a high concentration of data around the median. At 14 days both NIV groups have similar median adherence however at 30-, 60- and 90-days median adherence for volume targeted auto-adjusting EPAP is consistently greater than pressure targeted (Figure 3.3).

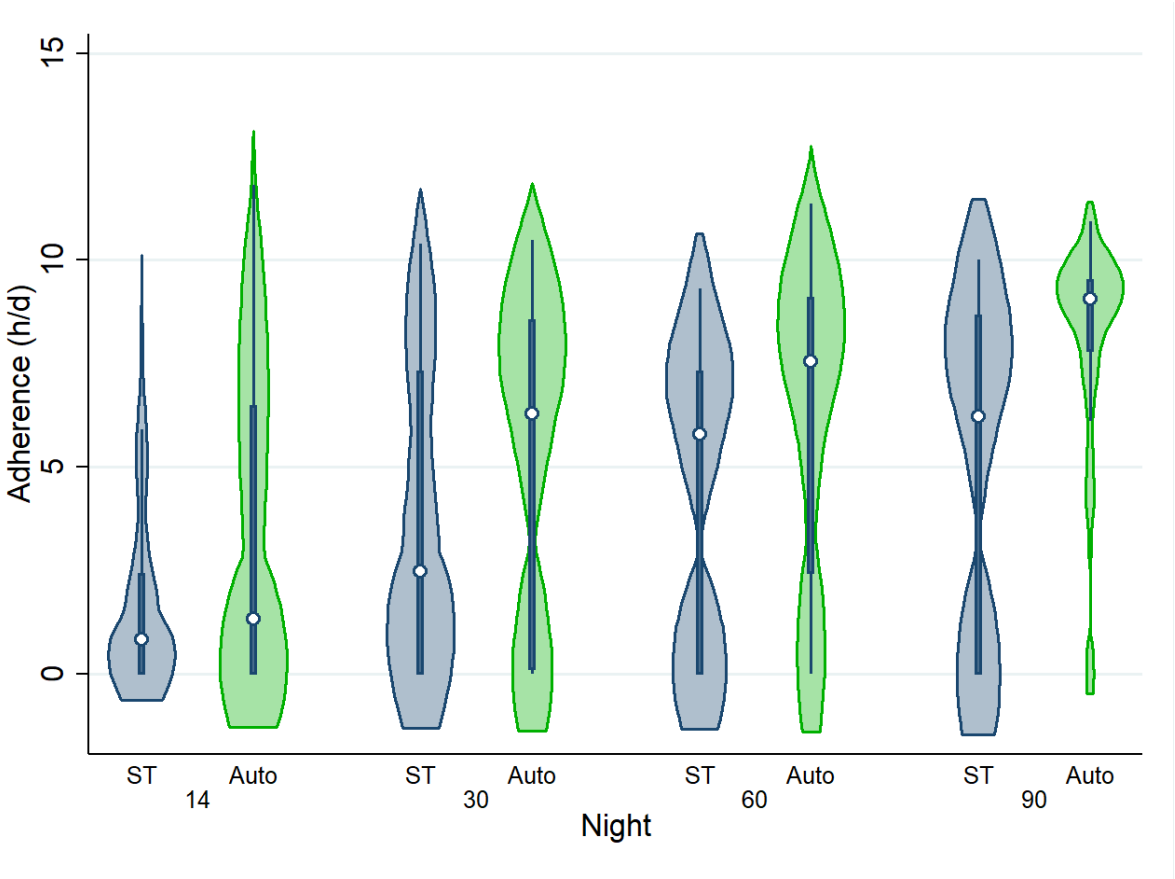

Figure 3.4. Violin plot of NIV adherence by timepoint for both NIV groups. Red line indicates adherence of 4h/d. White dot=median h/d. 0,14,30,60 and 90 are days. h/d=hours per a day. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP.

NIV adherence values for each of the 90 days in both groups are shown in Figure 3.4, with the fitted regression models overlaid. For volume targeted auto-adjusting EPAP there are very weak, positive, linear and curvilinear, relationships between NIV adherence and number of days of NIV use. There are significant outliers identified in the dataset. Linear, polynominal and quadratic regression lines provide poor fit for the dataset with R^2 values of 0.068, 0.077 and 0.112, respectively. For pressure targeted there are weak, positive, linear and curvilinear, relationships between NIV adherence and number of days. Linear, polynominal and quadratic regression lines provide poor fit for the dataset with R^2 values of 0.257, 0.291 and 0.303, respectively. Overall, all three regression lines suggest a higher starting and end adherence for volume targeted auto-adjusting EPAP compared to pressure targeted, that is, patients assigned to volume targeted auto-adjusting EPAP use NIV for longer and sooner after commencing use and continue to increase use over time (Figure 3.4).

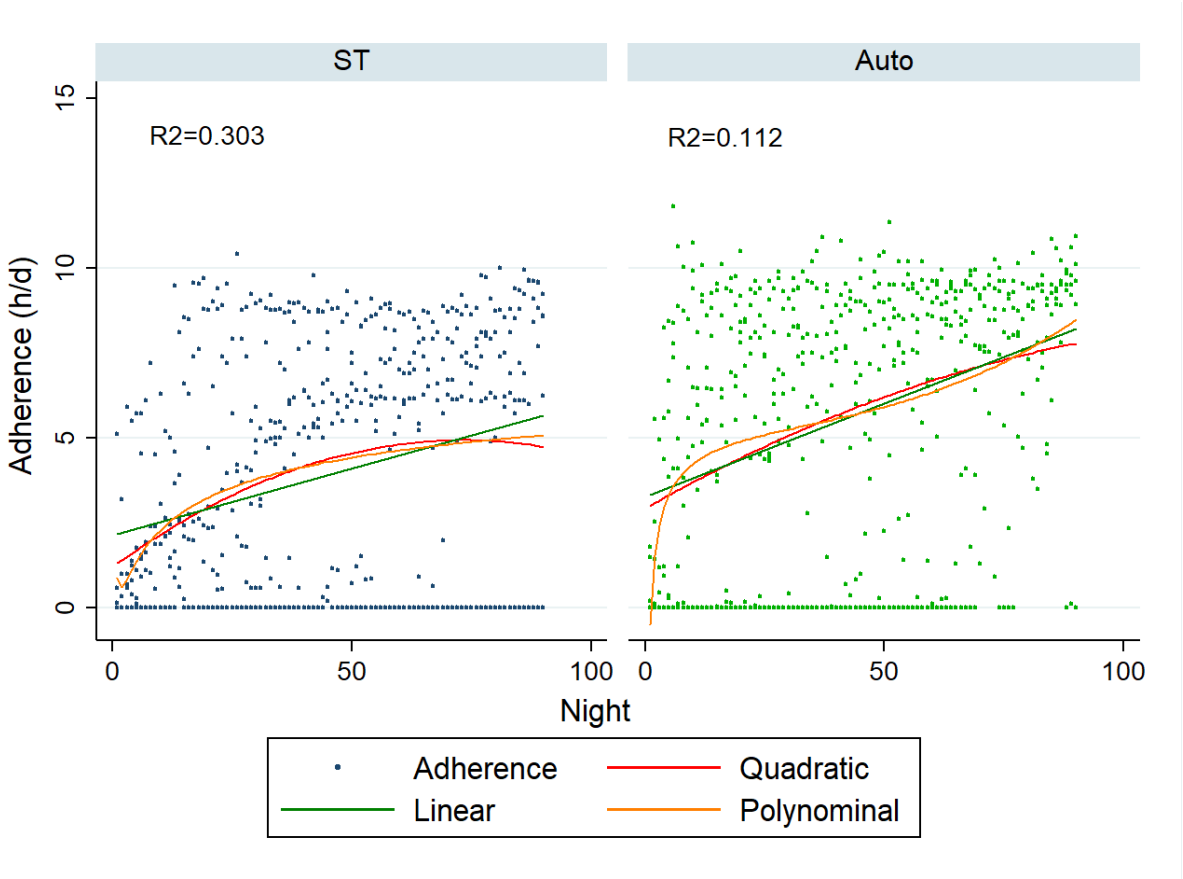

Figure 3.5. Scatter plots of NIV adherence over 90 days for both NIV groups. h/d=hours per a day. Scatter plots have been fitted with linear and non-linear models. R^2 is reported for the best fitting model (quadratic in both NIV modes). ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP.

It is however evident in Figure 3.4 that there are a large number of zero hour points in each NIV group, indicating that devices were often not used. This suggests a dichotomy in the participant population between those who did and did not use the device, irrespective of device mode. To understand whether NIV use patterns differed between device modes these differences were further interrogated. To do this, NIV adherence values over 90 days from each individual patient were plotted and are shown in Figure 3.5.

Visual inspection of each scatter plot identified patients 3, 4, 7,10, 11 and 13 as non-adherent with NIV. Patients 4 and 13 withdrew from the study at 14 and 13 days, respectively; patients 10 and 11 died at 69 days and 25 days respectively. Patients 3 and 7 were alive at 90 days. To enable detailed assessment of NIV use, patients who

were not adherent with NIV were removed from both groups and data was re-analysed.

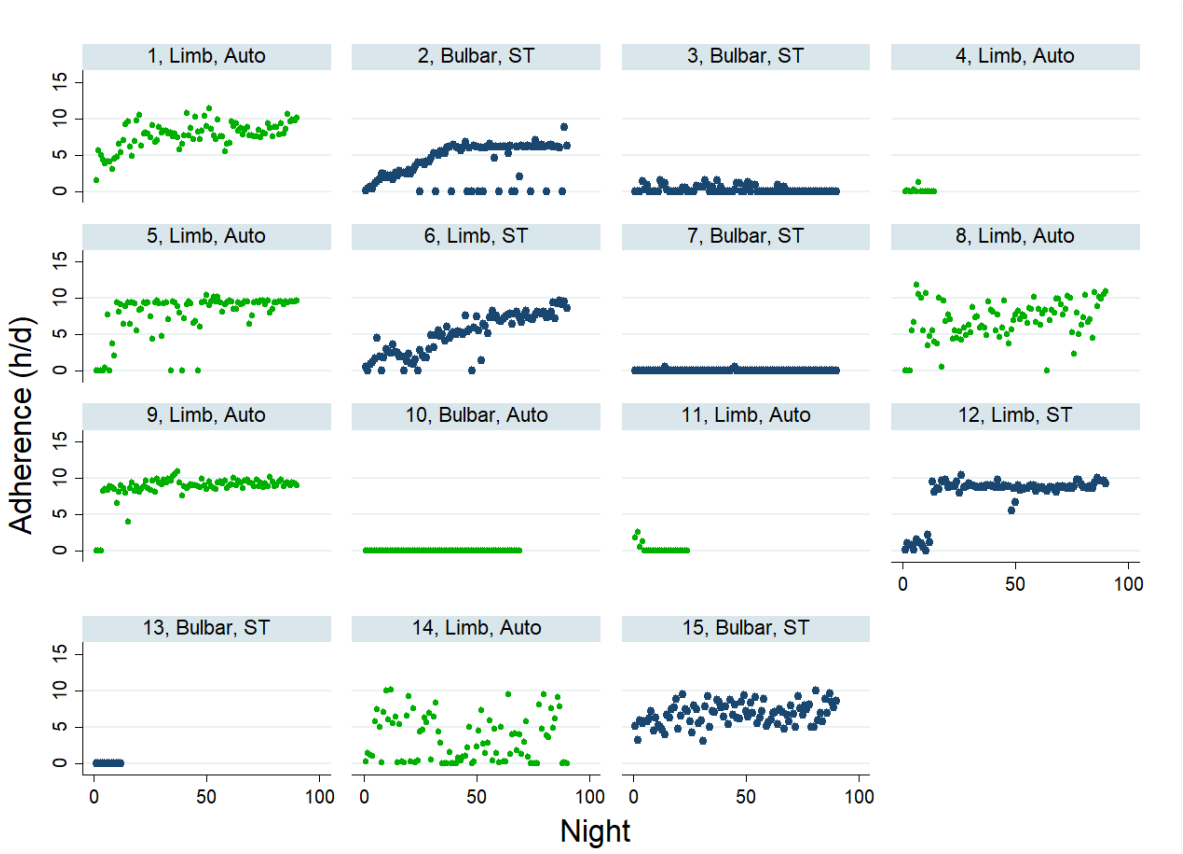

Figure 3.6. Scatter plot of NIV adherence over 90 days for each patient. Patient study identifier, ALS phenotype and NIV mode are shown in shaded box above each plot. h/d=hours per a day. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP.

Adherence of patients within each NIV group by timepoint are shown in Table 3.10. Patients using volume targeted auto-adjusting EPAP demonstrated statistically significantly greater adherence compared to pressure targeted at all timepoints (Figure 3.6).

Table 3.8. Adherence (h/d) of both NIV groups by timepoints for adherent patients

	Group		
Timepoint (days)	**Volume targeted auto-adjusting EPAP (n=5)**	**Pressure targeted (n=4)**	**p value**
14	5.54 (1.48-8.25)	2.01 (1-4.51)	0.000*
30	7.63 (5.4-9.1)	4.63 (2.48-8.76)	0.031*
60	8.41(6.5-9.4)	6.45(5.8-8.35)	0.004*
90	9.05(7.8-9.5)	8.1(6.22-9.16)	0.001*

Table entries are median (range); n=number of patients. * indicates variables that were significant with a p value <0.05 (nonparametric equality-of-medians test).

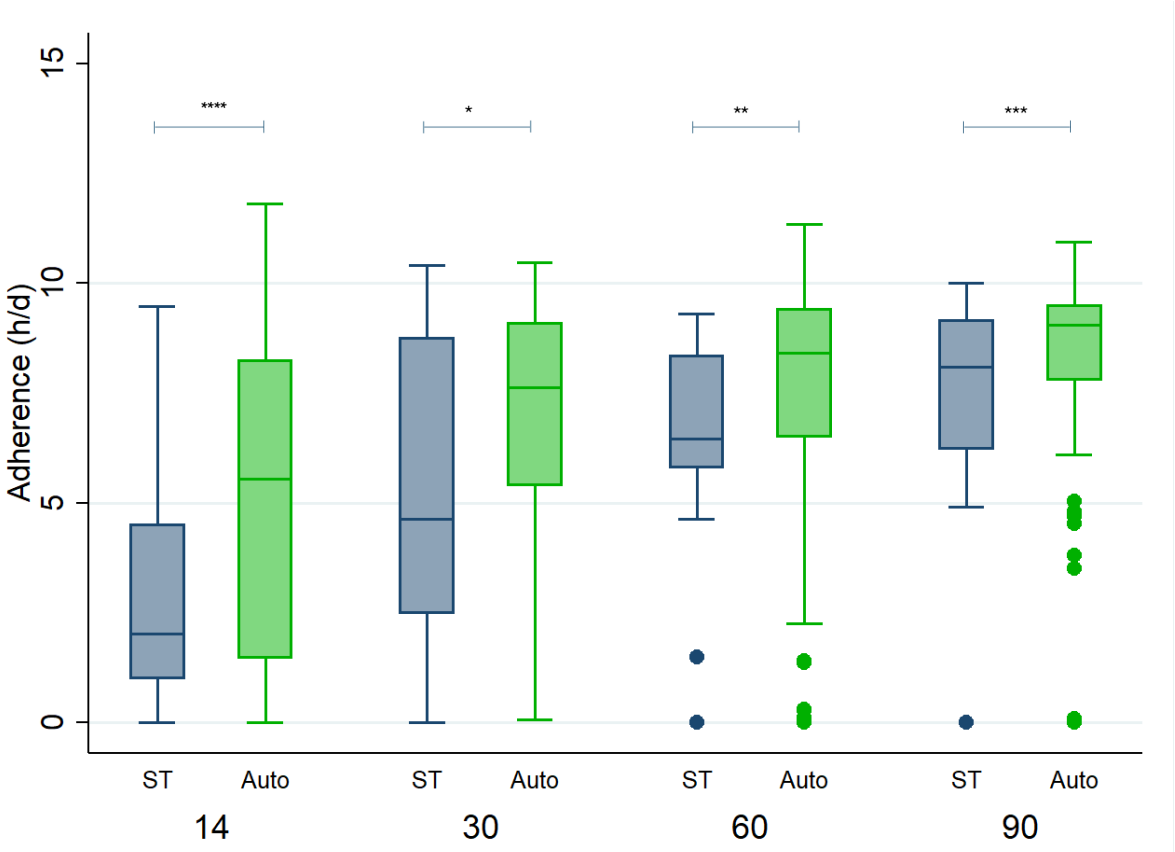

Figure 3.7. Box-plot of adherence by timepoints for both NIV groups for adherent patients. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset. Data points denoted as circles are outliers. ns=p value >0.05. P value ≤0.05 is designated with one (*) asterisk, ≤0.01 two (**) asterisk, ≤0.001 three (***) asterisk and

≤0.0001. Comparisons were made using Mann-Whitney test. pressure targeted=spontaneous/timed. h/d=hours per a day. 0,14,30,60 and 90 are days.

