Improving home mechanical ventilation

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Abstract

Home mechanical ventilation (HMV) is a complex assistive technology that can support individuals with respiratory failure to remain in the community. There is a lack of expert consensus regarding which disorders might benefit from HMV and also how best to apply the technology in order to achieve those benefits. Quality of care is therefore difficult to define for individuals receiving assisted ventilation as objective evidence is often lacking and broad consensus amongst expert clinicians remains elusive.

In this thesis, differences in the use of HMV are described and the available evidence that underlies different approaches is considered. Two similarly resourced HMV providers in Canada and Australia are shown to use very different care models with these differences persisting after adjustment for underlying population attributes. This suggests that the strategies represent true differences in approach. They were also not associated with the cross-sectional health-related quality of life (HRQoL) of users of HMV in a multivariable model.

To assist in the design of longitudinal studies involving non-invasive positive pressure ventilation (NIPPV), a systematic review of the literature considers the response of non-physiological outcome measures across different disease groups. This demonstrates that the subjective benefits of NIPPV are inconsistent and vary according to underlying diagnosis. Measures of somnolence and fatigue appear to be the most consistently influenced by NIPPV and these aspects of health should be incorporated in clinical studies in these often heterogeneous populations, along with relevant physiological and clinical endpoints.

Health policy makers frequently require cost-utility analyses to confirm the cost-effectiveness of new interventions or technology. Few of the available instruments have been evaluated in individuals receiving assisted ventilation. A comparison of responses to two generic preference-based HRQoL instruments is
presented. This demonstrates that the way in which mobility items are framed within the EuroQoL (EQ-5D-5L) and the Assessment of Quality of Life (AQoL-8D) contributes to the lack of agreement between the index scores produced with these instruments. This highlights critical measurement properties of the two instruments and underlines the need for careful consideration of HRQoL instruments in future research. In particular, the use of instruments that measure the behaviour of walking rather than the capacity to mobilise may be problematic in studies that may include individuals that are unable to walk.

Finally, a randomised controlled trial evaluating the role of polysomnography (PSG) titration of NIPPV is described, the design of which was guided by the preceding analyses. PSG is used routinely by only some HMV providers and it remains uncertain if it should form part of high quality care for users of HMV. Those undergoing PSG titration of NIPPV had significantly lower levels of patient-ventilator asynchrony and a trend towards improved adherence in comparison to the control group. However, there was no difference in the frequency of EEG arousals during sleep and there were no short-term differences between groups in measures of gas exchange, symptoms or HRQoL.

These findings suggest that practice differences between HMV providers are significant, reflect differences in approach to care, and are likely driven by a relative lack of both objective evidence and broad expert consensus. The heterogeneity of populations managed with HMV poses a challenge to evaluating the quality of care, and careful selection of non-physiological endpoints (particularly symptom scales and measures of HRQoL) is required to ensure important treatment effects are not missed in future studies. While PSG titration may have advantages over clinical titration, conclusive evidence of benefit has not been demonstrated in the short-term study presented in this thesis. It is therefore proposed that further multicentre randomised controlled trials are required to answer this and other important clinical questions for HMV users. Other study designs (including longitudinal observational studies with collaborative data sharing) should be used as part of comparative effectiveness research.
The current difficulty in defining high quality of care for individuals receiving assisted ventilation represents an extremely undesirable situation. A concerted effort involving users, carers, clinicians and policy makers could rectify this. This need will become more pressing as the prevalence of HMV – and the demand for high quality HMV services – increases over time.
Declaration

This is to certify that:

1. The thesis comprises only my original work towards the Doctor of Philosophy except where indicated in the preface

2. Due acknowledgement has been made in the text to all other material used

3. The thesis is less than 100,000 words in length exclusive of tables, figures, bibliographies and appendices

__________________________
Liam Michael Hannan
Preface

Studies presented in this thesis (Chapters Seven, Eight and Nine) were conducted in collaboration with other researchers. Over 50% of the work in each of these studies was original work performed by the PhD candidate (LMH). No third party editorial assistance was provided in preparation of this thesis.

For the data presented in Chapter Seven;

(Manuscript) HS provided assistance with data collection at the Australian site. JDR, CFM, DJB and MEH were involved in the conception, design, ethics approval, data analysis and writing of the manuscript. This contribution represented less than 50% of the work presented. The majority of the work was performed by LMH and is claimed as original.

For the data presented in Chapter Eight;

(Manuscript) WDR and JDR provided assistance with the conception and design of the PICO question for the review and selection of papers for inclusion. GSD assisted with the screening of titles and abstracts and Y-WC assisted with the data abstraction and analysis. All co-authors provided assistance with the production of the manuscript. This contribution represented less than 50% of the work presented. The majority of the work was performed by LMH and is claimed as original.

(Manuscript) JDR, CFM, DJB and MEH were involved in the conception, design, ethics approval, data analysis and writing of the manuscript. DGTW and SB assisted with the analysis and writing of the manuscript. This contribution represented less than 50% of the work presented. The majority of the work was performed by LMH and is claimed as original.
For the data presented in Chapter Nine;

LR, CC, NS, FJO, MEH, DJB and CFM were involved in the conception, design, ethics approval, and data analysis. LR provided significant assistance with the conduct of the study. DJB performed the randomisation procedures. MEH, FJO, NS and LR provided clinical interpretation of the polysomnography titration. This contribution represented less than 50% of the work presented. The majority of the work was performed by LMH and is claimed as original.

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For the survey data collection and systematic review presented in Chapters Seven and Eight, significant in-kind support was received from both the Department of Respiratory and Sleep Medicine at Austin Health and the Division of Respiratory Medicine at University of British Columbia and Vancouver Coastal Health.

The randomised controlled trial presented in Chapter Nine received funding from an Austin Medical Research Foundation project grant (grant number 2-1245 - $10,000) and a project grant from the Institute for Breathing and Sleep ($5,000). Significant in-kind support was received from the Department of Respiratory and Sleep Medicine at Austin Health and the Institute for Breathing and Sleep.
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Thanks also to the administrative and clinical staff of the Victorian Respiratory Support Service, the Department of Respiratory and Sleep Medicine (Austin Health) and the Provincial Respiratory Outreach Program for their assistance. I would like to specifically thank Linda Rautela for her considerable assistance during this research.

I also wish to thank my parents, Margaret and Mark Hannan who have always provided me with incredible support, encouragement, guidance, friendship and love. Thanks also to my extended family and friends, particularly my sisters Claire and Therese, for their love, support and understanding during my PhD.

A final thank you goes to my beautiful family - Danni, Eoin and Harper. Thank you for helping me to keep things in perspective and for continually providing me with enormous amounts of love and enjoyment. It has been a long road, but you have kept my focus on the important things in life, and this has made it fun.
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Appendix A

Glossary of Terms

ABG  Arterial blood gas
ALS/MND  Amyotrophic lateral sclerosis/Motor neuron disease
ALSFRS-R  Amyotrophic lateral sclerosis Functional Rating Scale (Revised)
AQoL-8D  Assessment of Quality of Life - Eight Dimension
BMI  Body mass index
CI  Confidence interval
cmH\textsubscript{2}O  Centimetres of water
COPD  Chronic obstructive pulmonary disease
CPAP  Continuous positive airway pressure
DMD  Duchenne muscular dystrophy
EEG  Electroencephalography
EMG  Electromyography
EOG  Electrooculography
EPAP  Expiratory positive airway pressure
EQ\textsuperscript{-5D-5L}  EuroQoL - Five Dimension (Five Level version)
ESS  Epworth Sleepiness Scale
FEV\textsubscript{1}  Forced expiratory volume (one second)
FSS  Fatigue Severity Scale
FVC  Forced vital capacity
GDP  Gross domestic product
GP  General practitioner
HMV  Home mechanical ventilation
HRQoL  Health-related quality of life
IMV  Invasive mechanical ventilation
IPAP  Inspiratory positive airway pressure
LVR  Lung volume recruitment
MBDS  Modified Borg Dyspnea Scale
MEP  Maximum expiratory pressure
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIP</td>
<td>Maximum inspiratory pressure</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimetres of mercury</td>
</tr>
<tr>
<td>MND</td>
<td>Motor neuron disease</td>
</tr>
<tr>
<td>NIPPV</td>
<td>Non-invasive positive pressure ventilation</td>
</tr>
<tr>
<td>NMD</td>
<td>Neuromuscular disorder</td>
</tr>
<tr>
<td>NREM</td>
<td>Non-rapid eye movement sleep</td>
</tr>
<tr>
<td>ODI</td>
<td>Oxygen desaturation index</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OHS</td>
<td>Obesity hypoventilation syndrome</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>PaCO$_2$</td>
<td>Partial pressure (arterial) of carbon dioxide</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>Partial pressure (arterial) of oxygen</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>PEEPe</td>
<td>Extrinsic positive end-expiratory pressure</td>
</tr>
<tr>
<td>PEEPi</td>
<td>Intrinsic positive end-expiratory pressure</td>
</tr>
<tr>
<td>PROP</td>
<td>Provincial Respiratory Outreach Program</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
</tr>
<tr>
<td>PtcCO$_2$</td>
<td>Partial pressure (transcutaneous) of carbon dioxide</td>
</tr>
<tr>
<td>PTP$_{dia}$</td>
<td>Pressure time product of the diaphragm</td>
</tr>
<tr>
<td>PVA</td>
<td>Patient-ventilator asynchrony</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement sleep</td>
</tr>
<tr>
<td>RTD</td>
<td>Restrictive thoracic disorder</td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>Oxygen saturation (arterial)</td>
</tr>
<tr>
<td>SpO$_2$</td>
<td>Oxygen saturation (peripheral)</td>
</tr>
<tr>
<td>SNIP</td>
<td>Sniff nasal inspiratory pressure</td>
</tr>
<tr>
<td>SRI</td>
<td>Severe Respiratory Insufficiency Questionnaire</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow wave sleep</td>
</tr>
<tr>
<td>TIL</td>
<td>Technology for Independent Living</td>
</tr>
<tr>
<td>TST</td>
<td>Total sleep time</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>VRSS</td>
<td>Victorian Respiratory Support Service</td>
</tr>
<tr>
<td>VWU</td>
<td>Ventilation Weaning Unit</td>
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</tbody>
</table>
Section 1 – Introduction

Chapter 1 – Thesis Overview

1.1 Problem Statement

Home mechanical ventilation (HMV) is an assistive technology used to treat individuals with chronic respiratory failure. HMV allows individuals to return to the community who previously might have required institutional care or have died. It provides symptomatic benefits, (Hannan, Dominelli, Chen, Reid, & Road, 2014) and can also prolong survival. (Bourke et al., 2006; Köhnlein et al., 2014; McEvoy et al., 2009) By design, HMV requires an interaction between the individual and the technology that is made difficult by the complexity of both the technology and the underlying disease process. The effective implementation of HMV therefore involves not simply the provision of a device for each user, but also requires clinical expertise and ongoing support in some form to maximise the possibility of successful management in the community.

For a number of possible reasons, the methods employed by HMV providers appear to differ, with a variety of care practices often performed routinely in the absence of objective evidence of benefit. There is also an apparent lack of expert consensus in the value of many of these methods. In combination these limit the ability to evaluate the quality of care for HMV users. Ineffective therapy or poor adherence can result in increased morbidity and mortality in individuals with chronic respiratory failure. (Aboussouan, Khan, Banerjee, Arroliga, & Mitsumoto, 2001; Bourke, Bullock, Williams, Shaw, & Gibson, 2003; Kleopa, Sherman, Neal, Romano, & Heiman-Patterson, 1999) However, many of the strategies employed with the intention of improving both adherence and effectiveness occur at considerable cost, and few have been subjected to scrutiny in controlled clinical trials. The costs of these strategies are
therefore incurred without an understanding of their benefits and in addition to the high cost of devices and consumables that are required for HMV. If particular measures are successful, they may lead to improvements in health and prolong survival within populations of individuals receiving assisted ventilation. On the other hand, if they do not have a positive effect, the resources allocated to them would be better redirected to other more beneficial strategies. Objective evaluation of these techniques is vital in order to ensure the sustainability of HMV services within a constrained health budget.

International comparisons can provide a broader perspective for clinicians, researchers and policy makers. Canada and Australia share a number of similarities in their healthcare systems, economies and demographics. (Thomson, Osborn, Squires, & Jun, 2012) This would suggest that comparisons between HMV providers from these countries might be reasonable. Contrasting practice in these two similarly resourced countries will allow discordant approaches to be evaluated further.

Controlled trials involving HMV are made difficult due to some uncertainty regarding the importance of certain physiological markers of success. Identifying and including appropriate non-physiological outcomes, particularly subjective measures and health-related quality of life (HRQoL), may assist in ensuring important treatment effects are not missed if they are present.

HMV providers from Australia have demonstrated a preference for the routine use of polysomnography (PSG) in the implementation of HMV. (Garner et al., 2013) This is one of a number of care practices that appears to vary between HMV providers internationally. While there are theoretical benefits to such an approach, the use of PSG for this purpose has not been subjected to controlled clinical trials. This represents a significant gap in the knowledge required to ensure safe and effective provision of HMV. In the absence of both a robust evidence base and international consensus in this field, appropriate benchmarks to measure quality of care for HMV users will remain unknown.
1.2 **Aim**

Thus, the aim of this thesis is to determine if the routine application of PSG to titrate non-invasive positive pressure ventilation represents an intervention that should be utilised by HMV providers that aspire to deliver high quality care.

1.3 **Overview**

In order to achieve this aim, Chapter Two provides a background discussion of the evidence and rationale for HMV, following which, details of the technical aspects of HMV and non-invasive positive pressure ventilation (NIPPV) are described in Chapter Three. Chapter Four provides an outline of the literature and rationale for different titration strategies for new users of NIPPV, including a discussion of patient-ventilator asynchrony. Chapter Five subsequently describes the evidence for the clinical structures and organisation used by HMV providers to support users. Also included is commentary regarding the current challenges of measuring quality of care for users of HMV. Subsequent to this, Chapter Six includes a comparison of Canadian and Australian healthcare systems, economies and demographics, in order to provide context for the subsequent examination of HMV providers from these countries. A qualitative comparison of two HMV providers from Australia and Canada follows at the conclusion of Chapter Six before quantitative results from a cross-sectional survey of HMV users from both sites are presented in Chapter Seven. This analysis enables an exploration of how differences in practice may have arisen and also generates hypotheses regarding the influence that the approach to care may have on HRQoL for individuals receiving assisted ventilation. Data from separate analyses is then presented in Chapter Eight, both intended to
identify appropriate subjective measures to include in longitudinal studies of individuals using HMV. The first of these is a systematic review evaluating patient-reported outcomes from longitudinal studies in new users of NIPPV. The second is an analysis of responses from current HMV users to two generic preference-based HRQoL instruments. Following these results, Chapter Nine details the methods and results of a randomised controlled trial comparing the routine use of PSG to titrate NIPPV with clinical titration alone. This study aims to determine if the use of PSG influences patient-ventilator synchronisation, sleep disruption and quality, adherence to therapy, gas exchange, symptoms and HRQoL in new users of NIPPV. Further discussion is provided in Chapter Ten with conclusions addressing the aim stated in this introduction.
Section 2 – Background

Chapter 2 - Home Mechanical Ventilation

2.1 INTRODUCTION

Breathing is a unique, essential and continuous behaviour in mammals, constantly adapting to changes in environmental and behavioural conditions in order to maintain blood gas homeostasis. (McKay, Atalla, & Morrell, 2010) Ventilatory (or breathing) failure is said to occur when the lungs fail to prevent carbon dioxide (CO₂) retention. (West, 2013) A variety of factors due to different pathological processes can interfere with ventilatory control and cause ventilatory failure. (Calverley, 2005) These include abnormalities in central drive, impaired gas mixing, mechanical inequalities, changes in respiratory muscles and excessive mechanical loading (see Figure 1). (Calverley, 2005) Frequently, multiple mechanisms contribute to the development of ventilatory failure in a given individual.

Mechanical ventilation can alleviate ventilatory failure both by resting respiratory muscles and improving alveolar ventilation, although for long-term therapy it remains uncertain which of these should be the primary physiological goal. For home mechanical ventilation (HMV), multiple clinical and physiological goals have been proposed. (Mehta & Hill, 2001) This may be a result of the heterogeneous population that is treated with this therapy. The care practices and interventions used by HMV providers to support individuals receiving assisted ventilation also appear heterogeneous.

The aim of this chapter is to discuss both the physiological and clinical rationale for mechanical ventilation and provide a commentary of the goals of long-term HMV and how providers attempt to achieve them.
2.2 **What is Mechanical Ventilation?**

Andreas Wesele Vasalius documented the first known attempt at assisted ventilation in 1555 which was reported to involve the use of a tube of reed or cane inserted into the trachea through which the proceduralist could blow to cause the “animal to take in air”. (Gali & Goyal, 2003) Through considerable technological advancements over time, assisted ventilation has not only become more sophisticated, but also become both safe and cost effective for long-term use outside of the hospital setting. During the polio epidemic of the 1950s both negative and positive pressure ventilation were used, (Gali & Goyal, 2003) however an increasing realisation that positive pressure techniques were less cumbersome and generally more liberating for users, has reduced the use of negative pressure techniques considerably. (Bach, Alba, Bohatiuk, Saporito, & Lee, 1987)

Positive pressure ventilation aims to support or manipulate pulmonary gas exchange, increase lung volume and decrease work of breathing. (Slutsky, 1993) The technique involves the delivery of air from the device to the airway at a
pressure that is greater than airway pressure. This produces a tidal volume (or breath) as air moves down a pressure gradient. During this inspiratory phase, lung volume increases and airway pressure also increases (the manner in which this occurs is determined by the compliance or distensibility of the respiratory system – which includes both the lungs and the chest-wall – and airway resistance) until inspiratory flow reduces, eventually to zero. As the device switches (or cycles) to its expiratory pressure level, expiratory flow occurs (from airway to device), again down a pressure gradient contributed to by the elastic properties of both the lungs and chest-wall, until the gradient between airway pressure and device pressure returns to zero. At this point the cycle can begin again.

In Chapter Three, there will be a discussion regarding the different interfaces (both invasive and non-invasive) used to deliver mechanical ventilation in the domiciliary setting. In the current section, and in all other parts of this thesis, all references to HMV will specifically relate to the use of non-invasive positive pressure ventilation (or NIPPV) unless specifically referred to as invasive mechanical ventilation (IMV).

2.3 **Physiological and Clinical Rationale for HMV**

Our understanding of the mechanism of action of long-term NIPPV in both stabilising and improving ventilation comes predominantly from studies in those with acute ventilatory failure. Most of these have focused on the efficacy of NIPPV in resting respiratory muscles. (Mehta & Hill, 2001) Carrey et al found that NIPPV reduced the diaphragmatic EMG signal in patients with either restrictive or obstructive ventilatory defects. (Carrey, Gottfried, & Levy, 1990) Diaphragmatic pressure swings have been shown to be reduced with NIPPV in obese subjects and in those with COPD suggesting an unloading of inspiratory muscles. (Appendini et al., 1994; Pankow et al., 1997) In individuals with COPD,
NIPPV is thought to both augment tidal volume for a given inspiratory effort (due to a driving pressure – so-called pressure support – delivered during the inspiratory phase) but also to reduce inspiratory work by applying a positive pressure throughout expiration (Figure 2). This application of extrinsic positive end-expiratory pressure (PEEPe) may act to counterbalance the presence of intrinsic positive end-expiratory pressure (PEEPi) if it is present. PEEPi, which may be present due to an elevated end-expiratory lung volume (dynamic hyperinflation) in individuals with COPD, imposes a threshold load on the inspiratory muscles which must be overcome before inspiratory flow can occur. (Tobin & Lodato, 1989)

![Figure 2 - Schematic of mask pressure trace demonstrating the inspiratory and expiratory phases of a positive-pressure ventilator 'breath'. IPAP=inspiratory positive airway, EPAP=expiratory positive airway pressure, PEEP=(extrinsic) positive end-expiratory pressure](image)

In addition to unloading the respiratory muscles, NIPPV augments alveolar ventilation, as demonstrated by the prompt improvements in PaCO₂.
following the commencement of this treatment in the acute setting. (Celikel, Sungur, Ceyhan, & Karakurt, 1998; Elliott, Steven, Phillips, & Branthwaite, 1990) Similar improvements in PaCO$_2$ have been demonstrated after the commencement of NIPPV in HMV cohorts. (Windisch, 2008) It is possible that NIPPV also produces an improvement in ventilation/perfusion ratio or shunt for certain individuals, (Mehta & Hill, 2001) through the application of PEEPe although how often this mechanism applies in long-term users is uncertain.

Many long-term users of NIPPV only use this therapy during sleep. Therapy for as little as four to six hours is not only able to stabilise gas exchange overnight but is also able to produce a stabilisation or improvement in daytime PaCO$_2$. (Annane et al., 1999; Nickol et al., 2005) This is felt to be predominantly due to a re-setting of chemosensitivity through a reduction in the accumulation of bicarbonate, although other theories such as the resting of fatigued respiratory muscles overnight or the resolution of microatelectasis have also been proposed. (Mehta & Hill, 2001)

Chronic ventilatory failure can result from a number of disorders. At its most basic level, this problem arises either due to an imbalance between the capacity of the respiratory system (the adequacy of the diaphragm and other muscles of respiration) and the magnitude of the load imposed on the system (reduced compliance of the lungs or chest-wall) or to an abnormality in the drive to breathe – or both (see Figure 1). An understanding of the mechanisms and mechanics that are contributing to ventilatory failure may, on an individual level, allow tailoring of NIPPV therapy to best overcome these mechanical impediments to ventilation. Both anecdotal evidence and limited published data suggest there are considerable differences in the benefits obtained from long-term NIPPV both between and within groups of disorders that all can result in ventilatory failure. (Bourke et al., 2006, 2003; Hannan et al., 2014; Köhnlein et al., 2014; McEvoy et al., 2009) This is likely to be an important driver of differences in practice between HMV providers.
2.4 DISORDERS ASSOCIATED WITH VENTILATORY FAILURE

2.4.1 Primary disorders of ventilatory control

This is a group of disorders characterised by primary abnormalities in ventilatory control leading to hypoventilation and central apnoea during sleep. (Piper, 2010) Individuals with the congenital form (known as congenital central alveolar hypoventilation syndrome) typically present in childhood and demonstrate little or no ventilatory sensitivity to CO$_2$ or hypoxia during sleep. (Piper, 2010) This produces severe nocturnal hypoventilation.

Evidence for the benefits of HMV (including IMV) for this group comes predominantly from case reports and case series. (Ellis, McCauley, Mellis, & Sullivan, 1987; Weese-Mayer et al., 1992) Even with HMV, early mortality is frequent in these conditions. (Weese-Mayer et al., 1992) While many can be managed with nocturnal support only, others require assisted ventilation when awake as well. (Weese-Mayer et al., 1992) Hypoventilation due to abnormal ventilatory control can also be acquired following neurologic insults affecting the brainstem or in those using opioids. (Piper, 2010)

2.4.2 Chronic obstructive pulmonary disease

The mechanisms leading to daytime hypercapnia in those with chronic obstructive pulmonary disease (COPD) are varied and appear to differ between individuals. Three broad groups of individuals with COPD who demonstrate abnormal gas exchange during sleep have been described: those with isolated nocturnal desaturations but with preserved daytime oxygenation; those with sleep hypoventilation in association with daytime hypercapnia; and, those with co-existent COPD and OSA (known as the overlap syndrome). (Piper, 2010)
Those with isolated nocturnal desaturations typically demonstrate these events predominantly during REM sleep and they are thought to occur due to a loss of accessory muscle tone during REM sleep in the presence of a mechanically disadvantaged diaphragm, (White, Drinnan, Smithson, Griffiths, & Gibson, 1995) although worsening ventilation-perfusion matching has also been implicated. (Mulloy & McNicholas, 1996) Those who demonstrate sleep hypoventilation and daytime respiratory failure can do so in the absence of morbid obesity or obstructive sleep apnoea, although BMI and indices of upper airway resistance are associated with its presence. (O’Donoghue et al., 2003) Those with COPD and overt OSA tend to develop hypercapnia with milder degrees of impairment in lung function, and also appear to be more predisposed to the development of pulmonary hypertension. (Chaouat et al., 1995) In addition to mechanical breathing abnormalities during sleep, alterations in chemosensitivity to CO₂ have also been suggested as contributors, (Piper, 2010) although it is uncertain whether these abnormalities represent cause or effect in these individuals. (Calverley, 2005)

The role of NIPPV for individuals with COPD remains unclear despite numerous studies attempting to address this question. The two most recent randomised controlled trials (RCTs) published have both demonstrated an improved survival with the addition of NIPPV to standard treatment in stable hypercapnic individuals with COPD. (Köhnlein et al., 2014; McEvoy et al., 2009) It should be noted that the study by McEvoy et al only demonstrated a survival advantage after adjustment for baseline measures of PaO₂, PaCO₂ and HRQoL – with the unadjusted survival hazard ratio not reaching statistical significance – and that some measures of HRQoL were actually worse in the group treated with NIPPV. (McEvoy et al., 2009) In the report by Köhnlein et al, a much larger survival advantage was demonstrated with NIPPV therapy that was implemented using comparatively high pressure settings (“high-intensity NIPPV”) in order to maximally increase alveolar ventilation. This study may have included individuals with comorbid OSA – as this disorder was not specifically evaluated.
for. This may have contributed to the higher than expected mortality in the control group. (Köhnlein et al., 2014; McEvoy et al., 2009) Although the authors reported positive results for HRQoL outcomes, these conclusions are less robust as a large proportion of participants did not complete these assessments. (Köhnlein et al., 2014) Other investigators have demonstrated a lack of effect of high-intensity NIPPV in reducing hospital admissions in those with persistent hypercapnia following exacerbations of COPD. (Struik, Sprooten, et al., 2014)

To date, there have been four systematic reviews and a further review of RCTs examining the role of NIPPV for individuals with hypercapnic COPD. (Chen et al., 2011; COPD Working Group, 2012; Kolodziej, Jensen, Rowe, & Sin, 2007; Struik, Duiverman, Bladder, & Wijkstra, 2008; Struik, Lacasse, Goldstein, Kerstjens, & Wijkstra, 2014) The methods used and the conclusions reached from these reviews have been mixed. One concluded that there is no effect of NIPPV therapy for the outcomes of mortality, lung function (FEV1), exercise tolerance or hospitalisations for individuals with stable hypercapnic respiratory failure secondary to COPD. (COPD Working Group, 2012) Others have suggested that there are modest benefits on gas exchange, (Chen et al., 2011) symptoms and HRQoL. (Kolodziej et al., 2007) The more recent review by Struik et al suggested a possible benefit in subgroups with very high baseline PaCO2 (55mmHg), those who utilised NIPPV with high inspiratory pressures (≥18cmH2O) and those who achieved more than 5 hours of use on average per night. (Struik, Lacasse, et al., 2014) These benefits were not seen in the overall populations included in the meta-analyses and benefits within these subgroups were limited to PaCO2 levels at 3 months. In addition, no longer-term influence on gas exchange, lung function or HRQoL could be identified. (Struik, Lacasse, et al., 2014)

The evidence supporting the use of NIPPV for individuals with COPD and daytime hypercapnia is therefore mixed and, presumably as a consequence, there is considerable regional variation in the use of NIPPV for this group. (Chu et al.,
2004; Garner et al., 2013; Lloyd-Owen et al., 2005) It appears likely that there are subgroups of individuals with COPD who can benefit from positive pressure therapy in some form,(Marin, Soriano, Carrizo, Boldova, & Celli, 2010; Struik et al., 2008; Struik, Lacasse, et al., 2014) however until these can be reliably identified, a consensus on whether this group should be offered long-term NIPPV is unlikely to be reached.

2.4.3 Neuromuscular disorders

The label of neuromuscular disorder (NMD) incorporates a broad and heterogeneous group of conditions that can produce ventilatory failure through a variety of mechanisms. The group includes conditions as varied as motor neuron disease (amyotrophic lateral sclerosis), Duchenne muscular dystrophy, and spinal cord injury as well as acquired and inherited myopathies and neuropathies. The grouping of these conditions in studies examining HMV is problematic but often necessitated due to the small numbers that each of these rarer conditions tend to contribute to clinical cohorts.(Windisch, 2008)

Those with NMD present with varying degrees and patterns of respiratory muscle involvement and often with differing ancillary features such as underlying lung disease, obesity, upper airway dysfunction or skeletal abnormalities.(Piper, 2002) The severity of respiratory muscle dysfunction (particularly of the diaphragm) is variable within and between these disorders and may be relevant clinically in determining the degree of dependence on assisted ventilation. The development of changes within the chest-wall or spine may add to mechanical disadvantage and therefore increase the load to which the weakened respiratory muscles are subjected.(Piper, 2010) Other potential contributors to ventilatory failure in this group include abnormalities of ventilatory control. These may be a primary consequence of the underlying neurological disorder or may occur secondarily due to bicarbonate retention.(Piper, 2010) Upper airway instability is
also seen in association with a number of these conditions and may be due to weakness or instability of the pharyngeal muscles or other disease-related changes to the resistance of the upper airway. (Berlowitz, Brown, Campbell, & Pierce, 2005)

Previous systematic reviews have evaluated the role of mechanical ventilation for individuals with NMD and specifically for motor neuron disease (MND; amyotrophic lateral sclerosis). A Cochrane systematic review reported by Annane et al examined the role of nocturnal mechanical ventilation for chronic hypoventilation in individuals with neuromuscular (and chest-wall) disorders. (Annane, Orlikowski, & Chevret, 2014) The review included ten studies, four of which were (short-term) crossover studies. The authors concluded that there was weak but consistent evidence to suggest NIPPV relieves symptoms of chronic hypoventilation in the short-term. They also concluded that NIPPV therapy led to prolonged survival mainly in users with MND. This review did not evaluate non-randomised studies and did not examine HRQoL. Another Cochrane systematic review reported by Radunovic et al examined the role of mechanical ventilation for individuals with MND. (Radunovic, Annane, Rafiq, & Mustfa, 2013) Their conclusions were based on the results of a single RCT. (Bourke et al., 2006) They concluded that NIPPV significantly prolongs survival and improves or maintains quality of life in people with MND. (Radunovic et al., 2013) Observational data also support the contention that NIPPV prolongs life in other progressive NMD such as Duchenne muscular dystrophy. (Bach & Martinez, 2011; Ishikawa et al., 2011; Toussaint, Chatwin, & Soudon, 2007) This is despite apparent harm from the use of NIPPV in normocapnic individuals with Duchenne muscular dystrophy described in an earlier RCT. (Raphael, Chevret, Chastang, & Bouvet, 1994)

Unfortunately, these systematic reviews and observational data provide fairly limited information on the role and potential benefits of NIPPV for individuals with NMD. They confirm the survival benefit of NIPPV for
individuals with MND and provide some support for short-term benefits on “daytime hypoventilation-related clinical symptoms” in individuals with other NMD. There is only limited information regarding the impact of NIPPV on subjective outcomes and HRQoL which may be perceived by users to be more important than survival or physiological endpoints. (Guyatt, G H, Cook, 1994)

2.4.4 Restrictive thoracic disorders

Restrictive thoracic disorders (RTD) include both congenital and acquired conditions that increase the rigidity of the thoracic cage. Ventilatory failure from these conditions is primarily attributable to the reduced compliance of the respiratory system and particularly the reduction in chest-wall compliance. (Calverley, 2005; Nickol et al., 2005) Additionally, abnormalities in chest-wall mechanics can alter the normal activity of respiratory muscles, reducing their efficiency and producing uncoordinated chest-wall movements that may alter V/Q distribution. (Piper, 2010) Changes in ventilatory control may also occur however the improvements demonstrated in daytime PaCO₂ following the commencement of nocturnal assisted ventilation suggest these problems are secondary and are ameliorated through the re-setting of chemoreceptors with improved nocturnal ventilation. (Calverley, 2005)

Studies evaluating individuals with RTD were included in the previously mentioned systematic review reported by Annane et al. (Annane et al., 2014) No long-term RCTs have been performed in this area, however benefits on some daytime symptoms have been reported with the use of NIPPV. (Nauffal et al., 2002) Data from non-randomised studies and case reports also supports the effect of NIPPV on improving PaCO₂ in individuals with RTD. (Ellis, Grunstein, Chan, Bye, & Sullivan, 1988; Zaccaria et al., 1995) Study quality in this area is generally poor and the evidence is therefore less clear regarding how subjective measures and HRQoL might be influenced by NIPPV.
2.4.5 Obesity hypoventilation syndrome

The obesity hypoventilation syndrome (OHS) is characterised by the presence of morbid obesity in combination with daytime hypercapnia, in the absence of other conditions that may produce hypercapnia. (Piper, 2011) Severe obesity is felt to be the primary abnormality predisposing to this condition. Obesity places an increased load on the respiratory system through alterations in chest-wall compliance and lung volumes. (Piper, 2010) In addition to this imposed load, the majority of those with the OHS will also demonstrate upper airway obstruction during sleep that further increases load and results in varying degrees of apnoea, periods of partial airway obstruction with hypoventilation, and periods of central hypoventilation. (Piper, 2010) Abnormalities in ventilatory control have been demonstrated during wakefulness in these individuals and some of these may be partially reversible with correction of sleep disordered breathing. (Chouri-Pontarollo et al., 2007) Neurohormonal abnormalities are also likely contributors to this condition, with elevated leptin associated with hypercapnia in obese individuals, (Phipps, Starritt, Caterson, & Grunstein, 2002) although a causative role has not been definitely demonstrated. (Malli, Papaioannou, Gourgoulianis, & Daniil, 2010)

The data supporting the use of NIPPV for individuals with OHS is not as strong as one would expect given the widespread use of long-term NIPPV for this indication. (Garner et al., 2013) Sham studies have generally not been performed and instead active controls (such as continuous positive airway pressure (CPAP)) have been used as comparators to NIPPV. (Masa et al., 2015; Piper, Wang, Yee, Barnes, & Grunstein, 2008) The study by Piper et al, which excluded individuals with severe hypoxaemia or hypercapnia on CPAP therapy, did not demonstrate a difference in daytime PaCO₂ at 3-months between CPAP and NIPPV, and there was no difference in treatment adherence. It is possible the exclusion criteria
used could have blunted evidence of benefit with NIPPV. Despite this, subjective sleep quality (using the PSQI) and psychomotor vigilance improved more in the NIPPV group compared to CPAP however there was no difference in daytime sleepiness (using the Epworth Sleepiness Score (ESS)). Masa et al demonstrated improvements in daytime PaCO$_2$ for both NIPPV and CPAP in comparison to lifestyle measures over two months.(Masa et al., 2015) Both CPAP and NIPPV were superior to control in improving symptoms (somnolence, headache, nocturia, morning confusion). There were between group differences for the CPAP and NIPPV arms (FVC% and 6-minute walk distance) however the differences were minor and only significant after adjustment for baseline values, age, gender, BMI and AHI.(Masa et al., 2015) An earlier study in individuals with mild OHS compared NIPPV with “lifestyle modifications”.(Borel et al., 2012) After one month of NIPPV there was a greater reduction in daytime PaCO$_2$, AHI and severity of overnight disturbances in SpO$_2$ in the NIPPV group compared with controls, however there was no significant difference in daytime somnolence (according to the ESS).(Borel et al., 2012) Despite these findings, NIPPV appears to be commonly prescribed for unselected populations with OHS.(Garner et al., 2013) The published evidence supports the suggestion that a considerable proportion of individuals with OHS can obtain equivalent benefits from CPAP however.(McKim et al., 2011)

### 2.5 Prevalence of Disorders Within HMV Cohorts

Previous publications have described the prevalence disorders within HMV cohorts across a number of regions (summarised in Table 1).(Chu et al., 2004; Farré et al., 2005; Garner et al., 2013; Hannan et al., 2016) Most notable is the considerable variation in the use of HMV for individuals with COPD and OHS.(Garner et al., 2013; Lloyd-Owen et al., 2005) This may be a reflection of differing philosophical approaches to the role of NIPPV. Anecdotally, this variation in practice is not isolated to patient-selection.
Table 1 - Comparison of populations according to underlying diagnosis* within home mechanical ventilation populations from published reports

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Australia</th>
<th>New Zealand</th>
<th>Europe</th>
<th>Hong Kong</th>
<th>Canada</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td>10%</td>
<td>1%</td>
<td>34%</td>
<td>57%</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>RTD</td>
<td></td>
<td>11%</td>
<td>5%</td>
<td>31%</td>
<td>19%</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>OHS</td>
<td></td>
<td>26%</td>
<td>54%</td>
<td>4%</td>
<td>8%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>NMD</td>
<td></td>
<td>33%</td>
<td>20%</td>
<td>35%</td>
<td>12%</td>
<td>76%</td>
<td>35%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>20%</td>
<td>20%</td>
<td>16%</td>
<td>20%</td>
<td>16%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Data from reported prevalence of HMV by underlying disease – diagnostic criteria for underlying conditions may have differed between studies/centres.

2.6 Goals of NIPPV

Although NIPPV appears to be an ideal therapy for individuals with chronic respiratory failure, acceptance of, and adherence to, this treatment is variable. (Bourke et al., 2003; Butz et al., 2003; Clini et al., 2002; Criner, Brennan, Travaline, & Kreimer, 1999; Ghosh, Rzehak, Elliot, & Windisch, 2012; Tsolaki et al., 2011) This would suggest that there are aspects of this therapy that are difficult to tolerate for some users. The task of implementing NIPPV for a new user therefore requires the HMV provider to counterbalance acceptability with the effectiveness of therapy. For example, by accepting what might be considered sub-optimal physiological measures in order to ensure that therapy is tolerated. Such compromises may achieve improved adherence but may negate some of the potential benefits of therapy. Conversely, if the rigid pursuit of physiological targets is preferred, poor adherence or complete intolerance could result.