Average (Mean +/- SEM) number of h/d for all adherent patients from both NIV groups was plotted across the 90 day period and 1 phase exponential non-linear regression was used to illustrate and assess differences to assess early NIV adherence. Although R^2 values were again relatively low at 0.300 and 0.131 for pressure targeted and volume targeted auto-adjusting EPAP respectively, the rate constant *k* was significantly different by an approximate t test ($p<0.0001$), and as illustrated by the clearly distinct exponential phases of the two lines in Figure 3.7. Patients using volume targeted auto-adjusting EPAP demonstrated an initial greater adherence compared to patients using pressure targeted.

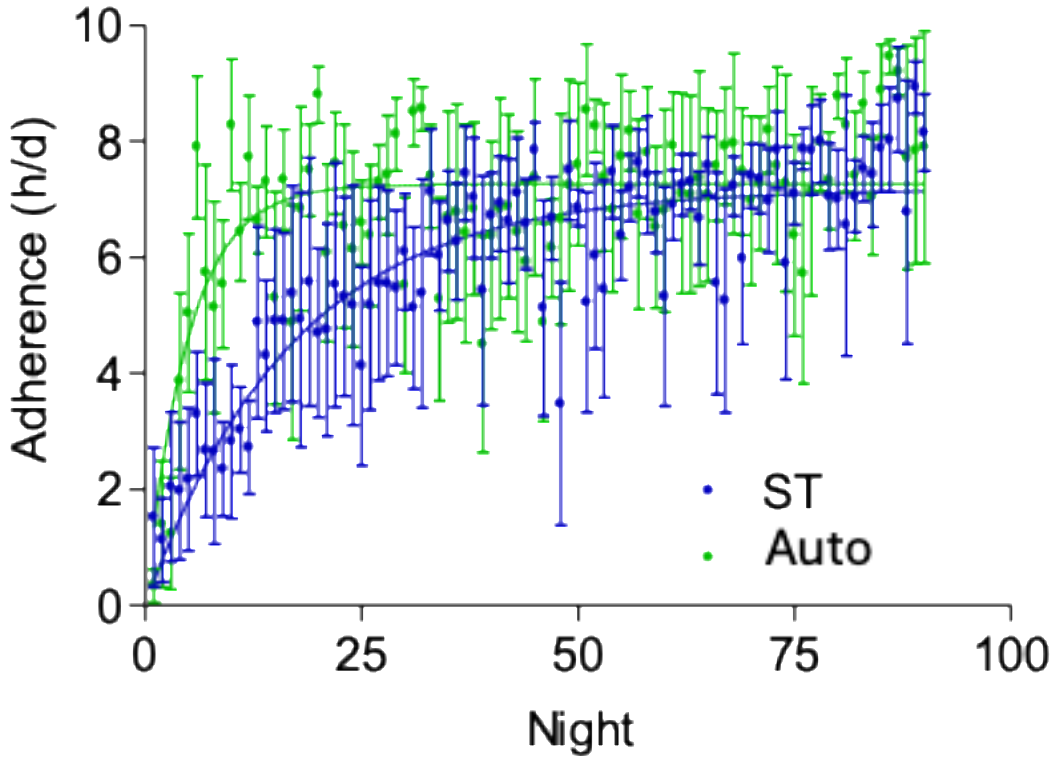

Figure 3.8. Scatter plots of NIV adherence over 90 days for adherent patients in both NIV groups (volume targeted n=5, pressure targeted n=4). h/d=hours per a day. Scatter plots have been fitted with 1 Phase Exponential Regression models. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP.

3.4.1.4 Effect and Sample Size Calculation

An *a priori* power analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2007) for sample and effect size estimation, based on data from the current pilot study (n=15). With a significance criterion of α = .05 and power = .80, the minimum sample size needed with an effect size of 0.45 is n=158 for a non-parametric equality of medians test to compare differences in adherence between NIV modes.

3.4.2 Secondary Outcomes

Although there was improved adherence with volume targeted auto-adjusting EPAP, respiratory blood gas parameters between groups were not statistically significantly different at 0, 14, 30, 60 and 90 days for PaO_2 and Bicarbonate. There is a wider spread of PaO_2 at baseline in the volume targeted auto-adjusting EPAP (Figure 3.8). $PaCO_2$ at 30 days was statistically and clinically significantly different between groups with a $PaCO_2$ of 5.33kPa for pressure targeted and 6.13kPa for volume targeted auto-adjusting EPAP (p=0.036; IQR 6.06-6.38, 5.26-5.8, respectively). Respiratory blood gas parameters for adherent patients are shown in Figure 3.9 and also did not differ significantly across timepoints for adherent patients.

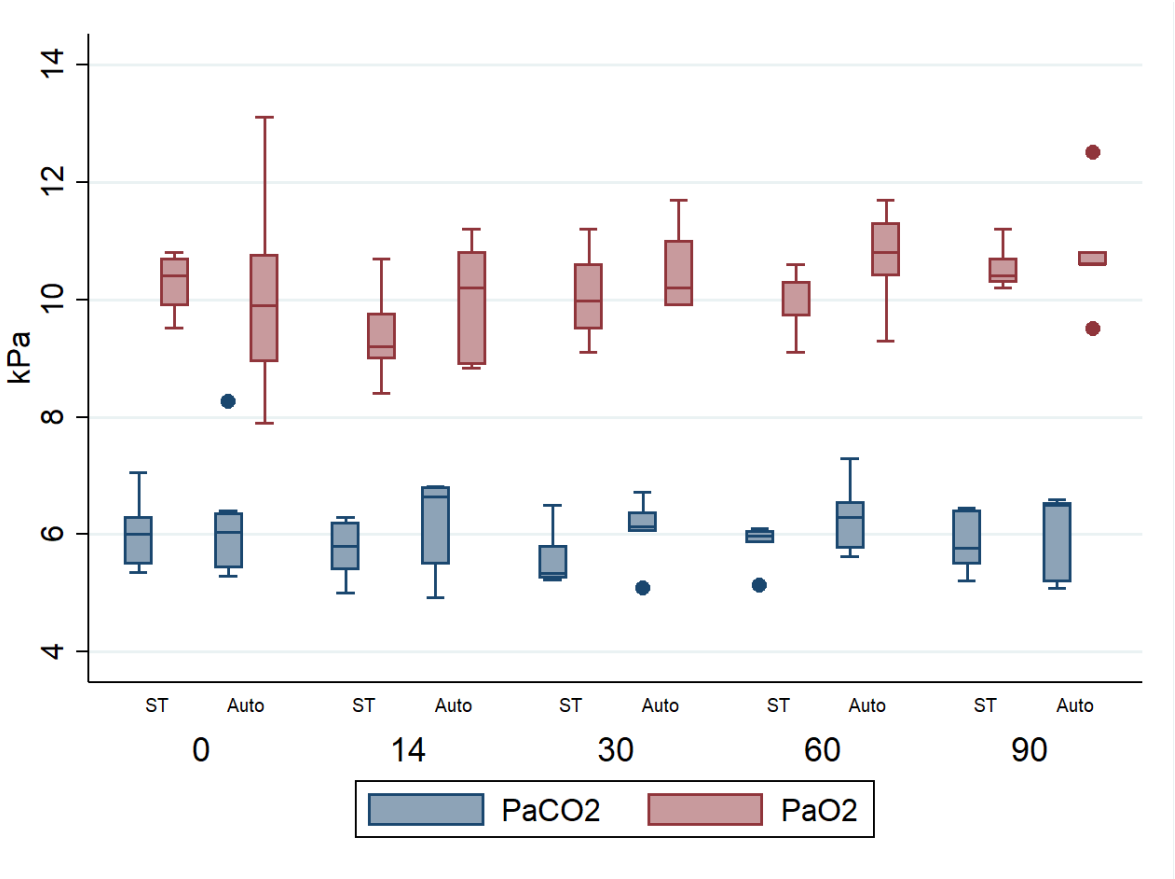

Figure 3.9. Box-plot of respiratory blood gas parameters by timepoints for both NIV groups. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset. Data points denoted as circles are outliers. PaO_2=arterial oxygen pressure. $PaCO_2$=arterial carbon dioxide pressure. kPa=kilopascal. 0,14,30,60 and 90 are days.

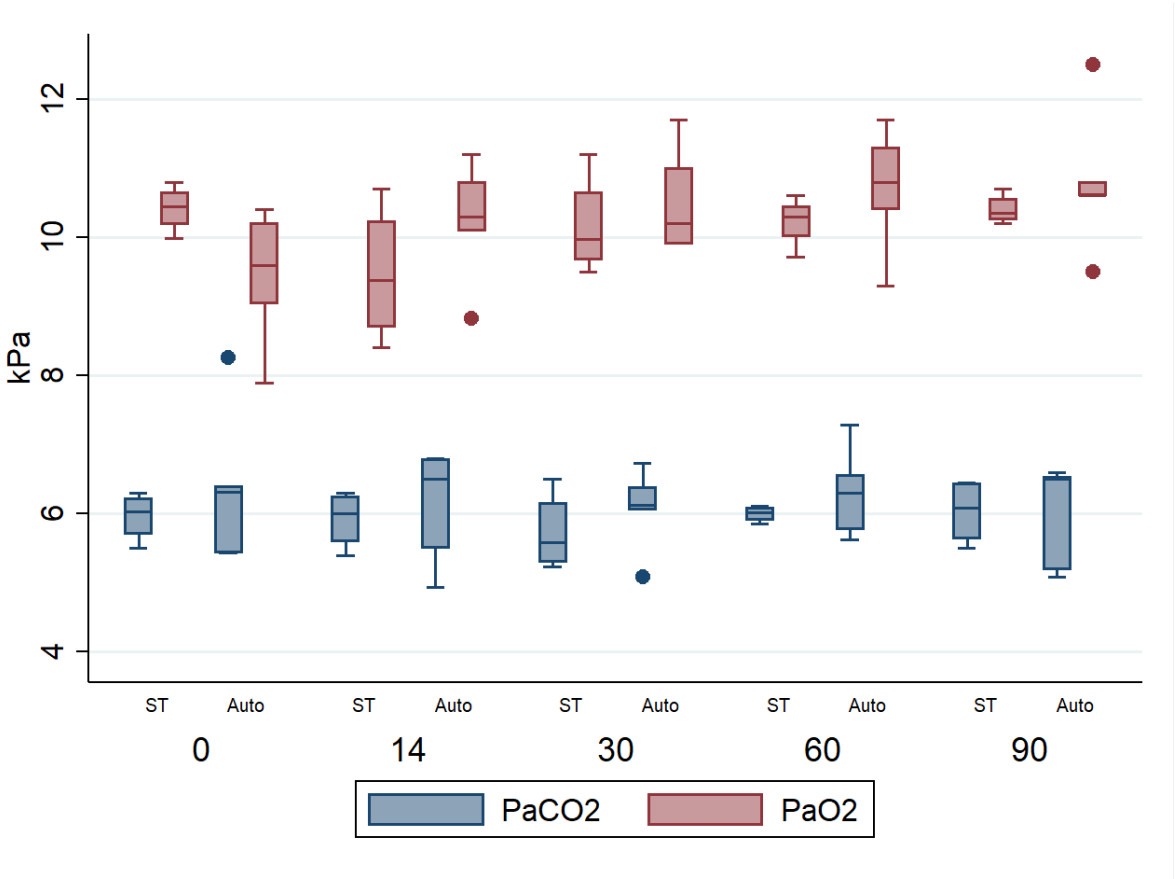

Figure 3.10. Box-plot of respiratory blood gas parameters by timepoints for both NIV groups for adherent patients. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset. Data points denoted as circles are outliers. PaO2=arterial oxygen pressure. PaCO2=arterial carbon dioxide pressure. pressure targeted=spontaneous/timed. kPa=kilopascal. 0,14,30,60 and 90 are days.

AHI also did not differ significantly between NIV groups across timepoints. Pressure targeted had a marginally higher AHI compared to volume targeted auto-adjusting EPAP over 90 days and is clinically significant (≥5 events/hour) (Figure 3.10). Overall, interface leak was higher in the volume targeted auto-adjusting EPAP group compared to pressure targeted. Interface leak was comparable between groups at 14 days but differed significantly at 30, 60 and 90 days (Figure 3.11).

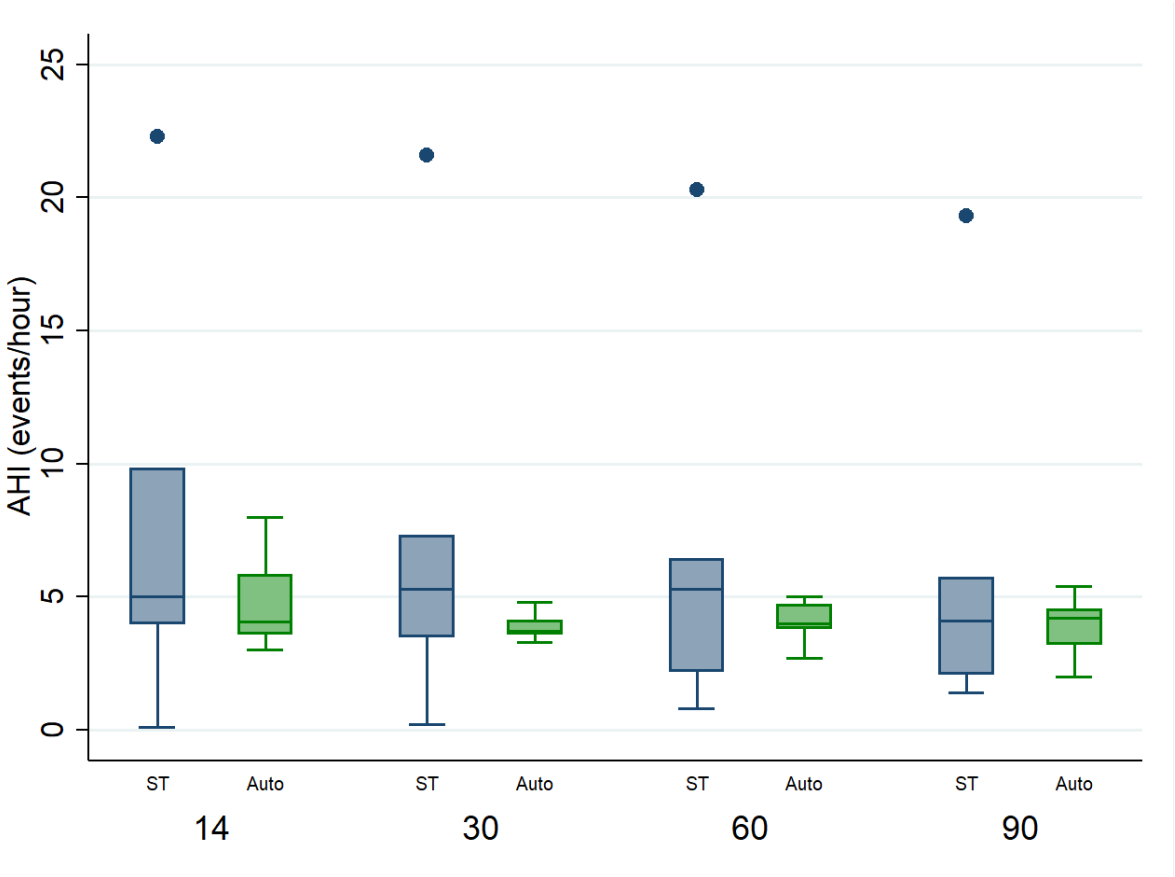

Figure 3.11. Box-plot of AHI by timepoints for both NIV groups. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset. Data points denoted as circles are outliers. AHI=apnoea hypopnoea index. pressure targeted=spontaneous/timed. 0,14,30,60 and 90 are days.