Even before considering whether such compromises are appropriate, there is an additional complication that arises due to the lack of consensus as to what
the primary physiological goal of NIPPV should be. (Tuggey & Elliott, 2006) This is problematic as depending on the ultimate goal of therapy, vastly different strategies may be appropriate. Some investigators have suggested that a reduction in respiratory muscle work (by unloading the inspiratory muscles) should be the goal, (Fanfulla, Delmastro, Berardinelli, Lupo, & Nava, 2005; Kimura, Takezawa, Nishiwaki, & Shimada, 1991) while others have suggested that increasing alveolar ventilation sufficiently to induce a relative and/or absolute hypocapnia should be the primary aim. (Dreher et al., 2011; Parreira et al., 1996; Windisch et al., 2002)

The implication is that different HMV providers may institute different pressure strategies depending on what their intended goal of therapy is. This is reflected in the previously discussed RCTs involving individuals with COPD. (Köhnlein et al., 2014; McEvoy et al., 2009) The pressures prescribed in the study by McEvoy et al (mean pressure support 7.8 cmH₂O) (McEvoy et al., 2009) were considerably lower than those reported by Köhnlein et al (mean pressure support of 16.8 cmH₂O) (Köhnlein et al., 2014). The procedures in the study by Köhnlein et al also explicitly targeted a reduction in PaCO₂ as part of their therapeutic approach. It is reasonable to hypothesize that these differences in approach could have an impact on clinical outcomes. This has been cited as a reason for the discordant results from these two RCTs, (Köhnlein et al., 2014) although other differences may have contributed. Different pressure strategies among a myriad of other care practices and techniques used by HMV providers could influence the effectiveness of NIPPV and the ability of users to adhere adequately to it.

Similar differences in the approach to titration of NIPPV are present for disease groups other than COPD. Masa et al describe increasing EPAP for individuals with OHS in response to the presence of apnoea during PSG but increasing IPAP in response to hypopnoea, flow limitation, snoring or nonapnoeic hypoventilation. (Masa et al., 2015) In contrast, Howard et al in their randomised
controlled trial of NIPPV versus CPAP in individuals with OHS titrated EPAP in order to “overcome obstructive events... [including] apnoeas or hypopnoeas, snoring or airflow limitation”. (Howard et al., 2017) Those using NIPPV in the study by Masa et al tended to have a lower EPAP (mean 7.8cmH2O versus 11.9cmH2O) and higher IPAP (20cmH2O versus 19.3cmH2O) than those using NIPPV in the study by Howard et al.(Howard et al., 2017; Masa et al., 2015) It appears likely that different approaches to titration contributed to some of these differences in the prescribed pressures for NIPPV.

It appears that the lack of a consensus regarding the primary goal of NIPPV is a contributor to these differences in approach. (Mehta & Hill, 2001) Mehta and Hill outlined short-term and long-term goals of NIPPV therapy (Table 2). This list incorporates many of the components of care that are used by HMV providers. Variations in resourcing, priorities of care and expertise would inevitably lead to the development of different service models.
Table 2 - Short-term and long-term goals of non-invasive positive pressure ventilation and the methods of evaluation that may be used by home mechanical ventilation providers to assess them*

<table>
<thead>
<tr>
<th>Short-term goals of NIPPV</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relieve symptoms</td>
<td>Clinical, subjective measures</td>
</tr>
<tr>
<td>Reduce work of breathing</td>
<td>Clinical, subjective, physiological measures</td>
</tr>
<tr>
<td>Improve or stabilize gas exchange</td>
<td>Physiological measures</td>
</tr>
<tr>
<td>Optimise patient comfort</td>
<td>Clinical, subjective measures</td>
</tr>
<tr>
<td>Good patient-ventilator synchrony</td>
<td>Clinical, physiological measures</td>
</tr>
<tr>
<td>Minimise risk</td>
<td>Clinical</td>
</tr>
<tr>
<td>Avoid intubation</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-term goals of NIPPV</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve sleep duration, quality</td>
<td>Clinical, subjective, physiological measures</td>
</tr>
<tr>
<td>Maximise quality of life</td>
<td>Subjective measures</td>
</tr>
<tr>
<td>Enhance functional status</td>
<td>Clinical</td>
</tr>
<tr>
<td>Prolong survival</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

*Adapted from (Mehta & Hill, 2001)

2.7 **How can HMV Providers Achieve These Goals?**

In pursuit of both short- and long-term goals, HMV providers have developed different care models and instituted an array of routine care practices to support their clients. (Hannan et al., 2014) Centralised HMV providers in various forms have been in existence for more than 40 years and have grown in size as the prevalence of HMV has increased over time. (Baydur et al., 2000; Simonds, 2003) In addition to the size of these services, the complexity of the medical problems managed in the community has also increased. The growth in these services has not been matched by the presence of objective data to support many of the care models and practices that they currently employ. Clinical inertia has meant that in many centres, interventions are applied routinely
despite the potential that they may be unnecessary, excessively burdensome or not cost-effective. Elsewhere, other HMV providers may perform these same interventions infrequently or not at all.

Why is it important to identify which techniques and strategies improve the effectiveness and adherence to HMV and outcomes for individuals receiving assisted ventilation? HMV is a resource intensive therapy. Many of the strategies employed by HMV providers (such as; polysomnography or polygraphy for the titration of settings, 24-hour phone support, home visits, routine airway clearance techniques, inpatient acclimatisation and training) are also associated with considerable expense. At the same time, intolerance and poor adherence to NIPPV are significant problems, with rates of up to 50% described in treatment naïve users of NIPPV. (Aboussouan et al., 2001) Individuals with chronic respiratory failure who are unable to tolerate NIPPV are likely to have increased morbidity and mortality. (Bourke et al., 2006; Butz et al., 2003; Petitjean et al., 2008; Priou et al., 2010) This could even add to costs through increased hospital admissions, poorer health status and reduced productivity. Identifying strategies that can support adherence and maintain the effectiveness of NIPPV therefore represents a significant therapeutic opportunity. On the other hand, redirecting resources away from measures that are not beneficial would also lead to improvements in the quality and cost-effectiveness of care.

2.8 Conclusion

Home mechanical ventilation provides a safe and effective therapeutic option for individuals with chronic ventilatory failure to be managed outside of the hospital setting. Although the primary physiological goal of long-term NIPPV remains debated, it is clear that increases in alveolar ventilation among other potential physiological benefits can result. Achieving physiological benefits alone are probably insufficient for a satisfactory outcome however, and this is
reflected in the multiple clinical and physiological goals previously described. (Mehta & Hill, 2001)

Different priorities of care, combined with heterogeneity of the population that require HMV, contribute to apparent differences in the way that individuals receiving assisted ventilation are supported and monitored. This situation is made more complicated by the technical challenges posed by the interaction between complex devices and abnormal respiratory mechanics. While acknowledging that technical expertise alone is insufficient to successfully establish HMV, an acute understanding of how this technology works is an essential attribute for clinicians in this area. The following chapter addresses the technical considerations and clinical challenges that must be negotiated to establish effective HMV.
Chapter 3 - Technical Considerations and Challenges to Achieving Effective Positive Pressure Ventilation

3.1 INTRODUCTION

Considerable technical expertise is required in order to successfully institute safe and effective NIPPV. The difficulties of negotiating the frequently complex respiratory and upper airway mechanics of the user and the increasingly modifiable parameters of the ventilators represent significant barriers to the success of this therapy. Multiple goals of therapy are described, (Mehta & Hill, 2001) however the relative weighting of these priorities may dictate the way in which NIPPV is implemented.

The aim of this chapter is to describe the technical considerations and clinical challenges required to successfully implement long-term NIPPV. To achieve this aim, there is first a discussion regarding invasive and non-invasive interfaces. A more detailed description of the important attributes of devices designed for long-term use is then provided. Subsequent to this there is a discussion contrasting pressure- and volume-targeted modes of NIPPV before further details regarding the trigger and cycling mechanisms commonly employed in HMV devices.

3.2 INVASIVE AND NON-INVASIVE METHODS

As mentioned previously, unlike negative pressure ventilation methods, positive pressure ventilation requires an interface between the device and the airway of the user. This may be an invasive interface (such as an endotracheal tube or tracheostomy) or a non-invasive interface (such as a mask or mouthpiece). Invasive interfaces have the advantage of the ability to form a closed system between the device and the large airways. This theoretically
reduces unintentional air leaks and provides a degree of airway protection for those with impaired cough or bulbar function. In addition, these interfaces remove the potential for upper airway obstruction to inhibit adequate ventilation. These technical advantages are countered by the need for either a surgical airway (tracheostomy) or an endotracheal tube that passes through the oropharynx. Either approach poses considerable impediments to speech, swallowing and normal mucociliary clearance and therefore long-term IMV is associated with increased complexity of care and possibly an increased frequency of respiratory tract infections. (Finder et al., 2004)

Longitudinal registry data has confirmed a considerable shift away from invasive interfaces in HMV cohorts over time, with an associated exponential increase in the number of users using NIPPV. (Simonds, 2003) The underlying drivers of this shift are likely to include; user preference; clinician preference; increased simplicity of NIPPV for home use; and reduced costs. (Bach, 1993a; Bach, Alba, & Saporito, 1993)

Although direct comparisons between the two methods have not been performed, results from a previous survey-based study of individuals receiving assisted ventilation who had used both methods have been described. (Bach, 1993a) Bach suggested that users prefer NIPPV due to this method being more convenient and having fewer impacts on speech, appearance and comfort. (Bach, 1993a) It was concluded that NIPPV was preferred overall by users. (Bach, 1993a) However, a similar study from a Swedish cohort reached an apparently conflicting conclusion, with those using IMV reporting a small but significantly higher score for perceived health status than those using NIPPV. (Markstrom et al., 2002) Both studies had significant methodological issues – most notably a failure to account for selection and responder bias within their samples. Neither study considered the influence on variables such as socioeconomic status or the adequacy of community supports that could significantly influence the perceived benefits of one approach over another. Conclusions regarding the relative merits
of IMV compared with NIPPV for individual patients are therefore not possible based on these studies – and randomised controlled trials are unlikely to ever be ethically justifiable. When determining the appropriate interface for users of HMV, most clinicians will consider factors such as safety, cost, complexity and comfort. Most individuals receiving assisted ventilation will be able to negotiate these criteria with the use of a non-invasive interface. IMV will therefore generally be reserved for those considered unable to be managed safely with NIPPV,(Lofaso, Orlikowski, & Raphael, 2006) or those already established on this form of therapy and with little prospect of a successful transition to NIPPV.

The following section describes many of the technical aspects of NIPPV and the challenges and difficulties that must be negotiated by HMV providers in order to achieve the short- and long-term goals of HMV discussed previously.

3.3 Interfaces

Despite the potential impact of the interface on important aspects of care such as tolerance to therapy and side-effects, the choice of interface for non-invasive ventilation has received little attention in the literature. As a consequence, there is relatively little evidence regarding the optimal interface for NIPPV.

3.3.1 Mask design

Over time there appears to have been a shift away from the use of nasal masks and towards oro-nasal interfaces for long-term NIPPV. This may be due to improvements in mask design or manufacture which has resulted in a reduced need for customised masks. A 2005 survey of home ventilation practices in Europe reported that a majority of individuals receiving assisted ventilation were
using nasal masks (Lloyd Owens 2005). In contrast, a 2013 survey of home mechanical ventilation in Australia found that an oro-nasal mask was being used by 62% of long-term NIPPV users, with 33% using a nasal interface (Garner et al 2013).

Comparisons between these two options have been performed however the available literature is relatively limited. Studies have generally comprised short-term clinical or physiological assessments, or bench studies. Navalesi et al suggested that nasal masks may produce smaller reductions in PaCO₂ and lower tidal volumes in comparison to oro-nasal masks, however their randomised crossover study was performed in participants who were awake and evaluated after only a 30-minute trial of therapy. (Navalesi & Fanfulla, 2000) This limits the strength of these conclusions when most use NIPPV during sleep. (Navalesi & Fanfulla, 2000) Wilson et al performed a comparison of nasal and oro-nasal masks and found no important clinical differences over consecutive nights apart from the need for the addition of a chinstrap to reduce leak from the mouth in those using nasal masks. (Willson et al., 2004) Fernandez et al performed a prospective observational study comparing nasal with oro-nasal masks for individuals commencing nocturnal NIPPV. (Fernandez et al., 2012) All participants trialled both mask options during both daytime and nocturnal therapy with NIPPV. They demonstrated similar efficacy between nasal and oro-nasal in lowering daytime PaCO₂ and no difference in nocturnal oxygen measures. More participants preferred the nasal masks initially however at three months the proportions using the two mask options were not different. (Fernandez et al., 2012) There were no differences in efficacy (determined by daytime arterial blood gas sampling) or adherence identified at three months. (Fernandez et al., 2012) They concluded that patient choice was a reasonable determinant of the interface for NIPPV. (Fernandez et al., 2012)

While the objective performance of an interface is important, its design and fit must also be acceptable for the user or adherence may suffer. These
studies do not suggest a uniform advantage with either nasal or oro-nasal interfaces. Although there may be individual factors (anatomical, psychological, among others) that may favour a particular mask option,(Schorr, Genta, Gregorio, Danzi-Soares, & Lorenzi-Filho, 2012; Vrijsen, Buyse, Belge, & Testelmans, 2014) individual choice will drive interface selection within most HMV services.(Fernandez et al., 2012)

3.3.2 Customised masks

Customised or semi-customised interfaces were once frequently used with NIPPV.(Schonhofer & Sortor-Leger, 2002) These are constructed with the use of moulds that allow the interface to be shaped to the user’s anatomy. Such interfaces are typically either nasal masks or mouth pieces.(Bach et al., 1987; Nava, Navalesi, & Gregoretti, 2009) With the expansion in the use of CPAP for obstructive sleep apnoea (OSA), a huge array of manufactured or commercial masks and other interfaces have become available for use with NIPPV. This has generally reduced the need for individually customised interfaces, as the majority of users will be able to find an appropriately fitting manufactured mask.

3.3.3 Intentional leak and risks

One of the additional reasons for a shift away from customised masks is that they do not incorporate any so-called intentional leak. This refers to the placement of vents within the mask that utilise the continuous airflow from the device during expiration. This airflow acts to vent expired air from the mask which reduces the re-breathing of carbon dioxide in the expired air.(Schonhofer & Sortor-Leger, 2002) Customised masks without in-built vents instead require the placement of an expiratory valve within the ventilator circuit or a separate
expiratory limb in order to reduce re-breathing. In-built anti-asphyxia valves are also generally absent in customised masks and therefore (primarily with oro-nasal masks) there is a risk of asphyxiation in the event of device malfunction. (Nava et al., 2009) In contrast, manufactured masks typically incorporate vents and anti-asphyxia valves. Aside from this safety issue, there is also evidence that non-vented interfaces do not cope as well in the face of large levels of unintentional leak. Carlucci et al demonstrated in a bench study that the delivered pressures and tidal volumes were lower for non-vented masks than for vented masks when unintentional leak was elevated. (Carlucci, Schreiber, et al., 2013) The level of intentional mask leak may influence ventilator performance in some circumstances – particularly if a mask that is not recommended by the manufacturer is used. Louis et al demonstrated significant differences in ventilator performance in a bench study and an in vivo comparison of recommended and non-recommended NIPPV masks. (Louis, Leroux, Isabey, Fauroux, & Lofaso, 2010) They recommended careful evaluation of ventilator performance when switching between masks with different levels of intentional leak. (Louis et al., 2010)

3.3.4 Unintentional leak

NIPPV interfaces are required to form a firm seal on the face of the user in order to ensure unintentional leak is minimised. This ensures that the positive pressure produced by the device is delivered to the upper airway of the user. Despite improvements in mask design, unintentional leak from around the mask or through the mouth is a frequently observed problem. It poses a considerable impediment to the delivery of effective NIPPV. At excessive levels it has been shown to interfere with sleep quality, (Bach, Robert, Leger, & Langevin, 1995; Meyer et al., 1997; Teschler, Stampa, Ragette, Konietzko, & Berthon-Jones, 1999) comfort, and ventilation. (Rabec et al., 2011; Teschler et al., 1999; Vignaux et al.,
Excessive unintentional leak can limit the acceptability of NIPPV. (Rabec et al., 2011) Ventilation may be compromised due to excessive leak limiting the ability of the device to detect inspiratory flow from the user, which is the parameter that most devices measure to detect inspiratory effort. (Carteaux et al., 2012) In addition, due to the loss of an adequate seal, the pressure delivered to the upper airway may be less than desired. The ability of devices to compensate for the presence of high levels of unintentional leak varies. (Carteaux et al., 2012) An understanding of the leak tolerance of a given device is important to ensure adequate performance in the face of excessive unintentional leak. (Carteaux et al., 2012; Oto, Chenelle, Marchese, & Kacmarek, 2013) Whether consistently high levels of unintentional leak produce demonstrable adverse clinical outcomes in long-term NIPPV users is unclear. (Alvarez et al., 2013) Aggressive attempts to minimise unintentional leak (through mask adjustments, tightening, addition of chinstraps) could even reduce the acceptability of NIPPV. In particular, iatrogenic damage to skin (particularly over the nasal bridge) from ill-fitting masks in an attempt to reduce leak, could itself produce adverse clinical outcomes due to the need to stop therapy in order to allow healing. (Mehta & Hill, 2001)

3.4 Humidification

The airway epithelium is susceptible to excessive drying from the cool, dry airflow from NIPPV devices and therefore humidification is generally used to avoid this. Humidification can ameliorate the increase in nasal resistance that can occur in the presence of mouth leak for users of nasal masks. (Richards, Cistulu, Ungar, Berthon-Jones, & Sullivan, 1996; Tuggey, Delmastro, & Elliott, 2007) Most long-term users of NIPPV use heated humidification, with many devices incorporating in-built humidifiers. Heat and moisture exchangers are an alternative, however in a randomised crossover study, Nava et al reported more (minor) side effects with these and strong preference amongst participants to
continue heated humidification at the conclusion of the study. (Nava et al., 2008)

Individual adjustment of heated humidification is usually required, again depending on the preference of the user as well as factors such as ambient room temperature. Avoiding excessive condensation within the mask and tubing may be important as this can precipitate ventilator malfunction by producing aberrant flow signals within the ventilator circuit. (Hannan, Rautela, Wilson, Berlowitz, & Howard, 2015)

3.5 NIPPV Devices

While there may be clinical factors that influence the choice of NIPPV device, it is reasonable to suggest price is probably a major driver within publically funded HMV services. Other non-financial considerations include the performance, functionality, reliability, portability, and acceptability of these devices.

3.5.1 Performance

Few studies have compared the performance of NIPPV devices for long-term use, although comparison bench studies have been described. (Battisti et al., 2005; Oto et al., 2013; Storre, Bohm, Dreher, & Windisch, 2009) These have predominantly shown that performance does vary between devices with regard to triggering (moving from expiratory pressure to inspiratory pressure) and cycling (moving from inspiratory pressure back to expiratory pressure), as well as the ability to compensate for excessive unintentional leak. (Storre et al., 2009) Whether these performance characteristics influence outcomes for long-term users of NIPPV is unknown.
3.5.2 Functionality

Clinician preference probably drives this aspect of NIPPV although users may report a preference for certain technologies or functions. Modern NIPPV devices often incorporate technology such as the ability to auto-titrate settings, (Jaye, Chatwin, Dayer, Morrell, & Simonds, 2009; Kelly et al., 2014) or to deliver a guaranteed tidal volume. (Murphy et al., 2012; Storre et al., 2006) Neither function has been demonstrated to have significant clinical advantages over standard fixed pressure devices. (Murphy et al., 2012; Storre et al., 2006) Other functions, such as pre-programmed alternative settings for daytime and nocturnal use, the recording of adherence, leak and other device derived measures, and remote monitoring over the internet are now available on many devices. (Hazenberg, Kerstjens, Prins, Vermeulen, & Wijkstra, 2014) It is unclear if the additional cost associated with these features is justifiable and their place in clinical practice remains to be defined. Some reports have suggested clinical utility, (Rabec et al., 2009; Sandoz, LeBlanc, & McKim, 2014) although the accuracy of the data measured by the devices is variable and therefore must be interpreted with caution. (Contal et al., 2012) The basic features of a device may actually be more important to users – such as the ease with which a device can be switched on or off, the presence of an internal battery and the presence (or absence) of alarms for certain parameters. Portability is often also very important to users, particularly for those that require daytime ventilation. The ability to easily transport or even use a device during transit may also be valued greatly.

3.5.3 Reliability

The reliability of NIPPV devices may be critically important for some users. Mechanical failure does occur and has been suggested to do so more frequently in newer models (those without a long period of post-market use) and
those with greater hours of use. (Chatwin, Heather, Hanak, Polkey, & Simonds, 2010) Regular servicing of devices is required to ensure adequate performance, accurate settings and appropriate alarms are in place. (Chatwin et al., 2010; Farré et al., 2006) Those using NIPPV for prolonged periods during the day (in addition to nocturnal use) should have an additional device to reduce risk in the event of device malfunction. (Chatwin et al., 2010) The need for battery back-up (internal or external) or access to an uninterruptible power source will depend on the specific clinical situation. A thorough assessment of risks for individual users is important in order to prepare for unexpected power failure or device breakdown. (“Brother pays tribute to men who died in Perth storm after power failure cut their breathing machines,” 2014; Simonds, 2006)

3.5.4 Acceptability

Many of the aspects covered above are incorporated into the acceptability of a device. Long-term users of NIPPV can become comfortable and familiar with their device and are frequently resistant to switching to newer alternatives. The acceptability of a NIPPV device primarily relates to its ease of use and how it fits with the user’s capabilities, patterns of behaviour and expectations. These concerns may be completely remote from the actual clinical performance of the ventilator or the specific parameters to which the device is set. Lofaso et al previously reported that users of HMV prioritised new technologies within home ventilators less highly than clinicians. (Lofaso et al., 2014) Issues that appear trivial to clinicians (i.e. aesthetics, noise (both presence or absence), size) may still represent impediments to a successful interaction between this technology and the user.

3.6 Device Settings
NIPPV devices allow a range of parameters to be adjusted in order to tailor therapy to the specific attributes of the user. There is however considerable variation between devices. (Battisti et al., 2005) An additional layer of complexity relates to the lack of consistency between device manufacturers in the terminology used to describe these parameters. Therefore, in the section that follows, device parameters will first be defined, and these definitions will subsequently be used throughout this thesis. For each of the parameters discussed, the theoretical benefits of adjustments will then be described, with an attempt to focus on condition-specific problems that can arise, as well as iatrogenic or ventilator-induced problems.

3.7 Mode

For the purpose of this thesis, device mode will refer to the parameter that the NIPPV device targets during inspiration. There are two predominant modes that are used for long-term NIPPV therapy; pressure (targeted) and volume (targeted).

3.7.1 Volume

In this mode, a desired target tidal volume is chosen and the device then delivers this volume over a given inspiratory time. In order to achieve the targeted volume in the face of potentially abnormal upper airway resistance or deranged respiratory mechanics, the device can adjust its inspiratory pressure. Airway pressures are therefore not constant, but vary according to the static mechanical properties of the respiratory system and the presence of inspiratory muscle activity from the user. The main theoretical advantage of this mode is that it allows the clinician to set a tidal volume targeted to achieve an adequate minute ventilation (when combined with an appropriate respiratory rate). Unfortunately, unintentional leak can limit the effectiveness this mode, as a
proportion of the set tidal volume will be lost in the presence of unintentional leak. This is less well compensated by volume-targeted modes. (Windisch, Storre, Sorichter, & Virchow Jr., 2005) An additional disadvantage is the relative inability of this mode to adjust to changing demands from the user. Attempts by the user to vary the size of the breath delivered (for example in the setting of illness) would be unsuccessful, as the tidal volume delivered is fixed. This mode also has the potential to generate very high mask or airway pressures when high levels of airway resistance or low compliance are present. This is seen commonly in those with upper airway obstruction or restrictive pathology. The resulting high pressures could overcome the ability of the mask to form a seal leading to increased unintentional leak.

3.7.2 Pressure

Now more frequently used, pressure-targeted ventilation delivers a set inspiratory positive airway pressure (IPAP) before returning to a set expiratory positive airway pressure (EPAP) level at the end of inspiration (see Chapter Two, Figure 2). The difference between these two pressures is commonly referred to as pressure support. Airflow is therefore adjusted by the device in order to establish and then maintain a constant IPAP during the inspiratory phase. (Rabec et al., 2011) In contrast to the volume-targeted mode, the delivered tidal volume is not fixed but varies according to the inspiratory time, the user’s own inspiratory muscle activity and the mechanics of the respiratory system. (Rabec et al., 2011) In this mode, a user can increase their minute ventilation in three ways; 1) by increasing their respiratory rate; 2) by applying additional inspiratory effort (thereby increasing respiratory compliance), or; 3) by prolonging their inspiratory time. It is for this reason that pressure-targeted modes are used almost exclusively in the treatment of acute ventilatory failure, and it is possible that this responsiveness may be beneficial in long-term users. The other potential
advantage of this mode is a greater ability to compensate for unintentional leaks. (Rabec et al., 2011) Elevated leak can be detected by the device as a fall in the inspiratory pressure. In response, increasing airflow will restore the desired IPAP and allows this mode to compensate for relatively large levels of unintentional leak. (Storre et al., 2009; Windisch et al., 2005)

3.7.3 Comparisons between Pressure and Volume modes

Comparison studies evaluating the two treatment modes have been limited by problems with study design. In their study, Meecham Jones and Wedzicha compared four nasal NIPPV devices (two volume-targeted, two pressure-targeted) in eight participants, most of whom had obstructive lung disease. They showed no significant difference between devices in gas exchange parameters or visual analogue scales of overall comfort and breathlessness. (Meecham Jones & Wedzicha, 1993) Their conclusions are limited however as all trials were performed during the daytime (not during sleep) and involved only short periods (approximately two hours) of treatment. (Meecham Jones & Wedzicha, 1993) A separate non-randomised crossover study in a mixed cohort with chronic respiratory failure concluded that pressure-targeted ventilation was suitable for the majority of those requiring NIPPV, although a group of ‘non-responders’ (identified as those with higher baseline daytime PaCO₂ and lower nocturnal oxygen levels) should be managed with volume-targeted devices. (Schönhofer, Sonneborn, Haidl, Böhrer, & Köhler, 1997) Investigators in this study used very low levels of EPAP for all participants that may have left some with persistent upper airway obstruction – particularly those with OHS who often have concomitant OSA. (Schönhofer et al., 1997) In direct contrast to the findings of Schönhofer et al, a retrospective study demonstrated that switching to pressure-targeted ventilation was actually effective for subjects with worsening PaCO₂ despite the use of a volume-targeted device. (Smith &
Shneerson, 1997) These conflicting results highlight the potential influence that local expertise and preferences may have on outcomes when evaluating modes of ventilation. Additional studies by Windisch et al and Struik et al also failed to demonstrate a clear advantage with either mode. (Struik et al., 2011; Windisch et al., 2005) Windisch et al demonstrated no difference in gas exchange or sleep quality with either mode, although side-effects were more frequent with volumetargeted devices. (Windisch et al., 2005) Subsequently, Struik et al demonstrated no significant difference in the time required to establish treatment naïve individuals with RTD who were randomly allocated either volume or pressure targeted NIPPV. (Struik et al., 2011) There were also no differences in nocturnal gas exchange measures. (Struik et al., 2011) Despite the absence of a clear advantage between modes, pressure-targeted devices tend to be used more frequently by HMV users. (Lloyd-Owen et al., 2005) Whether this is driven primarily by cost, clinician preference or user preference is uncertain.

Other newer ventilator modes have been developed. These include average volume-assured pressure support (AVAPS™, from Philips Respironics) and intelligent volume-assured pressure support (iVAPS™, from ResMed). Both AVAPS (tidal volume) and iVAPS (“alveolar ventilation target”) are intended to deliver a pre-set minimum tidal volume while essentially providing a pressure-targeted mode. This theoretically provides reassurance that the user will receive a safe minimum level of minute ventilation. In practice, the accuracy of device-derived estimates of minute ventilation is questionable – particularly in the presence of unintentional leaks. (Sogo et al., 2013) This potentially limits the efficacy of these modes in achieving their stated aim of ensuring a target volume of ventilation is achieved. (Lujan et al., 2015) Despite apparent enthusiasm for these devices, clinical benefits have not been demonstrated in comparison studies to date. (Crescimanno, Marrone, & Vianello, 2011; Janssens, Metzger, & Sforza, 2009; Murphy et al., 2012; Storre et al., 2006) Carlucci et al demonstrated that automated changes in IPAP in order to reach a targeted volume could induce sleep disruption. (Carlucci, Fanfulla, Mancini, & Nava, 2012) Janssens et al
reported improvements in ventilation parameters but at the expense of worse sleep quality in individuals with OHS using a volume-assured mode.\cite{Janssens2009} Another study in individuals with predominantly NMD demonstrated the reverse findings, with no difference in sleep quality but worse ventilation parameters (higher peak and average nocturnal PtcCO$_2$).\cite{Jaye2009} Murphy \textit{et al} subsequently demonstrated no clinical benefits with a volume-assured pressure support device in individuals with OHS in comparison with standard fixed pressure NIPPV.\cite{Murphy2012} The justification for any additional costs associated with such devices is therefore questionable.\cite{Crescimanno2011, Janssens2009, Murphy2012, Storre2006}

There are limited data for automatic titration of NIPPV settings using similar device technologies. Murphy \textit{et al} have described a pilot study evaluating auto-titrated NIPPV in stable individuals with COPD and OSA who were already established on therapy.\cite{Murphy2015} They reported that short-term measures of sleep quality and gas exchange were not different after transitioning to auto-titrated NIPPV and that adherence to therapy improved. Pressure support tended to be lower with the auto-titrated device and EPAP tended to be higher.\cite{Murphy2015} Other investigators have suggested a role for automatic titration of treatment naïve individuals.\cite{Kelly2014} Despite these interesting results, the lack of data from controlled clinical trials suggests that the widespread adoption of these methods cannot be supported currently.

3.7.4 Determining pressure settings

As described above, pressure settings (IPAP and EPAP) must be determined by the clinician in order to implement fixed NIPPV.
EPAP is typically set after considering three individual patient factors; 1) the likelihood of upper airway collapse during sleep (obstructive sleep apnoea or OSA); 2) the presence of PEEPi, and; 3) the need for mask venting during expiration to reduce CO$_2$ rebreathing. For individuals with upper airway collapse during sleep, NIPPV provides a pneumatic splint in a similar fashion to CPAP therapy and therefore EPAP can be set at a comparable level. Uncontrolled upper airway obstruction can impair the adequacy of ventilation when using NIPPV,(Rabec et al., 2011) and some investigators have described the use of auto-titrating CPAP devices in order to determine an appropriate EPAP level.(Borel et al., 2012) Such titrations are also performed during PSG or polygraphy or using nocturnal measures of gas exchange alone.(Berry, 2010; Berry et al., 2010; Borel et al., 2012; Janssens, Borel, & Pepin, 2011) Determining an EPAP can also involve consideration of the need to counteract PEEPi, although this may more frequently be a consideration in the acute use of NIPPV; for example during exacerbations of COPD.(Tobin & Lodato, 1989) For individuals without PEEPi or upper airway obstruction during sleep, a low EPAP setting (typically ~4cmH$_2$O) is recommended to ensure adequate mask venting of expired CO$_2$.

The IPAP level is typically set at least 4cmH$_2$O above the EPAP in order to provide a minimum level of pressure support.(Berry, 2010; Mehta & Hill, 2001) It may then be adjusted in order to target desired reductions in PaCO$_2$, improvements in nocturnal oxygenation, or reductions in inspiratory muscle work.(Berry et al., 2010; Borel et al., 2012; Fanfulla et al., 2005; Janssens et al., 2011) Pressure support adjustment may also take into account the tidal volume achieved – which is often estimated using device data. Some authors advocate a tidal volume of 6-8ml/kg using an ideal body weight,(Berry, 2010) while others have reported targeting a higher level of up to 10ml/kg.(Budweiser, Riedl, Jörres, Heinemann, & Pfeifer, 2007)
3.8 Triggering

The delivery of each breath from a NIPPV device involves it switching from the EPAP level to the IPAP level (see Chapter Two, Figure 2). This must be initiated or triggered in some way – either in response to an effort from the user (Spontaneous trigger) or when a pre-set time limit between breaths is reached (Timed trigger).

3.8.1 Spontaneous trigger

A Spontaneous trigger theoretically allows the NIPPV device to coordinate with the inspiratory efforts of the user. Flow triggers are commonly used in modern NIPPV devices. These are triggered when inspiratory effort from the user generates sufficient inspiratory flow to cause volume to accumulate above baseline flow (volume method) or when the inspiratory effort of the user distorts the expiratory flow waveform sufficiently (shape signal method). (Kondili, Prinianakis, & Georgopoulos, 2003) Pressure triggers (where a reduction in mask/circuit pressure due to inspiratory effort triggers the device) were previously utilised in some NIPPV devices although these may be less reliable and associated with greater work of breathing than flow trigger methods. (Kondili et al., 2003)

Modern NIPPV devices frequently allow adjustment of the sensitivity of the Spontaneous trigger in order to customise it to the needs of the user. Sensitivity can be increased by reducing the threshold inspiratory flow required to trigger the device, and vice versa. An insensitive Spontaneous trigger will tend to lead to ineffective efforts, where the device does not detect inspiratory efforts from the user. An overly sensitive Spontaneous trigger will tend to produce auto-triggering or autocycling, where the device is triggered by aberrant or random flow signals that are not due to inspiratory efforts from the user.
The major advantage of a Spontaneous trigger is its ability to adjust to changes in the demands of the user. Theoretically, it allows matching of the device breath rate with the respiratory rate of the user. However, this trigger strategy relies on the presence of both adequate central drive and peripheral muscle strength to generate sufficient inspiratory flow in order to trigger the device. These attributes are frequently not present in all users at all times. Therefore, the use of a Spontaneous trigger alone can lead to a mismatch between the user and the device. (Fanfulla et al., 2005) Other factors can also limit the effectiveness of the Spontaneous trigger. Excessive unintentional leak can result in a failure of the flow sensor to detect inspiratory effort. High levels of PEEPi, respiratory muscle weakness, alterations in central drive or upper airway obstruction can also produce a similar failure.

### 3.8.2 Timed trigger

An alternative trigger strategy is the Timed trigger. From a technological perspective, the Timed trigger is much more simple than the Spontaneous trigger. The clinician simply sets a preferred respiratory rate and this then dictates the interval between ventilator breaths. For example, a Timed trigger set to 12 breaths per minute would mandate that the device moves from EPAP to IPAP every five seconds. With this form of trigger, the device does not respond at all to the presence of inspiratory efforts by the user. The main theoretical advantage of the Timed trigger in comparison to the Spontaneous trigger is that it overcomes the potential for changes in central drive, upper airway obstruction and respiratory muscle function to influence the triggering of the ventilator. The inability to respond to changing demands from the user is a potential problem however, with this trigger strategy providing no capacity to increase or decrease the device respiratory rate in response.
Timed triggers are infrequently used in clinical practice, (Rabec et al., 2011) however are useful when a user has no ability to trigger breaths spontaneously. This situation is more commonly seen in users of IMV.

3.8.3 **Spontaneous/Timed trigger**

Due to the limitations of the two trigger methods described above, long-term NIPPV users are increasingly provided with a hybrid of these triggers – the Spontaneous/Timed trigger. This trigger strategy allows the clinician to choose a Timed trigger that provides a preferred respiratory frequency but also includes the capacity to respond to extra demands from the user through the retention of a Spontaneous trigger. Published reports suggest investigators use this hybrid trigger in different ways depending on whether the Timed trigger is set below or above the users’ own respiratory rate.(Contal, Adler, et al., 2013) A high respiratory frequency may be used in order to suppress spontaneous efforts,(Dreher, Storre, Schmoor, & Windisch, 2010; Windisch, 2008) while a low respiratory frequency would be considered more as a back-up in the event that inspiratory efforts by the user are not detected by the device.(Contal, Adler, et al., 2013)

3.8.4 **Choice of trigger strategy**

Contal *et al* evaluated three alternative trigger strategies over consecutive nights in ten long-term users of NIPPV with OHS. They compared PSG parameters using a Spontaneous trigger, and a Spontaneous/Timed trigger with a low (median 11bpm) or high (median 21bpm) respiratory rate. They demonstrated considerably less respiratory events during sleep (obstructive and central apnoeas and the frequency of 4% oxygen desaturations) using either of
the Spontaneous/Timed strategies in comparison to the Spontaneous trigger. Differences were reported between the two Spontaneous/Timed approaches also. (Contal, Adler, et al., 2013) There was better subjective sleep quality and a higher percentage of rapid-eye movement (REM) sleep using the lower respiratory rate Spontaneous/Timed trigger. (Contal, Adler, et al., 2013) A potential limitation of the study was that the initial pressure settings were not titrated using PSG. This may have meant that the Spontaneous trigger arm was disadvantaged, as uncontrolled upper airway obstruction could be more problematic in the presence of this trigger strategy. The study does provide some support for the use of a hybrid trigger, at least in individuals with OHS.

An earlier study in a mixed cohort of individuals with respiratory failure, did not demonstrate significant differences in nocturnal oxygenation when comparing a Spontaneous trigger with a Spontaneous/Timed trigger. (Restrick et al., 1993) This study also did not use PSG to titrate pressures, and also evaluated a relatively small sample. (Restrick et al., 1993)

No prospective studies have evaluated long-term outcomes with different trigger strategies. Two retrospective studies have compared outcomes in those using a Timed trigger with those using a Spontaneous/Timed trigger, with conflicting results. The report by Munoz et al from Spain, concluded that there was no significant difference in adherence, user satisfaction or blood gas parameters between the two methods. (Muñoz et al., 2006) Using data from a Japanese population, Tsuboi et al concluded that the use of a Timed trigger (with a high respiratory rate) was associated with significantly improved adherence and survival rates. (Tsuboi et al., 2009) The retrospective design of both studies and the presence of numerous unexplored confounders limit the weight of these findings considerably.

Despite a lack of high quality studies, most long-term users of NIPPV are prescribed a Spontaneous/Timed trigger. (Garner et al., 2013) Device manufacturers now infrequently produce devices that incorporate a Spontaneous
trigger exclusively, perhaps demonstrating clinician preference for the hybrid trigger. If a Spontaneous/Timed trigger is prescribed, it remains uncertain as to how the respiratory rate for the Timed component should be set. The lack of consensus on this approach further complicates comparisons between studies as the rate strategy selected may have significant implications on the effectiveness of therapy and the nature of events detected during nocturnal monitoring. It is also unclear whether a single rate strategy should be employed across all disease groups or if this aspect of management should be tailored to the individual and to their specific respiratory mechanics. An additional area of uncertainty regarding trigger strategy is the utility of detecting changes in the triggering patterns over time or what constitutes the ‘ideal’ frequency of spontaneously triggered breaths. Murphy et al in a post hoc analysis suggested there may be advantages in gas exchange and subjective measures associated with having a lower percentage of spontaneously triggered breaths (i.e. more passive ventilation). (Murphy et al., 2012) Sandoz et al also described cases where improvements in gas exchange were achieved coincidentally with changes in the frequency of spontaneously triggered breaths. (Sandoz et al., 2014) Neither of these findings are compelling and routine monitoring or targeting of this parameter has not been shown to be of clinical use to date.

Unless specified, ongoing commentary in this thesis will refer to Spontaneous/Timed trigger as the default method for long-term NIPPV. A similar method termed ‘Assist/Control’ is used in some reports however is sufficiently similar to Spontaneous/Timed that these two approaches can reasonably be considered interchangeable. (Lloyd-Owen, 2007)

3.9 Cycling

Cycling refers to the device moving from the set IPAP level back to the EPAP (see Figure 3). Again, many modern NIPPV devices allow the clinician to
tailor this parameter according to their preferences and the specific attributes of the user. Pressure-targeted devices will maintain the set IPAP until one of two events occur; 1) the device detects a drop in inspiratory flow that is below a threshold percentage of peak inspiratory flow (Spontaneous cycle – see Figure 3), or; 2) the pre-set maximum inspiratory time is reached (Timed cycle). Depending on the configuration of the device, either one of these two events will initiate the device to cycle.

Figure 3 - Schematic representation of Spontaneous trigger and cycle mechanisms in non-invasive positive pressure ventilation; representative mask pressure trace with simultaneous device flow trace;
(a) spontaneous trigger; increase in inspiratory flow is shown to reach a threshold level which triggers the ventilator to move from expiratory pressure to inspiratory pressure;
(b) spontaneous cycle; a decrease in inspiratory flow below a threshold level causes the ventilator to cycle back to expiratory pressure
3.9.1 Spontaneous cycle

Most devices utilise a flow sensor that is able to detect a drop in inspiratory flow below a threshold level. This threshold is commonly set at approximately 25-30% of the peak inspiratory flow but in many devices can be adjusted in order to accommodate the respiratory mechanics of the user. The threshold level that inspiratory flow must fall before cycling occurs is referred to as the cycle sensitivity. Increasing the cycle sensitivity therefore implies that a smaller fall (from peak inspiratory flow) is required to occur before the device moves from IPAP back to EPAP. The theoretical advantage of a Spontaneous cycle mechanism is that again it allows the device to respond to changes in demand from the user. If an individual augments their inspiratory effort, they may reach peak inspiratory flow earlier in inspiration and therefore a shorter duration at the IPAP is delivered for that breath. A Spontaneous cycle theoretically allows this to occur. In practice, the ability of ventilators to coordinate with the end of the inspiratory effort of the user is relatively limited and the users’ respiratory mechanics are probably the biggest influence on cycling. (Rabec et al., 2011) NIPPV devices tend to cycle late for individuals with airflow obstruction and prematurely in individuals with restrictive pathology. (Rabec et al., 2009) The potential risk of a purely Spontaneous cycling mechanism is that if it fails to detect a sufficient fall in inspiratory flow (such as in the presence of high levels of unintentional mask leak) the device may fail to cycle back to EPAP, thus leaving the mask pressure at the IPAP level during the users’ attempt to exhale. (Calderini et al., 1999) Few modern NIPPV devices now utilise a purely Spontaneous cycle due to this potential problem. Most now incorporate a maximum inspiratory time beyond which the device cycles back to EPAP regardless of whether the threshold drop in inspiratory flow has been detected. (Berry et al., 2010; Rabec et al., 2011)
3.9.2 Timed cycle

As for triggering, most modern NIPPV devices will incorporate the ability for the device inspiratory time to be set by the clinician. A Timed cycle allows the clinician to determine an appropriate inspiratory time based on the user's underlying pathology. (Rabec et al., 2011) For example, individuals with COPD may benefit from shorter inspiratory time which consequently provides a longer period for expiration and may reduce dynamic hyperinflation. (Tassaux, Gainnier, Battisti, & Jolliet, 2005) Modern devices typically allow the setting of a predetermined inspiration:expiration ratio or a preferred inspiratory time or range. (Rabec et al., 2011)

3.9.3 Spontaneous/Timed cycling

Commonly, both cycling mechanisms are utilised, producing what is essentially a hybrid cycling mechanism. This allows flexibility for changes in demand from the user while providing reassurance to the clinician that a safe inspiratory time will be delivered for each and every breath delivered by the device.

3.9.4 Choice of cycling strategy

Some investigators have advocated a preference for a specific cycling strategy. Dreher and Köhnlein have described using a fixed inspiratory time (in combination with high pressure support and high respiratory frequency) for individuals with COPD and daytime hypercapnia using long-term NIPPV. (Dreher et al., 2010; Köhnlein et al., 2014) While there may be merit in such an approach it has yet to gain widespread acceptance. Calderini et al evaluated NIPPV in a
critical care setting and demonstrated that using a Spontaneous/Timed cycle with a narrow range of inspiratory time (0.8-1.2 sec) in individuals with high levels of mask leak produced better coordination of NIPPV and less respiratory work than an alternative approach that relied purely on Spontaneous cycling. (Calderini et al., 1999) In another ICU based study in individuals with COPD ventilated invasively, increasing the cycle sensitivity was also associated with improved synchronisation between the ventilator and the user as well as reductions in PEEPi and respiratory muscle effort. (Tassaux et al., 2005) Vignaux et al also reported improvements in synchronisation between the ventilator and the user achieved by tailoring the cycle sensitivity to the individual. (Vignaux et al., 2013) The optimal cycling strategy for long-term NIPPV is uncertain. Given that unintentional leak is a frequent clinical issue, it seems likely that complete reliance on a Spontaneous cycle mechanism is unwise. Some form of hybrid strategy with consideration of the underlying respiratory mechanics (both with regard to an appropriate range of inspiratory time and cycle sensitivity) is likely to be appropriate for most users.

### 3.10 Rise Time

For NIPPV devices, the rise time or pressurisation time refers to the time the device takes to achieve the targeted IPAP once a breath has been triggered (see Figure 2). Apart from rise time, other factors also influence the pressurisation of the mask and ventilator circuit – these include; the level of pressure support, the compliance and resistance of the respiratory system and the level of inspiratory effort. (Rabec et al., 2011) While faster rise times are effective at unloading inspiratory muscles, (Bonmarchand et al., 1999) they may also increase dyspnoea, (Manning, Molinary, & Leiter, 1995) worsen synchronisation, (Thille, Rodriguez, Cabello, Lellouche, & Brochard, 2006) or promote unintentional leak. (Rabec et al., 2011) Rise time therefore is often set
according to comfort and tolerability, but with consideration of the underlying respiratory mechanics.

3.11 **CONCLUSION**

The complexity of the theoretical framework for NIPPV therapy is considerable, and evolving technological changes related to the indications, devices, modes and interfaces used adds to this complexity. To successfully implement new users with NIPPV, HMV providers must consider these issues in addition to user-specific challenges related to comfort, acceptability, anatomical variation, respiratory mechanics, safety and psychological issues. This often must occur in parallel with the management of severe degrees of underlying cardiac, respiratory, neuromuscular and metabolic disorders that may be associated with the condition that has led to respiratory failure. In the following chapter, titration strategies for NIPPV will be reviewed and the evidence supporting these often vastly different approaches will be discussed. A particular focus will be on the evidence regarding the identification and amelioration of problems with synchronisation between the device and the user.
Chapter 4 – Titration Strategies and Patient-Ventilator Synchronisation

4.1 Introduction

Once a decision has been made that an individual requires long-term NIPPV, the subsequent transition to assisted ventilation is not always straightforward. Adequate adherence to therapy is not universal and many will decide to discontinue therapy despite its potential benefits. HMV providers use a range of care practices and methods to maximise the likelihood that an individual will succeed in this transition process with differing priorities of care reflected in the approaches used.

The titration strategy (that is, the method of implementing NIPPV, how settings are chosen, and what parameters are targeted) appears to be one aspect of care that differs considerably in published reports. Whether these different approaches are driven by variations in resourcing, expertise, population or clinical priorities is uncertain. The lack of a single definitive clinical or physiological measure of success is a potential reason for these differences in approach.

Patient-ventilator synchronisation may be an important mediator of effective NIPPV although its evaluation is difficult. It remains uncertain whether titration strategies that allow the evaluation and optimisation of patient-ventilator synchronisation are superior at improving the rate of successful transition to long-term NIPPV.

The aim of this chapter is to describe the methods used to implement NIPPV, with a particular focus on the titration strategies described in the literature. These will be detailed and contrasted where possible. A discussion regarding patient-ventilator synchronisation follows this, including a review of
the available evidence regarding the possible impact of poorly synchronised NIPPV therapy.

4.2 Transition to Long-Term NIPPV

Prospective studies involving treatment naïve individuals with MND or COPD commencing long-term NIPPV have reported intolerance rates ranging from 0% to 50%.(Bourke et al., 2006, 2003; Butz et al., 2003; Clini et al., 2002; Criner et al., 1999; Domenech-Clar, Nauffal-Manzur, Perpina-Tordera, Compte-Torrero, & Macian-Gisbert, 2003) Such a range of intolerance rates suggests that a multitude of individual, technological and organisational factors may be contributing. Comparisons between studies and centres is difficult due to the clinical heterogeneity that is inherent within HMV cohorts, but also the variety of methods used to implement, and subsequently support and monitor users of NIPPV. It is uncertain whether the method of implementation, which is influenced considerably by the titration strategy (or target), influences clinical outcomes.

4.3 Titration Strategies

The range of pressures prescribed by different investigators evaluating NIPPV is large, reflecting stark differences in the approach to this therapy.(Mehta & Hill, 2001) Few comparison studies have compared approaches. Most have been limited to evaluating high- and low-intensity approaches in individuals with COPD.(Dreher et al., 2011, 2010; Lukácsovits et al., 2012) Arguably, there have been potential limitations in the titration strategy in the control arm (low-intensity) that will be discussed below. It remains unclear if there is an ideal approach or method.
Methods of titration range from clinical assessments (using qualitative evaluations of tolerance, comfort, usage, synchronisation), to objective targets measured during wake (oximetry, daytime PaCO₂, reductions in respiratory muscle work) to both simple (pulse oximetry, transcutaneous CO₂) and complex (PSG, polygraphy) nocturnal monitoring. Frequently, HMV providers utilise a range of approaches (see Table 3). The choice of technique presumably reflects the target parameter(s) of interest and therefore may also reflect treatment priorities. Few comparison studies have been performed to determine if there are advantages to a particular approach.
Table 3 - Comparison of reported methods for determining settings for new users of non-invasive positive pressure in prospective studies included in Hannan et al (2014).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Region</th>
<th>Clinical ABG</th>
<th>Oximetry</th>
<th>PtcCO₂</th>
<th>Machine PG</th>
<th>PSG</th>
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AUS=Australia, DEU=Germany, ESP=Spain, FRA=France, GBR=United Kingdom, GRC=Greece, USA=United States of America
ABG=arterial blood gas, Machine=device data, PtcCO₂=transcutaneous partial pressure of carbon dioxide, PG=polygraphy, PSG=polysomnography
4.3.1 Titration strategies: targeting maximal reduction in arterial CO$_2$

Increasing alveolar ventilation to induce relative and/or absolute hypocapnia is described by some as the primary therapeutic goal for NIPPV,(Parreira et al., 1996) and such an approach has been considered to be the standard of care for some HMV providers.(Windisch, 2008) Despite this assertion, there is no reliable data from individuals with COPD, OHS, NMD or RTD to indicate that a titration strategy targeting maximal suppression of PaCO$_2$ is more effective than other approaches. A lack of longitudinal studies means that it is also unknown if such an approach influences adherence or tolerability over long-term use.

There are very few studies that have attempted to link PaCO$_2$ levels with mortality in users of NIPPV. Marti et al reported that both daytime PaCO$_2$ ($\geq 50$mmHg) at one month and the Charleston comorbidity index at baseline were predictive of mortality during follow-up in a large Spanish cohort of individuals with RTD who were prescribed NIPPV.(Marti et al., 2010) Details of the initial titration of NIPPV were not provided although the investigators describe the use of arterial blood gas sampling after one hour of NIPPV in order to determine efficacy.(Marti et al., 2010) They noted that adherence to therapy was a potential confounder to their results, and they reported a trend to lower adherence in the deceased patients ($p=0.055$).(Marti et al., 2010) Retrospective data from individuals with RTD has been used to support a contention that both achieving and maintaining low PaCO$_2$ with NIPPV is associated with improved continuation rates.(Tsuboi et al., 2014) Tsuboi et al found an association between smaller changes in PaCO$_2$ measured over time and the likelihood of continuing NIPPV therapy.(Tsuboi et al., 2014) They subsequently hypothesised that to improve prognosis, PaCO$_2$ should not only be reduced “as low as possible... it should also be stabilized throughout long-term NIPPV” however this is not supported by their data.(Tsuboi et al., 2014) In fact, larger retrospective studies in individuals with COPD and post-tuberculous respiratory failure from Japan
suggested no adverse effect on survival associated with hypercapnia in those using long-term supplemental oxygen therapy (LTOT). (Aida et al., 1998) There was also an apparent prognostic advantage with higher levels of PaCO₂ in the post-tuberculous group. Ahmadi et al have also described a U-shaped association between mortality and PaCO₂ in a large Swedish cohort of individuals with COPD using LTOT, with modest levels of hypercapnia not associated with mortality. (Ahmadi, Bornefalk-Hermansson, Franklin, Midgren, & Ekström, 2014) Others have also noted a surprising lack of toxicity from chronically elevated PaCO₂, provided hypoxia is not present. (Feihl & Perret, 1994)

Despite this, PaCO₂ levels remain a preferred measure in some centres to determine efficacy of NIPPV. This is particularly so for individuals with COPD, where differences in titration strategies (particularly the failure to maximally suppress PaCO₂) have been postulated as the cause for the very modest benefits demonstrated in studies evaluating long-term NIPPV in this patient group. (Köhnlein et al., 2014)

Titration strategies that have attempted to maximally suppress PaCO₂ have therefore been advocated for stable individuals with COPD and hypercapnia. (Windisch, Haenel, Storre, & Dreher, 2009) Data to support this approach come from small randomised crossover studies comparing high-intensity NIPPV (mean pressure support = 24.1cmH₂O, respiratory rate 18/min) to low-intensity NIPPV (mean pressure support 10.6cmH₂O, respiratory rate 8/min). (Dreher et al., 2011, 2010) This study reported improved adherence with this approach without any difference in measures of HRQoL or symptoms, (Dreher et al., 2010) and a subsequent study suggested no detrimental impact on objective measures of sleep quality. (Dreher et al., 2011) These findings were balanced against increased levels of unintentional leak and the need for longer periods of inpatient acclimatisation. (Dreher et al., 2010) Other investigators have demonstrated similar reductions in PaCO₂ levels (and
measures of diaphragm work) with a high intensity approach but at the expense of lower non-invasive measures of cardiac output.(Lukácsovits et al., 2012)

It is important to note that settings in the control groups for these studies were not determined using PSG or polygraphy, but instead were also determined clinically.(Dreher et al., 2010) It is therefore uncertain if the apparent difference in adherence relates to the superiority of the high-intensity approach (which produced a lower PaCO$_2$) or the inferiority of the low-intensity approach.(Dreher et al., 2010)

In comparison to standard care, this high-intensity approach has been demonstrated to improve survival in individuals with hypercapnia due to COPD. As discussed in Chapter Two, the multicentre RCT reported by Köhnlein et al demonstrated a significant survival advantage for those managed with this form of NIPPV.(Köhnlein et al., 2014) Those with COPD and comorbid OSA were not excluded from this study. Observational data suggests this group could benefit considerably from positive pressure therapy directed at OSA.(Marin et al., 2010) It is therefore unclear if the large survival benefit demonstrated in the study by Köhnlein et al was mediated by the aggressive reduction in PaCO$_2$ or instead by a reduction in the frequency of upper airway collapse during sleep.

### 4.3.2 Titration strategies: targeting reductions in respiratory work

While higher levels of pressure support can maximally reduce PaCO$_2$, some investigators have suggested that the aim of titrating assisted ventilation should be to reduce measures of respiratory muscle work.(Kimura et al., 1991) The use of surface EMG of diaphragm and sternocleidomastoid to determine effective ventilation has been previously described by Goldstein et al in six individuals with chronic hypercapnic respiratory failure due to RTD and NMD. In this study, improvements in inspiratory muscle endurance (along with
reductions in daytime PaCO\textsubscript{2}) were reported. The rationale for targeting reductions in respiratory work is that inspiratory muscle fatigue may be an additional contributor to the development of hypercapnic respiratory failure – even in the presence of an essentially static excessive load and/or reduced capacity of the respiratory muscles. Therefore, respiratory muscle rest achieved with the application of intermittent NIPPV should provide sufficient support to ensure that the function of the respiratory muscles is optimised during periods of spontaneous breathing. The results described by Goldstein et al do not confirm this hypothesis, as diaphragm function may be influenced by changes in central ventilatory control mediated by reductions in PaCO\textsubscript{2} and bicarbonate. Others have suggested that diaphragm fatigue is unlikely to be a contributor to chronic hypercapnic respiratory failure. (Bégin, Mathieu, Almirall, & Grassino, 1997; Misuri et al., 2000) The diaphragm has been shown to be extremely resistant to fatigue, (McKenzie, Allen, Butler, & Gandevia, 1997; McKenzie & Gandevia, 1991) and imbalances between central drive and the load on the respiratory system are felt to be more important contributors. (Bégin et al., 1997; McKenzie et al., 1997; Misuri et al., 2000; Rochester, 1991) This suggests that while reducing respiratory muscle work with NIPPV may be an appropriate physiological goal, the mechanism of benefit is unlikely to be due to a reduction in fatigue of the diaphragm or other inspiratory muscles. It is possible, however, that the primary benefit of this approach is to support ventilation during sleep when central drive is reduced and when inspiratory muscles are placed under additional load. Positional changes, increases in upper airway resistance, loss of the central drive associated with wakefulness and periods of skeletal muscle atonia that occur during sleep all compromise ventilation. (Colrain, Trinder, Fraser, & Wilson, 1987; Naifeh & Kamiya, 1981; Trinder, Whitworth, Kay, & Wilkin, 1992) NIPPV that reduces respiratory muscle work may therefore allow consolidated sleep and stable ventilation to occur. Symptomatic benefits may then be obtained without a maximal reduction in PaCO\textsubscript{2} although a degree of relative hypocapnia in comparison to sleep without assisted ventilation would still be expected.
Using physiological measures of respiratory muscle work to titrate long-term NIPPV for clinical purposes is infrequently described. In the acute care setting, and in small physiological studies, transdiaphragmatic pressure swings, (Kimura et al., 1991) or the pressure time product of the diaphragm (PTP$_{\text{dia}}$ = the area under the curve of transdiaphragmatic pressure during inspiration), (Annat et al., 1990) are described, both of which require the insertion of an oesophageal catheter thereby limiting their clinical utility.

Reductions in PTP$_{\text{dia}}$ have been demonstrated in individuals with OHS using NIPPV although this technique was not used as a means of titrating settings. (Pankow et al., 1997) Tuggey and Elliott have previously demonstrated in individuals with RTD and COPD that reductions in respiratory work can be achieved with relatively low levels of inspiratory support. (Tuggey & Elliott, 2006) They also demonstrated that above a certain threshold pressure, further increases in pressure support were not associated with ongoing reductions in work – despite further increases in alveolar ventilation. (Tuggey & Elliott, 2006) This suggests that where respiratory muscle work is the target of therapy, lower levels of pressure support than those required for maximal suppression of PaCO$_2$ are sufficient. The study reported by Fanfulla et al supports this finding. (Fanfulla et al., 2005) They reported making adjustments to NIPPV settings in order to target a reduction in the transdiaphragmatic pressure swing in individuals with NMD. (Fanfulla et al., 2005) They evaluated parameters measured during sleep and compared results with those obtained using “usual settings”. (Fanfulla et al., 2005) Settings derived from measures of transdiaphragmatic pressure tended to be lower than those determined using clinical titration (which used the “maximal tolerated pressure support in order to reduce awake PaCO$_2$ by 5%”) and were associated with improvements in sleep quality. (Fanfulla et al., 2005) It is uncertain if the higher pressures delivered with the “usual settings” may have induced more sleep disruption.
Although an approach where NIPPV is titrated according to direct measures of respiratory muscle work is appealing, the use of invasive measures is unlikely to be acceptable to most users. Non-invasive measures of respiratory muscle work (such as surface EMG of the diaphragm or intercostal muscles) may be more acceptable. (Carrey et al., 1990; Goldstein, De Rosie, Avendano, & Dolmage, 1991) The clinical utility of this approach is uncertain however and there are also potential limitations for the use of surface EMG in practice. It is not clear that such a strategy would be effective outside the research setting. (Duiverman, Huberts, Eykern, Bladder, & Wijkstra, 2017) Problems related to electrical interference and signal acquisition issues due to body habitus may represent considerable impediments. (Kuiken, Lowery, & Stoykov, 2003)

4.4 Titration strategies: targeting tolerance and adherence

Many reports describing titration strategies for NIPPV include the use of clinical assessments of comfort and tolerability, (Bourke et al., 2006; Tsolaki et al., 2011; Windisch, 2008) with others incorporating the demonstration of a reduction in symptoms as a titration target. (Kim et al., 2011) From published reports, it appears uncommon that these assessments are utilised in isolation to guide pressure settings, (Vitacca et al., 2000) although tolerance is often described as providing a ceiling on desired pressures, regardless of the physiological parameter that is targeted. (Dreher et al., 2010; Fanfulla et al., 2005)

4.5 Titration strategies: targeting nocturnal gas exchange

The titration strategies outlined to this point have all involved daytime measures – specifically measures of PaCO₂ and respiratory muscle work. Given that NIPPV is commonly used only at night, nocturnal measures may be more
appropriate. Nocturnal pulse oximetry and capnography can be considered simple nocturnal monitoring on the basis that these can be performed overnight in almost any location. This frequently means that users undergo this form of monitoring at home.

**Pulse oximetry**

Titration strategies using simple nocturnal measures are frequently described, (Borel et al., 2012; Bourke et al., 2006, 2003; Gonzalez et al., 2003; Mustfa et al., 2006; Nickol et al., 2005; Storre et al., 2006) although they are often combined with other assessments. In two studies of individuals with MND, Bourke et al described titrating both inspiratory and expiratory pressures of NIPPV to target “optimum nocturnal oximetry” but provided no description of target parameters. (Bourke et al., 2006, 2003) The investigators also described the additional use of arterial blood gases and measures of adherence but again not how these measures influenced setting choice. In another group of individuals with MND, Mustfa et al reported the use of overnight oximetry on NIPPV “to determine the adequacy of ventilation” but again did not define how results influenced therapy. (Mustfa et al., 2006) In a study evaluating NIPPV in individuals with OHS, Borel et al reported target parameters for nocturnal oximetry where inspiratory pressure was adjusted in order to achieve “mean overnight SpO₂ >90% and >90% of the recording time without residual SpO₂ oscillations”. (Borel et al., 2012) No further details were described although the investigators supplemented their nocturnal oximetry data with the use of an auto-titrating CPAP device to determine the EPAP setting and they also targeted a “maximal reduction in PaCO₂ (immediately after awakening)”. (Borel et al., 2012) Gonzalez et al did describe target parameters for nocturnal oximetry during implementation of NIPPV (SpO₂>90% for at least 90% of the night) but again used other measures (including a nocturnal measure of partial pressure of transcutaneous carbon dioxide (PtcCO₂) less than 45mmHg) to adjust their
settings. (Gonzalez et al., 2003) Determining appropriate SpO₂ parameters for which an intervention is required may be difficult. (Nardi et al., 2012) Technical differences between these devices (averaging time, oxygen desaturation index (ODI) definitions, software algorithms) could also influence the results obtained and might limit the confidence in determining a threshold at which to intervene. (Netzar, Eliasson, Netzar, & Kristo, 2001)

Capnography

PtcCO₂ monitoring has been described as a method of titrating ventilator settings both during daytime evaluations, (Storre et al., 2006; Storre, Steurer, Kabitz, Dreher, & Windisch, 2007) and at night. (Nickol et al., 2005) There are limitations to this technique. The accuracy of PtcCO₂ measures is limited in the presence of high PaCO₂ levels, (Cuvelier, Grigoriu, Molano, & Muir, 2005) and if corrections for both drift and offset are not performed. (Berlowitz et al., 2011) Response times are often prolonged with these sensors, which could also limit their diagnostic accuracy. Despite this, some authors have suggested a role for this technique for ambulatory use. (Bauman et al., 2013) Specifically for titrating NIPPV settings, Nickol et al have previously described upwards titration of pressures “as tolerated to control nocturnal hypoventilation by ensuring there was a fall in both peak nocturnal PtcCO₂ and daytime PaCO₂”. (Nickol et al., 2005) Results from nocturnal PtcCO₂ tracings appear to be rarely used as the sole measure that dictates NIPPV settings. Daytime PtcCO₂ measures have been used to directly influence pressure settings, with investigators using changes in PtcCO₂ as a surrogate for changes in PaCO₂ and thus avoiding serial arterial blood gas sampling. (Storre et al., 2006) Measures of end-tidal CO₂ have also been suggested as a possible surrogate for PaCO₂ measures in order to guide NIPPV therapy. (Bauman et al., 2013; Berry, 2010) although the reliability of this approach for nocturnal monitoring, during NIPPV use, or in those with a high deadspace to
tidal volume ratio is questionable. (Huttmann, Windisch, & Storre, 2014; Janssens et al., 2011; Sanders et al., 1994)

Both oximetry and capnography suffer the same limitations with regard to a lack of consensus over what constitutes an abnormal result. Ogna et al retrospectively assessed combined nocturnal \( \text{SpO}_2 \) and \( \text{PtcCO}_2 \) monitoring in 232 consecutive recordings in spontaneously breathing individuals with NMD. (Ogna et al., 2015) They compared the prevalence of hypoventilation using the eight “most frequently used criteria” and reported that the prevalence of nocturnal hypoventilation ranged from 10.3% to 61.2%. (Ogna et al., 2015) Others have demonstrated differences in the prevalence of nocturnal hypoventilation using combined nocturnal oximetry and \( \text{PtcCO}_2 \) measures, which varied depending on which \( \text{SpO}_2 \) parameters were considered abnormal. (Nardi et al., 2012)

Apart from their reliability and uncertainty regarding appropriate clinical thresholds to intervene, there are other limitations to the use of either (or both) \( \text{PtcCO}_2 \) and \( \text{SpO}_2 \) for the titration of NIPPV. When performed without the simultaneous evaluation of sleep stage, body position, device performance (including leak) and synchronisation, these measures provide no additional information as to the cause of an abnormality in gas exchange. Derangements may be due to uncontrolled upper airway obstruction, excessive mask leak, device malfunction or inappropriate settings. It is also possible that acceptable results could be obtained in measures of gas exchange despite gross abnormalities in sleep quality, synchronisation or other unmeasured parameters that could limit the tolerance of NIPPV. (Fanfulla et al., 2007)

4.5.1 Titration strategies: targeting objective sleep quality

The use of PSG to evaluate long-term NIPPV is described by a number of investigators although whether the therapy is altered specifically in order to
improve measures of sleep quality is generally unclear in published reports. (Adler et al., 2011; Fanfulla et al., 2007; Guilleminault, Philip, & Robinson, 1998; Guo, Sforza, & Janssens, 2007; Katz, Selvadurai, Keilty, Mitchell, & MacLusky, 2004; Masa et al., 2015; McKim, Katz, Barrowman, Ni, & LeBlanc, 2012; Piper et al., 2008; Vrijsen et al., 2016) Although not all studies evaluating PSG measures pre- and post-institution of NIPPV therapy have demonstrated improvements, (Katzberg et al., 2013) many have. (Berlowitz, Detering, & Schachter, 2006; Elliott, Simonds, Carroll, Wedzicha, & Branthwaite, 1992; Khan, Beckmatt, & Dubowitz, 1996; Schönhofer & Kohler, 2000; Vrijsen et al., 2015) These have demonstrated an increased proportion of REM sleep, (Berlowitz et al., 2006; Schönhofer & Kohler, 2000; Vrijsen et al., 2015) as well as a reduction in EEG arousals during sleep, (Berlowitz et al., 2006; Khan et al., 1996; Schönhofer & Kohler, 2000) and improvements in sleep efficiency and total sleep time. (Berlowitz et al., 2006; Elliott et al., 1992; Schönhofer & Kohler, 2000) The effect of assisted ventilation on slow wave sleep appears inconsistent with some investigators reporting an increased proportion, (Schönhofer & Kohler, 2000; Vrijsen et al., 2015) some demonstrating no change, (Berlowitz et al., 2006) and others a reduction. (Khan et al., 1996) This inconsistency may relate to different underlying pathology, or it could possibly reflect differences in the degree of hypercapnia as this has been shown to be associated with the proportion of slow wave sleep. (Wang et al., 2011)

While the use of PSG has been advocated by some investigators as an important procedure to ensure adequate settings for NIPPV, (Fanfulla et al., 2005; Vrijsen et al., 2015, 2016) it does not appear that this is due to a specific attempt to target improvements in any particular sleep parameter. Because many parameters can by simultaneously evaluated during PSG, changes to NIPPV may be prompted by derangements in any or all of; nocturnal gas exchange, measures of respiratory muscle work, synchronisation, as well as sleep architecture. Therefore, the use of laboratory-based PSG titration (and other forms of attended complex nocturnal monitoring) allows real-time evaluations of objective physiological measures in order to both identify and rectify problems that arise.
during NIPPV therapy. (Berry et al., 2010) Whether or not changes are made in real time may depend on specific laboratory protocols or clinician preferences. (Vrijsen et al., 2016) Vrijsen et al have described a multiple night PSG protocol with changes made to NIPPV settings during the daytime after analysing nocturnal data. (Vrijsen et al., 2016) Such an approach would potentially be more costly and labour-intensive than adjustments in real-time.

The interaction between the user and an experienced clinician during this prolonged monitoring period may also provide additional benefits. It is possible for some individuals that this interaction could be as beneficial on the eventual outcome as the specific targeting of therapy to improve sleep and ventilation quality.

4.5.2 Titration strategies: automated titration

There is interest from some investigators in the use of device-derived data in order to titrate and evaluate NIPPV settings. (Janssens et al., 2011) Interrogation of device related data has been reportedly used as an adjunct to clinical assessment and measures of gas exchange in some centres. (Hazenberg et al., 2014; Sandoz et al., 2014) Overall, the reliability of the data extracted from these devices is generally uncertain and probably varies between devices and manufacturers. (Contal et al., 2012) The utility of this approach is therefore unknown.

Automated titration algorithms are contained within a number of NIPPV devices currently available and this alternative approach has been advocated as allowing the implementation of long-term NIPPV in less experienced centres. (Kelly et al., 2014) Murphy et al reported pilot data on such an approach, suggesting that auto-titrated NIPPV achieved similar nocturnal gas exchange measures to standard fixed pressure NIPPV in ten long-term users of NIPPV with
COPD and OSA. Adherence to therapy, sleep quality and subjective measures were not worse with the auto-titrated device. (Murphy et al., 2015) Kelly et al evaluated 18 treatment naive individuals (with COPD or restrictive disorders) and demonstrated similar nocturnal oximetry and capnography measures as well as similar sleep quality using either fixed NIPPV (titrated by an experienced clinician) or auto-titrated NIPPV. (Kelly et al., 2014) A small but significant increase in the median nightly use of the auto-titrating device was also reported. (Kelly et al., 2014) The investigators concluded that auto-titrating NIPPV could potentially improve access to NIPPV by reducing the requirement for expert clinical titration. (Kelly et al., 2014) It should be noted that setting adjustments were required more frequently with the auto-titrating device and no evaluation of cost-effectiveness or subjective measures was provided. (Kelly et al., 2014) In contrast to these findings, an earlier study from the same group reported a higher mean and peak PtcCO₂ and lower tidal volumes with an auto-titrating NIPPV device in a randomised crossover study of individuals already established on NIPPV. (Jaye et al., 2009) There was no difference in nocturnal SpO₂ measures and a small reduction in NREM1 sleep during use of the auto-titrating device. The authors suggested a potential role for this technology. (Jaye et al., 2009) These data do not confirm that the use of this technology would prove more effective than other approaches that represent standard practice in most HMV centres. Use of these devices in non-expert settings has not been evaluated. Auto-titrating or ‘intelligent’ modes (such as volume-assured pressure support) have demonstrated very little clinical advantages (if any) in comparison to fixed pressure NIPPV in studies to date. (Arellano-Maric, Gregoretti, Duivermann, & Windisch, 2017) While some have suggested a role in those with progressive disease to reduce manual adjustments to NIPPV settings, it is uncertain if this is a desirable metric of high quality care in these disorders. (J. E. Brown & Diaz-Abad, 2014) Further studies are required to determine if there are actual benefits for HMV services and users of HMV that can be achieved with the addition of these technologies.
4.5.3 Titration strategies: targeting patient-ventilator synchronisation

Patient-ventilatory asynchrony (PVA) has been defined as a situation in which there is a mismatching between neural (user) and mechanical (ventilator) inspiratory time. (Sassoon & Foster, 2001) Understanding of this phenomenon has developed from the critical care literature, (Chao, Scheinhorn, & Stearn-Hassenpflug, 1997; Leung, Jubran, & Tobin, 1997; Sassoon & Foster, 2001; Thille et al., 2006; Vignaux et al., 2009) however PVA has been increasingly identified and described in individuals using long-term NIPPV. (Adler et al., 2011; Atkeson et al., 2011; Fanfulla et al., 2007; Ramsay et al., 2015)

Reports describe the use of either subjective, or objective assessments of patient-ventilator synchronisation as part of their assessment of individuals commencing NIPPV, although only one previous study has described the observed frequency of PVA as the primary measure that influenced NIPPV settings. (Adler et al., 2011) Adler et al reported results from eight individuals with stable COPD who were using NIPPV and had reported morning dyspnoea. They underwent PSG primarily to optimise settings in order to reduce the severity of this symptom. (Adler et al., 2011) Participants had been established on NIPPV according to “prevailing recommendations”. Those included had to demonstrate adherence of greater than four hours per night and have no changes to settings for at least one month. After undergoing adjustment to settings following PSG, ineffective efforts were reduced with the PVA index falling from 40.5 +/- 31.0 to 6.7 (+/- 7.3). There were no differences in sleep parameters or nocturnal oximetry measures (oxygen desaturation index or mean SpO₂) although there was a trend towards a reduction in morning PaCO₂. (Adler et al., 2011) Participants reported symptomatic improvements, including a reduction in morning dyspnoea. (Adler et al., 2011) This observational data suggests an impressive response to PSG titration of settings in this group, however it should
be noted that the study was unblinded and there was no control group for comparison. (Adler et al., 2011) This apparent benefit in short-term subjective outcomes is therefore questionable. The improvements in nocturnal measures were also limited to measures of PVA. (Adler et al., 2011) It is noteworthy that on average the pressure support was reduced following PSG. Again, this raises the possibility that the primary mediator of any benefit was a reduction in excessively high pressures that were initially prescribed. These may have been contributing to dynamic hyperinflation and PEEPi in these individuals with COPD which could induce both PVA and dyspnoea. (O'Donnell, 2006) The reduction in pressure support therefore may have acted to reduce dynamic hyperinflation. The fall in PVA may therefore have been a concurrent phenomenon but not the physiological cause of the reduced dyspnoea.

The study by Adler et al therefore does not confirm the benefits of PSG titration but does identify a role for this procedure in identifying ineffective therapy or ventilator-induced phenomena. No other published report has demonstrated a benefit from a specific strategy aimed at reducing measures of PVA. Some investigators have reported the frequency of PVA during nocturnal recordings, both in stable long-term users of NIPPV, (Atkeson et al., 2011; Fanfulla et al., 2007) and in new users, (Ramsay et al., 2015; Vrijsen et al., 2016) although these observational studies did not report that demonstration of PVA prompted specific adjustments to treatment. As described above, the study by Fanfulla et al that did demonstrate an improvement in PVA after adjustment of NIPPV settings, performed adjustments based on measures of transdiaphragmatic pressure swings, rather than the observation of PVA itself. (Fanfulla et al., 2005) Nocturnal measurement of PVA in this situation therefore comprised an outcome measure by which the success of the titration strategy was judged, rather than a parameter that influenced the setting choice. (Fanfulla et al., 2005)

Therefore, based on published reports, it seems that the use of measures of PVA alone to determine NIPPV settings is an infrequent practice, if it is used at
all. More likely, measures of PVA are incorporated (either qualitatively or quantitatively) with other measures described above, such as gas exchange, measures of respiratory muscle work and clinical assessment.

4.6 Choice of Titration Strategy

There is no apparent clinical consensus regarding the optimal titration strategy for NIPPV, (Hannan et al., 2014) and the available literature does not provide convincing evidence of the superiority of any particular approach. This finding provides some justification for longitudinal studies comparing different approaches to NIPPV implementation. In the absence of a unifying physiological measure of success with HMV, the following section provides further details regarding the evaluation of patient-ventilator interaction and the possible methods of improving PVA during nocturnal monitoring with laboratory-based PSG.

4.7 Patient-Ventilator Interaction and Patient-Ventilator Asynchrony

PVA can occur due to factors related to the user, including; altered respiratory mechanics, changes in demand, abnormal respiratory muscle capacity and fluctuations in central drive. (Epstein, 2011) PVA can also arise due to factors related to the device including; the trigger and cycle strategy, interface problems (particularly leak) and the pressure and timing parameters chosen. (Epstein, 2011)

Previous reports have demonstrated associations between PVA and poorer tolerance of NIPPV as well as worse sleep quality, (Crescimanno, Canino, & Marrone, 2012; Fanfulla et al., 2005; Guo et al., 2007) and nocturnal gas exchange. (Fanfulla et al., 2007) Long-term adverse outcomes have not been demonstrated. In NIPPV for acute respiratory failure, PVA has been shown to
occur in over 40% of users and again has been associated with poorer tolerance of therapy. (Carlucci, Pisani, Ceriana, Malovini, & Nava, 2013; Vignaux et al., 2009) An association has not previously been demonstrated between adherence and PVA in long-term NIPPV users.