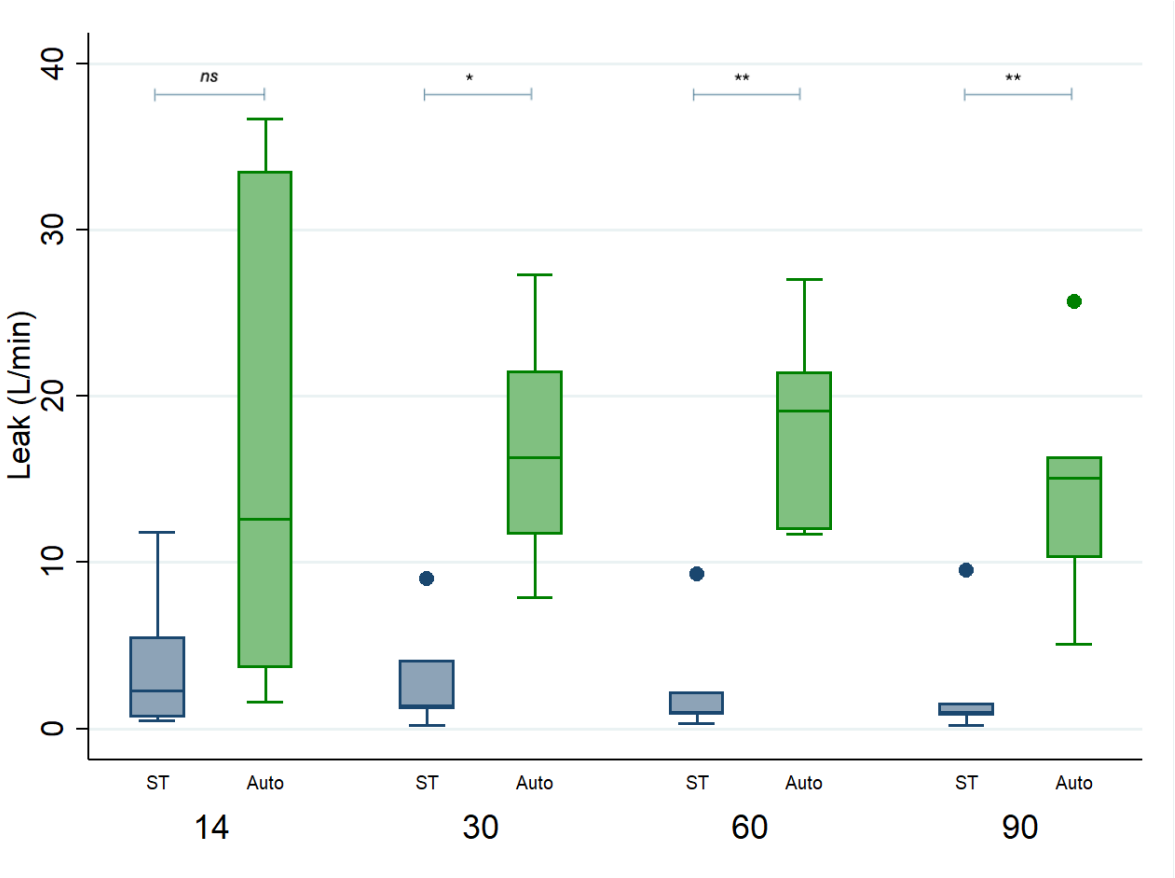

Figure 3.12. Box-plot of interface leak by timepoints for both NIV groups. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset. Data points denoted as circles are outliers. ns=p value >0.05. P value ≤0.05 is designated with one (*) asterisk, ≤0.01 two (**) asterisk, ≤0.001 three (***) asterisk and ≤0.0001. pressure targeted=spontaneous/timed. 0,14,30,60 and 90 are days. Interface leak for both NIV groups at each timepoint. Red line indicates interface leak threshold of 24L/min. L/min=litres per a minute.

3.5 Discussion

Data from this pilot study suggests NIV adherence is improved with volume targeted auto-adjusting EPAP in patients with CRF secondary to ALS. Data suggests patients who use volume targeted auto-adjusting EPAP have greater adherence sooner and for longer compared to patients using pressure targeted. Finally, data suggests that volume targeted auto-adjusting EPAP is no less effective than pressure targeted at facilitating gas exchange and improving or maintaining AHI, which are of particular importance in ALS.

Although the use of volume targeted auto-adjusting EPAP has been examined in other disease groups, including COPD and OHS (Patout *et al.*, 2020), this study provides data to support the use of volume targeted auto-adjusting EPAP in ALS, as part of evidence based clinical practice. Previous studies have reported volume targeted and pressure targeted NIV adherence rates in ALS ranging between 33 and 90% (Kleopa *et al.*, 1999; Gruis *et al.*, 2005; Coco *et al.*, 2006; Czudaj, Suchi and Schönhofer, 2009; Ristell *et al.*, 2019; Vitacca *et al.*, 2020; Rudnicki *et al.*, 2021; Russo *et al.*, 2021). Average adherence ranges between 6.5 and 12.3 h/d (Nicholson *et al.*, 2017; Sancho *et al.*, 2018).

Our data shows a total adherence for volume targeted auto-adjusting EPAP of 91% at 90 days for 9.05 h/d and 64% for 6.22 h/d for pressure targeted. Both groups demonstrated increasing adherence over time, with patients using volume targeted auto-adjusting EPAP achieving adherence of >4 h/d sooner and sustaining it for longer compared to pressure targeted. In comparison, previous studies have reported adherence of 90% for 8.30 h/d and 70% for 6.55 h/d using volume targeted NIV (Buttle *et al.*, 2015; Nicholson *et al.*, 2017). This further highlights the considerable variation in adherence rates in ALS, possibility because of the diseases natural heterogeneity.

A greater number of patients diagnosed with predominant bulbar disease were randomised to the pressure targeted group compared to volume targeted auto-adjusting EPAP. Previous studies have reported bulbar disease, especially severe bulbar dysfunction as a predictor of poor NIV adherence. However there is also evidence to support the contrary including one RCT, which demonstrated bulbar-onset disease predicted greater NIV adherence in ALS (Bertella *et al.*, 2017).

Sialorrhea, increased airways secretions, increased upper airway obstructive events and interface type (Peysson *et al.*, 2008; Georges *et al.*, 2016; Sancho *et al.*, 2018; Chatwin *et al.*, 2020) are all modifiable factors contributing towards poor NIV adherence. It is also clinically useful to acknowledge that respiratory blood gases did not significantly differ between groups, suggesting that patients with bulbar-onset disease demonstrate effective ventilation even if adherence, in some, is lower.

All patients were reviewed by a respiratory physiotherapist to assess and treat sialorrhea and airway secretions, to minimise the negative impact on NIV adherence. Interface leak is commonly reported in ALS NIV users and therefore interface type is an important decision. Often, interface leak can be resolved either by changing interface type, optimising NIV pressures or a combination of both strategies. All patients were provided access to all commercially available interfaces including full face, nasal and hybrid interface designs (Figure 1.22; 2.1). Both groups had access to all three interface types and selected the most comfortable option. Any interface issues which were identified either by the patient or via remote monitoring, especially interface leak, were resolved through patient coaching and education, visual demonstrations and ensuring the correct interface was chosen to meet patient specific needs.

Interestingly, our study reported a higher interface leak in volume targeted auto-adjusting EPAP despite a predominance of bulbar disease in the pressure targeted group which contrasts with previous studies observing comparable interface leak between both pressure targeted and volume targeted NIV (Nicholson *et al.*, 2017). This is an unexpected finding. A substantial explanation for this observation is beyond the scope of this pilot study, although it may be postulated that due to significant limb disease and therefore reduced limb function patients using volume targeted auto-adjusting EPAP were unable to adjust either their interface or sleep position to correct interface leak.

There is a significant gap in the literature regarding interface efficacy in ALS, and the findings of this study highlight the need for further work in this area. AHI between groups did not reach statistical significance, with a lower AHI in volume targeted auto-adjusting EPAP. This may hold clinical importance as at each time point, AHI in pressure targeted was >5 h/d with evidence to support a significantly reduced survival

in ALS with concomitant obstructive sleep apnoea syndrome (OSAS) (Carratù *et al.*, 2013). Volume targeted auto-adjusting EPAP can titrate pressures automatically to ensure that all obstructive episodes are effectively controlled, compared to pressure targeted that may not be able to fully prevent all obstructive episodes because of its fixed pressure limitations (Gay *et al.*, 1991; Kimura *et al.*, 1999; Boentert, 2020). Timing of the sleep study relative to severity of disease, weight loss and changes in upper airway stiffness may also contribute towards the discrepancies observed.

3.5.1 Study Limitations and Future Directions

The main limitation of this study is the small sample size, even for a pilot study, it is underpowered. There is no one guideline for sample size calculation in pilot and feasibility studies, with sample sizes ranging between 12-35 participants per arm (Kieser and Wassmer, 1996; Julious, 2005; Teare *et al.*, 2014). The challenges of recruiting patients with the context of a rarer disease may also contribute towards a small sample size. The randomised control approach in this pilot study, is inherently a meticulous design with explicit protocols, and although in many studies is considered a strength, in some, it may limit the ability to deliver patient specific care.

Although ALS phenotype was used to randomise patients, objective assessment of bulbar dysfunction was not assessed and as such we are unable to report the level of influence bulbar disease has on the discrepancies between adherence rates. Future studies should consider a formal assessment to mitigate the risk of this occurring again. The imbalance of bulbar phenotype between the NIV groups was most likely a result of the idiosyncratic nature of the randomisation methodology especially when applied to a small sample size.

Larger studies may benefit from using a pseudo-randomisation to ensure a balance of phenotypes across each NIV group. While, this study considered the impact of modifiable factors on NIV adherence, non-modifiable factors including, education level, marital status and household income were not assessed. For patient safety, this was a single blinded study only and this may have resulted in a degree of observer bias. This was minimised, where possible, by separating those investigators inputting data from those delivering patient care. Furthermore, due to disease progression in both groups, certain measurements including FVC were unable to be performed and therefore at risk of data bias, these data should therefore be interpreted with caution.

This study has presented several interesting trends in NIV adherence between volume targeted auto-adjusting EPAP and pressure targeted, which demonstrate clinical value in conducting a larger, multicentre study. A larger study would allow for sub-group analysis of ALS phenotype to accurately assess the impact of bulbar dysfunction on NIV adherence using both pressure targeted and volume targeted auto-adjusting EPAP modes. Survival should also be included as an endpoint in future studies. Remote monitoring is commonly used to support home NIV services, and this should be a focus of investigation in ALS and how it could be used to compliment out of hospital ventilatory care.

Healthcare utilisation is of particular interest within NHS hospitals and future RCT's should investigate if the automatic adjustment of volume targeted auto-adjusting EPAP is likely to reduce the number of hospital visits and tests required and improve patient experience. Future studies may also wish to focus on measurements of polysomnography to assess the impact of the automatic adjustment ability of volume targeted auto-adjusting EPAP to reduce the likelihood of sleep fragmentation and poor-quality sleep.

3.5.2 Conclusion

To my knowledge this is the first study with randomisation to compare adherence between two NIV modes in ALS, with the specific aim to assess the importance of NIV mode delivery, and whether a future, large scale, multicentre study would be appropriate to improve outcomes in those with respiratory compromise. The results indicate that improved NIV adherence may be achieved in ALS using volume targeted auto-adjusting EPAP compared to pressure targeted NIV, but the influence of ALS phenotype must be considered in these results. Data from our study is promising and contributes towards the existing literature of NIV in ALS.

4 Results: Improved HRQoL may be gained in ALS from using volume targeted auto-adjusting EPAP NIV

4.1 Introduction

During sleep there is a greater physiological strain on the load capacity-drive relationship of the respiratory system and the time tension index of the diaphragm muscle (D'Cruz, Murphy and Kaltsakas, 2018). In healthy individuals, RR, Vt and pharyngeal muscle tone decrease (Douglas *et al.*, 1982; Wiegand, Zwillich and White, 1989; Kubin, Davies and Pack, 1998). During REM sleep diaphragmatic muscle tone is well preserved with almost complete loss of intercostal muscle activity and therefore adequate diaphragmatic muscle strength is crucial to allow sufficient nocturnal ventilation (Kubin, Davies and Pack, 1998). In ALS, the combined effects of a weak diaphragm, reduced pharyngeal muscle activity and supine position result in SDB including nocturnal hypoventilation (Arnulf *et al.*, 2000).

Even in the early stages of ALS, respiratory function during sleep is adversely impacted even though respiratory and bulbar muscle weakness may not be significant enough to cause daytime symptoms of breathlessness. Nevertheless, as ventilation in ALS is further compromised during sleep, it is often the case that respiratory dysfunction in the sleeping state occurs sooner than signs and symptoms of daytime hypercapnic respiratory failure (Ward *et al.*, 2005).

As a consequence of SDB, patients with ALS have altered sleep architecture. Compared to healthy individuals, patients with ALS, have a greater number of arousals, more sleep stage changes per hour, shorter duration of REM, reduced sleep efficiency and overall less time spent asleep (Ferguson *et al.*, 1996; Arnulf *et al.*, 2000; Lyall *et al.*, 2001; Boentert *et al.*, 2015). Sleep disturbances can also be caused by dysphagia, muscle spasticity, fasciculations, cramps and reduced bed mobility (Hetta and Jansson, 1997).

Signs and symptoms of SDB include, daytime somnolence, morning headaches, altered mood and cognitive dysfunction including poor concentration and memory recall (Kelly, Claypoole and Coppel, 1990; Bédard *et al.*, 1991; Naëgelé *et al.*, 1995;

Ferguson *et al.*, 1996). Overall, SDB can significantly reduce HRQoL in ALS (Bourke, Shaw and Gibson, 2001; Bourke *et al.*, 2003).

The commencement of NIV to treat symptoms of SDB in ALS is both best and evidence based practice (NICE, 2016). NIV should be considered in patients diagnosed with ALS who present with signs and symptoms of SDB including, morning headaches, daytime somnolence, witnessed apnoeas and paradoxical breathing (NICE, 2016). In those patients who demonstrate sufficient adherence, NIV is associated with sustained improvements in HRQoL particularly those patient reported outcomes linked to sleep quality, despite an overall reduction of time spent in REM sleep (Lyall *et al.*, 2001; Bourke *et al.*, 2003, 2006).

Volume targeted auto-adjusting EPAP NIV (ResMed Ltd, Bella Vista, Australia) is a clinically enhanced version and can automictically adjust NIV settings to meet the patients ventilatory requirements. Pressure targeted NIV, has fixed pressure limitations and is unlikely to effectively, treat SDB and ensure an appropriate airway pressure is maintained across all sleep stages. As a result, volume targeted auto-adjusting EPAP has the potential to reduce the likelihood of sleep fragmentation caused by large fluctuations in pressure and thus improve sleep quality (Ambrogio et al., 2008; Boentert, 2020; Boentert et al., 2015; Ferguson et al., 1996; Gay et al., 1991; Kimura et al., 1999). Although pressure targeted is commonly used in ALS, neither pressure targeted or volume targeted auto-adjusting EPAP has been shown to be superior in terms of adherence or improvements in HRQoL.

4.2 Aims and Objectives

4.2.1 Primary Aim of the Study

The primary outcome variable was HRQoL measured by SRI, mHADS and ALSFRS-R questionnaire scores recorded at each study timepoint.

The primary aim of the study was to explore differences in SRI, mHADS and ALSFRS-R between pressure targeted and volume targeted auto-adjusting EPAP.

4.3 Methods

Methods are described in Chapter 2.

Patients were enrolled onto the study for 90 days. Study visits were completed at 14-, 30-, 60- and 90-days following commencement of NIV and were chosen to reflect our hospital's ALS pathway and NICE recommendation for patient assessment every 3 months. At each visit patients completed the SRI, ALSFRS-R and mHADS questionnaires to measure HRQoL (Windisch *et al.*, 2003; Gibbons *et al.*, 2011; Ghosh *et al.*, 2012; Walterspacher *et al.*, 2016; Moore, Young and Hughes, 2018).

HRQoL was measured by SRI, mHADS and ALSFRS-R questionnaire scores recorded at each study timepoint. Higher SRI scores describe better HRQoL (0=worst, 100=normal) (Ghosh *et al.*, 2012) and higher ALSFRS-R scores suggest less functional impairment by ALS (0=worst, 48=normal) (Cedarbaum *et al.*, 1999). A mHADS anxiety score of 7-8 suggests possible anxiety and ≥9 suggests probable anxiety. A mHADS depression score of 5-7 suggests possible depression and ≥8 suggests probable depression. A total mHADS score cut off point of 17 was used for a possible mood disorder and 21 for a probable mood disorder (Gibbons *et al.*, 2011).

4.3.1 Statistical Analyses

Statistical analyses were performed using STATA version 11.0 (Statacorp, California, USA). Statistical analyses were mostly descriptive using count and percentage for categorical data, mean with standard deviation and median with 25^{th}/75^{th} percentiles for continuous data. HRQoL score trends over time were visually examined using

histograms, boxplots, and time series charts. Continuous data was assessed for normality using the Shapiro–Wilk test. Where appropriate, parametric, and nonparametric testing was performed for between-group comparisons, using unpaired t-testing or the Mann–Whitney U test for continuous. A two-tailed level of significance less than 0.05 was chosen for all analyses.

4.4 Results

In total 24 patients were commenced onto NIV at the Department of Respiratory and Sleep Sciences, UHCW NHS Trust, between March 2021 and October 2023. Of these 24 patients, 15 patients consented and enrolled onto the pilot study. Patient demographics, ALS characteristics, baseline HRQoL and respiratory and sleep function are reported in section 3.4.1.

4.4.1 Primary Outcome

At baseline, HRQoL was comparable between group with no statistically significant differences, however patients assigned to pressure targeted demonstrated an overall lower SRI score. Patients allocated to volume targeted auto-adjusting EPAP demonstrated possible anxiety whilst both groups demonstrated possible depression. HRQoL for both groups are shown in Table 4.1.

Table 4.1 HRQoL characteristics of volume targeted auto-adjusting EPAP and pressure targeted groups

Characteristic	Volume targeted auto-adjusting EPAP (n=8)	Pressure targeted (n=7)	p value
Mean ALSFRS-R (SD)	27 (12)	31 (16)	0.54
Median mHADS Anxiety (SD)	8 (5)	6 (3)	0.39
Mean mHADS Depression (SD)	5 (4)	7 (3)	0.34
Mean SRI-SS (SD)	55 (21)	40 (14)	0.13

Table entries are median (range) or mean (SD); n=number of patients. Data points denoted as circles are outliers. ns=p value >0.05. P value ≤0.05 is designated with one (*) asterisk, ≤0.01 two (**) asterisk, ≤0.001 three (***) asterisk and ≤0.0001 four (****) asterisks.

4.4.1.1 Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

ALSFRS-R scores did not statistically significantly differ between volume targeted auto-adjusting EPAP and pressure targeted across time points. ALSFRS-R increased in the volume targeted auto-adjusting EPAP group. Scores at 0 days were higher in pressure targeted but higher in volume targeted auto-adjusting EPAP at 14, 30, 60 and 90 days. ALSFRS-R scores in the pressure targeted group decreased over time whereas scores in the volume targeted auto-adjusting EPAP group increased (Figure 4.1). Overall, there was a 1.3-point increase in patients using volume targeted auto-adjusting EPAP and an 8.4-point decrease in patients using pressure targeted. HRQoL related to physical disability is worse over 90 days in patients allocated pressure targeted (Table 4.2).

Table 4.2 ALSFRS-R scores for volume targeted auto-adjusting EPAP and pressure targeted groups

Time points	Volume targeted auto-adjusting EPAP	n	Pressure targeted	n	p value
0 days	26.7 (11.7)	8	31.2 (16.2)	7	0.542
14 days	27.6 (11.9)	6	22.4 (9)	5	0.439
30 days	29 (13.9)	5	24.5 (10)	6	0.549
60 days	28.4 (13.9)	5	21 (9.4)	5	0.357
90 days	29 (13.5)	5	22.8 (12.2)	6	0.448

Table entries are mean (SD) ; n=number of patients. * indicates variables that were significant with a *p* value <0.05.

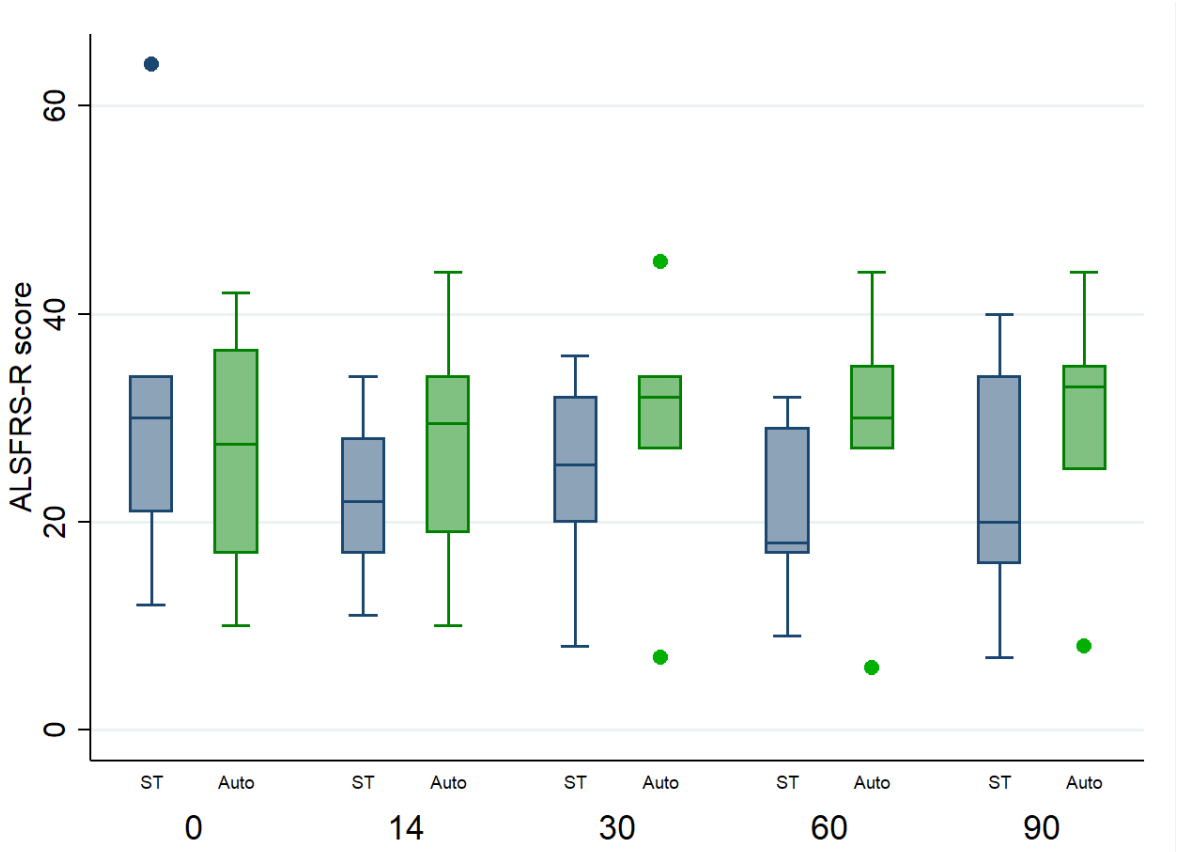

Figure 4.1. Box-plot of ALSFRS-R scores by timepoints for both NIV groups. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset.

4.4.1.2 Severe Respiratory Insufficiency Score

There were no statistically significant differences in SRI domains between NIV groups at any timepoint however there were clinically significant differences observed (Table 4.3). RC was higher in volume targeted auto-adjusting EPAP at 0 days but higher in pressure targeted at 30 days. PF was higher in pressure targeted at 0 days but higher in volume targeted auto-adjusting EPAP at 60 and 90 days. AS was higher in volume targeted auto-adjusting EPAP at 14, 30 and 60 days. SR and AX was higher in volume targeted auto-adjusting EPAP at 0, 30 and 90 days. WR was higher in volume targeted auto-adjusting EPAP across all time points. SF was higher in volume targeted auto-adjusting EPAP at 0, 14 and 30 days. SS was higher in volume targeted auto-adjusting EPAP at 0, 14, 30 and 90 days (Figure 4.2). Overall, SS was consistently higher in volume targeted auto-adjusting EPAP compared to pressure targeted.

Table 4.3 SRI Scores for volume targeted auto-adjusting EPAP and pressure targeted groups

	Volume targeted auto-adjusting EPAP	n	Pressure targeted	n	p value
Respiratory Complaints					
0 days	60(30.1)	8	48.7(20.2)	7	0.417
14 days	54.8(17.2)	6	58.8(22)	5	0.744
30 days	53(17.3)	5	67.6(11.4)	6	0.126
60 days	54.2(16.7)	5	57.6(26.3)	5	0.814
90 days	53.6(12.5)	5	57.5(15.3)	6	0.660
Physical Functioning					
0 days	31.2(34.5)	8	38.2(21.2)	7	0.649
14 days	32.5(32.2)	6	35.2(29.4)	5	0.889
30 days	35.8(25.2)	5	35.1(24.5)	6	0.967
60 days	34.2(26.6)	5	26(31.1)	5	0.666
90 days	40(21.9)	5	23.5(11.2)	6	0.140
Attendant Symptoms and Sleep					
0 days	59.6(18.1)	8	53(18.5)	7	0.496
14 days	58.5(16)	6	38.4(15.1)	5	0.063
30 days	61.4(15.7)	5	55.3(18.3)	6	0.574
60 days	66.6(16)	5	54.2(14.9)	5	0.240
90 days	61.4(14.5)	5	57.8(12.2)	6	0.668
Social Relationships					
0 days	73.5(17.2)	8	59.5(16)	7	0.131
14 days	66.6(12.5)	6	68.4(17.9)	5	0.855
30 days	69.2(13.6)	5	52(18.1)	6	0.115
60 days	68.4(16.9)	5	66.6(19.2)	5	0.879
90 days	64.2(18.5)	5	59(28.8)	6	0.737
Anxiety					
0 days	50.6(23)	8	39.2(18.1)	7	0.314

14 days	55.8(19.3)	6	52(24.1)	5	0.776
30 days	56(21)	5	47.5(24.4)	6	0.556
60 days	50(21.7)	5	50(26.4)	5	1
90 days	49(24.3)	5	42.5(21.8)	6	0.651
Psychological Well-Being					
0 days	53.2(15.9)	8	41.6(17.3)	7	0.200
14 days	53.6(23)	6	41.6(17.1)	5	0.359
30 days	59.4(18.3)	5	39.8(24.8)	6	0.179
60 days	55.6(20)	5	38.2(15.5)	5	0.164
90 days	54.4(14.6)	5	40.5(19)	6	0.215
Social Functioning					
0 days	54.3(27.7)	8	38.2(24)	7	0.254
14 days	52.8(25.3)	6	48(22.1)	5	0.746
30 days	57.6(24.8)	5	45(23.5)	6	0.411
60 days	49(30.1)	5	51.2(24.3)	5	0.902
90 days	45.8(25.1)	5	44.3(24.7)	6	0.924
Summary Score					
0 days	54.5(21.3)	8	45.5(13.6)	7	0.360
14 days	55.3(22.4)	6	49(18.5)	5	0.627
30 days	56.2(16.8)	5	49(14)	6	0.459
60 days	53.8(18.6)	5	49.2(17.8)	5	0.701
90 days	52.6(15.5)	5	46.5(12.3)	6	0.484

Table entries are mean (SD) ; n=number of patients. * indicates variables that were significant with a *p* value <0.05.

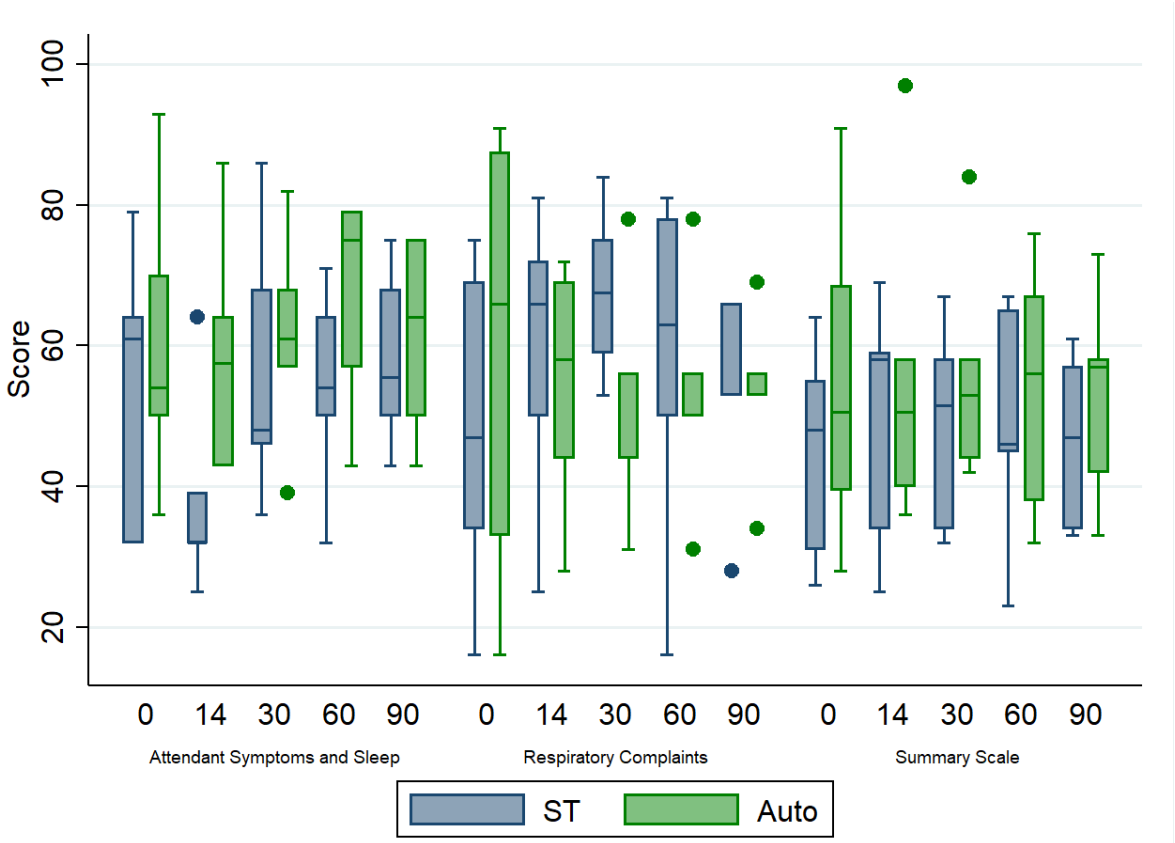

Figure 4.2. Box-plot of SRI domains by timepoints for both NIV groups. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset.

4.4.1.3 Modified Hospital Anxiety and Depression Scale

Baseline mHADS total scores were comparable between the groups. mHADS did not statistically significantly differ between volume targeted auto-adjusting EPAP and pressure targeted at any time point (Table 4.4). mHADS anxiety scores for both groups decreased over time with a greater decrease observed in patients using volume targeted auto-adjusting EPAP compared to pressure targeted (3 and 1 points, respectively). mHADS depression scores for both groups remained similar over time. mHADS total score for patients using volume targeted auto-adjusting EPAP decreased over time by 2 points compared to patients using pressure targeted where scores remained relatively unchanged over 90 days (Figure 4.3).

At baseline both groups had possible anxiety but at 90 days demonstrated no evidence of anxiety. Possible depression was observed in both groups at baseline and at 90

days probable depression was now evident in patients using pressure targeted. mHADS total scores for both groups demonstrated no evidence of a mood disorder at any time point.

Overall, patients using volume targeted auto-adjusting EPAP demonstrated the largest decrease in anxiety and were less depressed compared to patients using pressure targeted.

Table 4.4 mHADS for each domain for volume targeted auto-adjusting EPAP and pressure targeted groups

	Volume targeted auto-adjusting EPAP	n	Pressure targeted	n	p value
Anxiety					
0 days	8(5)	8	6(3)	7	0.398
14 days	6(5)	6	6(5)	5	0.964
30 days	5(4)	5	6(3)	6	0.893
60 days	6(4)	5	5(2)	5	0.654
90 days	5(4)	5	5(2)	6	0.846
Depression					
0 days	5(4)	8	7(3)	7	0.349
14 days	6(4)	5	7(3)	6	0.641
30 days	6(3)	5	6(4)	6	0.977
60 days	5(4)	5	7(4)	5	0.461
90 days	5(4)	5	8(4)	6	0.275
Total					
0 days	13(8)	8	13(5)	7	0.996
14 days	12(8)	5	13(8)	6	0.843
30 days	11(7)	5	11(7)	6	0.929
60 days	11(8)	5	12(5)	5	0.812
90 days	11(8)	5	13(6)	6	0.567

Table entries are mean (SD); n=number of patients. * indicates variables that were significant with a *p* value <0.05.