While it is possible that the clinical impact of PVA may be significant, there are considerable technical barriers in both its measurement and in efforts to improve it. Although referring to the critical care setting, Epstein previously concluded that the method used to detect PVA will frequently determine its prevalence. (Epstein, 2011) Different techniques have been described to identify PVA in long-term NIPPV users. These include the use of respiratory inductance plethysmography or strain gauges, surface EMG of inspiratory muscles, flow traces, and oesophageal pressure monitoring; often in combination. (Carlucci, Pisani, et al., 2013; Crescimanno et al., 2012; Fanfulla et al., 2007, 2005; Ramsay et al., 2015) Comparisons of these different methods for detecting PVA in long-term users of NIPPV have not been described. It also remains unclear whether PVA is more important than other physiological measures that can be obtained from NIPPV users. (Ramsay et al., 2015)

4.8 FORMS OF PATIENT-VENTILATOR ASYNCHRONY

It is useful to separate the different forms of PVA into trigger asynchrony and cycle asynchrony. (Ramsay et al., 2015) Trigger asynchrony appears to be the most prevalent form of PVA in NIPPV, although it is possible that this is because it is more readily identified than cycle asynchrony. (Crescimanno et al., 2012; Ramsay et al., 2015; Vrijsen et al., 2016)
4.9 **Trigger Asynchrony**

Three forms of trigger asynchrony are well described; 1) ineffective efforts – where an identifiable effort from the user is not associated with the delivery of a breath from the ventilator; 2) double triggering – where two breaths are delivered in rapid succession by the ventilator, and; 3) auto-triggering – where the ventilator erroneously detects inspiratory flow and delivers a breath or breaths in the absence of an actual inspiratory effort from the user.

4.9.1 **Ineffective effort**

Ineffective efforts occur when the device fails to move from the expiratory pressure to the inspiratory pressure despite the presence of inspiratory effort from the user. These constitute wasted respiratory work,(Thille, Cabello, Galia, Lyazidi, & Brochard, 2008) with the contraction of inspiratory muscles occurring without generating the same tidal volume (as a coordinated assisted breath).(Epstein, 2011)

The gold standard measure to detect inspiratory effort from the user is oesophageal pressure measurement or diaphragm EMG measured with an oesophageal catheter.(Epstein, 2011) Due to the difficulties obtaining these invasive signals in clinical practice, investigators have generally used respiratory movements (using respiratory strain gauges or respiratory inductance plethysmography),(Fanfulla et al., 2007, 2005) or changes in the inspiratory flow trace,(Thille et al., 2006) in order to detect ineffective efforts. Other detection techniques described include the use of parasternal intercostal EMG.(Ramsay et al., 2015)

Ineffective efforts are the most frequently identified form of PVA in NIPPV users.(Adler et al., 2011; Carlucci, Pisani, et al., 2013; Guo et al., 2007; Ramsay et al., 2015; Vrijsen et al., 2016) While scoring definitions and monitoring
techniques differ considerably between studies, this finding is fairly consistent, with the exception of the study by Crescimanno et al that reported less frequent ineffective efforts than auto-triggering. (Crescimanno et al., 2012) This study required three consecutive in-coordinated efforts to occur before a single ‘ineffective effort’ was scored, and this may have contributed to the comparatively low event rate. (Crescimanno et al., 2012) Across most other studies where the frequency of different types of PVA were compared, ineffective efforts were the most frequent event types – regardless of the use of daytime or nocturnal monitoring. (Adler et al., 2011; Carlucci, Pisani, et al., 2013; Ramsay et al., 2015; Vrijsen et al., 2016)

Ineffective efforts can be seen where unintentional mask or mouth leak is high, where upper airway obstruction is uncontrolled and when the trigger sensitivity is inappropriately low. (Jolliet, Tassaux, & Vignaux, 2009; Vignaux et al., 2009) Specific attributes of the user – particularly respiratory mechanics – may also contribute. Dynamic hyperinflation and PEEPi are associated with ineffective efforts. (Chao et al., 1997; Kondili et al., 2003) Similarly, alterations in drive or respiratory muscle strength may result in inspiratory efforts from the user that are insufficient to be detected by the flow (or pressure) sensor, even in the absence of PEEPi. (Kondili et al., 2003)

**Strategies to reduce ineffective efforts**

Once identified, strategies that may be effective at reducing ineffective efforts include the reduction of unintentional leak (by improving mask fit and seal), increasing the trigger sensitivity (which reduces the level of inspiratory flow required to trigger the device), increasing the EPAP (which can simultaneously provide control of upper airway obstruction and counteract PEEPi if present, (Nava et al., 1995)) and reductions in pressure support. (Leung et al., 1997) The addition of a Timed trigger (usually as a hybrid Spontaneous/Timed
trigger) may also be effective – particularly for those with severe respiratory muscle weakness or reductions in central drive, who may be unable to reliably trigger the device spontaneously during sleep. (Fanfulla et al., 2007, 2005)

4.9.2 Double triggering

Double triggering has also been variably defined, however can be considered to represent the presence of a single effort from the user (defined by the presence of respiratory movements, inspiratory muscle EMG or oesophageal pressure) but the delivery of two ‘breaths’ by the device. (Ramsay et al., 2015) These events can also be identified using the mask pressure trace where consecutive pressurisations occur with less than one second of (device) expiratory time. (Ramsay et al., 2015)

Double triggering commonly arises when there is a mismatch between the user’s inspiratory time and the set inspiratory time of the device. (Epstein, 2011) It may also occur when pressure support is insufficient. (Epstein, 2011) Where device inspiratory time is too abbreviated, or where pressure support is too low, the inspiratory effort of the user can extend into device expiration – which leads to the triggering of a second breath. Double triggering is more likely if the preset inspiratory time on the device is too short, (Branson, Blakeman, & Robinson, 2013) or if the back-up rate is higher than the user’s own respiratory rate (when using a Spontaneous/Timed trigger). In this second situation, the device delivers a (Timed triggered) breath before the user's inspiratory effort has begun. This then increases the likelihood that the inspiratory effort of the user will persist beyond the device inspiratory time, resulting in a second (Spontaneous triggered) breath to be delivered. (Sinderby, 2012) Double triggering could theoretically lead to (transient) dynamic hyperinflation by markedly limiting the time available for expiration, (Branson et al., 2013; Younes, Kun, Webster, & Roberts, 2002) although the presence of leaks from a non-invasive interface presumably makes this less
likely than when it occurs during invasive ventilation. If transient dynamic hyperinflation did occur, a subsequent ineffective effort in turn may be more likely, due to the additional load imposed by a transient increase in PEEPi. (Liao, Ou, & Chen, 2011; Younes et al., 2002)

Clinical consequences specifically attributed to double triggering have not been described in individuals using NIPPV and therefore the significance of these events (and the value of efforts to reduce them) is uncertain.

**Strategies to reduce double triggering**

Reducing the frequency of double triggering can be achieved by more closely matching the inspiratory time of the user with that of the device. Estimates of inspiratory time (of the user) can be made based on evaluations of the spontaneous breathing pattern or through assessments of respiratory movements and inspiratory muscle EMG (diaphragm, parasternal or scalene). Attempts to set the respiratory frequency at or below the user’s intrinsic respiratory rate (if using a Spontaneous/Timed trigger) may also be effective at reducing double triggering.

**4.9.3 Auto-triggering, autocycling and multiple trigger events**

There is some overlap in the literature between the terms autocycling and auto-triggering, and these events are similar. For the remainder of this thesis, auto-triggering will refer to a single ventilator ‘breath’ delivered without inspiratory effort from the user, (Branson et al., 2013) and not due to a Timed trigger. Autocycling will refer to the rapid delivery of multiple device breaths above the set respiratory frequency and without evidence that the breaths are due to inspiratory efforts from the user. (Harboe, Hjalmarsson, & Søreide, 2001)
During conventional nocturnal monitoring in a clinical setting, particularly without a reliable determinant of the presence or absence of inspiratory muscle activity, autocycling cannot be reliably differentiated from (multiple) rapid triggering due to rapid or very prolonged inspiratory efforts from the user. This is due to the frequent presence of respiratory movements (on respiratory inductance plethysmography) that may either be due to spontaneous efforts from the user (possibly indicating entrainment of the respiratory rhythm of the user during sleep with that of the malfunctioning ventilator), (Simon, Habel, Daubenspeck, & Leiter, 2000) or simply the passive rise and fall of the chest and abdominal wall during sleep in the presence of a patent upper airway. There are similar limitations to identifying single auto-triggered breaths when a Spontaneous/Timed trigger strategy is utilised.  

In flow-triggered devices, both autocycling and auto-triggering are felt to arise due to turbulence within the circuit which may be attributed to random noise, water in the tubing or mask, excessive leaks or cardiogenic oscillations. (Epstein, 2011; Harboe et al., 2001; Hess, 2011) An inappropriately sensitive trigger setting may contribute to these events. Autocycling and auto-triggering are also more frequent in individuals with low respiratory drive and respiratory rate and when dynamic hyperinflation is absent. (Kondili et al., 2003) Such factors produce prolonged periods of zero expiratory flow from the user before the next inspiratory effort occurs. This period leaves the flow sensor within the device more vulnerable to triggering from aberrant signals (or noise) within the circuit that are not due to inspiratory effort. (Kondili et al., 2003)

**Strategies to reduce autocycling and auto-triggering**

Again, there is limited data to suggest that autocycling (or auto-triggering) produces important clinical consequences in users of NIPPV. Theoretically there is the potential to produce significant hypocapnia and respiratory alkalosis due to
excessive ventilation during these events. Reducing unintentional leaks, lowering trigger sensitivity and reducing condensation within the ventilator circuit may all be effective in reducing autocycling and auto-triggering. In individuals with restrictive pathology who have a low respiratory rate and no dynamic hyperinflation, increasing the device inspiratory time may also be effective in reducing these events. (Hannan et al., 2015) (Appendix A) This approach acts to reduce expiratory time and this in turn reduces the time available during expiration where aberrant flow or pressure signals can inappropriately trigger the device. (Hannan et al., 2015)

4.10 Cycle Asynchrony

This form of PVA is less well described in users of NIPPV and may either occur less frequently or be more difficult to detect with confidence. (Crescimanno et al., 2012; Ramsay et al., 2015) Many investigators have not attempted to evaluate the frequency of these events. (Adler et al., 2011; Atkeson et al., 2011; Fanfulla et al., 2007, 2005) Those that have attempted evaluate these events have generally reported very low event rates and no apparent relationship with clinical consequences. (Crescimanno et al., 2012; Ramsay et al., 2015) The major limitation in identifying cycle asynchrony during standard clinical monitoring is the need for a reliable measure for the end of inspiration. Although surface EMG of inspiratory muscles could be useful for this purpose, their reliability for whole of night recording is somewhat questionable. (Aldrich, Sinderby, McKenzie, Estenne, & Gandevia, 2002) Effective NIPPV may also suppress signal amplitude from these recordings, therefore further limiting their usefulness. (Goldstein et al., 1991; Lake, Finucane, & Hillman, 1999)

It is possible that cycle asynchrony contributes to some of the forms of trigger asynchrony described above (particularly double triggering and ineffective efforts). (Younes et al., 2002) Modern ventilators frequently used for long-term
NIPPV now incorporate settings that minimise the frequency of severe forms of cycle asynchrony. The most obvious of these is the use of hybrid cycling mechanisms described previously in this chapter. Either the detection of a threshold reduction in inspiratory flow or the delivery of a pre-set maximum inspiratory time acting to ensure that the device cycles to the expiratory pressure. This mechanism avoids prolonged insufflations (synonymous with delayed cycling) that are described with the use of invasive ventilation. (Georgopoulos, Prinianakis, & Kondili, 2006) Conversely, premature cycling is possibly quite common in users of NIPPV, although undoubtedly it is more readily identified when it manifests as double triggering as described above.

4.11 Prevalence of PVA During NIPPV

PVA, in its many forms, has been recognised and described for many years – particularly in the ICU setting. (Fabry et al., 1995; Gurevitch & Gelmont, 1989; Tobin, Jubran, & Laghi, 2001) Attempts to quantify it and determine its clinical significance in users of NIPPV are relatively more recent. In a multi-centred study examining individuals with acute respiratory failure who were managed in ICU with NIPPV, over 40% of participants demonstrated an elevated asynchrony index (>10% of breaths during the monitoring period). (Vignaux et al., 2009) This study evaluated a very heterogeneous cohort with underlying disorders including COPD, congestive heart failure, OHS, RTD and NMD. (Vignaux et al., 2009) There were associations between the magnitude of mask leak and higher pressure support levels and an elevated PVA index on multivariate analysis, suggesting these were important drivers of PVA. (Vignaux et al., 2009)

In an earlier observational study by Fanfulla et al examining nocturnal NIPPV, asynchrony was demonstrated to occur frequently, even in clinically stable long-term users of NIPPV. (Fanfulla et al., 2007) PVA was generally not observed during wakefulness but was frequent during sleep. (Fanfulla et al., 2007)
They reported that over 4% of nocturnal breaths were asynchronous in individuals with a variety of causes of respiratory failure who had used NIPPV on average for over 18 months. (Fanfulla et al., 2007) Other studies using various measures of asynchrony have also shown similar frequencies of asynchronous breaths in individuals with MND, (Atkeson et al., 2011; Vrijsen et al., 2016) COPD, (Adler et al., 2011) and OHS, (Guo et al., 2007) although a variety of scoring rules were used in these studies.

4.12 **Clinical Outcomes and PVA**

Despite the prevalence of PVA in these reports, definitive evidence of adverse outcomes associated with these events in long-term users of NIPPV has not been demonstrated.

As described previously, the study by Adler et al suggested a possible contribution of PVA to early morning dyspnoea in individuals with COPD who were using nocturnal NIPPV. (Adler et al., 2011) Other studies have suggested an association between PVA (particularly ineffective efforts) and reductions in sleep quality. (Fanfulla et al., 2005) Fanfulla has also described associations between measures of PVA and worsening gas exchange. (Fanfulla et al., 2007, 2005) Greater degrees of asynchrony have been associated with increased discomfort with NIPPV although the magnitude of leaks and the level of pressure support may have been important contributors to comfort ratings. (Vignaux et al., 2009) Despite these potential adverse effects of PVA, in recent observational study, Vrijsen et al concluded that PVA and leaks while using NIPPV did not influence sleep architecture in individuals with MND. (Vrijsen et al., 2016)

The question therefore remains whether PVA represents an important clinical problem. Many reports suggest that a considerable proportion of HMV providers implement NIPPV without using techniques that could be expected to identify PVA if it is occurring. Could PVA simply represent a marker of
inappropriate NIPPV parameters that can be avoided with a less aggressive approach to clinical titration? Or is PVA a primary mediator of reduced adherence to therapy, regardless of the implementation strategy used? In clinical practice, such distinctions may not matter. HMV providers may want to use strategies they feel can improve unintentional mask leak, and tailor pressure support, EPAP and other device parameters to their users. If these are successful, PVA would be expected to be lower – as inappropriate settings or excessive leak (which appear to be drivers of PVA) would be less frequent. If this improves sleep quality, gas exchange, adherence, symptoms and HRQoL, then such strategies would represent high quality care for individuals receiving assisted ventilation.

4.13 CONCLUSION

A variety of titration strategies are described for determining appropriate settings for users of NIPPV. Unfortunately there is little evidence to suggest the superiority of a particular approach. While evaluating and improving patient-ventilator synchronisation through complex nocturnal monitoring could represent an important therapeutic approach, it is possible it may simply represent a costly and burdensome intervention.

Many questions therefore remain unanswered. Are clinical titration strategies performed during wakefulness sufficient for achieving adequate NIPPV? And if they are, how should success be defined? Also, should physiological measures (such as transdiaphragmatic pressure or measures of PaCO₂) be used routinely to dictate therapy? And, given that most require therapy only during sleep, how valuable is complex nocturnal monitoring in the form of PSG (or polygraphy)? Such questions also require consideration in a broader context. Even if the primary aim of HMV providers is to maximise the benefits of therapy in order to achieve better long-term outcomes, they must still
do so within a cost-constrained health system. Achieving universally successful NIPPV therapy is therefore impossible, but what should be the priority of care?

Differences between services regarding their level of experience and expertise, their use of community outreach, their ability to provide advice or assistance to users, the adequacy of medical supervision (including inpatient care), and the use of interdisciplinary teams (including physiotherapy, biomedical engineering, occupational therapy, speech pathology and case management) could all influence outcomes independently of the titration strategy used. Some of the interventions utilised routinely by HMV providers may primarily be beneficial by providing an opportunity for interaction between an experienced clinician and an individual receiving assisted ventilation. Others, however, may be critical for success. What would be sacrificed if it were decided not to perform them routinely for NIPPV users?

The subsequent chapter will discuss broader aspects of the care practices delivered by HMV services. Gaps in knowledge and a lack of expert consensus beyond geographic boundaries will be identified as limiting the ability to identify and define high quality care for HMV providers.
Chapter 5 – Providing Quality Care to Users of Home Mechanical Ventilation

5.1 Introduction

Perhaps due to the complexity of HMV and the medical, psychological and social needs of its users, those providing HMV must often negotiate complex networks of healthcare providers and funding systems in order to establish a functional service. While some of the apparent variability between regions in the way HMV is utilised may be driven by this, clinician preference, expertise, funding and accessibility may be considerable drivers of practice too.

Robust evidence, or where it is lacking, expert consensus allow quality of care to be assessed. Without these, defining quality of care is extremely difficult, and this means that quality improvement will be elusive. Interventions that are beneficial may be forgone, while others that are costly but with minimal clinical benefits, may be continued. (Walshe & Rundall, 2001) As the prevalence of HMV increases, providers must manage higher volumes of users with increasingly complex care needs. Within a cost-constrained health system, such expansions in care need to be accompanied by a reassessment of the strategies employed in order to determine their clinical efficacy and cost-effectiveness. This would ensure the sustainability of these services and that the highest quality of care achievable is delivered within a finite funding environment.

The aim of this chapter is to describe how quality of care may be measured within organisations such as HMV providers. The difficulty of this task is highlighted and attributed to the presence of gaps in knowledge and a lack of consensus as to what constitutes high quality care. Descriptions of HMV providers in published reports will be compared, as will guideline documents from different regions. The available evidence to support the use of certain strategies and organisational structures will also be discussed.
5.2 **HMV Providers and Quality of Care**

Ideally, health services develop their organisational model in order to ensure that they can deliver high quality patient care at a reasonable cost. However, both defining and measuring quality of care can be difficult and this can lead to the overuse, underuse or misuse of healthcare interventions. (Walshe & Rundall, 2001) This in combination with the expansion in HMV, (Simonds, 2003) has arguably contributed to very different care practices and strategies employed by HMV providers.

Because HMV therapy requires considerable equipment costs, some of these differences are likely to be due to variation in the way services are funded, constraints on access to certain interventions and expertise, as well as differences in demand for the therapy. Such a multitude of factors that will vary across different healthcare systems can be difficult to identify and quantify, but undoubtedly they play a role in how HMV provision is organised. Although the pursuit of high quality care may be preferred, in the end, economic drivers of practice are likely to be major factors in how HMV is delivered.

5.3 **Quality of Care**

The World Health Organisation (WHO) defines quality of care as occurring when the following factors are in place; 1) high professional standards; 2) effectiveness; 3) minimal risk for the patient; 4) high patient satisfaction; and 5) continuity of care. Frameworks for assessing the quality of care generally include measurement within these broad domains which can be summarised as access, effectiveness (and appropriateness), responsiveness, safety and equity. (Frølich, 2012)
Measuring quality of care is clearly an important aspect in determining if a health service is achieving its goals. This can be performed in a number of ways, however, a common approach, based on work by Donabedian, is to evaluate a health service based on structure (capacity, staffing, equipment), process (procedural frequency, waiting lists) and outcomes (mortality, morbidity, functional status, patient satisfaction). (Donabedian, 2005) Reliably and convincingly evaluating a health service generally involves measuring all three aspects, as measuring single factors and linking changes to outcomes is prone to bias. (Frølich, 2012)

The evaluation of quality of care within different levels of the healthcare system has been previously described. (Frølich, 2012) It was noted that in the assessment of organisations, the spectrum of quality of care is narrower than when assessing an entire healthcare system. Evaluating the outcomes at an organisational level (adverse events, waiting lists, length of stay, unplanned admissions) should occur with consideration of users (mortality, HRQoL, QoL, satisfaction) and interventions or care practices (physiological measures, adherence to guidelines). (Frølich, 2012) This suggests that to improve the quality of care requires both evidence that identifies the clinical practices that lead to better care, and knowledge of how to put this into practice. (Shortell, Rundall, & Hsu, 2007)
Such an approach requires that clinical evidence be known and described to clinicians to ensure evidence based practices are followed. Robust evidence allows a broader clinical consensus to be achieved that can then define best practice. Without it, quality of care at an organisational level will not be assessable in any meaningful way.

A number of HMV guidelines or consensus statements have been produced. ([No authors listed], 1999; McKim et al., 2011; Piper et al., 2010; Windisch, Walterspacher, Siemon, Geiseler, & Sitter, 2010) These were produced by clinicians and researchers from the United States, ([No authors listed], 1999) Australia, (Piper et al., 2010) Canada, (McKim et al., 2011) and Germany. (Windisch et al., 2010) A comparison of these documents identifies significant variations in their recommendations, particularly with regard to the use of NIPPV for individuals with COPD, the use of PSG to evaluate NIPPV and the use of routine airway clearance techniques, among others. ([No authors listed], 1999; McKim et al., 2011; Piper et al., 2010; Windisch et al., 2010) Because the majority of recommendations in each of the documents were reached on the basis of local
expert opinion, the discordant recommendations reflect a lack of objective data. Presumably they are influenced by historical practice and preferences given that such evidence is lacking. It is unsurprising that different conclusions are reached when only relatively low quality evidence is available to guide these recommendations. Arguably, local guideline recommendations are therefore likely to be a reflection of the care that these experts are currently delivering. Objective evaluation of the quality of care in this context is likely to be problematic. Certain strategies will be concordant with HMV guidelines in one setting but may be contrary to recommendations from experts based elsewhere.

5.4 HMV Provider Organisational Frameworks

There are limited data to describe the necessary organisational components of a high quality HMV service. Stuart et al previously described fundamental factors which they felt were crucial to success. (Stuart & Weinrich, 2004) Based on research evaluating the French model for HMV, they concluded the following factors were required; 1) physician leadership; 2) adequate financial support to ensure quality of care; 3) economies of scale; 4) continuity of care (allowing both inpatient and outpatient care); 5) personal care services; 6) quality of life; 7) access and tailoring of equipment and technology to individual needs; 8) national or regional organisation. (Stuart & Weinrich, 2004) The National Health Service (NHS) in the United Kingdom has also published a list of core standards for which HMV services managing individuals with “complex home ventilation” within the NHS need to adhere. (National Health Service (UK), 2013) This report emphasises the importance of specialist inter-disciplinary inpatient teams in order to manage patients with respiratory failure requiring long-term ventilation. They also provide details on the use of clinical nurse specialists, physiotherapists or physiologists to support ventilated patients at home. An outreach service is also described which incorporates home visits. The document also stresses the need for links with other units – specifically paediatric,
neuromuscular, palliative care, rehabilitation, ENT, nutritional and obesity management services. (National Health Service (UK), 2013)

5.4.1 Medical supervision and staffing

Where described, most HMV services employ subspecialty medical practitioners to determine the suitability of individuals to commence HMV. (Berry et al., 2010; Chatwin et al., 2010; Farré et al., 2005; Lujan et al., 2007) The specialty training of these physicians may vary however, with respiratory physicians, sleep physicians, critical care physicians, anaesthetists, paediatricians and neurologists all potentially providing clinical supervision. The subspecialty and expertise of the medical practitioner may influence patient-selection. (Lloyd-Owen, 2007) Greater proportions of individuals with underlying NMD or RTD were noted in units staffed predominantly by anaesthetists and critical care physicians in Europe. (Lloyd-Owen, 2007) Guideline recommendations on this issue vary with some explicitly recommending respiratory or sleep physicians, (Piper et al., 2010) while others emphasise the involvement of physicians “experienced in HMV”. (McKim et al., 2011) It is unclear whether patient-selection could be performed adequately by other clinicians, including non-physicians. A French working group recommended that physiotherapists be able to initiate NIPPV, but only with a prescription from a physician. (Rabec et al., 2010)

5.4.2 Interdisciplinary staffing

Most guideline documents support an interdisciplinary approach to the initiation of NIPPV. (McKim et al., 2011; Piper et al., 2010; Windisch et al., 2010) The German guideline, however, emphasises the responsibility of physicians to
“either directly carry out the initial set-up... or delegate the task to other specially trained medical assistants.” (Windisch et al., 2010) Such a physician-led model has been described by investigators previously, where the physician decided the type, model and interface for NIPPV, (Chatwin et al., 2010; Lujan et al., 2007) While some authors have suggested that nurses and “trained technicians” should be able to maintain the device but they should not initiate NIPPV alone, (Rabec et al., 2010) others describe a “nurse-led” model of care. (Mandal et al., 2015) There does not appear to be data specifically supporting nurse, or nurse-practitioner initiated NIPPV, although in many models of care, nurses, physiotherapists, (Moloney, Kiely, McDonnell, & McNicholas, 1999; Restrick et al., 1993) respiratory therapists, (Katzberg et al., 2013; Sandoz et al., 2014) and other clinicians play a role in the decision-making process. Sleep scientists at times may also be involved in the initial implementation of NIPPV – particularly when it is conducted within a sleep laboratory prior or during polysomnography. (Berry et al., 2010) No studies have evaluated differences in outcomes based on the type of clinicians that implement and monitor NIPPV. Literature on acute NIPPV therapy suggests that the expertise and experience of clinicians may play an important role in the success or failure of treatment. (Lopez-Campos et al., 2006) It is likely that expertise is similarly beneficial for long-term NIPPV users although the magnitude of any such benefit is uncertain.

5.4.3 Expertise and caseload

Differences in the size of an HMV provider and the volume of users they must manage could conceivably influence the quality of care. A centralised HMV provider model (where the service acts as a tertiary or quaternary referral centre) may be advantageous, to ensure expertise is concentrated within the service through increased patient volumes. (Mandal et al., 2013) This may act to up-skill clinicians regardless of their baseline qualifications. Smaller HMV providers
within a decentralised model may experience funding and access problems in addition to experiencing difficulty in maintaining sufficient levels of expertise due to smaller patient loads. (Leger & Laier-Groeneveld, 2002; Mandal et al., 2013) Such expertise issues presumably include both physician and non-physician team members and in this way, centralised medical supervision of HMV may be advantageous. (Simonds, 2004) Lloyd-Owen et al in the Eurovent study, demonstrated that smaller non-university hospital HMV centres tended to manage older patients with higher proportions having COPD or other lung disease. (Lloyd-Owen, 2007; Lloyd-Owen et al., 2005) Smaller centres also had a larger proportion of individuals with COPD in the study from Australia and New Zealand reported by Garner et al. (Garner et al., 2013) Centre size may also influence the timing of implementation of HMV, with smaller centres commencing therapy more frequently in the context of an episode of acute respiratory failure, in comparison to larger (university hospital-based) HMV centres that may have the structures and capacity to more easily institute therapy electively. (Lloyd-Owen, 2007; Lloyd-Owen et al., 2005)

While newer technologies such as auto-titrating NIPPV therapy have been suggested as a possible means of overcoming a lack of experience and expertise among clinical staff, (Kelly et al., 2014) the merits of such an approach remain to be seen. (Mandal et al., 2015)

5.4.4 Continuity of care

Continuity of care refers to “care over time by a single individual or team of healthcare professionals and to effective and timely communication of health information”. (Donaldson, Lohr, & Vanselow, 1996) Although there is support for this as a goal for chronic disease management programs, (Cabana & Jee, 2004) there remains some debate as to whether it represents a process or an outcome measure. (Christakis, 2003) While the use of larger, centrally administered HMV
services may have advantages regarding the expertise of clinicians, the size of these services may mean that continuity of care is more difficult, as direct oversight and frequent monitoring may not be possible. Clinicians and patients appear to differ regarding the importance of continuity in other chronic disease settings. (Van der Waal, Casparie, & Lako, 1996) Van der Waal et al demonstrated that individuals with diabetes, COPD and rheumatoid arthritis prioritised continuity of care more highly than physicians, while physicians prioritised efficiency more highly. (Van der Waal et al., 1996) This suggests the potential for competing priorities within HMV services. It is possible that individuals receiving assisted ventilation could actually be more satisfied by decentralised services, as these may be associated with a reduced requirement for travel, and potentially a greater likelihood for interaction with the same clinician. Simply measuring patient-satisfaction in this context may not resolve the issue, as patients may be satisfied by care that is of poor quality and not evidenced based. (Christakis, 2003; P. D. Cleary & McNeil, 1988) Despite this, continuity of care has been shown in general to be associated with higher quality of care. (Cabana & Jee, 2004) Vulnerable populations in particular (older age, chronic disease and lower socioeconomic status) have been shown to value continuity of care more than the less vulnerable. (Nutting, Goodwin, Flocke, Zyzanski, & Stange, 2003) The challenge for centralised services therefore is to provide continuity of care while at the same time leveraging the advantages of expertise and experience that come with larger caseloads.

5.4.5 Team care

Although team-based care has not been conclusively demonstrated to enhance patient or organisational outcomes, its use in healthcare continues to grow as the added pressures of restructuring, reorganisation, cost containment and the increasing complexity of healthcare knowledge and work have reinforced
the need for them. (Lemieux-Charles & McGuire, 2006) Team care could result in better patient outcomes as well as improved patient satisfaction, however the benefits are likely to vary depending on the setting. (Lemieux-Charles & McGuire, 2006) Within large, centralised HMV providers, team-based care may improve coordination and allow task delegation in order to maximise efficiency. A lack of coordination for individuals with complicated medical problems who may have reduced life expectancy could contribute to increased hospitalisations, (Roccaforte, Demers, Baldassarre, K.Teo, & Yusuf, 2005) wasted time and missed appointments, (Mason et al., 2013) and fragmented care. (Wagner et al., 2001) Adequate coordination within an HMV service is therefore likely to play an important role in facilitating the delivery of high quality care and it seems plausible that without it, quality of care would suffer. Given the increasing complexity of care required for many individuals receiving assisted ventilation, and the fact that many have advanced disorders associated with a high mortality, deliberate organisation of a team structure in order to facilitate safe and effective patient-centred care is likely to be beneficial.

Alternative methods to the use of team care in order to improve coordination have been described, although it should be noted that many of these overlap. (Mason et al., 2013) These methods include the use of keyworkers or nominated coordinators, shared or collaborative care models, integrated care pathways and the use of groupings comprising organisational or regional structures (‘networks’, ‘frameworks’, ‘programmes’ or ‘collaboratives’). (Mason et al., 2013) A variety of clinical outcomes (functional status, mental health and hospital admissions) have been reported to improve in studies in geriatric care through interventions which involved the implementation of a team care model. (Caplan, Williams, Daly, & Abraham, 2004; Cohen et al., 2002; Hughes et al., 2000) although results in other contexts did not demonstrate a difference. (Lemieux-Charles & McGuire, 2006) Study design in this area is often complex, and it may be difficult to determine whether improvements are attributable to the institution of team care per se, or simply a consequence of the
increased resources and attention associated with the implementation of a new approach to care.

### 5.4.6 Telephone support

Based on published reports, 24-hour telephone support is a frequent but not universal component of the care model provided to HMV cohorts. (Hannan et al., 2014) Few of the available HMV guidelines specifically mention this aspect of care. While there is no objective data to support the benefit of such a service, there is observational data that suggests a number of potential benefits from telephone support. (Chatwin et al., 2010) The most obvious of these is the ability of clients to alert HMV providers of either clinical deteriorations or malfunctioning equipment. A centralised telephone service may be the most affordable method of achieving this although it is possible that other methods (email, videoconferencing) may eventually supersede this approach. (Miyasaka, Suzuki, Sakai, & Kondo, 1997) Such interventions may provide for more timely evaluations of deteriorating patients. Other strategies, such as ‘walk-in’ clinics may be equally efficacious in removing some of the logistical barriers that can separate clinicians from deteriorating patients. (Simonds, 2007) It is likely that communication strategies which provide a simple but accessible link between HMV services, clients and their carers, play an important role in ensuring these individuals can be safely managed in the community. These measures may deliver an extra level of security and reassurance, particularly in the early phase of transitioning to HMV. (Miyasaka et al., 1997) These less tangible benefits may, in fact, be quite considerable. Contacts between individuals receiving assisted ventilation and HMV providers are often frequent (estimated at 5.5 per client annually) (Chatwin et al., 2010) Despite this, not all HMV services offer a dedicated outreach service to support users in the community. Garner et al reported that only 35% of HMV centres responding to their study (servicing just
over 50% of individuals receiving assisted ventilation in Australia and New Zealand) were supported by a dedicated outreach service. (Garner et al., 2013) Overall contacts were not reported but “visits” (presumably representing in-person contact) averaged 0.8 annually per client. (Garner et al., 2013) It is not known whether the lack of such a service influences clinical outcomes.

Formalised communication links could reduce unnecessary hospital presentations or admissions and may reduce the time commitment of both clinicians and users. (Miyasaka et al., 1997) Simultaneously, such a service provides a mechanism to rapidly facilitate the replacement of malfunctioning devices or initiate an urgent clinical review when necessary. (Chatwin et al., 2010)

5.4.7 Servicing

It has previously been suggested that when assessed over a number of manufacturers (and including both old and new devices) an average device failure rate of 8% could be expected within HMV services. (Chatwin et al., 2010) Others have suggested that one device failure for every 1.25 years of continuous use could be expected. (Srinivasan et al., 1998) This is consistent with the finding that failure rate appears higher in ventilator-dependent users (where hours of use accumulate quickly) and in older devices. (Chatwin et al., 2010; Srinivasan et al., 1998) These findings indicate the importance of both quality control (through regular servicing) and the need for mechanisms to respond to a malfunctioning device. It should be noted however that hospitalisations or other adverse outcomes related to device malfunction are infrequent. (Chatwin et al., 2010; Srinivasan et al., 1998) The Eurovent study identified significant regional disparities with regard to the performance of servicing of home ventilation devices. (Lloyd-Owen, 2007; Lloyd-Owen et al., 2005) Only 70% of centres reported performing regular scheduled servicing. (Farré et al., 2005) Larger HMV services were more likely to indicate that regular servicing was performed, and
that servicing included verification that pressure settings on the device were as prescribed. (Lloyd-Owen, 2007) Achieving adequate quality control and regular servicing of ventilators represents a significant medico-legal issue for HMV providers, particularly for individuals with high degrees of ventilator dependency. (Branthwaite & Garside, 2007; Simonds, 2006)

### 5.4.8 Funding

It seems likely that the infrastructure that is incorporated into a HMV service is important in order to ensure safe and high quality care is delivered to individuals receiving assisted ventilation. However, drivers other than the pursuit of high quality care may dictate the structure of a service. In particular, access to funding and the characteristics of the healthcare systems within which these services operate are likely to be significant. As an example, individuals receiving assisted ventilation residing in Greece must source their own equipment through a private company (in concert with a health insurer) while hospital or home visits to review therapy must be self-funded. (Lloyd-Owen, 2007) In contrast, those residing in France are able to access a fully publically funded system that incorporates both nursing and personal care, in addition to equipment needs. (Lloyd-Owen, 2007)

### 5.4.9 Population

While differences in the structure of HMV services therefore may be understandable, comparison studies suggest there is variation in both who is managed with HMV and, also, how they are managed. (Garner et al., 2013; Lloyd-Owen et al., 2005) Some of the regional variation in who is managed with HMV was outlined in Chapter Two (see Table 1), with particular reference to the lack of
consensus regarding the use of long-term NIPPV for individuals with COPD and OHS. (Chu et al., 2004; Garner et al., 2013; Lloyd-Owen et al., 2005)

Regarding the question of how individuals receiving assisted ventilation are managed, there is little published data comparing the practices of HMV providers from different regions. (Garner et al., 2013) A comparison of the descriptions of measures used to implement and support treatment naïve users of NIPPV in studies included in a systematic review, (Hannan et al., 2014) suggests that HMV providers do use very different approaches to care (see Table 4). Whether these differences influence clinical outcomes is unknown.
Table 4 - Comparison of reported care practices used to support users of non-invasive positive pressure ventilation in prospective studies included in a systematic review*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Region</th>
<th>Phone</th>
<th>Home visits</th>
<th>I/P</th>
<th>ACT</th>
<th>Nocturnal monitoring</th>
<th>PSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piper</td>
<td>2008</td>
<td>AUS</td>
<td>?</td>
<td>?</td>
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<td>✔</td>
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<tr>
<td>Butz</td>
<td>2003</td>
<td>DEU</td>
<td>?</td>
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<tr>
<td>Storre</td>
<td>2006</td>
<td>DEU</td>
<td>?</td>
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<td>✔</td>
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<tr>
<td>Windisch</td>
<td>2008</td>
<td>DEU</td>
<td>✔</td>
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<tr>
<td>Ferris</td>
<td>2000</td>
<td>ESP</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Nauffal</td>
<td>2002</td>
<td>ESP</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Domenech-Clar</td>
<td>2003</td>
<td>ESP</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Raphael</td>
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<td>FRA</td>
<td>✔</td>
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<tr>
<td>Borel</td>
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<td>FRA</td>
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<tr>
<td>Lyall</td>
<td>2001</td>
<td>GBR</td>
<td>?</td>
<td>✔</td>
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<tr>
<td>Newsom-Davis</td>
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<tr>
<td>Nickol</td>
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<tr>
<td>Tsolaki</td>
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<tr>
<td>Guilleminault</td>
<td>1998</td>
<td>USA</td>
<td>✔</td>
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</tbody>
</table>

AUS=Australia, DEU=Germany, ESP=Spain, FRA=France, GBR=United Kingdom, GRC=Greece, USA=United States of America, Phone=provision of on-call assistance by telephone, I/P=implementation performed during inpatient admission, ACT=prescription of airway clearance techniques or physiotherapy sessions, Nocturnal monitoring=use of oximetry, capnography or polygraphy (but not polysomnography), PSG=polysomnography

*Included inpatient re-assessments
*Adapted from (Hannan et al., 2014)
5.5 **Quality of Care in HMV Populations**

In the framework outlined previously for the evaluation of quality of care in healthcare organisations, (see Figure 4), both the effectiveness of interventions and adherence to guidelines were potential indicators of quality of care. Specifically for HMV providers, adherence to guidelines could be evaluated, provided that these are developed with knowledge of the effectiveness of interventions. However, given that guidelines are discordant and that evidence is lacking or of low quality, how can quality of care be evaluated objectively?