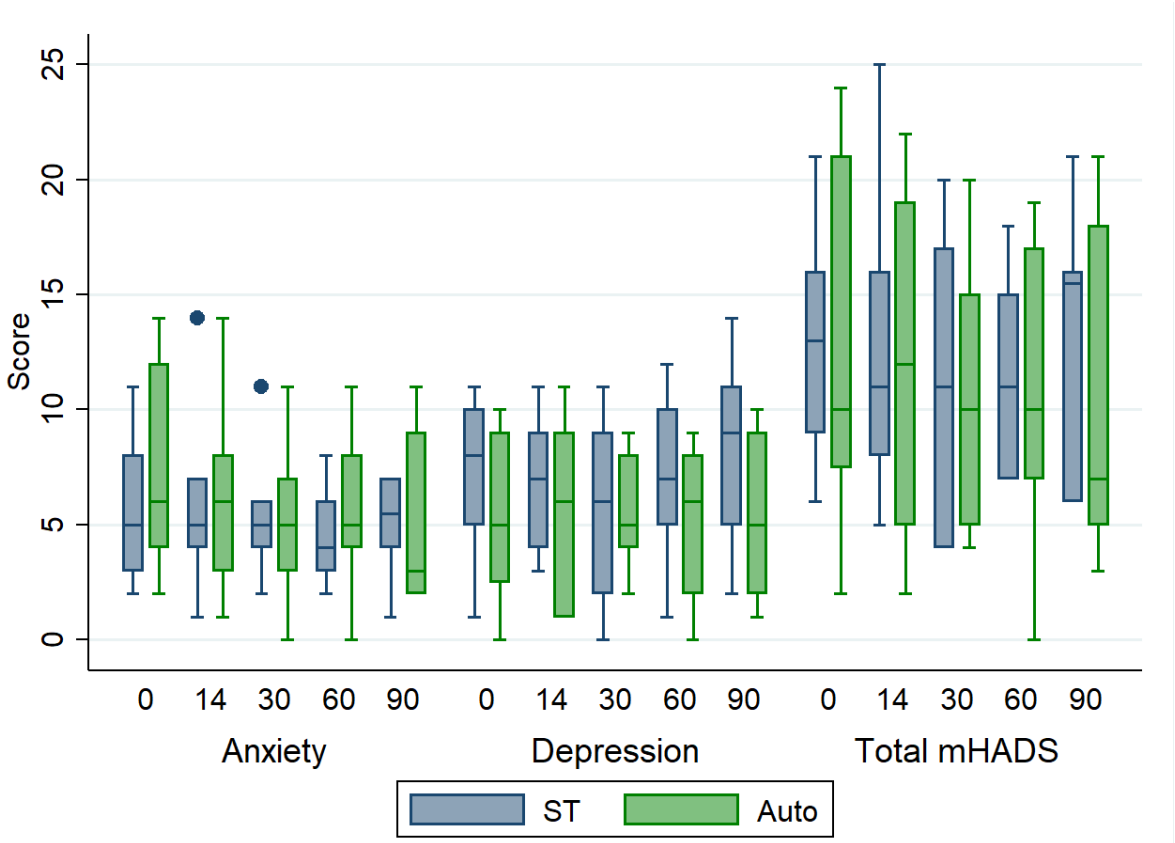

Figure 4.3. Box-plot of mHADS by timepoints for both NIV groups. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset.

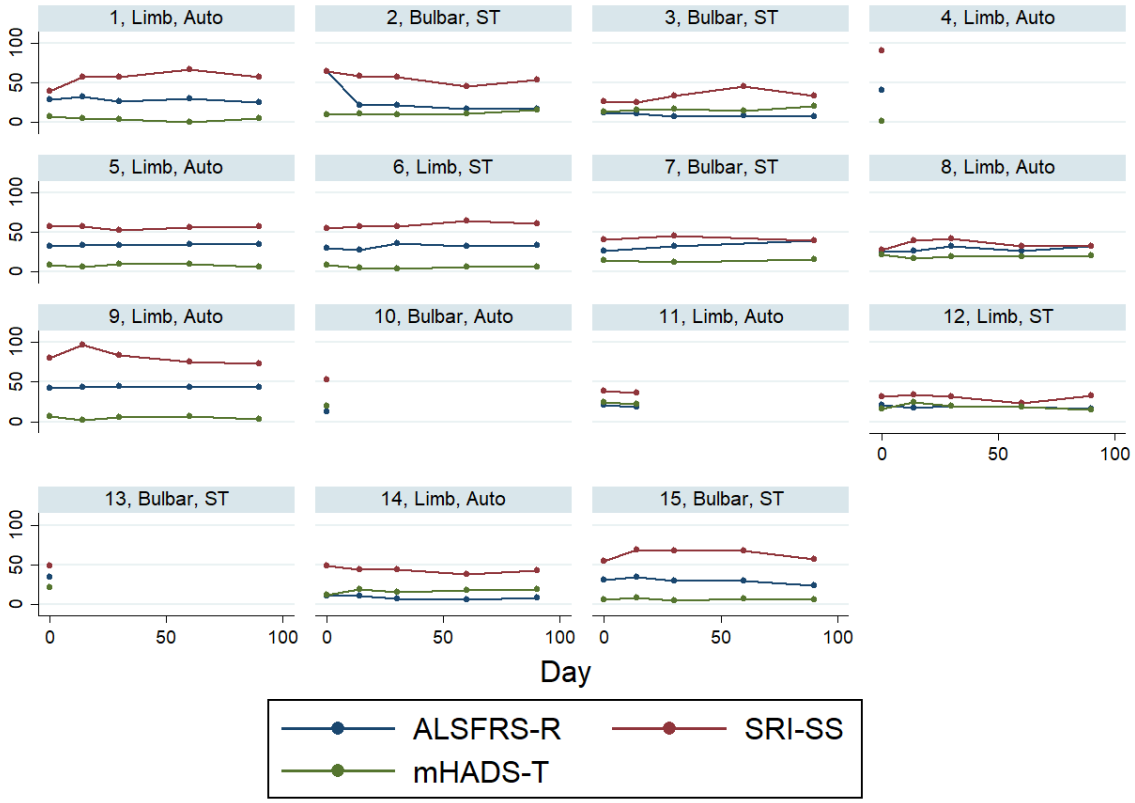

Figure 4.4. Scatter plot of HRQoL at each timepoint for each patient. Patient study identifier, ALS phenotype and NIV mode are shown in shaded box above each plot. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. ALSFRS-R=revised amyotrophic lateral sclerosis functional rating scale. mHADS-T= total modified hospital anxiety and depression score. SRI-SS=severe respiratory insufficiency summary score.

Figure 4.4 shows ALSFRS-R, SRI and mHADS scores for all patients and did not significantly differ between adherent and non-adherent groups for both NIV modes (section 3.4.1.3, p120) (Figures 4.5, 4.6, 4.7). Due to the small number of patients left in each group after removing non-adherent patients, it was not possible to assess for statistically significant differences. SRI scores for respiratory complaints and summary scale were comparable between both NIV modes across all timepoints, and attendant and sleep symptoms were higher in the volume targeted auto-adjusting EPAP at baseline and at 14 through to 90 days (Figure 4.5). Baseline ALSFRS-R scores were comparable between NIV modes, with higher scores observed in the volume targeted auto-adjusting EPAP group at 14, 30, 60 and 90 days (Figure 4.6). Anxiety, depression, and total scores did not differ significantly between NIV modes at baseline and up to

60 days. At 90 days anxiety, depression and total scores were lower in the volume targeted auto-adjusting EPAP group (Figure 4.7).

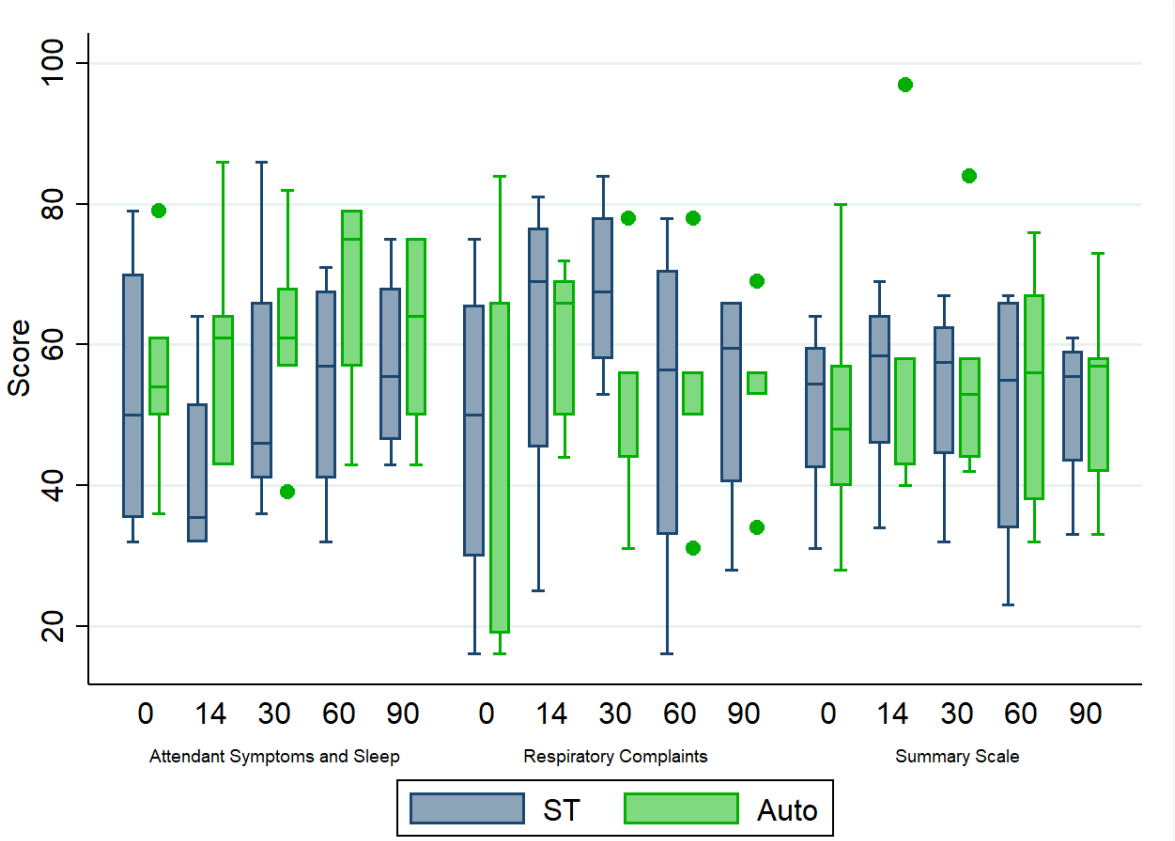

Figure 4.5. Box-plot of SRI by timepoints for both NIV groups for adherent patients. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset.

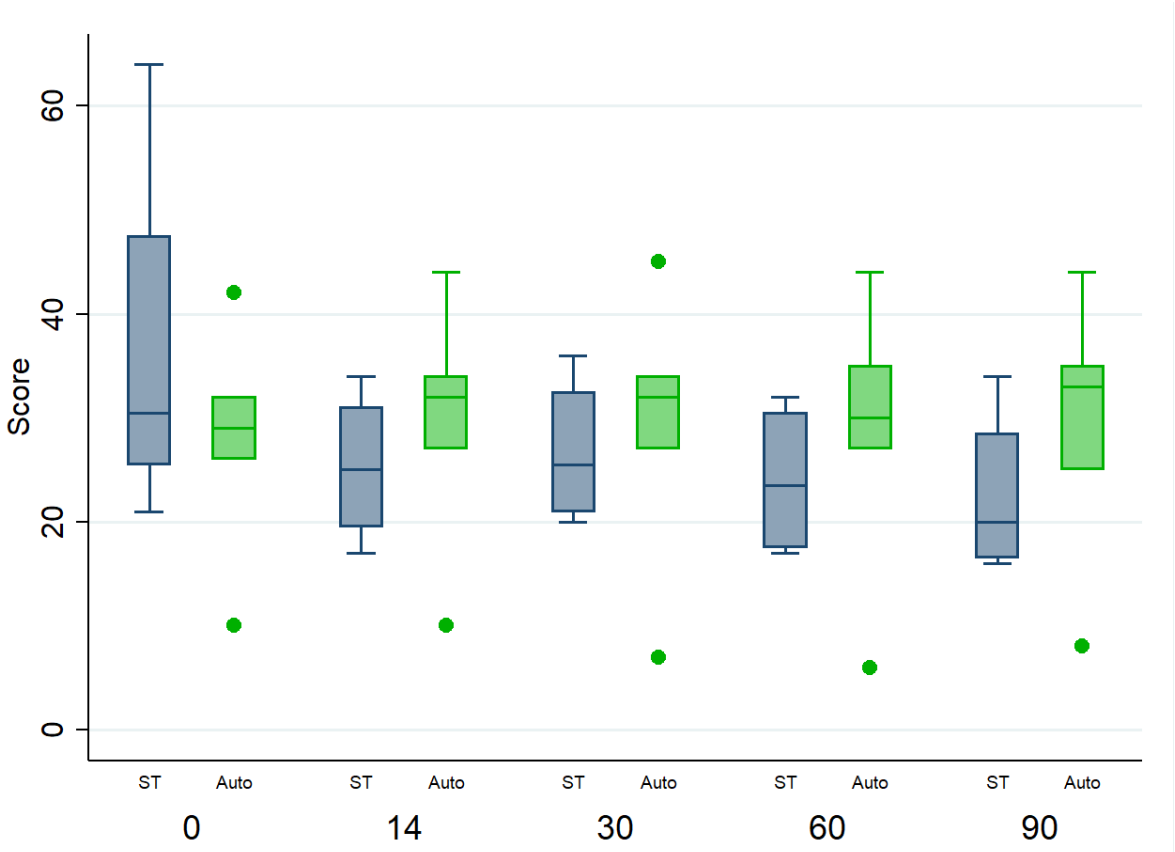

Figure 4.6. Box-plot of ALSFRS-R by timepoints for both NIV groups for adherent patients. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset.

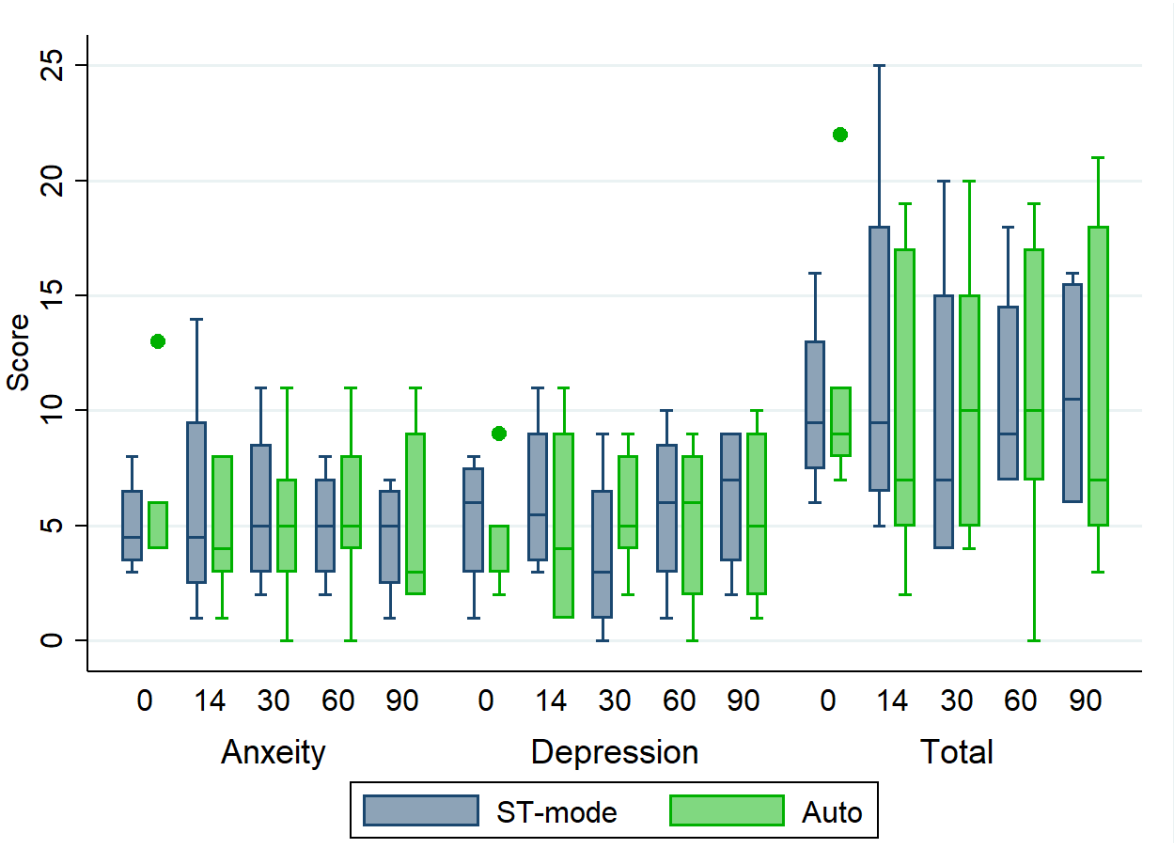

Figure 4.7. Box-plot of mHADS by timepoints for both NIV groups for adherent patients. ST = spontaneous timed. Auto = volume targeted auto adjusting EPAP. The length of the box represents the interquartile range (IQR) with the top edge of the box representing the third quartile and lower edge first quartile. The upper whisker representing the maximum number in the dataset and the lower whisker the smallest number in the dataset.

4.5 Discussion

The key findings of this pilot study are as follows: 1) There are no significant differences in anxiety scores between patients using volume targeted auto-adjusting EPAP and pressure targeted however a greater reduction in anxiety scores were observed in patients using volume targeted auto-adjusting EPAP; 2) Depression scores were lower in those patients using volume targeted auto-adjusting EPAP; 3) Treatment specific HRQoL tended to be better in the volume targeted auto-adjusting EPAP group; 4) Disease specific HRQoL tended to be higher in those patients using volume targeted auto-adjusting EPAP suggesting less disability was experienced as a result of ALS.