The subsequent section describes the available evidence that supports the effectiveness of some of the interventions employed by HMV providers. The discussion includes comparisons of published guidelines for HMV that highlight the considerable variation in expert opinion in this area. This situation makes adherence to guideline recommendations of dubious value as a marker of quality of care.

5.6 **Invasive Mechanical Ventilation**

The technical issues related to the use of IMV and limited comparisons with long-term NIPPV have been discussed previously in Chapter Three. Historically, large proportions of HMV cohorts were managed with IMV. (Robert et al., 1983) Perhaps due to improvements in the design and comfort of non-invasive interfaces, growth in NIPPV has significantly outpaced that of IMV. (Simonds, 2003) Some HMV services aggressively transition individuals managed with IMV onto NIPPV – even if assisted ventilation is required 24-hours per day. (Bach et al., 1993) Particularly for those individuals with progressive NMD such as MND or Duchenne muscular dystrophy (DMD), the merits of IMV are disputed by many clinicians. (Bach et al., 2007) While prolonged survivors have been reported in these groups, (Cazzolli & Oppenheimer, 1996) institutional
care is commonly required and this is generally associated with greater costs and poorer quality of life. (Moss et al., 1996) There is no evidence to support a consistent advantage with either IMV or NIPPV – even for those requiring continuous assisted ventilation. Studies evaluating preferences and HRQoL in users of IMV have produced conflicting results (as discussed in Chapter Three) and have been of questionable quality. (Bach, 1993a; Markstrom et al., 2002) Long-term IMV has been described in some localities to manage individuals with COPD, (Muir, Girault, Cardinaud, & Polu, 1994) as well as survivors of critical illness. (Donahoe, 2012; Unroe et al., 2010) Although this approach may be more cost-effective than (acute) hospital-based IMV, there is little debate that transitioning from IMV to NIPPV is associated with considerable cost savings regardless of the site of care. (Pilcher et al., 2005) As a result, it is very likely that cost acts as a major disincentive towards the use of domiciliary IMV. It is acknowledged that its relative contribution in comparison to clinician preference is unknown. Investigators have reported that users prefer NIPPV to IMV, particularly those that have experienced both therapies. (Bach, 1993a) Because IMV is frequently instituted in the setting of acute respiratory failure, anecdotal evidence suggests that few individuals are offered a discrete choice. Thus it is difficult to determine whether user preference contributes at all towards the use of IMV, or if such preferences are simply a reflection of the bias of clinicians towards one approach or another. (Bach et al., 2007; Lofaso et al., 2006) Regional differences in attitudes towards IMV are reflected in guideline documents, with some advocating the use of IMV for individuals with NMD when NIPPV is not manageable, (McKim et al., 2011; Windisch et al., 2010) while others instead emphasise the importance of advanced directives in order to avoid emergent intubation in the setting of acute respiratory failure. (Piper et al., 2010)
5.7 **Airway Clearance Techniques**

In comparison to many of the other interventions discussed in this section, the various guideline documents appear consistent in their recommendations that a variety of techniques be used to assist with airway clearance in individuals who demonstrate a reduced peak cough flow. (McKim et al., 2011; Piper et al., 2010; Windisch et al., 2010) Where graded, these recommendations were made on the basis of low quality evidence. (McKim et al., 2011; Piper et al., 2010) The techniques described include lung volume recruitment (LVR) which is achieved with the use of a resuscitation bag and mask/mouthpiece or through the use of a ‘breath-stacking’ technique using a ventilator; manually assisted cough which involves the augmentation of a spontaneous cough with the use of an abdominal or thoracic thrust by a carer or attendant; and mechanical in-exsufflation which requires the use of a proprietary device that delivers initially positive, then negative, airway pressures to promote the clearance of secretions. (McKim et al., 2011) Despite the apparent consensus of these recommendations, these measures are inconsistently applied by clinicians, (Katz et al., 2013) with a lack of controlled clinical trials cited as a significant barrier to more widespread use. (Chatwin et al., 2003; Katz et al., 2013) Anecdotally, there is little debate regarding their value during acute respiratory infection. Uncertainty exists regarding their benefits as a routine intervention for airway clearance during periods of stability. Evidence from retrospective studies suggests potential benefits with regular LVR strategies, including a possible slowing in the decline in respiratory function of individuals with DMD, (Katz et al., 2013; McKim et al., 2012) as well as the suggestion of reductions in morbidity (including avoidance of IMV) and prolonged survival. (Bach, Ishikawa, & Kim, 1997) Other studies have predominantly identified improvements in measures of cough strength without demonstrating significant longitudinal clinical benefits. (Chatwin et al., 2003; S. Cleary, Misiaszek, Kalra, Wheeler, & Johnston, 2013) Centres not currently recommending these techniques for users are departing from recommendations included in published guidelines. The
question remains, however, whether the low quality evidence on which these recommendations have been made is sufficient to support the widespread adoption of routine LVR and similar techniques.

5.8 **Site of Initiation of Therapy**

Historically, the initial implementation and acclimatisation of NIPPV always occurred during an inpatient hospital admission and this approach has a number of advantages. (Lujan et al., 2007) The most obvious of these is the potential to mobilise resources and expertise quickly to optimise therapy and to manage medical or technical problems that arise. (Lujan et al., 2007) Inpatient implementation allows close supervision and regular review which may provide the opportunity for the user to adapt to NIPPV quickly. (Leger & Laier-Groeneveld, 2002) Previously, authors have argued that inpatient implementation helps to create confidence, specifically to assist the user to sleep with NIPPV, and limits adverse effects. (Leger & Laier-Groeneveld, 2002) They have also postulated that inpatient implementation leads to a more rapid improvement in symptoms and hypercapnia. (Leger & Laier-Groeneveld, 2002) This has not been conclusively demonstrated in clinical trials. A number of studies have suggested equivalent outcomes between inpatient and outpatient implementation strategies, although generally in carefully selected populations. (Chatwin, Nickol, Morrell, Polkey, & Simonds, 2008; Domenech-Clar et al., 2008; Hazenberg et al., 2014; Lujan et al., 2007; Sheers et al., 2014) Inpatient implementation also poses a significant logistical barrier, particularly to users with complex care needs. The imposition of time away from home could disrupt care processes and procedures. (Hazenberg et al., 2014) It also requires the occupation of hospital beds that may be required for acute care and this imposes considerable costs. (Lujan et al., 2007)
A number of HMV services have adopted an outpatient model of NIPPV implementation and there are a small number of studies that support this practice. (Chatwin et al., 2008; Domenech-Clar et al., 2008; Hazenberg et al., 2014; Lujan et al., 2007; Sheers et al., 2014)

In a prospective RCT, Chatwin et al. allocated 36 clinically stable individuals with NMD or RTD who required NIPPV to either inpatient admission for implementation of therapy or an alternative outpatient model. (Chatwin et al., 2008) The investigators reported similar healthcare utilisation between the two groups with regard to contact with healthcare workers (although the length of inpatient admissions was discounted). (Chatwin et al., 2008) There were no reported differences between groups with regard to adherence to therapy or measures of gas exchange (daytime PaCO$_2$ and nocturnal SpO$_2$). It should be noted however that 18% (n=6) of participants dropped out of the study and were not included in the final analysis – four of whom were allocated to the outpatient group. (Chatwin et al., 2008) In a larger study, Domenech-Clar et al. reported results from a mixed cohort of individuals with either NMD, RTD or OHS who were managed either using an outpatient implementation model or a standard inpatient admission. (Domenech-Clar et al., 2008) They demonstrated no difference in HRQoL outcomes but significantly improved blood gas parameters in the ambulatory care group at six months. (Domenech-Clar et al., 2008) Despite these apparently positive findings, the study was limited by the presence of allocation bias, with group allocation dictated by the geographical area in which the participant resided. (Domenech-Clar et al., 2008) This non-randomised group allocation may have resulted in the presence of significant clinical, demographic and socio-economic confounders. Also, there was a trend towards higher baseline PaCO$_2$ and lower baseline PaO$_2$ in the inpatient group – perhaps suggesting more severe respiratory failure than the outpatient cohort. Both groups achieved a mean PaCO$_2$ that was within normal limits at six months and therefore the mean difference between the two groups (2mmHg) is also of uncertain clinical significance. (Domenech-Clar et al., 2008) More recently,
Hazenberg et al reported on an RCT comparing home-based implementation of NIPPV in comparison to a hospital-based for individuals with NMD and RTD in the Netherlands. (Hazenberg et al., 2014) The home-based group included the use of telemonitoring to support users. Similar to Chatwin et al, outcomes at six months (specifically PaCO$_2$, mean adherence) were not different between groups. Therapy failure (not defined) and deaths occurred in 18% of the home-based group and 10% of the hospital-based group at six months however these were not listed as study outcomes. The frequency of non-adherence (average daily use less than four hours) was also not reported. Subjective measures did not appear to differ significantly in survivors and those continuing in the study at six months and estimated costs were considerably lower in home-based arm. Costs in the hospital-based group may have been influenced by the standard use of monitoring within ICU in order to facilitate titration of NIPPV. (Hazenberg et al., 2014)

Despite their limitations, these studies do suggest a role for an outpatient implementation model for clinically stable individuals that require NIPPV. (Chatwin et al., 2008; Domenech-Clar et al., 2008) Definitive evidence is lacking, however, as to whether broader inclusion criteria and home-based implementation without the sophisticated telemonitoring described by Hazenberg et al is as safe and effective as inpatient care. Other studies evaluating outpatient models of NIPPV implementation have demonstrated shorter waiting times, (Sheers et al., 2014) which may have improved clinical outcomes for individuals with MND. Lower costs have also been demonstrated, with these predominantly achieved through a reduction in hospital bed days. (Lujan et al., 2007)

Despite these positive findings, HMV guidelines are inconsistent in their recommendations regarding the site of initial NIPPV implementation. Some do not address the site of implementation, ([No authors listed], 1999; McKim et al., 2011) while others explicitly recommend that implementation occur “on a
specialised general ward, in a sleep lab or on an observational ward". (Windisch et al., 2010) Others suggest that the site of care should be chosen at “the clinician’s preference”. (Piper et al., 2010)

On the available evidence it appears reasonable to suggest that selected clinically stable individuals can achieve equivalent outcomes with an ambulatory model for NIPPV implementation. Given the considerable costs associated with inpatient admissions, and the apparently equivalent clinical outcomes, it is likely that ambulatory models would be cost-effective. It is uncertain if the introduction of new technologies such as auto-titrating devices, (Jaye et al., 2009) systematic analysis of device-derived data, (Janssens et al., 2011; Pasquina et al., 2012) or telemonitoring, (Hazenberg et al., 2014; Pinto et al., 2010) could provide further support for this approach. Due to the costs associated with these new technologies, objective studies that can demonstrate a clinical benefit at a reasonable cost should be performed before they are implemented more widely. (Mandal et al., 2015)

5.9 Monitoring and Evaluation

Regardless of how the initial implementation procedure is performed, most HMV services perform some form of follow-up evaluation in order to determine if the therapy is achieving the desired clinical or physiological result. (Garner et al., 2013)

No studies have directly compared HMV services regarding how they monitor users after implementation, although the survey of HMV centres in Australia and New Zealand performed by Garner et al did compare the frequency of PSG use during follow-up. (Garner et al., 2013) Their results suggested much more frequent use of nocturnal PSG in HMV centres in Australia in comparison to New Zealand (90% vs. 33% during implementation and 50% vs. 0% during
follow-up). (Garner et al., 2013) The underlying drivers for this difference were not revealed in this study. A subsequent study by Rose et al based on survey responses from Canadian HMV providers reported that only 8% (of 105 providers) utilised polysomnography during follow-up. (Rose et al., 2015) Nocturnal oximetry was the predominant form of nocturnal monitoring used across Canadian centres, suggesting a similar approach to HMV centres in New Zealand. (Garner et al., 2013; Rose et al., 2015) No other comparison studies have evaluated this aspect of care. The data presented earlier in this chapter (Table 4) from prospective studies does suggest that very different approaches are used. This is also reflected in the disparate recommendations contained within HMV guidelines. Some recommend nocturnal monitoring (with PSG) for all patients to “ensure settings are appropriate to control sleep hypoventilation”, (Piper et al., 2010) while others do not recommend any nocturnal monitoring, instead advocating the use of daytime measures of gas exchange (PaCO$_2$, PtcCO$_2$ and SpO$_2$) to determine the effectiveness of therapy. (Windisch et al., 2010) The Canadian HMV guideline demarcates its recommendations to specific groups, with recommendations that PSG and measures of arterial blood gases are “not required” for individuals with MND, while noting that PSG is “useful for titrating and confirming efficacy” for individuals with OHS. (McKim et al., 2011)

5.10 Unrecognised Benefits of Care Models

Although the aim of the interventions used by HMV providers primarily relates to a desire to optimise respiratory status and achieve improvements in the effectiveness of ventilation, it is important to consider other potential benefits of a particular care model. Due to their underlying illness or to their reliance on assisted ventilation, users of HMV may be socially isolated, suffer from mood disorders or experience frequent clinical deteriorations. Regular or routine care practices that are instituted by HMV providers could theoretically provide support, not through a direct effect of the intervention itself, but by ensuring
regular contact between the individual receiving assisted ventilation and experienced clinicians. Thus the intervention – be it a home visit to service a device, an overnight PSG to evaluate therapy, or a session with a physiotherapist or nurse to learn airway clearance techniques – may produce benefits that occur as a result of the interaction between the user and the health professional. Reassurance, security, information and education may all be provided – even though these are not the primary aims of the intervention. By performing the intervention, this interaction also provides an opportunity to identify and remedy device or clinical problems. This may occur earlier than would have occurred without the routine contact. This opportunity may therefore produce significant clinical benefits. But the question is whether the interaction itself is enough, or does the intervention itself actually produce a measurable benefit? This issue needs to be considered in the design and interpretation of clinical studies.

5.11 Evaluating the Quality of Care Delivered by HMV Providers

Returning to the framework outlined earlier in this chapter (see Figure 4), evaluating quality of care for HMV providers requires consideration of outcomes related to the organisation, users and care practices. (Frølich, 2012)

Evaluating organisation outcomes is likely to already be occurring for most centralised HMV providers, as this is one of the advantages of a centralised administrative structure. Determining performance indicators that are broadly relevant between different HMV providers would allow comparisons between services. An example may include waiting periods between referral and implementation with HMV. (Sheers et al., 2014) Monitoring unplanned hospital admissions, machine servicing or failure rates and serious adverse events could also provide valuable benchmarks for which to evaluate organisations.
Similarly, measuring outcomes for users of HMV should again already be a consideration for centralised HMV providers who are likely to be equipped with structural advantages to collecting and reporting these data. Mortality data should be included in these measures although it is important that these are evaluated in an appropriate context given the prognosis of many of the underlying disorders that require long-term assisted ventilation. Comparisons between different HMV providers using mortality data alone could be problematic unless population differences are properly understood. Subjective measures, such as symptom ratings, measures of HRQoL and QoL and satisfaction with care may also be valuable. (P. D. Cleary & McNeil, 1988) Again, if consistently applied, these may provide valuable benchmarks for comparison with other HMV providers. The choice of instruments or scales for this population is not necessarily straightforward however, as the heterogeneity of the population and the potential for attrition or survivorship bias could create difficulties with comparisons. The inclusion of instruments or outcome measures that can account for deceased individuals could avoid reaching erroneous conclusions with these data. (Richardson, McKie, & Bariola, 2011) Data collection methods must also be acceptable and reliable across all groups included within HMV cohorts, particularly with regard to their format and the burden imposed. (Whitehurst et al., 2014)

Care practice evaluations for HMV providers are potentially more difficult and these may interact with both the user and organisation outcomes listed above. For example, the frequency of transition from NIPPV to tracheostomy for individuals with NMD may be considered by some to be a marker of the quality of NIPPV delivery. (Bach et al., 2007) Effective NIPPV delivery may therefore be assumed if the rate of tracheostomy use is low. However, if tracheostomy use is discouraged or rarely performed, the low rate of tracheostomy may essentially be a mandated outcome for some services that have chosen to avoid this intervention. Conversely, if tracheostomy is used relatively frequently, this could skew mortality data for individuals with progressive NMD when comparing this
with centres that discourage its use. A possible solution to this is to ensure that clinically appropriate and relevant outcomes are reported – in this example; tracheostomy-free survival would be more appropriate than overall survival.

Adherence to guideline recommendations is also problematic when evaluating the quality of care related to the interventions used by HMV providers. Using long-term NIPPV for those with COPD would be in keeping with expert advice in some settings, but not in others. The use of PSG titration of NIPPV would be similar. Therefore determining effectiveness by using a benchmark such as the frequency that PSG is used to titrate NIPPV cannot reasonably be used as a measure the quality of care. These gaps in evidence, and a lack of consensus, are therefore significant barriers to the evaluation of quality of care for HMV users. The reasons that this situation persists are numerous but may primarily involve a lack of clinical equipoise – that being a reluctance to not perform an intervention that is currently established within a particular model of care. Additional factors may be a lack of expertise or access to highly technical interventions. While such a scenario is not necessarily unique to HMV, it is perhaps more problematic in situations where the cost of care is high and the potential demands on care (depending on the approach) could be considerable.

A comparison of individuals receiving assisted ventilation from different regions who are managed by similarly resourced HMV providers would determine if the lack of expert consensus regarding these care practices is reflected in the care delivered. Comparing services from countries with similar economies, demographics and healthcare systems would limit some of the influence that resourcing may have on the structure of HMV providers.
5.12 Conclusion

Based on comparisons between prospective studies and guideline documents from different regions, there is clearly a lack of consensus as to what constitutes high quality care for users of HMV. These comparisons however, are limited due to presence of very different healthcare systems within which the HMV providers must operate. Comparisons between HMV providers from different regions but within similar healthcare systems may be more revealing. Comparing and contrasting HMV providers based in countries with similar economies, demographics and healthcare funding may provide some ability to control for the large influence that access to resources may have on the care model chosen by HMV providers. This would assist in determining if differences in care practices between regions – if they exist when directly compared – truly represent differences in the priorities of care.
Chapter 6 – Canadian and Australian Comparisons

6.1 Introduction

Multiple factors influence the care that is delivered to individuals receiving assisted ventilation. As discussed in Chapter Five, the lack of evidence for many care practices and the absence of a broad consensus between experts makes measuring quality of care difficult. The clinical heterogeneity of individuals receiving assisted ventilation also makes the measurement of clinical outcomes challenging. Comparing approaches to care between regions provides the opportunity to highlight differences and demonstrate associations with clinical outcomes if they are present. An examination of the similarities and differences between HMV providers allows further consideration of how these services have developed and evolved – but also how they may be improved.

The aim of this chapter is to first provide data comparing Canada and Australia with regard to demographics, economies and healthcare funding in order to support the contention that HMV providers from these countries should share similarities in resourcing. Available prevalence data for disorders and risk factors for diseases that may be managed with HMV is also discussed. Following this, details of two HMV providers, one from Canada and one from Australia are provided in order to provide a qualitative comparison of these services.

6.2 Performing International Comparisons

Comparing data from different countries can provide a broader perspective for researchers, policy makers and the general public. (Australian Institute of Health and Welfare, 2012) Such an approach can inform the development of new policies, health interventions or preventative measures. (Australian Institute of Health and Welfare, 2012) The validity of such
comparisons is reliant on issues such as data quality and the choice of countries. (Australian Institute of Health and Welfare, 2012) Regional comparisons of HMV providers have been reported which primarily examined the patterns of use in centres in Europe, (Lloyd-Owen et al., 2005) and in Australia and New Zealand. (Garner et al., 2013) These important studies have highlighted differences, predominantly in patient-selection for HMV, but also in certain care practices. (Garner et al., 2013) Both survey-based studies attempted to standardise data collection through the involvement of local representatives in the design and implementation of the surveys as well as by providing region-specific translations where required. (Garner et al., 2013; Lloyd-Owen et al., 2005) It is important to note that although patient-level data were incorporated into these results, this was not obtained directly from the individual users. Instead, the administering service provided summary data.

In both studies, regional differences in funding or reimbursement arrangements were mentioned as possible influences on some of the differences that were identified. (Garner et al., 2013; Lloyd-Owen et al., 2005) These, and other differences between the broader healthcare systems, economies and general populations within which HMV providers operate may impact on the care strategies employed.

6.3 **Comparing Australian and Canadian Healthcare Systems**

6.3.1 **Funding**

The Australian healthcare system incorporates universal health coverage for citizens and permanent residents through a national public health insurance scheme, Medicare. Medicare is financed through an income tax levy as well as through an additional levy on higher rate taxpayers who do not take out private health insurance. Uptake of additional private health insurance is therefore
encouraged through this mechanism, as well as through the provision of a means-tested rebate on premiums. Over half of the Australian adult population (57%) held private health insurance cover in 2011-12. (Australian Bureau of Statistics, 2013) It is felt to play both a complementary and supplementary role to the public health system by offering access to treatment within private hospitals and covering some ancillary health services. (Thomson et al., 2012) Approximately 70% of total health expenditure is funded by governments in Australia, with just over 60% of this funded by the Federal government and the remainder funded by State and Territory governments. (Thomson et al., 2012)

As the primary funder of healthcare within Australia, the Federal government, through the Medicare Benefits Schedule, defines appropriate subsidies for outpatient care including outpatient physician services. General practitioners (GPs) and physicians are able to set their own fees however. Despite this, most GP consultations are ‘bulk-billed’, meaning that the patient does not have an additional out-of-pocket cost.

The Canadian healthcare system also incorporates universal healthcare coverage for citizens and residents. (Thomson et al., 2012) In contrast to the Australian system, however, the Provincial or Territorial governments administer this with additional financial support provided by the Federal government. These fiscal transfers are conditional on the provision of universal coverage for medically necessary hospital, diagnostic and physician services in a system also known as Medicare. (Thomson et al., 2012) There is no cost sharing for publically insured physician, diagnostic and hospital services and therefore no out-of-pocket costs at the point of care for these services. The majority of specialist care is provided in hospitals and in this setting, physicians are not allowed to charge prices above the negotiated fee schedule.

Almost two-thirds of Canadians have additional private health insurance, frequently funded through employment-based group plans which cover services such as vision, dental care, prescription drugs, rehabilitation services, home care
and private rooms in hospital. Health insurance to provide faster access to publically-funded physician and hospital services is not available. (Thomson et al., 2012)

Public funding accounts for just over 70% of total health expenditures in Canada although the Federal government contributes only 20% of this. The Provincial or Territorial governments, through general taxation, contribute the remaining funds.

6.3.2 Health costs and outcomes comparison

Canada and Australia share a number of similarities related to their healthcare systems. Although Canada spends a larger percentage of gross-domestic product (GDP) on healthcare than Australia (11.4% vs. 9.1%) (Thomson et al., 2012) many of the other spending parameters, including the rate of growth and out-of-pocket spending on healthcare are similar. (Thomson et al., 2012) Within the general population, health risk factors such as smoking rates (16.3% vs. 15.1%) and obesity prevalence (24.2% vs. 24.6%) are similar. (Thomson et al., 2012) Specific health outcomes such as the mortality rate post admission with acute myocardial infarction (3.9% vs. 3.2%) and the rate of lower extremity amputation due to diabetes (10 vs. 11 per 100,000) are also similar. (Thomson et al., 2012) Consumer satisfaction rates related to public healthcare also do not appear different, with over half of those surveyed in each country reporting that fundamental changes are needed to the respective health systems. (Thomson et al., 2012)
6.3.3 Demographics and economic attributes

In considering the usefulness of comparing HMV services in different countries, it is also relevant to consider demographic and economic similarities. These may be important as older populations with more chronic disease may have different requirements and indications for HMV than younger, healthier cohorts. On this level, again Canada and Australia share a number of similarities. Although larger in population, Canada has a similar percentage of its population to Australia aged over 65yrs of age (14.1% vs. 13.0%)(Thomson et al., 2012) and a similar level of foreign born individuals (19% vs. 22%).(Migration Policy Institute, 2001) Both countries are members of the Organisation for Economic Co-operation and Development (OECD) and the G20 and share common heritage as former colonies of the United Kingdom. From an economic viewpoint, the two countries share many similarities with similar GDP per capita and similar contributions from primary production (manufacturing, mining, agriculture, forestry and fishing).(Organisation for Economic Co-Operation and Development, 2015; Reserve Bank of Australia, 2009) Both rank within the top third of OECD countries (first, Australia and sixth, Canada) on the OECD 'Better Life Index', a measure of wellbeing that incorporates 11 dimensions of life such as housing, income, employment, community, education, environment, civic engagement, health, life satisfaction, safety and work-life balance.(Organisation for Economic Co-Operation and Development, 2016)

While drawing firm conclusions regarding the appropriateness of comparing HMV services between Australia and Canada is difficult, there is little doubt that there are sufficient similarities to suggest that making such a comparison is not inappropriate.

When analysed further, undescribed differences in the funding of interventions, personnel or equipment for HMV providers may contribute significantly towards any differences in the care delivered. However, it is safe to
say that it appears that both Canada and Australia are relatively unencumbered when it comes to access to resources, knowledge and expertise in their potential to deliver high quality care for individuals receiving assisted ventilation. As such, while cost and access constraints may exist, they would not be expected to be larger drivers of practice than evidence from robust clinical studies, expert opinion or institutional preferences.

6.3.4 Prevalence of illnesses that may require HMV

As outlined in Chapter Two, one of the major areas of difference identified in previous comparisons of HMV services from different regions relates to patient-selection. (Garner et al., 2013; Lloyd-Owen et al., 2005) Lloyd-Owen et al demonstrated significant variation in the use of HMV for ‘lung users’ (comprising predominantly COPD) across the surveyed countries. (Lloyd-Owen et al., 2005) Providers in Italy, France, Germany, Austria and Portugal reported comparatively high proportions of ‘lung users’ in comparison to Denmark, Poland, Norway and the Netherlands. (Lloyd-Owen et al., 2005) They attributed this to a “greater interest in the ventilation of COPD patients” in some centres but also acknowledged the system of reimbursement limited the provision of HMV for some disease groups in some countries. (Lloyd-Owen et al., 2005) Garner et al discussed their observation of relatively low rates of HMV use in individuals with COPD in their study of 27 centres providing HMV in Australia and New Zealand. (Garner et al., 2013) They postulated that lower smoking rates in these two countries relative to Europe may have been a driver but no data were presented to support this conclusion. (Garner et al., 2013) They also noted local funding arrangements – particularly in New Zealand – which limit the prescription of HMV for those with COPD. (Garner et al., 2013) Garner et al also noted marked differences in the prevalence of HMV for users with OHS between Australia and New Zealand (25.6% vs 53.7% respectively). (Garner et al., 2013)
Interestingly, this finding may be a reflection of differences in the underlying prevalence in obesity (BMI>30) between the two countries (24.6% vs 27.8%)(Thomson et al., 2012) but the authors describe a possible reluctance to use CPAP as first line therapy for OHS in New Zealand centres as an additional explanation.(Garner et al., 2013)

Based on these reports, it seems likely that there will be differences in patient-selection between Canadian and Australian centres. Determining if there could be differences in the underlying prevalence of disorders that require HMV will allow a better understanding of the context of any variation between the two countries in the pattern of HMV provision. Unfortunately, there is relatively little prevalence data on many of these conditions. Some information can be drawn from the epidemiological data presented earlier – with similar age demographics, obesity and smoking rates.(Thomson et al., 2012) Whether there are regional differences (between states/provinces) in these attributes is unknown. Regarding specific prevalence for disorders that are frequently managed with HMV, only inferences can be drawn. The incidence of MND is generally reported to be approximately 2-3 in 100,000,(Alonso, Logroscino, Jick, & Hernán, 2009; Orrell, 2010) and there is no specific data from either Australia or Canada to suggest a marked variation from this level.(Wolfson, Kilborn, Oskoui, & Genge, 2009) Recent, region specific data for muscular dystrophy is similarly limited but prevalence rates between Canada and Australia have been reported to be broadly similar (26.2 vs 18.6 per 100,000 live male births, respectively).(Cowan, Macdessi, & Stark, 1980; Monckton, Hoskin, & Warren, 1982) For COPD, prevalence rates between Canada and Australia appear similar,(Buist et al., 2007) although there are no data to clarify if there are differences between the two countries in the prevalence of severe hypercapnic COPD which is the the group thought most likely to benefit from long-term NIPPV.(Köhnlein et al., 2014; McEvoy et al., 2009) No specific prevalence data is available for OHS. The previous published estimate (0.15 – 0.3% of the general adult population) was extrapolated from the rates of obesity and OSA in the general US
As such, obesity rates are the best available surrogate marker for the prevalence of OHS, and these are similar between Canada and Australia. (Thomson et al., 2012)

Although not definitive, these comparisons would suggest that although there may be variations in the underlying prevalence of these disorders between Australia and Canada, they are likely to be small and therefore should not be major drivers of differences between cohorts of HMV users if they are identified. This again supports the validity of comparing HMV providers from these two countries in order to explore differences in approach to care.

6.4 Canada: Provincial Respiratory Outreach Program (PROP)

PROP provides HMV to individuals residing in the province of British Columbia, which is located in western Canada. It was established in 2001 as a community organisation, in collaboration with the Technology for Independent Living (TIL) service. Prior to this, individuals receiving assisted ventilation were supported in the community by the Pearson Hospital Respiratory Program and it was the closure of this service that initiated a user-led push to develop a community-based (rather than hospital-based) service.¹(McKim, 2009)

The goal of PROP is to enable individuals receiving assisted ventilation to live outside of institutions and in the community where health-related costs are far less and quality of life and independence are much greater. (McKim, 2009)

The service is staffed on a contractual basis through Vancouver Coastal Health (the largest regional health provider in British Columbia, Canada). (McKim, 2009)

The clinicians providing the majority of direct contact with clients are respiratory therapists. These individuals are required to have completed a three-year training program (run at community colleges or institutes of technology) or a

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¹ Anonymous (unpublished; 2013); The Provincial Respiratory Outreach Program: A brief history
Prospective clients of PROP are referred by primary care physicians or respiratory physicians when they have developed, or are considered to be at risk of developing, respiratory failure. (McKim, 2009) Clients may be referred during an acute hospital admission or directly from the community. The service incorporates a set of entry criteria that are used to determine eligibility for enrolment (see Appendix B). New referrals are evaluated by the Medical Director of PROP and in general the entry criteria are in line with current Canadian Thoracic Society HMV guidelines. (McKim et al., 2011)

While many PROP clients are referred from the community during periods of medical stability, a number are referred in the context of an acute hospital admission. In this situation, team members from PROP provide assistance with the transition from hospital care to the community through direct involvement in discharge planning. This often includes onsite visits and assessments at acute care hospitals throughout the province. (McKim, 2009)

New clients are provided with up to two ventilatory support devices as well as associated consumables. Clients commenced on PROP devices while in hospital are visited at home within 48hrs of discharge. Those commencing therapy electively in the community are ideally implemented within seven days of their enrolment being approved.²

Communication with clients is through direct contacts in the form of home visits (at least annually) and phone calls, as well as indirect communication through a dedicated website and regular newsletter. (McKim, 2009) Clients have access to a 24-hour telephone advice line that is staffed by PROP respiratory

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² personal communication, Ms K Dickinson, PROP staff member, 2012
therapists. Emergency situations are referred to the emergency medical services in the province. Advice and assistance with equipment or technical issues is provided during telephone consultations. (McKim, 2009) The medical supervision for PROP clients remains the responsibility of the referring physician. This includes the prescription of preferred device settings and interfaces. PROP respiratory therapists will liaise with the referring physician regarding changes to settings or other technical issues. PROP does not incorporate a centralised medical outpatient service, nor do they have direct access to inpatient beds or other inpatient medical services.

PROP is co-located with the TIL service which allows collaboration between PROP respiratory therapists and TIL biomedical engineers to assist clients with complex requirements. The TIL service is tasked with implementing home modifications, mobility aids and other functional aids in order to support clients with disabilities to remain in the community. These adaptive technologies can hasten the transition back to the community for PROP clients who may otherwise require hospital or institutional care due to their functional limitations. (McKim, 2009)

PROP has no direct links or associations with a regional ventilation weaning service. Decisions regarding the use of long-term IMV are therefore made primarily by the referring physician or health service.

6.5 **Australia: Victorian Respiratory Support Service (VRSS)**

VRSS provides HMV to individuals residing in the state of Victoria, which is located in south-eastern Australia. Similarly to PROP, VRSS was established following the closure of a hospital-based program for long-term ventilation. The

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3 personal communication, Ms K Dickinson, PROP staff member, 2012
4 Anonymous (unpublished; 2006); Review of the Victorian Respiratory Support Service
Fairfield Hospital’s closure prompted the establishment of VRSS in 1996, however unlike PROP, the newly developed VRSS was created within the Department of Respiratory and Sleep Medicine at the Austin Hospital in Heidelberg.\textsuperscript{5}

VRSS provides for the implementation and ongoing management of individuals requiring assisted ventilation. Like PROP, VRSS provides a state-wide service and thus receives referrals from a wide geographic area. These are typically from specialist physicians or inpatient services. Unlike PROP, referral from inpatient services typically prompts a direct inter-hospital transfer with VRSS infrequently assisting onsite at the referring centre. VRSS also does not implement ventilation in client’s homes but instead arranges admission to the ward for this purpose. Due to competing patient flows for inpatient beds, these policies have the potential of delaying the implementation of assisted ventilation. A recently developed ‘day-admission’ model reduced waiting times and was associated with fewer adverse events and similar daytime PaCO\textsubscript{2} levels to that achieved with inpatient admissions,(Sheers et al., 2014). Anecdotally, day-admissions are now the preferred option for the implementation of NIPPV for medically stable individuals residing in the community for VRSS.\textsuperscript{6}

Through its incorporation with Austin Health, VRSS maintains access to inpatient beds (up to eight) and an inpatient medical team consisting of a consultant respiratory and sleep physician, an advanced trainee and a resident medical officer. Medical staff are required to manage VRSS inpatients, attend outpatient clinics and provide a consultation service within Austin Health. Medical staff also provide expertise to a separate tracheostomy management service and inpatient ventilation weaning unit (VWU). The VWU may house up to four inpatients with prolonged failure to wean from IMV.(Hannan et al., 2013) The co-location of VRSS and the VWU potentially allows simpler transfers between services – for example where individuals fail to wean from assisted

\textsuperscript{5} VRSS Registrar Handbook (unpublished; 2012)

\textsuperscript{6} Anonymous (unpublished; 2006); Review of the Victorian Respiratory Support Service
ventilation and therefore require ongoing therapy in the community. This approach also allows VRSS to play a gatekeeper role in determining the suitability of individuals for long-term ventilation – particularly long-term invasive ventilation. Given admission to the VWU is typically required for all those who require long-term IMV in the community, this provides an opportunity for rationalisation of the ventilation approach and potentially a switch to non-invasive modalities. (Hannan et al., 2013) Outcome data from the VWU suggest this model is safe and generally successful in reducing the need for long-term IMV in the community. (Hannan et al., 2013)

VRSS incorporates allied health staff to ensure comprehensive management of their clients. Occupational therapists provide aids and equipment to assist in the transition to assisted ventilation. A social worker, speech pathologist and musculoskeletal physiotherapist all form part of the team and are tasked with tailoring the approach to optimise the chance of successful home-based therapy.

VRSS also incorporates an outreach service staffed by specially trained nurses experienced in the management of ventilators, non-invasive interfaces, tracheostomies and gastrostomy tubes. Outreach nurses are responsible for client and carer education, perform annual ventilator servicing and clinical reviews, and are available for both home visits and telephone consultations where required. Annual contact between outreach team members and clients of VRSS is considered the standard of care. Outpatient clinical review with a physician on at least an annual basis is also considered standard. Regular home visits are not part of standard practice, however, are used for servicing and clinical reviews where attendance at an outpatient clinic for this purpose is problematic. Similarly to PROP, there is 24-hour phone support for VRSS clients. After hours this is staffed by advanced trainees who are able to provide advice on device issues as well as medical advice where required. Acute clinical

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7 Anonymous (unpublished; 2006); Review of the Victorian Respiratory Support Service
8 VRSS Registrar Handbook (unpublished; 2012)
deteriorations are referred to local emergency medical services although clients are prioritised to be transferred to the Austin Hospital where an inpatient stay is required.

For the clinical management of assisted ventilation, specialised respiratory physiotherapists are tasked with the implementation of therapy for all new clients of VRSS. In addition, these team members are tasked with the management of respiratory and ventilation issues for VWU admissions and VRSS clients during acute inpatient admissions. The physiotherapist's role includes assisting in the interpretation of overnight PSG that is performed routinely for individuals commencing NIPPV. PSG is also available for diagnostic purposes (prior to commencement of therapy) and during follow-up if deemed necessary by a VRSS physician. PSG for VRSS clients is performed within a specialised sleep laboratory housed adjacent to the acute inpatient ward. This provides the ability for individuals with complex care needs to undergo PSG – a procedure that is often difficult in standard sleep laboratories where nursing care is generally less available.