I believe this to be the first study which has explored HRQoL between two different modes of NIV in ALS. Quality of life (QoL) in ALS is poor and significantly worse than patients living with cancer and indeed the general population (Caballero-Eraso *et al.*, 2023). At diagnosis strategies to improve or maintain quality of life should be implemented alongside any clinical intervention to ensure quality of life is not adversely affected.

The impact on QoL should be carefully assessed with patients, families, and careers, before, during and after any clinical intervention, for example NIV or PEG to ensure there is a balance that one does not negatively impact the other. Previously, research had focused on assessing QoL enhancements using NIV compared to standard care (no NIV), however this study provides preliminary indications that further increases in HRQoL could be gained by using volume targeted auto-adjusting EPAP as an alternative to the commonly used pressure targeted NIV.

There is significant evidence which demonstrates an improved HRQoL in ALS with the use of NIV. Historical evidence suggested that nocturnal hypoventilation caused cognitive dysfunction in ALS and that this could be reversed using NIV with most patients reporting overall satisfaction with the continued use of NIV (Aboussouan *et al.*, 1997; Newsom-Davis *et al.*, 2001).

Previous studies using pressure mode NIV have reported improvements in HRQoL using the SF-36 questionnaire with a 25% increase in the ‘vitality’ domain (Lyall *et al.*,

2001), sustained improvements in mental health and sleep related issues for up to 452 days and significant improvements in SF-36 mental component summary, sleep apnoea quality-of-life index symptoms domain and time maintained above 75% of baseline (Bourke *et al.*, 2006).

Prospective HRQoL data from the Breathe-MND 1 trial cohort, demonstrated reductions in ALSFRS-R (median [IQR] 13.9 [9.4 to 28.4]%) and SRI (1.7 [−7.1 to 10.5]%). Data from our volume targeted auto-adjusting EPAP group is comparable to the Breathe-MND 1 trial cohort, with an increase in ALSFRS-R of 8.6% and 3.5% in SRI-SS. Interestingly, for pressure targeted, there was a similar increase in SRI score of 2.2% but a contrasting 26.9% decrease in ALSFRS-R. Previous studies, albeit few, have explored the effect of NIV mode in ALS. Of note, these studies focused of assessing the impact of different NIV modes on survival, breathing mechanics, cough effectiveness and NIV adherence (Sancho *et al.*, 2014, 2018; Nicholson *et al.*, 2017). Therefore, we consider our study to be the first which has investigated the impact that NIV mode has on HRQoL in ALS.

A greater number of patients with bulbar dysfunction at NIV setup were allocated to the pressure targeted group. Early studies have reported bulbar dysfunction, as a significant factor which influences both NIV adherence and QoL in ALS (Aboussouan *et al.*, 1997). Patients who develop moderate to severe bulbar dysfunction have been shown to have less improvement in HRQoL (Bourke *et al.*, 2003).

Although the most noteworthy RCT investigating NIV versus standard care in ALS, reported similar findings in mild to moderate bulbar disease it also reported opposing results to previous studies, regarding patients with severe bulbar disease. Although no significant survival benefit was identified, those patients with severe bulbar disease demonstrated improvements in both HRQoL and sleep symptoms, likely due to better treatment of nocturnal hypoventilation (Bourke *et al.*, 2006; Vrijsen *et al.*, 2015).

Furthermore, a single centre, review of ALS patients using NIV, found that bulbar patients are as likely to achieve sufficient NIV adherence at 30 and 90 days as patients who have predominant limb disease (Ristell *et al.*, 2019). As higher HRQoL scores are achieved in patients who demonstrate adherence with NIV (Jackson *et al.*, 2021), there is an emphasis on addressing any modifiable factors which can negatively impact NIV use. Problems with bulbar dysfunction which can limit NIV adherence

include increased upper airway secretions, chocking, drooling and upper airway obstruction.

All considering, we believe that the use of a standard care patient pathway to underpin the study's design has where reasonably possible, controlled the influence a greater number of patients with bulbar disease in the pressure targeted group, and as such limit the potential effect of interface discomfort/leak, upper airways secretions and obstructions on the observed differences in HRQoL between volume targeted auto-adjusting EPAP and pressure targeted groups. Of note, Chapter 3 has shown greater NIV adherence in those patients using volume targeted auto-adjusting EPAP compared to pressure targeted; this may further contribute towards the higher HRQoL observed in the volume targeted auto-adjusting EPAP group.

HRQoL in ALS is commonly measured using ALSFRS-R, mHADS, SF-36, SRI and EQ-5D questionnaires (Cedarbaum *et al.*, 1999; Jenkinson *et al.*, 2002; Windisch *et al.*, 2003; Gibbons *et al.*, 2011; Moore, Young and Hughes, 2018). QoL in any patient is specific and personalised and as such standardised questionnaires may lack sensitivity and specificity to identify those items which provide patients with happiness and quality of living in their final stages of life.

In ALS, QoL cannot be measured by assessment of functional status, strength and mobility alone (Goldstein, Atkins and Leigh, 2002), particularly as this may overestimate HRQoL in ALS patients with predominant bulbar disease where mobility may not be limited. Preliminary HRQoL data from the Breathe-MND 1 trial cohort, demonstrated larger percentage reductions ALSFRS-R scores after 2 months of using NIV compared to SRI or AQoL-8D (Aiyappan, 2017). Similarly, QoL after initiation of NIV may not necessarily improve, as the use of NIV may negate another aspect of a patient's quality of living and therefore emphasis should be placed on using the right QoL questionnaire, for the right patient at the right time. For ALS, accurate assessment of QoL over time to allow meaningful intervention may not be possible by HRQoL measurements alone, especially for non-disease modifying interventions such as NIV or PEG.

Several studies encourage the use of treatment specific QoL assessments to not only assess improvements in HRQoL but also predict survival in ALS (Aiyappan, 2017; Markussen *et al.*, 2019). We have utilised disease and treatment specific QoL

assessments to assess the impact of NIV mode on HRQoL which we believe to be a strength of the study and improve the external and internal validity of results. Further consideration should be given to the protocols which are implemented to assess the effectiveness of complex interventions, including NIV in ALS, with an aim to move away from rigid systems using one measure to define if the intervention has been successful. The use of NIV in ALS goes beyond simply asking if it has worked using a single measure but presents a broader range of questions including, what other impact NIV may have on patients, the value obtained by patients versus the healthcare resources required to deliver NIV and how the impact on one patient can be used in real time to support clinical decision making for the next patient (Skivington *et al.*, 2021).

Certainly, with the use of questionnaires in ALS, there is a risk of precise unbiased answers to narrow questions and more uncertainty around more broader questions (Skivington *et al.*, 2021). It may therefore add greater value to patient care, if questions which are most useful to patients and caregivers are asked, before, during and after care to provide the most certainty about what to do next. This may allow the development of assessment with a more tailored and personalised approach to assessing the overarching QoL benefit in ALS patients using NIV.

4.5.1 Study Limitations and Future Directions

The main limitation of this study is the small sample size, even for a pilot study, it is underestimated. There are no specific guidelines, for sample size calculation in pilot and feasibility studies, with sample sizes ranging between 12-35 participants per arm (Kieser and Wassmer, 1996; Julious, 2005; Teare *et al.*, 2014). The randomised control approach in our pilot study, is inherently a meticulous design with explicit protocols, and although in many studies is considered a strength, in some, it may limit the ability to deliver patient specific care.

Despite, randomisation by ALS phenotype, objective measurement of bulbar impairment was not assessed and as such we are unable to evaluate the extent if any, bulbar disease has on the discrepancies between HRQoL scores. Whilst, our study considered the impact of modifiable factors on NIV adherence, non-modifiable factors

including, education level, marital status and household income were not assessed. The impact of caregiver support using NIV was not explored as part of this study.

Studies have shown that patients with family caregivers who describe a sense of meaningfulness and purpose in caring for a family member are more likely to tolerate NIV compared to those patients without caregivers (Cousins *et al.*, 2013). Furthermore, caregivers report periods of stress, anxiety, and disturbed sleep during the initial period of NIV which is followed by periods of opposite emotions (Sundling *et al.*, 2009).

Our pilot study has provided initial evidence to support the performance of a larger, multicentre study to test if these results are replicated. A larger study would allow for sub-group analysis of ALS phenotype to accurately assess the impact of bulbar dysfunction on HRQoL using both pressure targeted and volume targeted auto-adjusting EPAP modes. Future studies should focus on exploring the relationship between polysomnography indices and HRQoL domains and include survival as an endpoint. Remote monitoring is commonly used to support home NIV services, and this should be a focus of investigation in ALS and how it could be used to compliment out of hospital ventilatory care.

Most QoL questionnaires are tiresome and would add considerable time to hospital appointments, therefore future work should investigate how technology could incorporate electronic QoL questionnaires into virtual clinic appointments. Future RCT's should investigate if the automatic adjustment of volume targeted auto-adjusting EPAP is likely to reduce the number of hospital visits and tests required and improve patient experience and overall HRQoL.

4.5.2 Conclusion

HRQoL in ALS is poor and worsens over time. NIV has been shown to improve HRQoL in ALS. To our best knowledge this is the only study with randomisation to compare HRQoL between two NIV modes in ALS. The results from our study suggest improved HRQoL may be gained from using volume targeted auto-adjusting EPAP. Data from our study is promising however a large, multicentre trial is required to substantiate any findings. Our study contributes towards the existing literature of how NIV can be used to improve HRQoL in ALS.

5 Discussion

This thesis highlights the significance of improving NIV adherence to obtain the greatest survival benefit and QoL status. The study has explored differences in adherence and HRQoL between two different modes of NIV in patients diagnosed with ALS. The results show that adherence and HRQoL are no worse in volume targeted auto-adjusting EPAP compared to pressure targeted, with greater 90-day adherence and higher ALSFRS-R and SRI scores seen in those patients using volume targeted auto-adjusting EPAP.

5.1 Comparisons to Adherence Findings

This thesis has demonstrated greater NIV adherence when using volume targeted auto-adjusting EPAP compared to pressure targeted. Largely, NIV adherence, irrespective of mode significantly varies with the number of patients using NIV for ≥4 h/d reported to range from 46% to 100% (O'Brien *et al.*, 2019). We have shown NIV adherence rates for volume targeted auto-adjusting EPAP and pressure targeted at 90 days of 9.05 h/d and 6.22 h/d, respectively. Previous studies have reported volume targeted NIV adherence of 6.5h/d, 9.4h/d, 9.5h/d and 9.8h/d and 6.6h/d, 8.6h/d, 9.5h/d and 10.5h/d (Bourke *et al.*, 2006; Sancho *et al.*, 2014; Martínez *et al.*, 2015; Nicholson *et al.*, 2017).

Although similar studies have investigated the impact of volume targeted NIV on adherence in ALS, this study has focused on understanding how the additional features of enhanced volume targeted auto-adjusting EPAP NIV above those of the more traditional mode of volume NIV, including automatic algorithms to maintain a patient's unique alveolar ventilation, intelligent backup rate and automatic titrating EPAP impact adherence. The natural heterogeneity of ALS and the unpredictable pace of disease progression are likely to contribute towards the broad range of NIV adherence rates, which may never be addressed by NIV mode alone.

One previous study investigating the use of volume targeted to reduce the time to first NIV optimisation and the total number of NIV related interventions over a 6-month period also reported adherence rates (Panyarath *et al.*, 2022). The study reported a statistically significant difference after 1 week with a mean adherence of 2.2 h/d for

volume targeted and 4.6 h/d for pressure targeted. Adherence at 1 month and 6 months were comparable for volume targeted and pressure targeted and did not reach statistical significance. AHI was significantly higher patients using volume targeted compared to pressure targeted at 1 week, 3 and 6 months whereas interface leak was comparable between groups at all 3 time points. This study differs from the current study in several ways. It contains a greater number of patients with bulbar dysfunction in the whole group and volume targeted group, patients were not blinded to NIV mode, the AE feature was not used meaning EPAP titration was manual, and the study methodology did not include NIV adherence as a primary end point. These are significant factors contributing towards the differences observed in NIV adherence. Furthermore, the study by Panyarath *et al.* (2022) was published after the current study had begun recruitment and as such was not included in the original literature review.

Although this study was underpinned by a robust protocol with randomisation, it followed our hospital's standard ventilatory care pathway for patients with ALS, which I believe to be a strength of the study. In a clinically complex group of patients, this allowed timely and co-ordinated access to ventilatory care, which was adaptable for those patients who presented with complex needs and required support by an MDT to gain input from or referral to other clinical teams for specialist advice. This will allow the early identification of barriers to either accepting or adhering to NIV, creating opportunity for assessment and resolution to promote acceptable NIV adherence and the associated survival and HRQoL benefits.

Our standard ventilatory care pathway has where possible, reduced the overall negative impact of modifiable factors, namely airway secretions, interface leak, upper airway obstructions and cough strength (Peysson *et al.*, 2008; Georges *et al.*, 2016; Sancho *et al.*, 2018; Chatwin *et al.*, 2020) on NIV adherence. Prior to commencing NIV, all patients were reviewed by a respiratory physiotherapist with a specialist interest in MND. Patients cough strength and secretion burden were assessed and treated if clinically appropriate with lung volume recruitment (LVR) or mechanical exsufflation-insufflation (MI-E). Any pharmacological intervention for secretion reduction was discussed and approved at the MDT. This is of particular importance as previous studies have made associations between increased oropharyngeal and/or airway secretions and poor NIV adherence along with observations of increased NIV

adherence following treatment with subcutaneous glycopyrrolate (Bach, Bianchi and Aufiero, 2004; Sheers *et al.*, 2014; Servera *et al.*, 2015; Khamankar *et al.*, 2018).

Substandard NIV interface fit and discomfort are major factors associated with poor NIV optimisation and low NIV adherence. A patient's inability to tolerate the NIV interface is a significant barrier to achieving sufficient NIV adherence and subsequent survival and HRQoL benefits. Aerophagia, effect on eating and speaking, dry mouth, sore eyes, interface leak and pressure sores all contribute to low NIV adherence, optimisation and effectiveness (Sundling *et al.*, 2009; Baxter *et al.*, 2013; Martínez *et al.*, 2015; Vrijsen *et al.*, 2015).

To ensure a high likelihood of interface tolerance our standard care pathway made accessible all commercially available NIV interfaces and after patient education and training, an interface, either full face, nasal or hybrid, was selected based on the patient's personal preferences, fit, comfort and clinical suitability. Of particular interest, is the higher interface leak observed in the volume targeted auto-adjusting EPAP group which did not negatively impact on adherence nor on respiratory blood gas parameters, which disagrees with previous studies observing comparable interface leak between both pressure targeted and volume targeted (Nicholson et al., 2017). This, of course, maybe a spurious finding and a considered scientific explanation is beyond the scope of this pilot study. However, given that a greater number of limb disease patients were present in the volume targeted auto-adjusting EPAP group, it is reasonable to assume more difficulty was experienced to adjust the NIV interface during sleep, especially in the absence of family or careers.

Whilst the use of a standard ventilatory care pathway limited the negative impact of modifiable factors, single marital status, household income <£50,000 and low education status have been shown to have a significantly adverse impact of NIV adherence. Although routine clinical practice offers limited support to address these factors, they should be used to help identify those patients who may need more extensive NIV training, education, optimisation and follow up plan.

Previous studies identified that ALS patients with a lower FVC at NIV commencement tended to achieve lower adherence compared to those with a higher FVC (Gruis et al., 2005). However, in contrast to this a more recent study reported no significant

difference in adherence rates between those patients with an FVC < or > 80% predicted value (Vitacca et al., 2020).

Similarly, studies have reported no difference in NIV adherence between those patients who present with symptoms, measured by ALSFRS-R scores and those without (Parkes *et al.*, 2019; Jackson *et al.*, 2021). Both ALFRS-R and FVC were comparable between both NIV groups and therefore we don't believe either to overly influence NIV adherence more so in one group than the other. It is important to note that most patients in this study were unable to produce quality assured spirometry according to ARTP standards and was more common in patients who had bulbar impairment. It may therefore be somewhat difficult to apply the prognostic power of FVC within clinical practice, especially if patients with ALS find it challenging to perform technically acceptable and clinically meaningful spirometry.

All considering, we believe that the use of a standard ventilatory care patient pathway to underpin the study's design has where reasonably possible, controlled the foremost modifiable factors which can influence NIV adherence and as such limit the potential effect of interface discomfort/leak, upper airways secretions and obstructions on the observed differences in adherence between volume targeted auto-adjusting EPAP and pressure targeted groups. Largely, we believe the current study represents 'real world' clinical practice and in addition, as our standard ventilatory care pathway is underpinned by national and international guidelines, the results of our study can be clearly incorporated into other NHS systems, processes and clinical practices to ensure the best possible outcomes for ALS patients using NIV.