Regular outpatient reviews are centralised through one of three weekly VRSS clinics conducted at Austin Health or satellite sites in metropolitan and regional centres. The medical care of VRSS clients is shared between the referring clinician (who manages pre-existing medical problems) and VRSS medical staff (who predominantly manage the assisted ventilation and any associated issues). Decisions on the method and adjustment of assisted ventilation are primarily the responsibility of the VRSS medical staff. Guidelines are provided for non-medical members of the VRSS team to perform empirical adjustments (see Appendix C).
<table>
<thead>
<tr>
<th>Feature</th>
<th>Australia</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-based</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Invasive and non-invasive ventilation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Onsite visits at referring centre</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Home implementation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Direct access to inpatient beds</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Centralised medical management</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Outreach service</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>24-hour phone support</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Routine polysomnography</td>
<td>Yes</td>
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</tr>
<tr>
<td>Routine oximetry</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Aids and equipment</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Annual home visits</td>
<td>No&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Annual contact with clients</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Advanced Care Planning</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>(Routine) airway clearance</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Data represent responses to questions posed in personal communications to staff members of each service as well as information extracted from reports that evaluate and describe the respective services. (McKim, 2009)

<sup>a</sup> For complex cases, clinicians may visit referring hospitals prior to transfer

<sup>b</sup> (Minimum) annual review with a physician team member at an outpatient clinical appointment is part of standard care

<sup>c</sup> Aids and equipment are generally provided by external services

<sup>d</sup> Aids and equipment are specific to those provided by the Technology for Independent Living service

<sup>e</sup> Annual home visits are not standard although many receive them for combined device servicing and clinical review by an outreach team member
6.6 COMPONENTS OF HMV PROVIDERS

As discussed in Chapter Five, Stuart et al has described fundamental factors which they felt were crucial to the success of a HMV service. (Stuart & Weinrich, 2004) These provide an appropriate framework to perform a qualitative comparison of these two HMV providers.

6.6.1 Physician leadership

Both PROP and VRSS incorporate highly trained physicians in their model of care but there are clear differences between the two services in the degree of physician oversight. PROP employs a physician medical director who approves all new clients to the service. By nature of their expertise, this physician also manages a number of PROP clients in their clinical practice. The PROP medical director, in effect, performs an administrative function to ensure the appropriateness of referrals and is generally not tasked with direct oversight of clinical matters. Medical management of PROP clients (assuming an individual fits the inclusion criteria) therefore remains primarily the responsibility of the referring physician. Again, due to experience and expertise, referrals tend to be clustered from clinicians with an interest in assisted ventilation and these physicians will generally manage a number of PROP clients. Their level of expertise with assisted ventilation is not necessarily determined or mandated by PROP. In contrast, VRSS has a centralised medical model. The management of assisted ventilation is the primary responsibility of VRSS physicians. Other clinical management issues remain with the referring team or GP. While this centralised medical management adds considerably to the administrative burden on VRSS, the volume of clients within the service allows the development of sufficient expertise in multiple clinicians to ensure the delivery of highly specialised care.
6.6.2 Financial support

Comparisons of the two services with regard to the level of financial support they receive are problematic due to their different structures and staffing. At face value, the reported funding allocations for the two services are similar. For the 2015-2016 financial year, the operating budget of VRSS was $2.92M (AUD) while the PROP operating budget was $3.56M (CAD). There are differences between the two services with regard to funding models and reimbursement for certain activities. For example, PROP does not provide or administer inpatient or outpatient medical services, with these funded separately by the provincial government. While VRSS does provide these services, some (such as inpatient hospitalisations) are reimbursed separately through alternative federal or state funding sources. Whether there are differences in overall health costs per client between the two services is therefore unknown.

6.6.3 Economies of scale

The potential benefits of economies of scale for HMV providers are multiple, and both PROP and VRSS leverage these to a similar extent. From a financial perspective, they create the opportunity for efficiently managing equipment and consumable purchases that produces significant purchasing power. As discussed previously, the management of a ‘critical mass’ of individuals that require assisted ventilation also ensures that clinicians are adequately exposed to these clinical problems in order to maintain competency. Nursing, allied health and medical staff all benefit from consistent exposure and throughput of new referrals. This may be of particular importance for HMV as in comparison to other assistive technologies, individuals requiring HMV are

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9 personal communication, Mr I Batchelder, VRSS staff member (2016)
10 personal communication, Dr J Road, PROP staff member (2016)
typically “low volume but high complexity”.” If a higher caseload improves expertise, it is also possible that it may produce improvements in efficiency. Garner et al previously reported that more experienced and larger HMV providers had significantly higher numbers of clients per fulltime staff member than less experienced or smaller services in Australia and New Zealand. (Garner et al., 2013) While this analysis did not consider the quality of care delivered, it does suggest that large, experienced and centrally administered HMV providers may have structural advantages in catering for increased demands for their services.

6.6.4 Continuity of care

Although PROP and VRSS offer different models of care with regard to medical supervision of assisted ventilation, it cannot be inferred they offer different levels of continuity of care. Both offer a dedicated outreach service that provides clients with the opportunity to be managed by a specialised interdisciplinary team. The decentralised medical supervision model of PROP, through maintaining a single physician contact, might offer particular advantages for some individuals with complicated medical histories or pathophysiology. Such longitudinal relationships may be impossible with the shared care model used by VRSS. It is therefore unclear whether there are true differences between the two services with regard to continuity of care. Both maintain a centralised database of clients and this allows for the recording of clinical and equipment information that can be readily accessed by all staff of the respective organisations. These databases therefore form a crucial plank in establishing effective and timely access to information on specific clients. This may aid clinical care when personal knowledge of the medical history or progress of particular clients is lacking.

Anonymous (unpublished; 2006); Review of the Victorian Respiratory Support Service
6.6.5 Personal care services

Neither PROP nor VRSS directly provide personal care services to clients. Both services will facilitate or advocate on behalf of clients, where necessary, to ensure there are adequate supports in place for successful home-based care. This may include the provision of specific training for carers in the use of assisted ventilation techniques. HMV services in some countries do coordinate the provision of personal care services for their clients. (Stuart & Weinrich, 2004) This could be supportive of overall satisfaction with care and quality of life, particularly for highly disabled individuals. Federal, state/provincial or local governments in both Canada and Australia provide funding for some personal care services that may be accessed by PROP and VRSS clients where necessary.

6.6.6 Quality of life

This aspect of care provision is not explicitly addressed by either PROP or VRSS. Anecdotally, both services strive to ensure their interventions and care can maximise quality of life for their clients. Formal evaluations of satisfaction with care, HRQoL, QoL and wellbeing measures are not part of standard practice for either service.

6.6.7 Access and tailoring of care

Both services have developed care models that aim to maximise access to care for individuals that require assisted ventilation and in particular those with disabilities. Because PROP is entirely community-based (with no physical links to a hospital or health service), their model is perhaps more flexible in this regard. The lack of access to dedicated inpatient beds or a designated physical
space for outpatient implementation means that PROP routinely performs outpatient implementation of NIPPV within clients’ homes. For clients that are current hospital inpatients, PROP will perform implementation at essentially any of the inpatient medical services within the province. This effectively means that PROP brings HMV to the client. In contrast, VRSS does not implement HMV in clients’ homes and instead almost exclusively performs this task onsite at Austin Health or one of the regional nodes. Implementation is performed either as an inpatient (which may require transfer from other acute medical facilities) or as an outpatient (using a day-admission model). Whether this more inflexible model imposes a burden on clients is unknown. Any such burden is balanced by the capacity to ensure the provision of HMV occurs with clinical monitoring in a hospital setting.

Both services are resourced to ensure care is tailored to individual needs. As described above, PROP is co-housed with the TIL service. This allows the PROP team to work collaboratively with biomedical engineers to ensure adequate home modifications are in place to allow care to occur in the home. A similar service is provided by VRSS through the use of occupational therapists although the capacity to provide home modifications (including environmental control systems) are more limited and would require the involvement of external services (Table 5).

6.6.8 Regional organisation

As state/province wide organisations, both VRSS and PROP service a defined geographic region. VRSS also supports individuals in Tasmania who require HMV. Stuart et al suggested that regional organisation such as this provides a model for innovation and for the diffusion of new technology. (Stuart & Weinrich, 2004) There are examples of both PROP and VRSS involvement in the use of new technology and respiratory care practices, such as direct diaphragm
pacing for ventilator dependent individuals with spinal cord injury. (Nikfarjam, Story, Nunn, & Howard, 2011; Onders et al., 2009) While centrally administered services may facilitate the diffusion of new technology, their size and organisation may also provide capacity to scrutinise and evaluate both new and old methods in clinical trials.

6.7 CONCLUSION

Canada and Australia have similar demographics, measures of economic activity and have a broadly similar approach to the funding of healthcare. While differences exist between the two countries, these do not appear to be sufficient to invalidate comparisons of the two HMV providers described.

A cross-sectional evaluation of the populations of individuals receiving assisted ventilation managed by these HMV providers will allow a comparison of the underlying disorders managed with HMV, an opportunity to contrast the care practices employed at each site, and the potential to link these with an important outcome measure - HRQoL. It would not be surprising if differences in the underlying diagnoses of users are identified between the two sites as these have been a consistent finding in previous comparison studies. (Garner et al., 2013; Lloyd-Owen et al., 2005) While anecdotally, the two services have developed different care practices, it is unknown whether the experience of clients of the respective services is truly different. It is also unknown if these differences influence HRQoL.

Would an individual with MND or muscular dystrophy who required assisted ventilation be managed differently if they resided in Australia or Canada? And would any such difference influence their HRQoL? Answering these questions may allow an evaluation of aspects of care that may (or may not) be
associated with HRQoL across the two sites. This generation of hypotheses will allow costly or burdensome interventions to be scrutinised further.
Section 3 – Results

Chapter 7 – Cross-National Comparison of Home Mechanical Ventilation Providers from Canada and Australia

7.1 INTRODUCTION

Cross-national comparisons can provide a broader perspective for clinicians, researchers and policy makers. (Australian Institute of Health and Welfare, 2012) Examining HMV providers situated in countries with similar economies, demographics and healthcare systems, improves the validity of these comparisons. Previous studies have suggested that regional differences are likely to be identified in the populations managed with HMV. (Garner et al., 2013; Lloyd-Owen et al., 2005) The available evidence discussed in the Chapter Six suggests that differences in disease prevalence within the Canadian and Australian general population should be small. Large differences in the populations managed by these two HMV providers, if identified, would suggest at least a degree of variation in patient-selection. In addition to identifying population differences, this comparison may reveal variation in the care practices employed. If present, these may be attributable wholly to differences in population attributes, or alternatively may reflect varying priorities in the approach to care. To extend these comparisons, cross-sectional HRQoL will be evaluated across the two cohorts. Population attributes (demographic, socioeconomic, functional, clinical) will be explored and the relationship between HRQoL and care practice differences examined.

There are multiple aims for this chapter. The first is to provide a quantitative comparison of the two HMV providers that were qualitatively described in Chapter Six. The second is to confirm whether there are differences
in the underlying diagnoses of users of HMV within the two populations. The third is to determine whether they employ different care practices to support their clients. The fourth aim is to examine whether differences in care practices are due to population differences alone, or in fact reflect differences in the approach to care. The final aim of this chapter is to determine whether differences in care practices between the two sites are associated with cross-sectional HRQoL.

7.2 Hypotheses

1. That the proportions of individuals receiving assisted ventilation within the two cohorts with COPD, OHS, NMD and ALS/MND will be different

2. That there will be differences in the care practices employed by the two HMV providers that are not entirely explained by population differences

3. That there will be overall differences in cross-sectional HRQoL (using the AQoL-8D index score and the SRI summary scale) between the two populations of individuals receiving assisted ventilation

4. That cross-sectional HRQoL will be associated with differences in the care practices used by the two HMV providers

7.3 Overview

In 2013, individuals receiving assisted ventilation from two HMV providers in Canada and Australia were invited to participate in a postal survey. The survey included both clinical and demographic items, as well as a number of HRQoL instruments. Detailed methods are provided in the manuscript (see page 157), along with the main results (page 158) and discussion (page 161). (Hannan et al.,
Tables and figures from the online supplement that accompanied the manuscript are provided in Appendix E. Additional methods (page 150), results (page 166) and discussion (page 175) are also provided.

7.4 ADDITIONAL METHODS

7.4.1 Data collection methods

Questionnaire

The non-standardised portion of the survey was developed by the investigators and piloted with five individuals receiving assisted ventilation to ensure it was acceptable, understandable and that it included minimal jargon. Feedback from this pilot group necessitated a small number of alterations to terminology and format (see Appendix D for a copy of the questionnaire).

Clinical data

The centralised databases managed by the two HMV providers were interrogated to allow comparisons between responders to the study (participants) and non-responders. These data were also used as the primary source of clinical data used in the analysis. The validity of responses to the questionnaire and data contained in the respective databases was not independently verified. Additional clinical data was collected in the questionnaire. These included items evaluating type and duration of therapy, average usage, details of initial implementation, use of PSG, adequacy of community support, use of airway clearance techniques and advanced care planning (Appendix D).
Diagnosis

Individuals were grouped according to the diagnosis listed in the respective database. The diagnostic groupings were COPD, OHS, RTD, NMD and ALS/MND. It was determined that ALS/MND should be categorised separately from NMD due to it being a (rapidly) progressive neuromuscular disorder. A broad group of either stable or (generally) slowly progressive neuromuscular disorders were labelled NMD, including but not limited to; muscular dystrophies; phrenic nerve dysfunction, post-polio syndrome, spinal cord injury, congenital and acquired neuropathies and myopathies. No attempt was made to determine actual clinical trajectory.

7.4.2 Additional analysis

Invasive mechanical ventilation

A post hoc exploratory analysis was performed to evaluate domain (SRI) and dimension (AQoL-8D) scores according to HMV type (IMV or NIPPV). This aimed to explore patterns within these components of HRQoL that are incorporated in the summary measures (AQoL-8D index score and SRI summary scale). It was hypothesised that lower measures of physical function in those using IMV may offset higher ratings in non-physical aspects of health when compared to users of NIPPV.

7.4.3 Health-related quality of life

Assessment of Quality of Life questionnaire (AQoL-8D)

The AQoL-8D is a preference-based health-related quality of life (HRQoL) instrument. (Richardson, Iezzi, Chen, Khan, & Maxwell, 2013) The instrument has
35 items and evaluates eight separately scored dimensions (independent living, relationships, mental health, coping, pain, senses, self-worth and happiness). Mental and Physical ‘superdimensions’ are generated from responses and the AQoL-8D also produces a single index of health based on the “time trade-off” method of scaling (AQol-8D index score). (Richardson et al., 2013) The AQoL-8D index score (utility) provides a valuation of a given health state with anchors at full health (=1.00) and death (=zero). AQoL-8D index scores using the current scoring algorithm (version 14) range from 0.09 to 1.00. (“www.aqol.com.au’ Accessed June 2016, http://www.aqol.com.au/index.php/scoring-algorithms,” 2016)

A priori it was determined that the AQoL-8D index score and dimensions would be used as the primary indicator of generic HRQoL for the initial evaluation of the two groups of individuals receiving assisted ventilation. The inclusion of an additional generic preference-based HRQoL instrument (the EQ-5D-5L [see below]) provided the ability to compare the two instruments in this population (with these results presented in Chapter Eight of this thesis).

**EuroQOL (EQ-5D)**

The EQ-5D is a preference-based generic HRQoL instrument that comprises five domains; mobility, self-care, usual activities, pain/discomfort, anxiety/depression. The version used in this study was the EQ-5D-5L that incorporates a five-level (5L) scale for each domain as well as a visual analogue scale for the respondent to estimate their current health (zero to 100). A number of value sets are available for scoring the EQ-5D-5L. Canadian weights were used for the entire population (i.e., Australian EQ-5D-5L responses were assigned Canadian values). (Xie et al., 2016) Similarly to the AQoL-8D, the EQ-5D-5L index score is anchored at full health (=1.0) and death (=zero) however unlike AQoL-8D, the EQ-5D-5L includes health states that are valued as ‘worse than death’
with those indicated by negative values (less than zero). EQ-5D-5L index scores obtained using the Canadian value set range from −0.148 to 0.949. (Xie et al., 2016)

Severe Respiratory Insufficiency (SRI) questionnaire

The SRI is a multi-dimensional disease-specific HRQoL questionnaire specifically designed for use in individuals receiving assisted ventilation. (Windisch et al., 2003b) The instrument was originally designed and validated in German however an English translation has been developed and was the form used in this study. (Ghosh et al., 2012) The SRI includes seven subscales or domains across 49-items. The subscales include respiratory complaints (SRI-RC), physical functioning (SRI-PF), attendant symptoms and sleep (SRI-AS), social relationships (SRI-SR), anxiety (SRI-AX), psychological wellbeing (SRI-WB) and social functioning (SRI-SF). The seven subscales can be summarised into one summary scale (SRI-SS). Each subscale and the summary scale are scored from 0 to 100, with higher scores indicating better HRQoL.

7.4.4 Multivariable regression

This was performed using SPSS version 21 (IBM, Arkmonk, NY). A forward stepwise multivariable regression model was constructed in an iterative fashion with variables selected based on factors demonstrated to influence HRQoL in normal populations (age, gender, employment, household income), (D. W. Brown et al., 2003; Centers for Disease Control and Prevention (CDC), 2003; Fryback et al., 2007; Jiang & Hesser, 2006) and in individuals receiving assisted ventilation (diagnosis), (Windisch et al., 2003a, 2003b) in addition to factors that appeared to have a significant association with HRQoL measures based on inspection of
summary data. Model diagnostics were used to ensure validity; scatter plots of residuals and lack of fit tests. Initially, model constructions were performed using separate data sets for each site (Australia and Canada). Due to similarities in summary data and model constructions, it was determined that pooling the data from both sites was appropriate and to include site as a factor in the model construction in order to determine its significance.
7.5 **MANUSCRIPT — CARE PRACTICES AND HEALTH-RELATED QUALITY OF LIFE FOR INDIVIDUALS RECEIVING ASSISTED VENTILATION: A CROSS-NATIONAL STUDY**


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Care Practices and Health-related Quality of Life for Individuals Receiving Assisted Ventilation
A Cross-National Study

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Abstract

Rationale: Considerable evidence demonstrates comparable regional variation in patient populations managed with this therapy. This review includes the outcomes for individuals receiving assisted ventilation for those patients.

Objectives: We sought to identify and describe the respiratory care practices of home ventilation provision in two different regions and determine whether practice differences influence health-related quality of life.

Methods: We conducted a cross-national survey of individuals receiving assisted ventilation by two state-wide home mechanical ventilation providers, one in Victoria, Australia, and the other in British Columbia, Canada. The survey was used to evaluate care practices, functional and physical measures, socioeconomic attributes, and health-related quality of life.

Measurements and Main Results: Overall, 495 individuals receiving assisted ventilation responded (57.2%) to the survey. Responders had clinical attributes similar to those of nonresponders. The Canadian population had a greater proportion of individuals with neuromuscular disorders and lesser percentages with obesity hypoventilation syndrome and chronic obstructive pulmonary disease.

We also found marked differences in the reported care practices in Canada that were not fully explained by population differences. Subjects in the Canadian sample were more likely to use invasive mechanical ventilation (24.2% vs. 25.5%, P < 0.001), to use routine airway clearance techniques (28.9% vs. 14.8%; P < 0.001), and had more home implementation of noninvasive ventilation (39.9% vs. 3.6%; P < 0.001). Subjects in the Australian population were more likely than those in Canada to undergo polysomnography to evaluate their ventilatory function (93.9% vs. 37.4%; P < 0.001). There was no difference in summary measures of health-related quality of life between the two sites. In a multivariable regression model, age, ability to perform activities of daily living, functional status, employment, and household income were all independently associated with health-related quality of life, but neither geographic location (Canada vs. Australia) nor underlying diagnosis were significant factors in the model.

Conclusions: In two cohorts of individuals receiving assisted ventilation, one in Australia and the other in Canada, we found marked differences in both the care practices provided and the populations served. Despite these regional differences, measures of health-related quality of life were not different. Further research is required to examine costly or burdensome interventions that are currently not used routinely in the management of individuals receiving assisted ventilation.

Keywords: noninvasive ventilation; quality of life; respiratory insufficiency
Although the benefits of home mechanical ventilation have been established for people with a number of clinical conditions (1–5), a lack of consensus remains for others (6–9). Consequently, there are marked differences in patient selection for home mechanical ventilation, with regional differences highlighted in previous studies (10–12). Regional variations in approach appear to extend further than simply patient selection, however, with descriptions in published reports suggesting that a wide range of techniques are used to implement, support, and monitor patients receiving assisted ventilation (1). Whether this variation is purely a function of differences in patient populations or if it represents a true variation in clinical practice is unclear. Would a person using assisted ventilation receive similar care in Europe, North America, and Australia? And how would any differences in care influence their health-related quality of life (HRQoL)?

A number of care practices appear to be used frequently in some settings and sparingly in others. Examples include the use of polysomnography (PSG) in the implementation and monitoring of noninvasive ventilation (NIV) (11), regular lung volume recruitment or assisted coughing (13), and domiciliary invasive mechanical ventilation in patients with progressive neuromuscular disorders (NMDS) and chronic obstructive pulmonary disease (COPD) (10, 12). Many of these care practices are supported by relatively limited evidence apart from observational data and expert opinion (13–19). A lack of clarity regarding the true clinical impact of these and other care practices would appear to be a significant impediment to more widespread use, and possibly to more consistent and higher-quality care.

In this study, we undertook a cross-sectional assessment of respiratory care practices and HRQoL across two cohorts of individuals receiving assisted ventilation, one in Australia and the other in Canada. These countries share an aspiration to provide universal health care, have similar health care costs per capita, and have approximately 70% of their total health system spending covered by public funding (20). We surveyed individuals receiving assisted ventilation managed by the Victorian Respiratory Support Service, based in Victoria, Australia, and the Provincial Respiratory Outreach Program, in British Columbia, Canada. Both services are publicly funded; are affiliated with large public hospitals (in Melbourne, Australia, and Vancouver, Canada); and offer a state- or province-wide, interprofessional, team-based approach to care that incorporates an outreach service, 24-hour telephone support, ambulatory models for elective NIV implementation, and transition to domiciliary ventilation for hospital inpatients. Despite a number of similarities, anecdotally the two services have developed different models of care in the way that they treat, monitor, evaluate, and support individuals receiving assisted ventilation. Further descriptions of the two services are provided in the online supplement.

Our aims in this study were to describe the two populations of individuals receiving assisted ventilation and identify and characterize differences in care practices between the two sites, as well as to determine whether any identified differences were related to variations in the underlying patient populations or were truly reflective of alternative approaches to care. We also aimed to determine whether differences in care practices between the two sites influenced the HRQoL of individuals receiving assisted ventilation. Previous cross-sectional examinations of HRQoL in similar populations have suggested that underlying diagnosis is a major influence on HRQoL (21, 22). However, these studies did not consider factors that might support or impair HRQoL, such as physical functional status and socioeconomic attributes. Therefore, we also aimed to determine if the association between diagnosis and HRQoL remained after adjustment for these factors.

**Methods**

The study protocol was approved by the University of British Columbia Clinical Research Ethics Board (H12-01479) and the Austin Health Research Ethics Committee (H2012/04850).

Informed consent was obtained from all participants.

**Home Mechanical Ventilation Providers**

Participants in this cross-sectional study were recruited from two home mechanical ventilation providers, one based in Victoria, Australia, and the other in British Columbia, Canada. We identified participants by accessing the centralized databases of their respective home mechanical ventilation providers. All those receiving home mechanical ventilation as of February 2013 were invited to participate. We collected responses from English-speaking recipients of the postal survey who were able to provide consent. Further details on the survey procedures are included in the online supplement.

**Study Questionnaire**

Before being sent to participants, the study questionnaire was developed by the investigators and piloted with a small group of individuals receiving assisted ventilation in order to ensure the terminology and format were acceptable.

The questionnaire included items to capture the type and duration of, as well as the reason for, home mechanical ventilation. Data from the client databases were used to supplement questionnaire responses. Specific questions regarding aspects of care (site and circumstances of initial implementation of home mechanical ventilation, completion of advanced care plans, use of routine airway clearance techniques [including lung volume recruitment and assisted cough], and previous PSG while using home mechanical ventilation) were also included. Items used to evaluate demographic and socioeconomic information were adapted from examples obtained from the 2010 U.S. Census.

We also included the Assessment of Quality of Life questionnaire (AQoL-8D) (23), which is a generic, 35-item HRQoL instrument that incorporates eight domains of health and produces a global health utility index anchored at 0.0 (death) and 1.0 (full health). Australian weights were used for the AQoL-8D utility, as Canadian weights were not available. We also included the English translation of the Severe Respiratory Insufficiency (SRI) questionnaire (24), which is a
Figure 1. Participant flow through the study. The Australian cohort was derived from the Victorian Respiratory Support Service, Victoria, Australia. The Canadian cohort was derived from the Provincial Respiratory Outreach Program, British Columbia, Canada. HMV = home mechanical ventilation.

disease-specific, multidimensional HRQoL questionnaire designed for use with individuals receiving assisted ventilation (22, 24).

Physical function and independence in activities of daily living (ADL) were evaluated using the Physical Function subscale of the SRI (SRI-PF) (24) and the Katz ADL scale (25), respectively. The Katz ADL scale is a six-item instrument used to measure level of independence (1 point) or dependence (0 points) for each of six basic ADLs: bathing, dressing, toileting, transferring, continence, and feeding (25). Lower scores represent greater dependence on others for basic ADL tasks.

Table 1. Summary of socioeconomic attributes and diagnosis, by site

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Australia (n = 284)</th>
<th>Canada (n = 211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD</td>
<td>56.3 ± 15.0</td>
<td>56.0 ± 18.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>55.6%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Socioeconomic attributes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population center ≥100,000</td>
<td>160 (56.3%)</td>
<td>106 (50.2%)</td>
</tr>
<tr>
<td>Employed or self-employed</td>
<td>38 (13.4%)</td>
<td>29 (13.7%)</td>
</tr>
<tr>
<td>Household income ≥$60,000</td>
<td>45 (15.8%)</td>
<td>59 (30.3%)*</td>
</tr>
<tr>
<td>Higher than secondary education level</td>
<td>104 (36.6%)</td>
<td>96 (45.5%)</td>
</tr>
<tr>
<td>Residential care</td>
<td>17 (6.0%)</td>
<td>15 (7.1%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS/MND</td>
<td>18 (6.3%)</td>
<td>33 (15.6%)*</td>
</tr>
<tr>
<td>NMD</td>
<td>106 (37.0%)</td>
<td>102 (62.6%)</td>
</tr>
<tr>
<td>RTD</td>
<td>34 (12.0%)</td>
<td>23 (10.5%)*</td>
</tr>
<tr>
<td>COPD</td>
<td>88 (31.0%)</td>
<td>17 (8.1%)*</td>
</tr>
<tr>
<td>OHS</td>
<td>31 (10.9%)</td>
<td>6 (2.8%)*</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.8%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: ALS/MND = amyotrophic lateral sclerosis/motor neuron disease; Australia = Victorian Respiratory Support Service, Victoria, Australia; Canada = Provincial Respiratory Outreach Program, British Columbia, Canada; COPD = chronic obstructive pulmonary disease (includes COPD, non-cystic fibrosis bronchiectasis, cystic fibrosis, and overlap syndrome [COPD with obstructive sleep apnea]); NMD = neuromuscular disorders (includes muscular dystrophies, phrenic nerve dysfunction, post-polio syndrome, spinal cord injury, and congenital and acquired neuropathies and myopathies); OHS = obesity hypoventilation syndrome; RTD = restrictive thoracic disorders (includes congenital and acquired kyphoscoliosis, posttuberculous and postsurgical).

*P < 0.05.

Results

In February 2013, 1,074 individuals receiving assisted ventilation were identified across both sites (Australia, n = 645; Canada, n = 429) (see Figure 1). Of these, 208
A greater proportion of individuals at the Canadian site had amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) or NMDs, whereas a greater proportion at the Australian site had COPD or obesity hypoventilation syndrome (OHS).

**Physical and ADL Function**

Canadian participants were more likely to report an inability to complete most basic ADL tasks independently (Katz ADL scores of 0–2) than were those from Australia (46.4% vs. 25.0%, respectively; \( P < 0.001 \), and they also had a lower median SRI-PF (41.7 vs. 45.8; \( P = 0.01 \). However, when analyzed within diagnostic categories, no significant difference was observed between sites with regard to these physical function measures, suggesting that they were entirely attributable to the excess of individuals in the Canadian cohort who had NMDs or ALS/MND (see Figure 2).

**Care Practices**

Overall, individuals receiving assisted ventilation in Canada were more likely to use invasive ventilation (24.2% vs. 2.5%; \( P < 0.001 \), to require daytime ventilation (23.7% vs. 8.1%; \( P < 0.001 \), to have completed an advanced care plan (27.7% vs. 18.3%; \( P = 0.02 \), to routinely use airway clearance techniques (28.9% vs. 14.8%; \( P < 0.001 \), and to have had home mechanical ventilation implemented while

---

**Table 2. Comparison of care practices, overall and by diagnosis**

<table>
<thead>
<tr>
<th>Care Practice</th>
<th>Overall</th>
<th>ALS/MND</th>
<th>NMD</th>
<th>RTD</th>
<th>OHS</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Can</td>
<td>Aus</td>
<td>Can</td>
<td>Aus</td>
<td>Can</td>
<td>Aus</td>
</tr>
<tr>
<td></td>
<td>(n = 211)</td>
<td>(n = 284)</td>
<td>(n = 18)</td>
<td>(n = 105)</td>
<td>(n = 23)</td>
<td>(n = 34)</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>24%</td>
<td>2%*</td>
<td>18%</td>
<td>0%</td>
<td>33%</td>
<td>7%</td>
</tr>
<tr>
<td>Advanced care plan</td>
<td>37%</td>
<td>94%*</td>
<td>18%</td>
<td>100%</td>
<td>38%</td>
<td>95%</td>
</tr>
<tr>
<td>Routine airway clearance techniques</td>
<td>28%</td>
<td>16%*</td>
<td>57%</td>
<td>60%</td>
<td>33%</td>
<td>22%</td>
</tr>
<tr>
<td>Home NIV implementation</td>
<td>40%</td>
<td>4%*</td>
<td>64%</td>
<td>0%</td>
<td>35%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: Advanced care plan = active/current advanced care plan; ALS/MND = amyotrophic lateral sclerosis/motor neuron disease; Aus = Victorian Respiratory Support Service, Victoria, Australia; Can = Provincial Respiratory Outreach Program, British Columbia, Canada; COPD = chronic obstructive pulmonary disease; Home NIV = home implementation/Initiation of noninvasive ventilation; NMD = neuromuscular disorders; OHS = obesity hypoventilation syndrome; Polysomnography = polysomnography while using assisted ventilation; Routine airway clearance techniques = routine/regular performance of airway clearance techniques (includes airway suctioning, lung volume recruitment, and other assisted cough techniques) in the absence of respiratory infection/deterioration in symptoms; RTD = restrictive thoracic disorders. Invasive mechanical ventilation refers to assisted ventilation delivered via tracheostomy or endotracheal tube.

\(^* P < 0.05\).
Table 3. AQoL-8D health utility and domain health utility values, by site

<table>
<thead>
<tr>
<th></th>
<th>Australian</th>
<th></th>
<th>Canadian</th>
<th></th>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health utility</td>
<td>0.56</td>
<td>0.41–0.77</td>
<td>0.56</td>
<td>0.43–0.73</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Mental SD</td>
<td>0.29</td>
<td>0.18–0.44</td>
<td>0.31</td>
<td>0.19–0.43</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Physical SD</td>
<td>0.48</td>
<td>0.34–0.62</td>
<td>0.44</td>
<td>0.31–0.53</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>IL</td>
<td>0.52</td>
<td>0.42–0.71</td>
<td>0.46</td>
<td>0.37–0.58</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>0.75</td>
<td>0.63–0.85</td>
<td>0.79</td>
<td>0.63–0.85</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>MH</td>
<td>0.60</td>
<td>0.51–0.71</td>
<td>0.65</td>
<td>0.51–0.71</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.77</td>
<td>0.61–0.85</td>
<td>0.77</td>
<td>0.61–0.85</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>0.57</td>
<td>0.51–0.74</td>
<td>0.55</td>
<td>0.51–0.71</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>SW</td>
<td>0.76</td>
<td>0.63–0.89</td>
<td>0.76</td>
<td>0.63–0.89</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.71</td>
<td>0.46–0.85</td>
<td>0.71</td>
<td>0.42–0.85</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>0.84</td>
<td>0.75–0.92</td>
<td>0.82</td>
<td>0.73–0.92</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AQoL-8D = Assessment of Quality of Life-8D; Australian = Victorian Respiratory Support Service, Victoria, Australia; Canadian = Provincial Respiratory Outreach Program, British Columbia, Canada; C = coping; H = happiness; IL = independent living; IQR = interquartile range; MH = mental health; P = pain; R = relationships; S = senses; SD = super-dimension; SW = self-worth.

at home (rather than in a hospital or a sleep laboratory) (39.9% vs. 3.6%; P < 0.001) (see Figure 3 and Table 2). Those managed by the Australian service were significantly more likely to have undergone PSG to evaluate their home mechanical ventilation therapy (93.9% vs. 37.4%; P < 0.001), with differences in the use of PSG persisting even after we analyzed only those individuals who were prescribed nocturnal NIV (93.3% vs. 42.3%). The differences in care practices (with the exception of advanced care plans) remained significant after adjustment for underlying diagnosis, suggesting that they represented different approaches to care between the two home mechanical ventilation providers (see Table 2). The reported frequency of contact with health care workers and the number of hospital admissions in the previous 12 months were not different between the two sites.

**Health-related Quality of Life**

Despite the significant differences identified in both the reported care practices and the underlying diagnoses within the two cohorts, there was no overall difference in AQoL-8D health utility between the two sites (Table 3). There were no differences in subgroups separated by sex, diagnosis, or home mechanical ventilation type (Table 3 and Figure 4).

Regarding the domains of the AQoL-8D, Canadian participants had lower scores than their Australian counterparts in the Physical super-dimension and Independent Living domain of the AQoL-8D, but this did not translate to significant differences in health utility. When these domains of the AQoL-8D were analyzed according to diagnostic groups, the differences between the two sites were not significant, again suggesting that they were a result of the excess number of individuals within the Canadian cohort who had NMDs or ALS/MND.

The results were similar when we used the disease-specific HRQoL instrument (see online supplement). We found no differences between sites in either the SRI summary scale or the domains of the SRI, with the exception of the SRI-PS differences outlined previously.

**Multivariable Regression**

For the AQoL-8D health utility, the final multivariable model included measures of physical function and ADL performance (SRI-PS and Katz ADL scale) as well as measures of socioeconomic status (annual household income [>$60,000] and employment [for wages]) and age (Tables 4 and 5). The final model explained 44.9% of the variance of the AQoL-8D health utility. Neither underlying diagnosis nor site of care (Australia vs. Canada) was independently associated with either measure of
HRQoL in the multivariable model (Figures E1 and E2). Figure 5 illustrates the apparent lack of influence of diagnosis on AQoL-8D health utility following adjustment for the factors contained within the final model.

Discussion

This cross-national, cross-sectional study demonstrated marked regional differences in the clinical characteristics of individuals receiving assisted ventilation and the care practices used to support them. Yet, in spite of these differences, HRQoL was not different between the two sites.

There were significant differences between the Canadian and Australian services in the proportions of clients who had NMDs (including ALS/MND), OHS, and COPD. Data to confirm that the prevalence of these disorders is similar within the two general populations are limited (26–32); however, on the basis of available studies, the differences in proportions we found seem to exceed what could reasonably be expected. In addition, there were also considerable differences in the proportions of individuals using invasive ventilation, and undergoing PSG, home implementation of NIV, or using routine airway clearance techniques. These differences in care practices were not simply the result of the variation in underlying diagnoses between sites, as they persisted when analyzed according to diagnostic groupings. This suggests that both patient selection and care practices differ between these two otherwise very similar home mechanical ventilation services – despite their location within predominantly publicly funded health care systems and within countries with considerable socioeconomic similarities (20–22). Yet, despite these clear variations in approach, we did not observe any difference in summary measures of HRQoL, either overall or by diagnosis.

Domiciliary mechanical ventilation has now been used for over 50 years, and yet the methods and manner in which it is used continue to vary according to region. Our study is certainly not the first to identify some of these regional variations in approach (10, 11). Patient selection has undoubtedly been the most apparent aspect of differences in previous studies. In the Eurovent study, Lloyd-Owen and coworkers demonstrated considerable differences between European countries with regard to both the prevalence of home mechanical ventilation and the proportions of those treated who had COPD and NMDs (10). In a subsequent article, Garner and colleagues compared home mechanical ventilation services in Australia and New Zealand and reported significant differences between these two countries in the proportions using assisted ventilation who had NMDs, OHS, restrictive thoracic disorders, and COPD. Some regional differences in care practices have also been described (10, 11, 35), with Garner and coworkers highlighting the more frequent use of PSG to implement therapy in Australian centers.

We postulate that the primary drivers of the differences demonstrated in these studies and in our data are cost (or access) constraints, a relative lack of evidence or conflicting evidence regarding certain approaches, and a historical or philosophical preference for certain techniques. Cost and access constraints are the most straightforward of these to consider, as these factors tend to influence most aspects of health care provision. Ambulatory care models (including implementation of NIV in the home) are an example of a potentially lower-cost model for the implementation of home mechanical ventilation. Although a number of home mechanical ventilation services still use inpatient stays to implement and review therapy (8), in selected patients, ambulatory care models appear to provide equivalent clinical outcomes and are associated with fewer delays (36, 37). Another aspect of care that is driven by cost is the use of invasive ventilation. Financial incentives (or disincentives) for this form of therapy differ by region (10) and may be dependent on the method of funding (public or private) and the capacity of community services to safely manage these patients. Financial incentives could also influence the use of certain
Table 4. Univariable regression estimates of effect

<table>
<thead>
<tr>
<th>Factors Associated with AQoL-8D Health Utility</th>
<th>β Value</th>
<th>Range</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0*</td>
<td>(−0.01 to 0.01)</td>
<td>0.9</td>
</tr>
<tr>
<td>Sex</td>
<td>0.03</td>
<td>(−0.01 to 0.07)</td>
<td>0.12</td>
</tr>
<tr>
<td>Labor force participation</td>
<td>0.12</td>
<td>(0.07 – 0.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALS/MND</td>
<td>−0.10</td>
<td>(−0.25 to 0.06)</td>
<td>0.01</td>
</tr>
<tr>
<td>NMD</td>
<td>−0.02</td>
<td>(−0.16 to 0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RTD</td>
<td>0.06</td>
<td>(−0.10 to 0.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OHS</td>
<td>−0.01</td>
<td>(−0.16 to 0.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>0.03</td>
<td>(−0.13 to 0.19)</td>
<td>0.01</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katz ADL scale score</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>−0.16</td>
<td>(−0.20 to 0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0–2</td>
<td>−0.12</td>
<td>(0.16–0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SRI physical function</td>
<td>0.06*</td>
<td>(0.04–0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Employment for wages</td>
<td>0.15</td>
<td>(0.10–0.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Household income &gt;$60,000</td>
<td>0.06</td>
<td>(0.01–0.10)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Definition of abbreviations: ADL = activities of daily living; ALS/MND = amyotrophic lateral sclerosis/motor neuron disease; AQoL-8D = Assessment of Quality of Life-8D; COPD = chronic obstructive pulmonary disease; NMD = neuromuscular disorders; OHS = obesity hypoventilation syndrome; RTD = restrictive thoracic disorders; SRI = Severe Respiratory Insufficiency questionnaire.
*β value for a change in the parameter equal to 0.5 of the standard deviation of that parameter (age = 0.5 × SD = 7.9 yr; SRI-PF = 0.5 × SD = 11.6).

investigations or procedures in some settings (38). The ability to access dedicated units with the aim of removing patients from invasive mechanical ventilation may also influence both the number of patients managed with invasive ventilation during acute illnesses and the numbers downstream who need to be managed in this way in the community (39–42).