Several studies have reported comparable effects of volume and pressure mode NIV on respiratory blood gases, ventilatory patterns, nocturnal hypoventilation and hypoxia (Jones and Wedzicha, 1993; Restrick *et al.*, 1993; Elliott *et al.*, 1994). Even though there is evidence which demonstrates significantly more effective ventilation is achieved using volume mode NIV in those patients with severe chronic hypercapnic respiratory failure caused by other conditions, including COPD, OHS and RCWD, this may not necessarily be reflected in clinical practice (Schonhofer *et al.*, 1997). This is also similar for ALS patients, where there is evidence to support more effective ventilation and better adherence when using volume mode NIV compared to pressure

mode NIV. This may well be due to the natural heterogeneity of ALS but may also be explained in part by the variance in NIV use both in the UK and across Europe.

Results from the EuroVent study (Lloyd-Owen *et al.*, 2005) showed that overall, the UK is less likely to use volume targted NIV with volume targeted NIV used most commonly in NMD (41%). Non-University Hospital Trusts used volume taregted NIV more frequently compared to University Hospitals who more commonly used pressure targeted NIV for their neuromuscular disease patients. The current study contributes evidence to support and indeed promote the wider use of volume targeted auto-adjusting EPAP NIV within both University and non-University Hospital Trusts across the UK, improving accessibility to safe, comfortable and clinically effective NIV.

All NIV setups were conducted either in outpatient clinics or at the patients place of residence either at their home or hospice. Previous studies have examined the place of setup and how this may impact on NIV adherence (Volanti *et al.*, 2011; Nixon *et al.*, 2015; Heiman-Patterson *et al.*, 2018). Most studies have considered the impact of day case NIV setup versus an overnight inpatient admission with combined NIV titration (Bertella *et al.*, 2017). Overall, there were no significant differences in early adherence rates and adherence rates at 3 months (76% versus 80%, p=0.733) and at 3 months (68% versus 76%, p=0.529). Importantly, improvement in patient symptoms was similar between groups at both timepoints and in addition pulmonary function and clinician satisfaction did not differ between groups.

Beyond elective admission for an overnight NIV setup, a multi-day inpatient visit has been compared against a single day hospital attendance. Although, this study was subject to a possible selection bias as only ‘suitable’ patients were included, median wait time for NIV setup decreased from 30 to 13.5 days ($p<0.04$), time to either death or emergency admission and overall survival were improved when patients attended hospital for a single day for NIV setup (278 to 580 days; hazard ratio 0.41, p=0.04). Effective ventilation was similar between groups (Sheers *et al.*, 2014). This study reports no safety or clinical effectiveness concerns with volume targeted auto-adjusting EPAP and location, and therefore place of setup can be determined by the patient and caregivers, based on preference and individual need, both at hospital, home and hospice without negatively impacting on adherence.

An international survey has reported that hospital admission for NIV setup in ALS is most common in Europe compared to the USA (41% versus 0%) (Heiman-Patterson *et al.*, 2018) and in a UK based audit NIV setup at a patients home with support from a specialist nurse has been reported to be as successful as hospital based NIV setup (Nixon *et al.*, 2015).

Hospital related anxiety is of particular concern in ALS and has been reported as a significant barrier to excepting NIV, and therefore attempts should be made to limit hospital visits without compromising the safety, effectiveness and quality of ventilatory care. In a study using volume targeted and pressure targeted, the number of NIV setting changes at 1 week, 3 and 6 months were similar between groups (Panyarath *et al.*, 2022). The study however did not measure patient anxiety, had a greater number of patients with bulbar-onset disease and did not use the AE feature of volume targeted. As these are significant factors which can influence NIV adherence and overall effectiveness it was unable to accurately assess the impact of volume targeted on reducing hospital visits.

Our hospital's standard ventilatory care pathway, was incorporated into this study's protocol and therefore it is anticipated the benefits reported from the previous studies are being received by our patients. This study has reported improved NIV adherence using volume targeted auto-adjusting EPAP compared to pressure targeted and consequently there should now be a focus on how volume targeted auto-adjusting EPAP can be introduced into our standard ventilatory care pathway.

Current practice is to change pressure targeted settings in response to a deterioration in the patient's symptoms, or respiratory and sleep function, which is expected to require a hospital visit. The ability of volume targeted auto-adjusting EPAP to automatically adjust ventilator settings according to the patient's individual requirements, to overcome upper airway obstructions or increase alveolar ventilation is expected to reduce the number of hospital visits and physiological tests required, improving patient and career experience by reducing overall anxiety.

Furthermore, the rate of progression of muscle weakness in ALS varies greatly between patients and the adaptability provided by the auto-adjustment features of volume targeted auto-adjusting EPAP is likely to improve effectiveness, tolerability and compliance despite unpredictable disease progression (Gay *et al.*, 1991; Ferguson *et*

al., 1996; Nicholson *et al.*, 2017). Certainly, this is beyond the extent of this pilot study, but nevertheless as there are no current guidelines which refer to the optimal place of NIV setup, this should highlight the importance of exploring how volume targeted auto-adjusting EPAP can ensure that only those patients where it is essential, attend hospital. This reduces the anxiety related to travelling to the hospital, waiting in the outpatient clinics, moving around the hospital departments, the possible risk of infection from other patients, time and cost burdens and overall, the prospect of patients accepting and tolerating NIV.

There is still uncertainty about which NIV mode, pressure or volume, offers the most effective level of ventilation. It is however clear that irrespective of which NIV mode is used to treat CRF in ALS, emphasis should be placed on timely review of NIV effectiveness and subsequent NIV optimisation. NIV which is targeted to achieve patient specific ventilation outcomes is likely to confer advantages related to NIV acceptance, tolerance, adherence and benefits related to survival and HRQoL.

This study has demonstrated NIV adherence is achieved sooner using volume targeted auto-adjusting EPAP compared to pressure targeted and as such special consideration should be made regarding the use of volume targeted auto-adjusting EPAP over pressure targeted in those patients who present with significant predictors of poor NIV adherence and who may face challenges related to attending hospital due to poor mobility, physiological and/or psychological stress. In addition, in those hospitals where time from NIV setup to first follow up is prolonged due to increased clinical demand or operational limitations, volume targeted auto-adjusting EPAP may be employed, under the assumption that adherence will be achieved sooner and therefore a delayed follow up appointment may not necessarily have an undesirable impact on the assessment or optimisation of effective ventilation.

Conversely, given the complexity of ALS and the significant inter-patient variation in disease presentation and progression, this study does not recommend an extended follow up period beyond that advised by published guidelines (NICE, 2016) and indeed, suggests a patient specific (rather than disease specific), follow up period to identify the causes of poor ventilation or adherence and offer clinical support to optimise ventilator settings including interface and humidification preferences. Our hospital's standard ventilatory care pathway offered patients a 3 day follow up period

using remote monitoring data and telephone consultation with the outcome from the patient's assessment dictating the next appropriate follow up period which could be between a few days or weeks. Of course, consideration should be given to patients with additional complexity, including those with moderate to severe bulbar impairment and physiological evidence of a rapidly progressing ALS.

In certain patients, NIV optimisation may not be aimed at reducing daytime hypercapnia or improving SDB but instead symptom improvement. For patients where NIV setup was weighted against improving symptoms rather than physiology, NIV optimisation may not require respiratory blood gases or alternative testing. Reducing healthcare utilisation but without jeopardising the quality of patient care, in place of a more traditional hospital assessment, a combination of telephone consultation, review of remote monitoring data and the adaptive features of volume targeted auto-adjusting EPAP may be recommended.

5.2 Health Reported Quality of Life Considerations in ALS

It may be assumed that patients who have been diagnosed with a terminal disease, such as ALS, will accept a treatment which has been shown to improve both duration and quality of life. However, around a third of ALS patients decline the use of NIV despite patients and caregivers being provided with the evidence-based benefits including improved HRQoL and survival (Cousins *et al.*, 2013). Although many studies have investigated the advantages of NIV, focus has mainly been on the differences observed between adherent and non-adherent patients (Coco *et al.*, 2006; Mustfa *et al.*, 2006). There is evidence to suggest that caregiver involvement is of particular importance when supporting ALS patients use NIV however, overall, there is a lack of evidence to fully account for the reasons why patients diagnosed with ALS decline NIV (Ando *et al.*, 2015).

Four themes have been identified as contributors towards non-acceptance and poor adherence of NIV, these are, not needing NIV, previous bad experiences of healthcare, negative perceptions of NIV and preservation of 'self'. Patients tended to dismiss NIV as they felt it was not required and although some patients admitted physical changes, they were not prepared to associate these with ALS. After a terminal diagnosis, patients have been reported to compare their current self to their previous self or in some situations others who have the same disease, this may force patients to protect

parts of their ‘self’ which the disease cannot affect, including autonomy, dignity and some aspects of QoL (Harman and Clare, 2006; Ando *et al.*, 2015). This indeed may also be true for patients with ALS, who could prioritise maintaining dignity or autonomy, over breathlessness or poor-quality sleep and thus deciding to reject the use of NIV.

A significant factor which contributed towards the negative view of NIV was inherent to the treatment itself. Patients complained of issues with the NIV interface and the pressure of the ventilator when delivering therapy, commonly experienced side effects across all patients using NIV irrespective of disease. However, withdrawal from NIV was not exclusively related to NIV interface or pressure discomfort but rather the negative experiences of using NIV, the panic when using the therapy along with the feeling of being powerless when using the interface and ventilator (Torheim and Gjengedal, 2010; Ando *et al.*, 2015). In addition, maintaining the interface and ventilator, including cleaning, replacing consumables and overcoming any technical issues caused further challenges. Overall, this can lead to heightened levels of anxiety for both patients and caregivers, which are further intensified by negative views or experiences of healthcare providers.

The overpowering number of hospital appointments combined with the physical and emotional stress of travelling to and from the hospital and the ‘requirement’ to comply with the use of NIV were reported to challenge patients self-value and resulted in disempowerment (Coyle, 1999; Sundling *et al.*, 2009). The significant complexity of these issues cannot be solved by NIV mode alone however the use of volume targeted auto-adjusting EPAP may contribute towards a reduction in NIV related anxiety.

Current practice at our hospital, and indeed what is reflected nationally, is to change pressure targeted settings in response to alterations in $PaCO_2$, results of polygraphy or overnight pulse oximetry and patient symptoms which is likely to require a hospital visit. The automatic adjustment of volume targeted auto-adjusting EPAP may contribute towards a reduction in the number of hospital visits and clinical tests required and improve patient experience.

The rate of progression of ALS varies greatly between patients and the flexibility provided by the auto-adjustment of the volume targeted auto-adjusting EPAP mode is likely to improve effectiveness, tolerability and compliance despite unpredictable disease progression. The natural heterogeneity of ALS dictates that one clinical

treatment strategy which has proven beneficial for one patient may not be as effective for another and indeed the application of volume targeted auto-adjusting EPAP is similar to pressure targeted, employing an interface and tubing to deliver ventilatory care.

To contribute solving this clinical phenomenon, this study has provided evidence to support the use of volume targeted auto-adjusting EPAP to 'boost' adherence soon after setup and overall act as an additional clinical tool to support patients who are finding NIV challenging to accept and tolerate. It is clear, albeit beyond the scope of this study, that medical manufactures of NIV interfaces, need to invest resources to develop innovative strategies aimed at minimising the invasive nature of currently available NIV interfaces and how current negative perceptions of NIV interfaces can be changed to maintain a patient's identity throughout the progression of ALS.

Despite decades of research aimed at exploring HRQoL in ALS, there is still no universally accepted 'gold' standard assessment of QoL. The ALSFRS-R is a disease specific questionnaire focusing on assessing functional disability and ALS progression and is recommended as a primary outcome of HRQoL in clinical trials (Cedarbaum *et al.*, 1999; Leigh *et al.*, 2004). There are several advantages of using the ALSFRS-R assessment in both clinical trials and clinical practice, its relatively easy to comprehend and complete by patients, caregivers and healthcare professionals, its well validated and reliable and serves as a proxy for prognosticating survival (Hartmaier *et al.*, 2022).

Amid these advantages there are still concerns with the multidimensionality and non-linearity of the ALSFRS-R and as such challenge its ability to accurately and meaningfully assess HRQoL related to changes in physical disability across all patients diagnosed with ALS. Rasch analysis has identified some aspects of functional status are difficult to measure in the context of the disease (Hartmaier *et al.*, 2022; Fournier, James and Glass, 2023). ALSFRS-R has been shown to either decline or remain stable after the commencement of NIV (Jackson *et al.*, 2001; Lyall *et al.*, 2001; Vrijsen *et al.*, 2015) using pressure cycled modes of NIV.

ALSFRS-S scores for alternative NIV modes have not been fully explored. One study comparing NIV effectiveness in ALS patients using volume and pressure modes reported ALSFRS-R only at baseline and did not perform any between group comparisons. Another study compared ALSFRS-R scores in ALS patients using

volume mode NIV, however ALSFRS-R scores were compared between adherent and non-adherent patients and not part of the primary data analysis or outcomes (Sancho *et al.*, 2014; Martínez *et al.*, 2015).

The current study has explored the differences in ALSFRS-R scores between two groups of ALS patients using two different modes of NIV; volume targeted auto-adjusting EPAP and pressure targeted. We have reported an improved ALSFRS-R score in those patients using volume targeted auto-adjusting EPAP compared to pressure targeted and provide data to contribute towards this clear gap in evidence relating to HRQoL in ALS patients using NIV. Interestingly, we have reported a slower rate of ALSFRS-R decline for volume targeted auto-adjusting EPAP but an increased rate for pressure targeted. When using pressure targeted a median change in ALSFRS-R of -1.2 points per a month has been reported (Jackson *et al.*, 2021).

In contrast, this study has demonstrated a median change in ALSFRS-R of -0.76 in patients using volume targeted auto-adjusting EPAP compared to a median change of -2.8 in the patients using pressure targeted. Overall, ALSFRS-R scores remained stable in patients using volume targeted auto-adjusting EPAP compared to those using pressure targeted. Interestingly, patients allocated to use pressure targeted demonstrated a 8.8-point decrease in ALSFRS-R from day 0 to starting NIV.

This noteworthy decline in ALSFRS-R is supported by data published in a real-world survey of HRQoL across all disease stages in ALS. This study reported that when assessing the severity of ALS using the Kings staging criteria the steepest decline in HRQoL occurs between stages 3 and 4 which are associated with the introduction of either NIV or PEG (Stenson *et al.*, 2024). The use of volume targeted auto-adjusting EPAP over pressure targeted may soften the reduction in HRQoL when NIV is required to support the patient's own ventilation.

Of particular discussion is the application of ALSFRS-R to monitor HRQoL after intervention with NIV. ALS is a complex disease where QoL in its broadest sense, can be defined by physical health, psychological state, relationships with others, relationships with the environment and level of independence, all of which vary significantly in ALS patients over differently timed courses of disease progression and changes in severity.

The ALSFRS-R may be considered to focus more on the assessment of the patients physical functioning which is expected as HRQoL decline is associated with disease progression (Ilse *et al.*, 2015). HRQoL scores are therefore expected to fall irrespective of NIV which is unable to directly improve physical functioning. ALS patients report the loss of strength and mobility as the most significant factors contributing towards a reduced HRQoL. Of secondary concern is fatigue affecting between 44-86% of patients with ALS (McElhiney *et al.*, 2009; Lo Coco and La Bella, 2012).

The origin of fatigue in ALS is multifactorial and is likely the accumulation of neuromuscular pain, respiratory impairment, side effects of medication, poor quality sleep and psychological factors (Lo Coco and La Bella, 2012). The ALSFRS-R provides incomplete assessment of fatigue, including sleep quality and as such offers limited use in assessing the effectiveness of NIV to improve HRQoL. Interestingly, breathlessness is reported to be of limited concern to patients diagnosed with ALS and this may certainly reflect the effectiveness of NIV itself, nationally recognised guidelines to manage respiratory failure in ALS, an MDT approach to delivering care or a combination of all three.

The ‘response shift’ concept, in which patients shift their life goals and expectations of themself, to match their ‘new’ reality, may also negate the use of the ALSFRS-R to assess HRQoL in response to NIV. Patients may develop new perspectives of what is required to maintain HRQoL, above and beyond physical strength and mobility, including personal relationships and satisfaction with their environment (Raheja *et al.*, 2016). Understanding what is problematic to the patient is of central importance as this will drive interventions which offer meaningful support, symptom control and on-going clinical management. As a result, there may be more value in applying a global QoL assessment, including psychological factors, which offers a wider and more holistic assessment of QoL in ALS. This could allow patients to dictate how QoL is defined considering relationships with family, friends and the use of non-medical support systems. Patients can then be educated on the likely benefits of NIV, allowing expectations on how it will improve QoL to be managed with care.