A lack of conclusive evidence, as well as conflicting evidence from clinical trials, also underlies some of the regional variation in the use of home mechanical ventilation. Lloyd-Owen and colleagues clearly demonstrated geographic variation in the use of long-term NIV for individuals with COPD, and, in spite of more recent studies suggesting a mortality benefit in this group (8, 9), there remains no clear consensus regarding the role of long-term NIV for this indication. Our data also suggest the presence of regional preferences in the use of NIV for individuals with OHS, and in this area, too, recent evidence does imply that continuous positive airway pressure therapy may provide equivalent benefits to NIV in a significant proportion of those with OHS (5, 43).

Other practices, including the use of long-term invasive ventilation for individuals with progressive neurological disorders (such as ALS/MND), the routine use of airway clearance techniques (including lung volume recruitment and mechanically assisted cough), and the use of PSG (or polygraphy) to evaluate home mechanical ventilation, are supported by observational literature and expert opinion (13–19). However, they appear to be used infrequently by a number of home mechanical ventilation providers, presumably because of a lack of controlled clinical trials. Our results emphasize the need for further research in this area, not only to improve the quality of care but also to ensure that limited resources are used appropriately.

The results of this project provide support for previous qualitative studies that emphasized the importance of physical function and socioeconomic status on the overall HRQoL of individuals receiving assisted ventilation (44–46). In fact, the influence of these factors on HRQoL in our present study appeared to be more than that of the underlying diagnostic label or the respiratory care practices used. This extends the findings of previous studies in which researchers identified diagnosis as an important predictor of HRQoL in cohorts of individuals receiving ventilator assistance (21, 22). The results of our analysis demonstrate that the differences in HRQoL between diagnostic groups are explained more by physical functional status and socioeconomic factors than by any intrinsic aspect of the diagnosis itself. We acknowledge that the underlying disorder which has contributed to the need for assisted ventilation is likely to be an important determinant of physical function, and possibly socioeconomic status; however, our results suggest that there is no diagnostic category that is intrinsically associated with poor HRQoL.

Table 5. Multivariable regression estimates of effect and final model

<table>
<thead>
<tr>
<th>Factors Associated with AQoL-8D Health Utility</th>
<th>β Value</th>
<th>Range</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.02*</td>
<td>(0.01–0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Katz ADL scale score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>−0.04</td>
<td>(−0.07 to 0.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0–2</td>
<td>0.07</td>
<td>(0.03–0.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SRI physical function</td>
<td>0.07*</td>
<td>(0.05–0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Employment for wages</td>
<td>0.06</td>
<td>(0.01–0.10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Household income &gt;$60,000</td>
<td>0.04</td>
<td>(0.8–0.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted R² value</td>
<td>0.449</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: ADL = activities of daily living; AQoL-8D = Assessment of Quality of Life-8D; SRI = Severe Respiratory Insufficiency questionnaire.
*β value for a change in the parameter equal to 0.5 of the standard deviation of that parameter (age = 0.5 × SD = 7.9 yr; SRI-PF = 0.5 × SD = 11.6).
among individuals receiving assisted ventilation.

One interpretation of our data suggests that unemployed, financially insecure, and functionally limited individuals receiving ventilator assistance are likely to have a poor HRQoL, regardless of whether they have a diagnosis of COPD, ALS/MND, or OHS, whereas the reverse is likely to be true for those who are employed, financially stable, and less physically dependent. This finding is important for both patients and clinicians, as there is considerable clinical heterogeneity within these broad diagnostic groups and the decision to commence home mechanical ventilation may be influenced by predictions of HRQoL on treatment. Our data support the use of more holistic assessments to better inform these decisions. Our cross-sectional data do not capture potential differences in the trajectory of HRQoL with different diagnoses; however, longitudinal studies have not consistently demonstrated a diagnosis-related impact on HRQoL trajectory (47, 48).

Given the significant differences identified in both the clinical attributes and the respiratory care practices of the two home mechanical ventilation services, it is somewhat surprising that overall HRQoL was not different, even after adjustment for differences in diagnoses and other important baseline variables. Does this mean that the choice of respiratory care practices does not really matter? Our observational data cannot answer this question conclusively. We examined two well-established, centrally administered, interprofessional home mechanical ventilation providers, and it is possible that these structural similarities, combined with adequate clinical expertise, allow the two models of care to achieve similar outcomes for their patients. Our data suggest a lack of association between the care strategies identified and HRQoL outcomes; therefore, we speculate that, on a population level, the magnitude of benefit obtained from individual strategies aimed at optimizing ventilation and respiratory care may be quite small. We acknowledge, however, that such strategies could be beneficial within smaller subgroups. As such, it is vital that care practices that are employed routinely are carefully and critically evaluated, particularly those that are either costly or burdensome for patients. For example, given the marked difference between the sites in the use of PSG, further evaluation is warranted to evaluate the burden, costs, and clinical impact of this practice.

This study has a number of limitations that require consideration. Although we used evidence-based methods to optimize our response rate (49), we acknowledge the potential for responder bias, particularly the possibility that individuals receiving assisted ventilation with better HRQoL may be more likely to respond to a voluntary postal survey such as ours. Also, we note that the Australian site had more clients who did not receive the postal survey than the Canadian site, although we did not identify any systematic reason for this to have occurred. Reassuringly, our comparison of responders with nonresponders demonstrated that our samples provided a good representation of the respective cohorts.

We also acknowledge that, owing to our use of a postal survey, a caregiver or support person may have assisted with or completed the survey on behalf of some respondents, which may have introduced an unknown degree of bias. Although we evaluated data from two statewide and publicly funded services, some individuals could access privately funded NIV devices and therefore may not have been captured within this study. It is uncertain whether this practice occurs to a degree at either site sufficient to influence our findings, although we do not suspect this to be the case. It is also possible that the outcome measures used may not have been sufficiently sensitive to detect a difference that could be attributed to differences in care practices. We attempted to reduce this likelihood through the inclusion of a disease-specific HRQoL instrument. The results obtained with the SRI were not different from those derived from the AQoL-8D (see online supplement); however, this possibility remains. We identified only associations (and the lack thereof) with HRQoL in this study; therefore, these observations should be considered as hypotheses until proven in prospective longitudinal studies. Conducting qualitative studies designed to increase understanding of drivers of patient selection biases at the patient, clinician, organizational, and community levels is also important.
Conclusions  
In this study, we found considerable differences between two home mechanical ventilation providers in different regions with regard to both the care practices employed and the populations served. Geographic heterogeneity in patient selection and the methods used to implement, support and monitor individuals receiving assisted ventilation therefore remains an ongoing challenge to clinicians and researchers in this area. Despite these marked differences between the Australian and Canadian services, there appeared to be no influence on HRQoL, either overall or by diagnostic group. This apparent lack of influence on HRQoL highlights a need for further research to examine interventions that are currently used routinely in the management of individuals receiving assisted ventilation, particularly those interventions that are either costly to administer or burdensome to perform. A focus on strategies that can improve the physical function, independence, employment opportunities, and financial security of individuals receiving assisted ventilation may be more beneficial.

Author disclosures are available with the text of this article at www.atjs.org.

Acknowledgment: The authors acknowledge the contributions of Simon Cox and the staff of the Provincial Respiratory Outreach Program, as well as the staff of the Victorian Respiratory Support Service. The authors also specifically acknowledge the contribution of Marg Bakewell for her assistance with data collection.

References


7.6 **Supplementary Data**

Tables E1-4 and Figures E1-2 from the online supplement included with the manuscript are provided in Appendix E.

7.7 **Additional Results**

There were similar age distributions and a male predominance at both sites (Table 6). Marked differences were identified in the portions with ALS/MND and NMD between the two sites. The Canadian cohort was comprised of greater than 75% of individuals with an underlying neuromuscular diagnosis (either ALS/MND or NMD) in contrast to the Australian cohort for which this group comprised just over 40% ($p<0.001$, Table 6). The Australian cohort had a greater proportion with OHS (35% vs. 8%, $p<0.001$, Table 6). Few individuals with COPD were managed with HMV at either site, although the Australian site had a higher proportion (11% vs. 2%, $p<0.001$, Table 6).

Over 22% of the Canadian cohort used a tracheostomy for ventilation (IMV) in comparison to less than 4% of the Australian cohort ($p<0.001$, Table 6). Consequently, a greater proportion of the Australian population used NIPPV therapy (Table 6). The need for assisted ventilation for more than nocturnal use was relatively infrequent at both sites, although more common within the Canadian cohort (22% vs. 9%, $p<0.001$, Table 6).
Table 6 - Attributes of eligible individuals receiving assisted ventilation from Australian and Canadian providers

<table>
<thead>
<tr>
<th></th>
<th>Australia (n=502)</th>
<th>Canada (n=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54.6 (15.7)</td>
<td>53.0 (17.8)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td>286</td>
<td>226</td>
</tr>
<tr>
<td></td>
<td>57.0%</td>
<td>62.1%</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>ALS/MND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>8.0%</td>
<td>15.7%*</td>
</tr>
<tr>
<td></td>
<td>NMD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>165</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td>32.9%</td>
<td>60.7%*</td>
</tr>
<tr>
<td></td>
<td>RTD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>10.6%</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td>OHS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>173</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>34.5%</td>
<td>8.2%*</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10.8%</td>
<td>2.2%*</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Prescribed use</strong></td>
<td>nocturnal only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>456</td>
<td>285</td>
</tr>
<tr>
<td></td>
<td>91.0%</td>
<td>78.5%*</td>
</tr>
<tr>
<td></td>
<td>&gt;nocturnal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>9.0%</td>
<td>21.5%*</td>
</tr>
<tr>
<td><strong>HMV type</strong></td>
<td>NIPPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>484</td>
<td>281</td>
</tr>
<tr>
<td></td>
<td>96.4%</td>
<td>77.2%*</td>
</tr>
<tr>
<td></td>
<td>IMV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>3.6%</td>
<td>22.8%*</td>
</tr>
</tbody>
</table>

* p<0.05; Pearson’s χ² for proportions

Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, SD=standard deviation, ALS/MND=Amyotrophic lateral sclerosis/Motor neuron disease, NMD=Neuromuscular disease, RTD=Restrictive thoracic disease, OHS=Obesity hypoventilation syndrome, COPD=Chronic obstructive pulmonary disease, HMV=Home mechanical ventilation, NIPPV=Non-invasive ventilation, IMV=Invasive mechanical ventilation

There were very few significant demographic differences between participants from the two cohorts (Appendix E, Table E2). Most were not living in residential care facilities or supported accommodation, with the majority owning the home they lived in. Employment for wages was uncommon across both groups, with the majority retired, receiving a pension or unable to work (Appendix E, Table E2). Most were educated to a secondary level or above and lived in cities. A greater proportion of the Australian cohort reported an annual household income of less than $60,000 (Appendix E, Table E2). Cost of living differences between the two sites were unaccounted for.
7.7.1 Duration of home mechanical ventilation

There was no difference in the proportion of participants that had commenced assisted ventilation in the context of an acute admission (Australian 37.3% vs. Canadian 35.3%, \( p=0.817 \)). The Canadian population contained more users with greater than five years of HMV use (54.0% vs. 42.6%, \( p=0.02 \), Table 7). Users of IMV were over-represented in this group within the Canadian population (n=35, 30.7%). None of the current users of IMV within the Australian population had used assisted ventilation for less than five years (see Table 7).

Table 7 - Duration of home mechanical ventilation; by site and by interface type (overall; invasive mechanical ventilation, and; non-invasive positive pressure ventilation); values represent number (%) except where indicated

<table>
<thead>
<tr>
<th></th>
<th>Australia (n=284)</th>
<th>Canada (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of HMV use (overall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>41 (14.4)</td>
<td>26 (12.3)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>118 (41.5)</td>
<td>71 (33.6)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>121 (42.6)</td>
<td>114 (54.0)*</td>
</tr>
<tr>
<td>No response</td>
<td>4 (1.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Duration of HMV use (IMV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>0 (0.0)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>0 (0.0)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>7 (100.0)</td>
<td>35 (68.6)</td>
</tr>
<tr>
<td>No response</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Duration of HMV use (NIPPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>41 (15.0)</td>
<td>24 (15.0)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>118 (43.2)</td>
<td>57 (35.6)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>114 (41.8)</td>
<td>79 (49.4)</td>
</tr>
<tr>
<td>No response</td>
<td>4 (1.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

\* \( p<0.05 \); Pearson’s \( \chi^2 \) for proportions

Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, HMV=Home mechanical ventilation, IMV=Invasive mechanical ventilation, NIPPV=Non-invasive mechanical ventilation
7.7.2 Healthcare utilisation and community supports

Hospital admission rates and healthcare worker contacts in the preceding 12-months were also not different between sites (Table 8). The (self-reported) mean number of healthcare worker contacts (including specialist, local medical officer and nursing/outreach support) was just over eight contacts per client at both sites in the preceding 12-months (Table 8). Most respondents rated their level of community supports as adequate (“I feel very well supported, I feel well supported, I feel supported”) while less than 5% rated their level of support as poor or very poor. No comparison of personal healthcare costs was performed (Table 8).

Table 8 - Healthcare utilisation and community supports; values represent number (%) except where indicated

<table>
<thead>
<tr>
<th></th>
<th>Australia (n=284)</th>
<th>Canada (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital admissions</strong>(^a)</td>
<td>None</td>
<td>118 (55.9)</td>
</tr>
<tr>
<td>(preceding 12 months)</td>
<td>1 or more</td>
<td>93 (44.1)</td>
</tr>
<tr>
<td>No response</td>
<td>4 (1.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Healthcare worker contacts</strong>(^a)</td>
<td>None</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>(preceding 12 months)</td>
<td>1-6</td>
<td>93 (44.1)</td>
</tr>
<tr>
<td></td>
<td>7 or more</td>
<td>108 (51.2)</td>
</tr>
<tr>
<td><strong>Healthcare worker contacts</strong>(^a)</td>
<td>Mean (SD)</td>
<td>8.3 (6.2)</td>
</tr>
<tr>
<td>(preceding 12 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Perceived level of support</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Poor</td>
<td>2 (0.7)</td>
<td>9 (4.2)</td>
</tr>
<tr>
<td>Adequate(^b)</td>
<td>271 (95.4)</td>
<td>192 (91.0)</td>
</tr>
<tr>
<td>No response</td>
<td>9 (3.2)</td>
<td>10 (4.7)</td>
</tr>
</tbody>
</table>

\*p<0.05; Pearson’s \(\chi^2\) for proportions
\(^a\) Self-reported
\(^b\) Combined ratings of “supported”, “well supported” and “very well supported”
Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, HMV=Home mechanical ventilation, SD=standard deviation
7.7.3 Exploratory analysis

Current users of IMV from both sites more frequently commenced therapy in the context of an acute hospital admission when compared to current users of NIPPV (71% vs. 32%, p<0.001, see Table 9). It was not able to be determined from survey responses whether the current type of HMV used was the same as that instituted during the initial acute hospital admission. There was no difference in the proportion reporting a hospital admission in the previous 12-months between IMV and NIPPV users (Table 9). Contacts with healthcare workers in the previous 12 months were more frequent on average for users of IMV than those using NIPPV (11.3 vs. 7.8, p=0.004; independent samples t-test); ratings of perceived support were similar (Table 9).
Table 9 - Duration of use, healthcare utilisation and community support ratings according to type of ventilation (invasive or non-invasive); combined responses from both Australian and Canadian sites; values represent number (%) except where indicated

<table>
<thead>
<tr>
<th></th>
<th>IMV (n=58)</th>
<th>NIPPV (n=437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of HMV use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>2 (3.4)</td>
<td>65 (14.9)*</td>
</tr>
<tr>
<td>1-5 years</td>
<td>14 (24.1)</td>
<td>175 (40.0)*</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>42 (72.4)</td>
<td>193 (44.2)*</td>
</tr>
<tr>
<td>No response</td>
<td>0 (0.0)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Commenced HMV during acute admission</td>
<td>41 (70.7)*</td>
<td>139 (31.8)*</td>
</tr>
<tr>
<td>Hospital admissions&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>32 (55.2)</td>
<td>225 (51.5)</td>
</tr>
<tr>
<td>1 or more</td>
<td>26 (44.8)</td>
<td>208 (47.6)</td>
</tr>
<tr>
<td>No response</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Healthcare worker contacts&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (8.6)</td>
<td>17 (3.9)</td>
</tr>
<tr>
<td>1-6</td>
<td>18 (31.0)</td>
<td>209 (47.8)*</td>
</tr>
<tr>
<td>7 or more</td>
<td>35 (60.3)</td>
<td>211 (51.2)</td>
</tr>
<tr>
<td>Healthcare worker contacts&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mean (SD)</td>
<td>11.3 (8.5)</td>
</tr>
<tr>
<td></td>
<td>7.83 (6.1)&lt;sup&gt;#&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Perceived level of support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>0 (0.0)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Poor</td>
<td>2 (3.4)</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Adequate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54 (93.1)</td>
<td>409 (93.6)</td>
</tr>
<tr>
<td>No response</td>
<td>2 (3.4)</td>
<td>17 (3.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Self-reported; in the 12-months prior to completing the survey
<sup>b</sup> Combined ratings of “supported”, “well supported” and “very well supported”

*<sup>p</sup><0.05; Pearson’s χ² for proportions
#<sup>p</sup><0.05; independent samples t-test

IMV=Invasive mechanical ventilation, NIPPV=Non-invasive positive pressure ventilation
There was no difference between users of IMV and NIPPV in summary measures of HRQoL using either the AQoL-8D or SRI (see manuscript Figure 4 (page 161) and Appendix E, Table E4). The exploratory analysis of domain (SRI) and dimension (AQoL-8D) scores was performed using pooled responses from both sites from those with ALS/MND and NMD.

For those with NMD, those using IMV had lower scores for the SRI Physical Function domain and the AQoL-8D Independent Living and Physical Superdimension scores in comparison to those using NIPPV (all $p<0.05$; independent samples Mann Whitney U test; Table 10 and Table 11). There were no significant differences in other domains or dimension scores for those with NMD (Table 10 and Table 11).

For those with ALS/MND, the only significant difference between users of IMV and NIPPV with either instrument was in the AQoL-8D Coping dimension that favoured users of IMV ($p=0.016$; independent samples Mann Whitney U test; Table 10 and Table 11). There were trends in other domains (SRI Attendant Symptoms and Sleep, AQoL-8D Mental Health, Pain and Mental Superdimension) that appeared to favour those using IMV, however these did not reach statistical significance. There was also a trend in the AQoL-8D Independent Living dimension that favoured users of NIPPV (Table 11).
Table 10 - Domain and summary scores for the disease specific HRQoL instrument (SRI) from responders with ALS/MND and NMD; invasive and non-invasive interfaces; figures represent median (interquartile range) except where indicated

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HMV type</th>
<th>n=</th>
<th>RC</th>
<th>PF</th>
<th>AS</th>
<th>SR</th>
<th>AX</th>
<th>WB</th>
<th>SF</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS/MND</td>
<td>IMV</td>
<td>6</td>
<td>53.1 (50)</td>
<td>14.6 (27)</td>
<td>78.6 (36)</td>
<td>79.2 (13)</td>
<td>47.5 (43)</td>
<td>68.1 (20)</td>
<td>54.7 (29)</td>
<td>56.4 (20)</td>
</tr>
<tr>
<td></td>
<td>NIPPV</td>
<td>46</td>
<td>40.6 (39)</td>
<td>20.8 (35)</td>
<td>57.1 (32)</td>
<td>70.8 (29)</td>
<td>50.0 (45)</td>
<td>58.3 (31)</td>
<td>50.0 (31)</td>
<td>48.8 (28)</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td></td>
<td>0.638</td>
<td>0.322</td>
<td>0.058</td>
<td>0.199</td>
<td>0.787</td>
<td>0.135</td>
<td>0.539</td>
<td>0.281</td>
</tr>
<tr>
<td>NMD</td>
<td>IMV</td>
<td>50</td>
<td>60.9 (19)</td>
<td>33.3 (18)</td>
<td>57.1 (26)</td>
<td>75.0 (26)</td>
<td>70.0 (38)</td>
<td>72.2 (28)</td>
<td>66.7 (28)</td>
<td>60.5 (15)</td>
</tr>
<tr>
<td></td>
<td>NIPPV</td>
<td>186</td>
<td>62.5 (31)</td>
<td>41.6 (29)</td>
<td>60.7 (25)</td>
<td>70.8 (29)</td>
<td>65.0 (35)</td>
<td>66.7 (25)</td>
<td>65.6 (28)</td>
<td>59.5 (24)</td>
</tr>
<tr>
<td></td>
<td>p-value*</td>
<td></td>
<td>0.781</td>
<td>&lt;0.001</td>
<td>0.332</td>
<td>0.277</td>
<td>0.257</td>
<td>0.203</td>
<td>0.795</td>
<td>0.964</td>
</tr>
</tbody>
</table>

*p-value from independent samples Mann Whitney U test

HRQoL=Health-related quality of life, SRI=Severe Respiratory Insufficiency questionnaire, IMV=invasive mechanical ventilation, NIPPV=non-invasive positive pressure ventilation, ALS/MND=Amyotrophic lateral sclerosis/motor neuron disease, NMD=neuromuscular disorder, SS=Summary Scale, RC=Respiratory Complaints, PF=Physical Function, AS=Attendant symptoms and Sleep, SR=Social Relationships, AX=Anxiety, WB=Psychological Well-being, SF=Social Functioning
Table 11 - Dimension and index scores for the generic HRQoL instrument (AQoL-8D) from responders with ALS/MND and NMD; invasive and non-invasive ventilation; figures represent median (interquartile range) except where indicated

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HMV type</th>
<th>n=</th>
<th>index</th>
<th>pSD</th>
<th>mSD</th>
<th>IL</th>
<th>H</th>
<th>MH</th>
<th>C</th>
<th>R</th>
<th>SW</th>
<th>P</th>
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</tr>
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<td>ALS/MND</td>
<td>IMV</td>
<td>5</td>
<td>0.61 (0.3)</td>
<td>0.36 (0.2)</td>
<td>0.42 (0.2)</td>
<td>0.35 (0.0)</td>
<td>0.79 (0.2)</td>
<td>0.69 (0.2)</td>
<td>0.87 (0.3)</td>
<td>0.56 (0.1)</td>
<td>0.80 (0.2)</td>
<td>0.80 (0.4)</td>
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<td></td>
<td>NIPPV</td>
<td>45</td>
<td>0.48 (0.3)</td>
<td>0.40 (0.2)</td>
<td>0.23 (0.2)</td>
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<td>0.966</td>
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<td>0.058</td>
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<td>0.319</td>
<td>0.813</td>
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</table>

<sup>a</sup> p-value from independent samples Mann Whitney U test

Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, HMV=Home mechanical ventilation, IMV=invasive mechanical ventilation, NIPPV=non-invasive positive pressure ventilation, ALS/MND=Amyotrophic lateral sclerosis/motor neuron disease, NMD=neuromuscular disorder, index=AQoL-8D index score, pSD=Physical Super Dimension mSD=Mental Super dimension, IL=Independent Living, H=Happiness, MH=Mental Health, C=Coping, R=Relationships, SW=Self-Worth, P=Pain, S=Senses
7.8 **Additional Discussion**

These data have confirmed the first hypothesis stated in this chapter by demonstrating considerable variation in the underlying diagnoses of individuals receiving assisted ventilation within populations managed in Australia and Canada. As outlined in Chapter Six, the available data related to risk factors for OHS (obesity) and COPD (smoking) suggest there should be similarities in population prevalence between Canada and Australia. (Thomson et al., 2012) There are also no data to suggest there should be differences in the incidence or prevalence of NMD or ALS/MND. The population differences are therefore very likely to be greater than could be explained by variation in disease prevalence within the general populations. They may represent true differences in the provision of HMV by these providers to certain diagnostic groups.

The second hypothesis was also confirmed with differences demonstrated in the care practices employed by the two HMV providers. Despite a number of organisational similarities, distinctly different approaches were demonstrated in the frequency of IMV, use of PSG to evaluate therapy, implementation of NIPPV at home, and the prescription of airway clearance techniques. Such differences have been suggested in previous publications, (Garner et al., 2013; Hannan et al., 2014) but have not been previously detailed.

The third hypothesis was not proven, with no overall difference demonstrated in cross-sectional HRQoL between the two populations. It was expected that differences in both population and care practices would lead to overall differences in cross-sectional HRQoL using unadjusted estimates. Unexpectedly, both generic and disease-specific HRQoL measures were remarkably similar across the two sites. While the Canadian population tended to score lower in the physical function domains (for both AQoL-8D and the SRI), this did not translate into overall differences in summary measures of HRQoL using either measure.
The fourth hypothesis was also not proven, as no relationship was demonstrated between care practice differences and HRQoL. As discussed in the manuscript, this was the case even after adjustment for other variables that influence HRQoL in normal populations and those that have been associated with the HRQoL of individuals receiving assisted ventilation in previous studies.

### 7.8.1 Population differences and care practices

It was thought that differences in care practices might be explained by differences in the underlying diagnoses of those managed with HMV at the two sites. This was not shown, as when analysed according to diagnostic group, care practices were still significantly different (see manuscript, Table 2). The two findings may however still be linked. It is speculated that the care practices themselves could influence population attributes when evaluated in cross-section. Prolonged survival in progressive NMD with the use of IMV is acknowledged. (Bach, 1993b; Cazzolli & Oppenheimer, 1996) Therefore it is possible more liberal use of IMV at the Canadian site may be a contributor to the relative excess of those with NMD and ALS/MND in the Canadian cohort. This is tentatively supported by the observation of significantly more users of HMV with greater than five years of therapy in the Canadian population. Many of these (30.7%) were using IMV. Of particular note is that only six participants with ALS/MND reported more than five years of HMV, and all of these were managed at the Canadian site with five currently using IMV. This possibility would not account entirely for the population differences demonstrated. A more liberal policy towards ventilatory assistance for OHS and COPD at the Australian site may be a contributor also.

Nevertheless, anecdotally there has been a shift away from IMV at the Australian HMV provider and this could be inferred by the observation that no
current IMV users at this site reported less than five years of HMV. This is not the case for the Canadian cohort, with more current users of IMV reporting shorter durations of HMV (~30% reporting less than five years since commencing). It is acknowledged that respondents were not asked to specify whether their current HMV type (IMV or NIPPV) was that used for the duration of therapy. Disease trajectories for these heterogeneous disorders were also not assessed. This limits the confidence of linking IMV use with the unexpectedly high proportion of individuals with NMD and ALS/MND in the Canadian cohort, however it remains a plausible explanation as a contributor to this observation.

7.8.2 Drivers of IMV at the Canadian HMV provider

A number of factors may underlie the apparent excess of IMV users at the Canadian site apart from the possibility of prolonged survivors. This observation may reflect an institutional (and societal) expectation for therapy that can achieve prolonged survival and thus a lower threshold for commencing IMV. Excess use of IMV may also be an indication of more restricted access to specialised inpatient medical services that are familiar with long-term HMV, with individuals switching from NIPPV in the context of an acute deterioration. The lack of a regional ventilation weaning service could additionally reduce the likelihood that individuals are transitioned off assisted ventilation completely or at least back onto NIPPV, thus increasing demand for long-term IMV in the community. (Pilcher et al., 2005) It is also possible that excess use of IMV could reflect an increased rate of NIPPV failure.
7.8.3 Access to specialised inpatient medical services

Most of those who commence long-term IMV do so in the context of an acute respiratory deterioration requiring hospitalisation. (Cazzolli & Oppenheimer, 1996) Results from the current study suggest that current users of IMV more frequently commenced HMV in the context of an acute hospital admission than those currently using NIPPV. As outlined above, limitations in the format of the survey mean that it is not possible to confirm that those currently using IMV were not initially managed with NIPPV during their original acute hospital admission. Some may have commenced assisted ventilation with NIPPV during an acute admission, and subsequently transitioned onto IMV electively. Even with this limitation, it is still possible that the excess use of IMV in the Canadian service does reflect a lack of access to inpatient medical services familiar with the acute management of individuals receiving assisted ventilation. This may mean that decision-making in the acute setting could be performed in peripheral or less experienced centre and by clinicians that are unfamiliar with long-term HMV users. Reports suggest that inpatient services that specialise in the management of HMV users may be effective in avoiding IMV during acute illness. (Tzeng & Bach, 2000) They may also facilitate a return to NIPPV for those unable to avoid intubation. (Bach & Martinez, 2011)

7.8.4 Regional non-ICU weaning service

The absence of a regional ventilation weaning service may also be a contributor to the greater numbers of those using IMV in the Canadian service. Regional non-ICU weaning centres in various forms are described, (Hannan & Howard, 2013) with most reporting considerable success in liberating individuals from IMV, (Damuth, Mitchell, Bartock, Roberts, & Trzeciak, 2015) as well as
important cost-savings in comparison to ongoing ICU care. (Pilcher et al., 2005)

In contrast to the Canadian service, the Australian HMV provider maintains a
direct link with a specialist inpatient medical service, which facilitates admissions
for current clients, and inter-hospital transfers of those admitted elsewhere. The
Australian service also incorporates a dedicated non-ICU ventilation weaning
unit. This may act to minimise the number of people who require this type of
assisted ventilation at the time of hospital discharge. (Hannan et al., 2013)

7.8.5 Effectiveness of non-invasive positive pressure ventilation

Additional hypotheses for the excess use of IMV at the Canadian site relate
to the effectiveness of NIPPV. Two aspects of the Canadian model for
implementing NIPPV differ considerably from that of the Australian service; 1) the implementation of NIPPV in the users home, and; 2) the routine use of
clinical titration alone (with PSG titration infrequent). Implementation of NIPPV
may be less effective at home than in a hospital setting. While the previously
described reports have suggested equivalent outcomes between these two
approaches, there were some methodological issues that limit these conclusions
including possible allocation bias, (Domenech-Clar et al., 2008) limitations in
analysis regarding drop-outs or treatment failure, (Chatwin et al., 2008;
Hazenberg et al., 2014) and the use of PaCO$_2$ as a primary outcome. (Hazenberg et al., 2014) Routine use of home-based implementation is therefore not confirmed as equivalent to hospital-based, although it is acknowledged that for carefully
selected individuals it may well be. The lack of access to inpatient medical
services may mean the Canadian HMV provider has less capacity to appropriately
target the use of home-based implementation. This could mean that individuals
that may benefit from a period of inpatient acclimatisation are less able to access
this. This is potentially compounded by the use of clinical titration combined
with nocturnal oximetry alone. Daytime clinical titration for NIPPV could produce less effective NIPPV. (Fanfulla et al., 2007) While there are no studies that demonstrate a benefit of routine PSG monitoring over clinical titration, previous investigators have hypothesised that this would be beneficial. (Fanfulla et al., 2005) It is conceivable that if either of these factors contributed to less effective NIPPV, the proportion of users transitioning to IMV (as rescue therapy) could be expected to be higher. The current study was not intended to test this hypothesis and therefore this remains speculation only.

7.8.6 Exploratory analysis

The high proportion of IMV users in the Canadian population did not appear to influence measures of HRQoL between the two sites. In fact, summary measures of HRQoL did not differ between users of IMV and NIPPV overall (manuscript Figure 4 (page 161) and Appendix E, Table E3). The exploratory analysis presented indicates lower physical function measures for those using IMV with NMD (SRI Physical Function, AQoL-8D Independent Living and Physical Superdimension) and ALS/MND (AQoL-8D Independent Living). These scores were offset for individuals using IMV with ALS/MND in the AQoL-8D Coping and Pain dimensions but there were no differences in other domain or dimension scores for those using IMV with NMD. It is of interest that the differences in physical components of health for IMV users did not translate into significant differences in the SRI-SS or AQoL-8D index score. This would suggest the presence of slightly higher ratings in some non-physical aspects of HRQoL that were not statistically significant, but were still sufficient to offset decrements in physical aspects of HRQoL. This could be a reflection of responder or attrition (survivorship) bias as discussed in the manuscript. Alternative explanations include the possibility for response-shift; where “changing internal standards,
values and the conceptualisation of quality-of-life” lead to adaptation. (Sprangers & Schwartz, 1999) This has been described as the ‘disability paradox’, where psychosocial adaptation to severe physical limitation and loss of independence supports quality-of-life. (Lulé et al., 2013) One final possibility to explain the similarity in ratings of HRQoL between users of NIPPV and IMV is the possibility of a bias in patient-selection. Those offered and accepting IMV may have had sufficient personal or community resources (financial, intellectual, spiritual) that allowed this choice to be appropriate for them in spite of poor or deteriorating physical function. It suggests the provision of a service that is able to provide adequate support for those using IMV in order for them to be successfully managed in the community. Those using IMV and NIPPV had similar views on the adequacy of community support. Although representing only a crude representation of healthcare utilisation, users of IMV reported significantly more contact with healthcare workers on average, but no apparent difference in the frequency of hospital admissions in the previous 12-months.

As discussed previously, there are conflicting conclusions from studies that have attempted to address the preference of users of IMV and NIPPV. (Bach, 1993a; Markstrom et al., 2002) Previous commentary suggests that there are strong views from clinicians about the relative merits of these options for assisted ventilation, particularly for those requiring continuous support. (Bach et al., 2007; Lofaso et al., 2006) Societal expectations for access to life-prolonging interventions were not considered in this study but may also be an important driver of the use of IMV. These may be important drivers of differences in practice, particularly with regard to the use of IMV in individuals with progressive neuromuscular disorders such as MND. (Rabkin et al., 2012) The current results were not intended to address this question. Given the ethical barrier to RCTs to determine the superiority of a liberal or restrictive approach to IMV, well-designed longitudinal observational studies would be a reasonable alternative. Such studies would need to include measures of mortality, robust
and reliable measures of HRQoL and life-satisfaction (of both users and their carers), and cost estimates (both direct and indirect) in order to provide assistance with clinical decision-making in this area.

7.8.7 Differences in care practices between providers

Even in apparently similar (and similarly resourced) HMV providers, care practices are different. Apart from the use of IMV and home-based implementation of NIPPV, other differences in approach were also identified. These included the prescription of routine airway clearance techniques such as LVR and mechanical in-exsufflation. Current practice at the Australian HMV provider represents a departure not only from practice at the Canadian site and the Canadian HMV guideline,(McKim et al., 2011) but also from local expert consensus opinion.(Piper et al., 2010) As discussed previously, more convincing objective evidence may be required to convince clinicians of the merits of these approaches. Given the proposed benefits of performing these manoeuvres routinely may be avoidance or delay of HMV, as arguably the hypothesised benefits may be greater in those not already requiring assisted ventilation, and in whom clinical equipoise is likely to be greater. Dedicated neuromuscular or paediatric services may be best placed to evaluate these approaches.

In contrast, routine PSG titration represents an intervention that is considered a fundamental part of the delivery of NIPPV for the Australian HMV provider but not the Canadian. It is both costly to perform and potentially burdensome for individuals receiving assisted ventilation. It is also specifically discouraged in the Canadian guideline with regard to its use in individuals with MND, and therefore current practice in Australia represents a significant departure from this recommendation.(McKim et al., 2011) Avoidance of laboratory-based overnight monitoring would represent a significant financial
saving, but at what cost? Would NIPPV be less effective at improving gas exchange, sleep quality, patient-ventilator synchronisation, symptoms and HRQoL? And could this lead to increased non-adherence or treatment failure?

7.9 CONCLUSION

These results have confirmed cross-sectional differences in the underlying diagnoses of individuals receiving assisted ventilation managed by the Canadian and Australian services and also considerable differences in the care practices employed to support them. Despite this, there was no difference overall in summary measures of HRQoL, and the care practice differences identified were also not associated with HRQoL. These findings have generated a number of hypotheses that could be tested in longitudinal studies. In particular a number of questions remain regarding the actual clinical benefit of care practices such as the routine use of PSG titration of NIPPV. While it is possible that not performing PSG could lead to less effective NIPPV, it is uncertain whether any advantages justify performing it routinely.

The following chapter of this thesis details two studies that provide an examination of subjective outcome measures for use in studies involving users of NIPPV. It includes a systematic review that included prospective studies of NIPPV in treatment naïve users to determine its effect across different diagnostic groups. Following this, a comparison of responses from individuals receiving assisted ventilation to two generic preference-based HRQoL instruments is provided. The findings from these analyses were intended to guide the choice of outcome measures used in longitudinal studies involving NIPPV.
Chapter 8 – Evaluation of Subjective Outcome Measures

8.1 INTRODUCTION

Physiological measures are used in studies evaluating the effect of NIPPV, as these measures are easily interpretable, generally reliable and available in most healthcare settings. While these measures remain valuable to identify the physiological effects of an intervention, they do not always translate into clinical benefits. Subjective measures, when applied appropriately, may provide a better indication of the effect of an intervention that balances both its burdens and its benefits. Patient-reported outcomes include self-reported symptom scores or scales and preference-based measures of health-related quality of life (HRQoL). Such measures are particularly beneficial when so-called ‘hard’ clinical endpoints, such as mortality, are unable to be measured.