Twenty years ago, a treatment specific instrument was developed to assess QoL in those patients using NIV. The SRI contains 7 domains and scores can range from

between 0 -100, with higher scores representing a better HRQoL (Windisch *et al.*, 2003). There are a limited number of studies which have used the SRI to assess HRQoL in ALS patients using NIV. In 2006, a RCT reported better HRQoL in ALS patients using NIV compared to those receiving standard care (no NIV) where HRQoL was measured using the SF-36, SAQLI and CRQ (Bourke *et al.*, 2006). A review of the studies previously performed concluded that there is too much variability in study methodology, study design and QoL endpoints to draw clear and concise conclusions about which HRQoL instruments should be used to accurately and meaningfully assess QoL in ALS patients using NIV (Piepers *et al.*, 2006).

Many studies use the generic SF-36 to assess HRQoL however instruments including the SRI were not used as study endpoints (Bourke *et al.*, 2003, 2006). To address this concern, the current study used disease specific, treatment specific and psychometric specific patient reported questionnaires to offer a more compressive assessment of QoL in ALS patients using NIV. The current study has presented SRI scores similar to other studies. In a study using volume targeted and pressure targeted NIV modes, SRI was not significantly different at baseline or at 3 months (Panyarath *et al.*, 2022). One previous study compared SRI scores between two groups of patients receiving NIV. One group was exclusively ALS patients and the other group comprised of a range of diseases including non-ALS neuromuscular diseases, kyphoscoliosis and OHS (Hazenberg *et al.*, 2016). SRI scores for patients using pressure targeted were comparable however SRI scores for the volume targeted auto-adjusting EPAP tended to be higher at baseline and 90 days.

One challenge to overcome when comparing HRQoL scores, are the different time points at which these measurements are made, which vary from study to study. This is particularly important in a disease such as ALS where there can be significant disease progression and therefore deterioration in a patient's QoL over a short period of time. This may lead to significantly decreases from one point of measure to the next or from the start to the beginning of a study. The current study measured HRQoL over a period of 90 days at 14-, 30- and 60-day timepoints which were aligned to our hospital's standard ventilatory care pathway. Other studies have measured HRQoL over a longer period and at fewer timepoints, for example over a 6-month period with measurements at baseline, 2 and 6 months (Hazenberg *et al.*, 2016). Hazenberg and colleagues showed that at 2 months the domains for attendant symptoms and sleep,

respiratory complaints and anxiety significantly improved whereas at 6 months only the domain for attendant symptoms and sleep was still significantly improved.

The current study reports SRI summary scores which do not significantly change over time after commencing NIV (both modes) however for the attendant symptoms and sleep domain there are observed improvements over each time point. This may reflect the greatest clinical benefit of NIV in ALS being associated with improving sleep quality and treating SDB. Interestingly, in the current study, patients using pressure targeted demonstrated a significant fall in attendant symptoms and sleep at 14 days. Although, anecdotal, this may be related to challenges in using the interface which is a commonly reported problem in ALS that were then resolved with scores returning to baseline (Torheim and Gjengedal, 2010; Ando *et al.*, 2015).

Overall, there is too much variation in the scores of different QoL instruments within ALS. When comparing SRI, MRF-28, HADS and SF-36 scores between a group of ALS and a group of other disease, SRI (3 domains) was the only instrument which identified improvements in HRQoL at 2 and 6 months after using NIV in the ALS group. SF-36 identified changes in HRQoL at 6 months only. All HRQoL instruments were able to identify changes in QoL at 2 and 6 months in the other disease group. This highlights not only the variability in HRQoL measurements in ALS but also the differences observed using the same HRQoL instruments in other disease.

Time from diagnosis, time from symptom(s) onset, presence of bulbar dysfunction, FVC and secretion burden are all factors which can influence a patients HRQoL at any given point in time and it seems that despite extensive validation, current instruments to measure QoL in ALS patients using NIV do not offer the required level of sensitivity and specificity to accurately measure and monitor disease progression, symptoms and overall HRQoL. Although, commonly used as endpoints in studies investigating effectiveness of interventions in ALS, there still may be question about the validity of use within clinical practice.

Despite using mHADS to identify depression, the current study has reported similar low levels of depression and anxiety as reported previously (Kurt *et al.*, 2007; Wicks *et al.*, 2007; Vignola *et al.*, 2008; Grabler *et al.*, 2018). Interestingly, even when using the same depression scoring tool, for example BDI, varied results have been observed (Grabler *et al.*, 2018). The current study has reported low levels of anxiety and

depression within 15 patients diagnosed with ALS and commenced onto NIV. mHADS for anxiety, depression and total domains remained relatively constant over 90 days for both volume targeted auto-adjusting EPAP and pressure targeted groups which is in agreement with previous studies (Dorst, Behrendt and Ludolph, 2019). No patients in either group demonstrated evidence of a mood disorder during the 90 day study period.

Overall, it appears that anxiety is marginally improved after commencing volume targeted auto-adjusting EPAP and depression remained unchanged. Previous studies have identified that patients with a high degree of depression/depressive symptoms are more likely to decline NIV, lending to a loss of their dignity, identify and autonomy. The current study was unable to assess this as all patients reported low levels of depression and accepted to commence NIV.

The HADS has been previously used in MND trials to measure a patients mood determined by levels of anxiety and depression (Goldstein *et al.*, 2006; Wicks *et al.*, 2007). Originally, HADS was applicable across all diseases and interventions, however, overtime it became apparent that in its current form it did not hold the level of validity to accurately measure levels of anxiety and depression in patients diagnosed with ALS. After Rasch analysis its questioning was revised providing stronger evidence for it use in an ALS population (Gibbons *et al.*, 2011). Similarly, the HADS has been modified to show adequate validity for use in patients diagnosed with cancer, musculoskeletal and Parkinson's disease (Smith *et al.*, 2006; Pallant and Tennant, 2007; Forjaz *et al.*, 2009).

Anxiety and depression are commonly reported in MND, including ALS (Annunziata *et al.*, 2023) with a greater prevalence of anxiety and depression in those patients who are non-adherent with NIV (Russo *et al.*, 2021). Of note, there is no reported association between anxiety and depression scores and the time taken for ALS patients to demonstrate adherence with NIV nor is there evidence to suggest that depression scores improve after patients commence NIV (Dorst, Behrendt and Ludolph, 2019; Russo *et al.*, 2021).

Previous studies which have measured depression have done so with the BDI and not mHADS. Both methods of scoring depression have been validated in other disease including adult congenital heart disease (ACHD) and end stage renal disease (ESRD)

with a comparable sensitivity and specificity permitting use within clinical practice (Loosman *et al.*, 2010; Westhoff-Bleck *et al.*, 2020), however there is limited evidence comparing BDI and mHADS in ALS. A negative correlation between ALSFRS-R and depression measured by BDI has been previously reported. Patients with a high level of functional disability measured by ALSFRS-R are more likely to be depressed (Grabler *et al.*, 2018) and as such we would of expected a greater degree of depression in both volume targeted auto-adjusting EPAP and pressure targeted groups.

Given the moderate degree of impairment of both the SRI and ALSFRS-R, mHADS appears to be relatively well preserved and disproportionately low. For this reason, it could be suggested that receiving a diagnosis of ALS may not inevitably be reason for anxiety and depression and indeed some patients, their relatives and care givers who demonstrate remarkable resilience may find positive meaning to their lives whilst living with ALS (Grabler *et al.*, 2018). Furthermore, it may be the functional impairment which leads to anxiety and depression and not necessarily as a result of commencing NIV and as such the diagnosis and subsequent treatment of mood disorders may lead to improved NIV adherence in ALS.

5.3 Study Limitations, Bias and Confounding Factors

Although this is a pilot study with the main aim to trial and evaluate the randomised methodology, identify any issues with the study design and inform sample and effect size for future definitive RCT's, the most notable limitation is the small sample size from a single hospital. It is recommend that 35 patients per group for continuous outcomes and 60 patients per group for categorical outcomes are used in order to ensure sufficient statistical precision (Teare *et al.*, 2014).

The current study recruited 15 patients, permitting 8 patients for group 1 and 7 patients for group 2. Using historical data from our hospital we anticipated between 20-25 ALS patients to commence NIV per a year. This study had proposed a 3-year recruitment period and therefore aimed to recruit a total of 40 patients. Due to the COVID-19 pandemic, recruitment was deferred until March 2022. The recruitment was revised to a total of 15 patients and was completed by October 2023. Although this pilot study is statistically 'underpowered' there is still significant value gained regarding sample

sizes for future RCT's. The current study has provided data which considers both target and final recruitment, providing useful information as to whether target and final sample sizes for future studies are realistic and achievable in ALS (Totton *et al.*, 2023).

Nevertheless, this study has demonstrated a promising recruitment rate of 75%, in a single centre, where 20 patients are commenced onto NIV every year. To achieve a sample size of 158 patients, a multicentre approach would be required, with a recruitment target of 0.83 patients per a month, across 6 similar sized centres, recruiting for 2.6 years. Furthermore, although the final sample size is significantly lower than pilot studies in other disease, for example COPD, it is crucial to consider the frequency of commencing NIV in ALS and our final sample size is, in some hospitals, proportionate to what is expected annually.

This pilot study was designed to replicate larger scale RCT's and therefore its design was to be inclusive of all ALS patients, irrespective of bulbar impairment, social support, level of physical and mental disability, or personal views and beliefs on survival or using life prolonging therapy. Consequently, as a result there were a greater proportion of ALS patients with bulbar dysfunction in the pressure targeted group compared to the volume targeted auto-adjusting EPAP group and despite the small sample size this was a statistically significant difference. Firstly, we acknowledge the negative impact bulbar dysfunction has on NIV adherence however an objective measure of bulbar dysfunction, for example the Norris scale bulbar sub score, was not performed and therefore the influence of bulbar impairment on NIV adherence in the pressure targeted group is unknown. In addition, the small sample size did not allow for statistical analysis stratified by ALS phenotype.

NIV settings were configured according to the study's setup protocol which followed a standard ventilatory care pathway, however NIV setting changes over time were not recorded and therefore a limitation of this study is the inability to report average IPAP, EPAP, BR and PS for both groups at setup and at each study time point. This data would allow review to ensure that both modes are delivering a comparable level of PS at NIV setup and over time as to prevent either mode delivering supra-physiological target tidal volumes which may counterintuitively induce arousals, worsen sleep quality and potentially impact adherence.

The inclusive nature of the pilot study saw patients enrolled who had different levels of social support in the form of family, friends or caregivers. A limitation of this study was not assessing the impact of NIV on caregivers or vice versa, the impact of caregivers on NIV adherence. There was significant variability in the social support of the patients enrolled not just at the beginning of the study but as changes occurred throughout the study period. Combined with non-modifiable factors, this creates additional challenges when assessing which changes are required to improve NIV adherence and HRQoL.

Given the significant negative impact of poor-quality sleep on HRQoL, only basic sleep function, in the form of overnight pulse oximetry, was measured. Not employing the use of cardiorespiratory polygraphy or full polysomnography may be a limitation of the study. These sleep tests do not form part of our hospital's standard ventilatory care pathway for ALS patients and as such would incur significant study costs and would not represent real world clinical practice.

To provide a robust measure of HRQoL, the current study used disease and treatment specific instruments as well as an instrument with validated psychometric properties in ALS. Of, course there are additional QoL instruments available, and it would be interesting to collect data from these, however it was often reported that patients found completing the mHADS, ALSFRS-R and SRI, tedious, time consuming and at times upsetting. We therefore don't necessarily see this as a limitation of the study but instead a more selective use of the QoL questionnaires available and were cautious that completing large sets of questionnaires would discourage patients, family and caregivers from taking part in the study.

To ensure patient safety it was not possible to blind the investigators or members of the clinical research team collecting data from NIV mode. Although this may have incurred observer bias, I believe the objective nature of the measurements specifically NIV adherence mitigated this to a degree. Furthermore, the lead researcher who completed data validation and performed statistical analysis was not involved, were possible, during patient consultations, including completing the QoL questionnaires and as such minimised reporter and observer bias. Whilst the use of remote monitoring is part of our hospital's standard care pathway, for some patients, the thought of being monitored may subconsciously improve NIV adherence in the attempt to 'please' the

clinical research team. The study may also be subject to the Hawthorne effect as some measurements including HRQoL were only made as part of the study and not routine clinical practice.

Although this study was discussed by a patient representative at a local MND forum, there was no formal public and patient involvement or indeed involvement of clinical stakeholders, including neurology or palliative care in the design, conduction or outcomes of the study.

5.4 Clinical Implications and Changes to Clinical Practice

It is important that the completion of this study provides learning and the opportunity to improve clinical care for patients diagnosed with ALS. I believe that this study improves the equity of access to an alternative mode of NIV that has the potential to improve clinical outcomes. I have identified the challenges which patients with ALS experience when performing physiology investigations however we advocate that all patients, even those with bulbar disease should not be denied the opportunity to take part in testing, which provides valuable data to direct clinical management. We have a greater awareness of the importance of diagnosing SDB in ALS at the earliest opportunity and therefore all patients will receive an overnight pulse oximetry at their first clinical appointment. Furthermore, for those patients who present with significant signs and symptoms of SDB there will be access to cardio-respiratory polygraphy.

Within our hospital's NIV service there is now an improved focus on measuring QoL and these quantitative measurements will now be incorporated into our patient pathway and home NIV policy. There will also be attention to asking patients to describe what provides QoL and ensure that the initiation of NIV and its on-going use does not contest this. This study has also provided an opportunity for the clinical care team to improve the understanding of how modifiable and non-modifiable factors can influence NIV adherence and what options are available across the MDT to overcome these to promote a 'further faster' approach to clinical problem solving. The clinical care team have an improved understanding of volume targeted auto-adjusting EPAP as an alternative mode to pressure targeted combined with a new set of clinical skills allowing the initiation and optimisation of volume targeted auto-adjusting EPAP within out standard ventilatory care pathway for ALS patients.

Given the heterogeneity of ALS and the need to provide patient specific ventilatory care, I believe this study and the use of volume targeted auto-adjusting EPAP contributes towards the development of personalised medicine pathways aligned with the Personalised Medicine Strategy from the Chief Scientific Officer for England. Finally, this study provides evidence to support the review of local systems, processes and clinical practices and contribute towards our hospital's UKAS IQIPS accreditation.

5.5 Future Research

The primary recommendation from this study will be the performance of a large-scale multicentre study investigating the differences in adherence and HRQoL between pressure targeted and volume targeted auto-adjusting EPAP. Further research is required to assess the impact of all severities of bulbar disease on NIV adherence and how volume targeted auto-adjusting EPAP may overcome these clinical challenges. The impact of caregivers on NIV adherence using any NIV mode should also be more rigorously investigated. Furthermore, future studies should investigate the ability of volume targeted auto-adjusting EPAP to treat SDB quicker, achieving effective ventilation sooner and prolonging survival. Titration of NIV in ALS by PSG has been recommended however there are no studies investigating impact of volume targeted auto-adjusting EPAP versus pressure targeted on sleep staging and how PSG measurements correlate to HRQoL indices.

The performance of respiratory physiology diagnostic tests to investigate for the presence of respiratory impairment in ALS is recommended by NICE. Due to the natural heterogeneity of ALS and indeed the physical consequences of the disease further studies are required to assess the feasibility of performing respiratory function tests in ALS, to ensure the right patient has the right diagnostic test at the right time.

There appears to be considerable evidence demonstrating poor HRQoL in ALS and its subsequent consequences including poor NIV adherence. Further QoL studies exploring longitudinal relationships between HRQoL, global QoL, religiosity, anxiety and depression in large ALS populations are required. Studies investigating the psychological strategies including mindfulness, cognitive behavioural therapy to improve QoL in ALS despite disease progression would allow significant progression in this area of ALS care.

Finally, and with the results of this study to provide support, the development of national guidelines for the provision of complex home ventilation detailing place of NIV initiation, interface, humidification, secretion management, patient and caregiver education and training, NIV mode and settings and telemonitoring are required to move towards a nationally adopted standard of ventilatory care in ALS.

5.6 Conclusions

To our knowledge this is the only study with randomisation comparing adherence and HRQoL between two NIV modes in ALS. QoL in ALS is poor and clinically worse compared to patients diagnosed with Cancer. Improved NIV adherence, ALSFRS-R, mHADS and SRI scores were achieved using volume targeted auto-adjusting EPAP compared to pressure targeted. There is an unmet need for clinical strategies to maximise QoL in ALS and therefore volume targeted auto-adjusting EPAP could be considered as an additional ventilatory adjunct in the clinician's toolbox to improve outcomes associated with NIV adherence. Our study provides promising data which compliments the current evidence base for the use of NIV in ALS. We recommend a large-scale, multicentre study to fully investigate the impact of volume targeted auto-adjusting EPAP on adherence rates and HRQoL in ALS.

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