The choice of patient-reported outcome measures can be difficult however, as the format, structure, content and reliability of these may not be known or may not have been adequately evaluated. Interpreting the results obtained can also be difficult, particularly in heterogeneous populations, as treatment effects may differ between different disease groups despite the application of an apparently uniform intervention. Even within apparently homogeneous populations, for example those with the same diagnostic label, heterogeneity may exist and could influence the acceptability of certain instruments. This may influence the performance of instruments that are not designed specifically for use in such populations.

Although there is a disease-specific measure of health-related quality of life developed specifically for use with individuals receiving assisted ventilation,(Windisch et al., 2003b) generic preference-based HRQoL instruments are still commonly used in clinical studies in this group.(Bourke et
In theory, this allows comparisons between studies and with other disease groups. However, little is known about the performance of many of the commonly used generic preference-based HRQoL measures in individuals receiving assisted ventilation. Evaluating instruments in this population therefore provides the opportunity to identify issues with their performance. Specifically, understanding the limitations of certain instruments may ensure more valid interpretation of these results.

The first aim of this chapter is to determine the subjective benefits of NIPPV across different disease groups and therefore identify aspects of health that could be expected to respond to this therapy in longitudinal studies. The second aim is to evaluate the performance, and identify limitations, of two generic preference-based HRQoL instruments in a population of individuals receiving assisted ventilation.

8.2 HYPOTHESES

The hypotheses that will be tested in this chapter are;

1. that the subjective benefits (determined using patient-reported outcomes) obtained from NIPPV will not be uniform across all disease groups that require this therapy, and;

2. that there will be poor agreement between the summary measures generated by two generic preference-based measures of HRQoL (the AQoL-8D and EQ-5D-5L) in a population of individuals receiving assisted ventilation, and that the framing of mobility items contained within the two instruments will be a contributor to the lack of agreement.
8.3 **ADDITIONAL BACKGROUND**

8.3.1 **Physiological changes and subjective benefits**

A disconnect exists between the physiological benefits that can be obtained from NIPPV and the subjective effects that can result. It is not uncommon to observe an individual who experiences a significant reduction in PaCO$_2$ with short-term use of NIPPV who reports an apparent lack of efficacy regarding symptoms and subsequent poor long-term adherence. Clearly, multiple factors influence the perceived benefit obtained – many of which are not obvious to the clinician and cannot be reliably identified using physiological measures of success alone.

Given the pathophysiology of ventilatory failure it is reasonable to ask why a large reduction in PaCO$_2$ (from elevated levels) may not be subjectively beneficial to a user of HMV. PaCO$_2$ can potentially be dramatically reduced with the use of very large amounts of pressure support delivered by NIPPV (Dreher et al., 2010) – yet higher pressures generally produce increased volumes of mask and mouth leak, (Dreher et al., 2010; Storre et al., 2009) which may actually increase sleep disruption. (Meyer et al., 1997; Teschler et al., 1999) High levels of leak are generally not well tolerated, and may contribute to patient-ventilator asynchrony. (Carlucci, Pisani, et al., 2013) Therefore despite achieving a large reduction in PaCO$_2$, high levels of pressure support may not be conducive to longer-term adherance. Conversely, a lower pressure support level may be better tolerated by users but may not achieve a significant reduction in PaCO$_2$, and may represent less effective therapy. (McEvoy et al., 2009) Balancing these competing interests is one of the difficulties of both clinical practice and clinical research in this area. With this in mind, focusing primarily on physiological outcomes in a clinical trial may be problematic. (Leger et al., 1994; Raphael et al., 1994; Vianello, Bevilacqua, Salvador, Cardaioli, & Vincenti, 1994)
This example also highlights that individuals are likely to evaluate the benefits and burdens of any therapy with different weightings to clinicians. While physiological effects may be desired by clinicians, users generally want a therapy that makes them feel better. (Guyatt, G H, Cook, 1994) They may even weigh the reliance on assisted technology as a burden or a mixed blessing, (Ingadottir & Jonsdottir, 2006) thereby effectively raising the bar above which any perceived benefit must reach. Clinical trials that attempt to demonstrate benefits from particular strategies or interventions must therefore consider this. When the interventions themselves impose a burden, this may negate any physiological benefit obtained by discouraging groups of users from continuing therapy.

Physiological benefits (or the lack thereof) may also prove misleading in clinical studies. An example of this is the use of pulmonary rehabilitation for individuals with COPD. Consistent evidence exists of important clinical and psychosocial benefits from pulmonary rehabilitation. (Puhan, Scharplatz, Troosters, Walters, & J, 2011; Ries, Kaplan, Limberg, & Prewitt, 1995; Wijkstra et al., 1994) Despite this, an acknowledged physiological marker of disease severity (forced expiratory volume in 1-second; FEV1) does not improve following pulmonary rehabilitation. (Ries et al., 1995; Wijkstra et al., 1994) Examples from other areas of medicine also exist. Improvements in the levels of glycosylated haemoglobin (HBa1c) were consistently demonstrated in short-term studies using rosiglitazone in individuals with type-2 diabetes mellitus. Reductions in HBa1c levels suggest improved glycaemic control, (Nathan, Singer, Kurxthal, & Goodson, 1984) and should produce improved clinical outcomes. (UK Prospective Diabetes Study (UKPDS) Group, 1998) However, subsequent meta-analyses including longer-term data suggested this apparent physiological benefit of rosiglitazone was associated with excess myocardial infarction and admissions due to congestive heart failure. (Nissen & Wolski, 2007)
Physiological measures alone are therefore generally not useful endpoints in studies evaluating healthcare interventions. As a consequence, measures of HRQoL and other patient-reported outcomes (PROs) are frequently utilised. A number of these instruments can be used to produce economic (cost-utility) analyses to determine cost-effectiveness,(Guyatt, King, Feeny, Stubbing, & Goldstein, 1999) however the choice of instrument may influence these analyses.(Grieve, Grishchenko, & Cairns, 2009) Instrument selection therefore is extremely important to ensure treatment effects are not missed, as this could lead to mistaken health policy or treatment decisions. The selection process is made more difficult by the wide array of instruments and their different applications and measurement properties. Simply choosing a popular and validated instrument may not be appropriate for certain study populations.(Kersten, Mullee, Smith, McLellan, & George, 1999)

8.3.2 Patient-reported outcomes

Hundreds of standardised measures have been developed to capture patient-reported outcomes including symptoms status, physical function, mental health, social function and wellbeing.(Nelson et al., 2015) They include simple visual analogue scales, rating scales, and other standardised measures. The multitude of instruments available for clinicians and researchers has meant that comparability across studies is often difficult. The interpretability of these instruments is often also limited – particularly when determining if a difference is clinically meaningful within a given patient population. Routine use of these measures in clinical practice is not widespread but they are consistently used in clinical research settings.(Nelson et al., 2015) They are particularly useful if objective clinical outcomes such as mortality, hospital admission or other clinical events are difficult to measure or beyond the scope of the research project.
While these subjective measures are important, their interpretability for clinicians and relevance to individual patients is questionable. (Guyatt, Feeny, & Patrick, 1993) Many clinicians are unfamiliar with these instruments and this poses difficulty in interpreting study results. This is important as increasingly patients and carers desire objective information on the relative benefits and risks of particular treatment options. (Baxter et al., 2013)

8.3.3 Generic preference-based HRQoL instruments

In economic evaluations of healthcare interventions, generic preference-based HRQoL instruments are used in order to provide a value of a given health state. (Weinstein, Torrance, & McGuire, 2009) Differences that occur in a given population’s health over time (pre- and post-intervention) can then be determined and the costs required to achieve this change can be evaluated. A critical element of this process, therefore, is to produce reliable, responsive and empirically valid estimates of health. (Brazier & Deverill, 1999)

The generic preference-based HRQoL instruments that are used for cost-utility analyses generate a single index of health from the results obtained within the questions or items in the instrument. (Feeny, 2000) There are a number of methods for generating this single index score of health, but in essence, large scaling studies incorporate the use of a community sample to evaluate the desirability of different health states. (Weinstein et al., 2009) Using scaling techniques, a scoring algorithm can be generated that allows the calculation of an index score from any combination of responses to the items contained within the instrument. (Brazier, Ratcliffe, Salomon, & Tsuchiya, 2007) The benefit of producing a single index of health (commonly referred to as ‘utility’) in this way is that it allows changes that occur within different dimensions of health to be viewed within the context of the overall health of an individual or sample population. (Feeny, 2000) For example if an intervention improves aspects of the
mental health of a population but reduces its physical health, the net effect on
the index score may be zero – meaning that the health of that population remains
unchanged. In addition, this also allows for differing effects of an intervention on
an individual to be detected. For example where an intervention produces an
improvement in physical function in some participants, but produces an
improvement in mental function in others. In this situation, the index score
would improve across the population as a result of the intervention, despite the
different responses of individuals. The characteristics of this approach make it
useful as a measure of HRQoL independent of its usefulness in economic
evaluation studies. (Feeny, 2000) Generic preference-based HRQoL instruments
that produce an index score based on this method can therefore help to answer
the question; if health status improves on some dimensions and diminishes on
others, is the patient overall better or worse off? (Feeny, 2000)

8.3.4 Subjective benefits – what should we expect?

While NIPPV can be considered a ‘one-size-fits-all’ therapy for ventilatory
failure, clearly the disorders that can produce this type of respiratory failure are
heterogeneous. Should we therefore expect the subjective benefits of NIPPV to
be uniform across all diagnostic groups? Individuals with obesity-
 hypoventilation who use long-term NIPPV have often suffered from long-
standing poor health and may have acquired significant additional co-morbidities
or complications related to morbid obesity. They may also be more cognoscente
of the healthcare system and therefore more comfortable with medical
interventions such as NIPPV or have had previous experience with treatments
such as CPAP. In contrast, individuals with MND may have relatively little co-
morbidity and generally have had less time to adjust to their life-limiting illness
when they commence NIPPV. The need for assisted ventilation also often
represents a pre-terminal phase in their illness and thus their capacity to manage the technology may be more limited, and the consequences of an inability to continue therapy more acute. It is doubtful whether similar benefits should be expected following NIPPV for these two groups, despite it providing an apparently similar physiological benefit.

Patient-reported outcomes can be useful in this context, however, because of the multitude of instruments available, it may be difficult to determine the meaning or relevance of improvements in a given instrument. Clinicians (and other researchers) may have difficulty interpreting results obtained with unfamiliar instruments. Distilling this information in order to inform individuals contemplating NIPPV may be problematic in this context.

As an example, Radunovic et al reported on a systematic review they performed evaluating NIPPV for individuals with ALS/MND and concluded that therapy “improves or maintains quality of life in people with ALS/MND”. (Radunovic et al., 2013) This conclusion was based on results obtained from a single RCT which included 41 participants, n=22 were treated with NIPPV and n=19 were untreated controls. (Bourke et al., 2006) The RCT by Bourke et al showed a significant survival advantage in those treated with NIPPV. There was also a longer median time maintained above 75% of the baseline SF-36 mental component summary and a longer median time maintained above 75% of the baseline SAQLI symptoms domain. Raw data for this study have not been published and were not provided for the systematic review. For the clinician, the ‘take-home’ message from both the RCT and the subsequent systematic review is that individuals with ALS/MND live longer if treated with NIPPV and have improved or maintained quality of life. It is clear however, that only certain aspects of HRQoL improved or were maintained with NIPPV. These aspects were limited to those evaluated within the SF-36 mental component summary. It is unclear from the reported results whether simultaneous deteriorations in other
aspects of HRQoL related to physical health occurred. These may have offset gains in the mental health component summary. While the results of this RCT and the weight of non-randomised studies and anecdotal reports all indicate that individuals with ALS/MND do benefit from NIPPV therapy, broad conclusions such as those from the systematic review may be misleading. The oversimplification of these results, while understandable, could lead to misunderstandings regarding the potential benefits of NIPPV for individuals with ALS/MND. This may create difficulties if the expectations of therapy are unable to be met.

8.4 OVERVIEW

The following systematic review (page 194) includes prospective studies evaluating NIPPV in new users in order to determine which domains or dimensions of health may respond to therapy and whether there are differences between diagnostic groups in their response. Additional discussion (page 209) follows the manuscript. Supplementary Files 1 (search strategy), 2 (generation of composite effect sizes) and 3 (excluded studies) that are referred to in the manuscript are included in Appendix F.
8.5 MANUSCRIPT – SYSTEMATIC REVIEW OF NON-INVASIVE POSITIVE PRESSURE VENTILATION FOR CHRONIC RESPIRATORY FAILURE

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REVIEW

Systematic review of non-invasive positive pressure ventilation for chronic respiratory failure

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KEYWORDS
Non-invasive ventilation;
Ventilation;
Chronic respiratory failure;
Quality of life

Summary
Background: This systematic review examined the effect of non-invasive positive pressure ventilation (NIPPV) on patient reported outcomes (PROs) and survival for individuals with or at risk of chronic respiratory failure (CRF).
Methods: Randomised controlled trials (RCTs) and prospective non-randomised studies in those treated with NIPPV for CRF were identified from electronic databases, reference lists and grey literature. Diagnostic groups included in the review were amyotrophic lateral sclerosis/motor neuron disease (ALS/MND), Duchenne muscular dystrophy (DMD), restrictive thoracic disease (RTD) and obesity hypoventilation syndrome (OHS).
Results: Eighteen studies were included and overall study quality was weak. Those with ALS/MND had improved somnolence and fatigue as well as prolonged survival with NIPPV. For OHS, improvements in somnolence and fatigue, dyspnoea and sleep quality were demonstrated, while for RTD, measures of dyspnoea, sleep quality, physical function and health, mental and emotional health and social function improved. There was insufficient evidence to form conclusions regarding the effect of NIPPV for those with DMD.

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Introduction

Non-invasive positive pressure ventilation (NIPPV) is an established, effective long-term treatment for individuals with or at risk of chronic hypercapnic respiratory failure due to a number of heterogeneous conditions. Most commonly, these conditions include obesity hypoventilation syndrome (OHS), restrictive thoracic diseases (RTD), chronic obstructive pulmonary disease (COPD) as well as amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) and other neuromuscular diseases [1,2]. Rapid expansion in the use of domiciliary NIPPV has been described in a number of countries [3,4], and it is a preferred method of providing long-term ventilatory support (in comparison to negative pressure methods or invasive mechanical ventilation) due to a variety of factors including cost and patient preference as well as a possible reduction in ventilator associated complications [5–7].

Increasingly, investigators who have evaluated domiciliary NIPPV therapy have recognised and emphasised the reporting of patient reported outcomes (PROs). These outcome measures generally evaluate the presence or severity of symptoms and/or determine health-related quality of life (HRQoL). In general, instruments that evaluate HRQoL attempt to measure those aspects of overall quality of life that can clearly be shown to affect health — either physical or mental [8]. PROs are considered to be useful outcome measures in studies involving NIPPV — particularly where a mortality benefit is unlikely to be identified. This focus on PROs contrasts earlier studies that more frequently evaluated physiologic outcome measures, such as daytime carbon dioxide tension (PaCO₂), pulmonary

Conclusions: This review has demonstrated that NIPPV influences PROs differently depending on the underlying cause of CRF. These findings may provide assistance to patients and clinicians to determine the relative costs and benefits of NIPPV therapy and also highlight areas in need of further research.

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function, or sleep parameters. Unfortunately, the large range of instruments used in NIPPV studies has made comparison of outcomes difficult. In addition, it is likely that only specific facets of an individual’s health and wellbeing are influenced by NIPPV, and that these will differ depending on the underlying disease process that has led to respiratory failure. This review therefore attempts to clarify the impact of NIPPV therapy by synthesising subscales of PROs in order to better describe how this therapy influences specific components of health and wellbeing.

Three previous systematic reviews and a further review of randomised controlled trials have examined NIPPV for individuals with hypercapnic respiratory failure secondary to COPD [9–12]. We conducted a targeted search of electronic databases from the conclusion of the most recent review and did not identify additional RCTs that could be included in a meta-analysis. We therefore elected not to perform a further evaluation of NIPPV for the treatment of individuals with COPD.

Two previous systematic reviews have evaluated the role of long-term NIPPV for individuals with neuromuscular and chest wall disorders [13], and for ALS/MND [14], but neither included non-randomised studies, thereby omitting a significant number of the studies performed in this area. Annane et al. concluded that weak but consistent evidence supports the use of NIPPV to relieve symptoms of chronic hypoventilation in the short-term for individuals with neuromuscular and chest wall disorders, while Radunovic et al. concluded that NIPPV improves or maintains quality of life in people with ALS/MND. Both reviews concluded that NIPPV significantly prolongs survival in people with ALS/MND.

In spite of a bias towards a positive treatment effect [15,16], non-randomised studies are able to provide important data that can assist clinicians. Provided their limitations are understood, data from well conducted non-randomised studies evaluating therapy may be similar to that obtained from RCTs in similar populations [17]. Consideration of non-randomised studies is further necessitated in situations where the likelihood of further RCTs is low [16]. This is particularly relevant to NIPPV therapy (most notably for individuals with progressive neuromuscular diseases such as Duchenne muscular dystrophy (DMD) and ALS/MND) where it may be considered unethical to perform an RCT when subjects in the control arm would have a potentially life-prolonging treatment withheld [18–20]. Furthermore, no previous review has evaluated the impact of NIPPV on dyspnoea, sleep quality or examined how therapy influences specific components of HRQoL. This is significant, given that many of these outcomes may be perceived by patients to be more important than survival or physiological endpoints [21]. We have therefore included both RCTs (for survival and PRO data) and non-randomised prospective studies with a repeated measures design (for PRO data) to examine whether NIPPV improves survival and PROs in individuals with or at risk of developing chronic respiratory failure due to ALS/MND, DMD, RTD and OHS.

Methods

A systematic review was performed using the methodology outlined by the Centre for Reviews and Dissemination [22].

Search for relevant studies

Databases were searched from the date of their inception until December 3rd 2012. These included: MEDLINE, EMBASE, CINAHL, the Centre for Reviews and Dissemination, The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials, ACP Journal Club, Database of Abstracts and Reviews of Effects (DARE), Health Technology Assessment, and the NHS Economic Evaluation. We also searched grey literature including: Proceedings First, Papers First, National Guideline Clearing House, ProQuest Dissertations and Theses (PQDT). The electronic searches were supplemented by manually scanning the reference lists from included articles to identify additional studies that may have been missed during the search of databases.

Search strategy

Population (disease) specific search terms (obesity hypoventilation syndrome, kyphoscoliosis, muscular dystrophy and amyotrophic lateral sclerosis) were combined with intervention specific terms (positive pressure respiration, artificial respiration, mechanical ventilation, non-invasive) together with modifications to meet the requirements of particular databases in all our searches. For a detailed description of the search strategy please refer to Supplementary File 1. A flow chart that illustrates the search strategy and study selection is shown in Fig. 1. Two researchers reviewed all abstracts and titles identified in the electronic and manual search independently. Full text articles were also independently reviewed by two researchers. Disagreements were resolved at each stage of the search by consensus.

Study selection

Studies were included if they; (1) described participants with or at risk of respiratory failure due to ALS/MND, DMD, RTD, or OHS with an indication to commence NIPPV therapy according to published criteria [23,24]; (2) were an RCT or prospective study with a repeated measures design; (3) examined NIPPV (defined as any form or mode of positive pressure ventilation delivered via a non-invasive interface [i.e. nasal, oronasal, total face mask or mouthpiece] for a minimum of 4 weeks); (4) reported survival or PROs using standardised instruments evaluating HRQoL, symptoms, sleep quality, mental health and physical health.

Studies were excluded if they; (1) did not report outcomes according to diagnostic groups; (2) included participants with obstructive lung diseases (COPD, asthma, cystic fibrosis, bronchiectasis), spinal cord injury, stable (or non-progressive) neuromuscular diseases, muscular dystrophies other than Duchenne type and congenital or acquired central alveolar hypoventilation syndromes, and obstructive sleep apnoea (except that co-existing in individuals fulfilling diagnostic criteria for OHS); (3) utilised continuous positive airway pressure (CPAP), negative pressure ventilation, diaphragm or phrenic nerve pacing or invasive ventilation (delivered via an endotracheal tube or tracheostomy); (5) reported only the presence or absence of
symptoms or did not use a standardised PRO instrument or; (6) appeared to report on similar groups of patients [25,26].

Data abstraction

From each selected article, the following information was abstracted: author, journal, year of publication, study design, participant characteristics, exclusion criteria, comparison group (if present for RCTs), use of supplemental oxygen therapy, other concurrent interventions, method of NIPPV titration, mode and method of NIPPV, treatment period, change in PaCO₂, drop-outs, compliance (usage), PRO outcomes, and survival. PRO data were abstracted from RCTs and prospective studies with a repeated measures design whereas survival data was only abstracted from studies with a parallel group RCT design comparing NIPPV with an appropriate ‘standard care’ (defined as any or all of; oxygen therapy, medications, supportive care and lifestyle interventions). When studies reported outcomes at multiple time-points, we preferentially used data from between 1 and 6 months (defined as short-term treatment).

A number of authors were approached for additional data [19,25,27–35], and this was received to complement several reports [19,34,35].

Study outcomes

Quality assessment of studies

All articles were assessed using the Quality Assessment Tool for Quantitative Studies by two investigators independently. Discrepancies were resolved by consensus. This tool provides a global rating and component scores for six components (selection bias, study design, confounders, blinding, data collection method and withdrawal and dropouts) [36,37].

Data analysis

Meta-analyses could not be performed on the included studies due to the heterogeneity of study design and outcomes. Two reviewers (LWH and YWC) grouped appropriate domains (subscales) of PROs independently into 6 discreet categories; dyspnoea, sleep quality, somnolence and fatigue, mental and emotional health, social functioning, and
physical function and health. The methodology has been described previously [38], and is detailed in Supplementary File 2. Not all instruments/domains were able to be assigned into the categories devised.

Only studies that presented repeated measures data for PROs (mean and standard deviation) were able to be included in our calculation of effect sizes. These were calculated for each of the PRO domains as the difference between the means of the baseline and post-treatment scores (change from baseline) divided by the standard deviation of change. Composite effect sizes and 95% confidence intervals (CI) for each of the combined categories were then calculated. We used Cohen’s categories for classifying effect sizes; 0.80 = large, 0.50 = medium, and 0.20 = small. Further details are provided in Supplementary File 2.

Results

Our systematic search identified 1533 records after the removal of duplicates (Fig. 1). After screening titles and abstracts, 178 studies were retrieved in full text version and of these, 18 studies were included in our synthesis. Excluded full-text articles are listed in Supplementary File 3 and reasons for exclusions are summarised in Fig. 1. The included studies and an overview of study attributes are displayed in Tables 1 and 2.

Quality assessment

A summary table of the quality assessment of the included studies is provided in Table 3. Table 2 demonstrates the number of studies with a particular design for each condition; only three studies were RCTs with the remaining being multi-centre (n = 2) or single centre prospective cohort studies (n = 13). Most included studies rated as strong for data collection methods and for reporting of withdrawals and dropouts. Selection bias (10/18), controlling for confounders (15/18) and blinding (15/18) were frequently rated as weak with the large number of non-randomised study designs contributing significantly to these ratings. Global ratings of studies were most often weak (13/18).

Patient reported outcomes

Twenty-three PROs were used across the included studies (Table 1 and Supplementary Data File 2). These included instruments that evaluated sleepiness, dyspnoea, fatigue, morning headache, mood, anxiety, depression and generic and disease-specific health-related quality of life. Fig. 2(a)–(c) – Forest plots.

Amyotrophic lateral sclerosis/motor neuron disease

Randomised studies

The study by Bourke et al. randomised individuals with ALS/MND to NIPPV or standard care and demonstrated: median survival in the NIPPV group of 219 days (range 75–1382 days) vs 171 days (range 1–878 days), improved mental component summary (MCS) of the SF-36 and all domains of the Sleep Apnea Quality of Life Index (SAQI) and Chronic Respiratory Questionnaire. Repeated measures data for PROs was unavailable for this study.

Non-randomised prospective studies

Five studies reported outcomes for individuals with ALS/MND after commencing NIPPV [18,28,30,39,40], and additional data was provided by one author who originally grouped their subjects with ALS/MND in a combined ‘neuromuscular disease’ group [35]. Fig. 2(a) summarises the composite effect size according to our combined categories for PROs. A consistent beneficial effect of NIPPV on somnolence and fatigue was demonstrated across the included studies. There was no apparent effect on physical function and health associated with NIPPV therapy, and dyspnoea, mental and emotional health and social function were inconsistently influenced across studies. No data from included studies was available to evaluate the effect of NIPPV on sleep quality for individuals with ALS/MND.

Duchenne muscular dystrophy

Randomised studies

One randomised controlled trial was identified that reported outcomes for individuals with Duchenne muscular dystrophy (DMD). Raphael et al. reported results from a multicentre randomised controlled trial conducted in France from 1986 until 1991 [41]. The randomly allocated individuals with DMD and preserved lung function (forced vital capacity between 20 and 50% of predicted) to either ‘conventional treatment’ or ‘conventional treatment + NIPPV’. The primary outcome was overall survival and three secondary endpoints (time to occurrence of hypercapnia >45 mmHg, time to decrease FVC below 20% of the value obtained at randomisation, time to necessary NIPPV ventilation for respiratory failure) were also examined. Changes in symptoms or HRQoL were not evaluated in this study. Results were reported for 70 participants (n = 35 per group) due to a planned interim analysis demonstrating significantly more deaths in the NIPPV group. At the reference date 8 deaths were observed in the NIPPV group compared with 2 deaths in the conventional treatment group. 2-year survival rates (77% vs 96%) and 3-year survival rates (65% vs 89%) demonstrated persistent differences between the two groups. There were no significant differences between the groups with regard to secondary endpoints.

Non-randomised prospective studies

Only one prospective study including individuals with DMD and with a repeated measures design evaluating PROs was identified that reported outcomes specific to diagnosis. The study by Guillemainault et al. reported pre- and post- treatment values for the Epworth Sleepiness Scale (ESS) in only one of three included participants with DMD. This participant with DMD (who received supplemental oxygen in addition to NIPPV treatment) demonstrated an ESS of 15/24 (at baseline) that fell to 9/24 (at 1 month).
Table 1  Studies included in the systematic review.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Diagnostic group</th>
<th>n</th>
<th>Gender (F:M)</th>
<th>Comparison</th>
<th>Survival</th>
<th>PROs reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourke* 2006</td>
<td>RCT (single centre, parallel groups)</td>
<td>ALS/MND</td>
<td>NIPPV = 22 Control = 19</td>
<td>8:14 9:10</td>
<td>&quot;Standard care&quot;</td>
<td>Yes</td>
<td>SF-36, CRDQ, SAQLI</td>
</tr>
<tr>
<td>Mustafa 2006</td>
<td>PC (single centre)</td>
<td>ALS/MND</td>
<td>26</td>
<td>6:20</td>
<td></td>
<td></td>
<td>SF-36, CRDQ, SAQLI, ESS, McGill HRQoL HADS</td>
</tr>
<tr>
<td>Lyall 2001</td>
<td>PC (single centre)</td>
<td>ALS/MND</td>
<td>16</td>
<td>1:15</td>
<td></td>
<td></td>
<td>SF-36, ESS</td>
</tr>
<tr>
<td>Newsom-Davis 2001</td>
<td>PC (single centre)</td>
<td>ALS/MND</td>
<td>9</td>
<td>0:9</td>
<td></td>
<td></td>
<td>ESS, HAD Anxiety score HAD Depression score</td>
</tr>
<tr>
<td>Butz* 2003</td>
<td>PC (single centre)</td>
<td>ALS/MND</td>
<td>36</td>
<td>N/R</td>
<td></td>
<td></td>
<td>ESS, PSQI, VAS Sleep quality, Fatigue scale, Beck's Depression Inventory, von Zersen Mood Scale</td>
</tr>
<tr>
<td>Bourke* 2003</td>
<td>PC (single centre)</td>
<td>ALS/MND</td>
<td>17</td>
<td>5:12</td>
<td></td>
<td></td>
<td>SF-36, CRDQ, SAQLI, ESS</td>
</tr>
<tr>
<td>Raphael 1994</td>
<td>RCT (multicentre, parallel groups)</td>
<td>DMD</td>
<td>NIPPV = 35 Control = 35</td>
<td>0:35 0:35</td>
<td>&quot;Conventional treatment&quot;</td>
<td>Yes</td>
<td>SF-36, CRDQ, SAQLI, ESS</td>
</tr>
<tr>
<td>Ferris 2000</td>
<td>PC (single centre)</td>
<td>RTD</td>
<td>16</td>
<td>N/R</td>
<td></td>
<td></td>
<td>Sadoul Dyspnoea Scale VAS Dyspnoea, Morning headache, Fatigue, Diurnal drowsiness, Sleep quality</td>
</tr>
<tr>
<td>Borel 2012</td>
<td>RCT (single centre, parallel groups)</td>
<td>OHS</td>
<td>NIPPV = 19 Control = 18</td>
<td>11:8 11:7</td>
<td>&quot;Lifestyle counselling&quot;</td>
<td>No</td>
<td>ESS</td>
</tr>
<tr>
<td>Murphy 2012</td>
<td>PC (multicentre)</td>
<td>OHS</td>
<td>25</td>
<td>14:11</td>
<td></td>
<td></td>
<td>SRI, ESS, FSS, VAS Fatigue, Sleep comfort, Physical activity</td>
</tr>
<tr>
<td>Piper 2008</td>
<td>PC (single centre)</td>
<td>OHS</td>
<td>18</td>
<td>9:9</td>
<td></td>
<td></td>
<td>SF-36, ESS, PSQI</td>
</tr>
<tr>
<td>Storrie 2006</td>
<td>PC (single centre)</td>
<td>OHS</td>
<td>14</td>
<td>2:8</td>
<td></td>
<td></td>
<td>SRI</td>
</tr>
<tr>
<td>Windisch 2008</td>
<td>PC (multicentre)</td>
<td>Mixed</td>
<td>135</td>
<td>2.7</td>
<td></td>
<td></td>
<td>SF-36, SRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(OHS)</td>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(RTD)</td>
<td>(29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsolaki 2011</td>
<td>PC (single centre)</td>
<td>Mixed</td>
<td>101</td>
<td>10:18</td>
<td></td>
<td></td>
<td>SF-36, ESS, MRC Dyspnoea Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(OHS)</td>
<td>(28)</td>
<td>6:11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(RTD)</td>
<td>(17)</td>
<td>N/R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ALS/MND)</td>
<td>(10)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Time</td>
<td>Outcome</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nauffal 2002</td>
<td>PC (single centre)</td>
<td>Mixed (RTD)</td>
<td>62 (35)</td>
<td>14:21</td>
<td>SF-36 Borg Dyspnoea scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domenech-Clari* 2003</td>
<td>PC (single centre)</td>
<td>Mixed (RTD)</td>
<td>67 (36)</td>
<td>11:17</td>
<td>SF-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickol 2005</td>
<td>PC (single centre)</td>
<td>Mixed (RTD)</td>
<td>20 (8)</td>
<td>4:4</td>
<td>ESS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilleminault* 1998</td>
<td>PC (single centre)</td>
<td>Mixed (DMD)</td>
<td>20 (3)</td>
<td>0:3</td>
<td>ESS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These studies fulfilled the inclusion criteria for the review however missing or unavailable data have not allowed incorporation into the calculation of composite effect sizes.

RCT — randomised controlled trial, PC — prospective cohort, NIPPV — non-invasive positive pressure ventilation, AVAPS — average volume assured pressure support, CPAP — continuous positive airway pressure, M — male, F — female, PRO — patient reported outcome, ALS/MND — amyotrophic lateral sclerosis/motor neurone disease, OHS — obesity hypoventilation syndrome, RTD — restrictive thoracic disease, DMD — Duchenne muscular dystrophy, S mode — spontaneous mode, T mode — timed mode, S/T mode — spontaneous/timed mode, A/C mode — assist/control mode, SRI — Severe Respiratory Insufficiency Questionnaire, SF-36 — Medical Outcomes Study Short Form Health Survey, SAQLI — Calgary Sleep Apnea Quality of Life Index, FSS — Fatigue Severity Score, PSQI — Pittsburgh Sleep Quality Index, SSS — Stanford Sleepiness Score, ESS — Epworth Sleepiness Scale, FSS — Fatigue Severity Scale, CRQD — Chronic Respiratory Disease Questionnaire, HADS — Hospital Anxiety Depression Score, MRC — Medical Research Council, McGill HRQoL — McGill Quality of Life Questionnaire, VAS — Visual Analogue Scale.

* Study design was determined by the reviewers and is reported according to the method in which the data from the study was analysed in this review (and not necessarily how the authors of the study reported the study design) — for example; the study by Murphy et al. was reported by the authors to be a randomised controlled trial however in order to attempt to answer this review question, the data was analysed as a prospective cohort study (with repeated measures) and therefore has been reported in this manner.

* Diagnostic groups listed include only those where results were reported according to specific diagnosis — for example if a study reported results for a group with 'neuromuscular disease' but did not separate outcomes according to a specific diagnosis (ie Duchenne muscular dystrophy or amyotrophic lateral sclerosis), these groups/diagnoses were not included in our analysis.

* Only comparison group data that is included in this review is reported.

* Only randomised controlled trials were evaluated for survival analysis.
<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>% Not analyseda</th>
<th>NIPPV</th>
<th>Titration method (site; technique)b</th>
<th>Co-interventionsc</th>
<th>Treatment intervald</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS/MND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bourke* 2006</td>
<td>NIPPV = 22</td>
<td>0</td>
<td>Pressure; S/T mode</td>
<td>Inpatient; ABG, Overnight monitoring</td>
<td>Riluzole, Vaccinations, Airway clearance techniques, Palliative care</td>
<td></td>
</tr>
<tr>
<td>Control = 19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mustfa 2006</td>
<td>26</td>
<td>33.3%</td>
<td>Pressure; mode not described</td>
<td>Inpatient; ABG, Overnight monitoring</td>
<td>Phone support</td>
<td>3 months</td>
</tr>
<tr>
<td>Lyall 2001</td>
<td>16</td>
<td>6.3%</td>
<td>Pressure; mode not described</td>
<td>Uncertain; ABG</td>
<td>Airway clearance techniques</td>
<td>1-month</td>
</tr>
<tr>
<td>Tsolaki 2011</td>
<td>10</td>
<td>9.9%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pressure; S/T mode</td>
<td>Inpatient, Clinical, ABG</td>
<td>Inpatient training, home visits</td>
<td>3 months</td>
</tr>
<tr>
<td>Newsom-Davis 2001</td>
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<tr>
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<td>36</td>
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<td>1-month</td>
</tr>
<tr>
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<td></td>
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<td>3</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pressure; T mode</td>
<td>Uncertain; PSG</td>
<td>Supplemental oxygen (n = 1), Home visits</td>
<td>1-month</td>
</tr>
<tr>
<td>RTD</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pressure;</td>
<td>Inpatient; ABG</td>
<td>Supplemental oxygen (n = 19), Phone support, Clinic visits</td>
<td>3 months</td>
</tr>
<tr>
<td>Windisch 2008</td>
<td>29</td>
<td>37.0%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pressure and Volume; A/C mode</td>
<td>Inpatient; Clinical, ABG</td>
<td>Inpatient re-assessments</td>
<td>1-month</td>
</tr>
<tr>
<td>Tsolaki 2011</td>
<td>17</td>
<td>9.9%&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Inpatient, Clinical, ABG</td>
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<td>3 months</td>
</tr>
<tr>
<td>Domenech-Clari* 2003</td>
<td>36</td>
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<td>Pressure;</td>
<td>Inpatient; ABG</td>
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</tr>
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<td>Nickol 2005</td>
<td>8</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pressure;</td>
<td>Inpatient; ABG, Overnight monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferris 2000</td>
<td>16</td>
<td>0</td>
<td>Pressure; T mode Volume; A/C mode</td>
<td>Inpatient; Clinical, ABG, Overnight monitoring</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Pressure; S/T mode</td>
<td>Inpatient; not described</td>
<td></td>
<td>1-month</td>
</tr>
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<td>Study</td>
<td>Patients</td>
<td>%</td>
<td>Methodology</td>
<td>Inpatient; Clinical, ABG</td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
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<td>----------------------------------</td>
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<td></td>
</tr>
<tr>
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<td>Pressure; S/T mode</td>
<td>Inpatient; Overnight monitoring</td>
<td>3 months</td>
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</tr>
<tr>
<td>Piper 2008</td>
<td>18</td>
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<td>Pressure; S mode</td>
<td>Uncertain; PSG</td>
<td>3 months</td>
<td></td>
</tr>
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<td>28.6%</td>
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<td>Uncertain; Clinical, Overnight monitoring</td>
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<td></td>
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<tr>
<td>Tsolaki 2011</td>
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<td>9.9%*</td>
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<td>Windisch 2008</td>
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<td>37.0%*</td>
<td>Pressure and Volume; A/C mode</td>
<td>Inpatient; Clinical, ABG</td>
<td>Inpatient re-assessments 1-month</td>
<td></td>
</tr>
</tbody>
</table>

* These studies fulfilled the inclusion criteria for the review however missing or unavailable data have not allowed incorporation into the calculation of composite effect sizes.
*# For studies with mixed cohorts, the % not analysed is the value for the overall study population and is not specific for diagnosis.
NIPPV — non-invasive positive pressure ventilation, AVAPS — average volume assured pressure support, CPAP — continuous positive airway pressure, M — male, F — female, PRO — patient reported outcome, ALS — amyotrophic lateral sclerosis = motor neurone disease, OHS — obesity hypoventilation syndrome, RTD — restrictive thoracic disease, DMD — Duchenne muscular dystrophy, S mode — spontaneous mode, T mode — timed mode, S/T mode — spontaneous/timed mode, A/C mode — assist/control mode, SRI — Severe Respiratory Insufficiency Questionnaire, SF-36 — Medical Outcomes Study Short Form Health Survey, SAIQ — Calgary Sleep Apnea Quality of Life Index, FSS — Fatigue Severity Score, PSQI — Pittsburgh Sleep Quality Index, SSS — Stanford Sleepiness Score, ESS — Epworth Sleepiness Scale, FSS — Fatigue Severity Scale, CRQD — Chronic Respiratory Disease Questionnaire, HADS — Hospital Anxiety Depression Score, MRC — Medical Research Council, McGill HRQoL — McGill Quality of Life Questionnaire, VAS — Visual Analogue Scale.
*% Not analysed includes those not analysed due to reported deaths, drop-outs or ‘lost to follow-up’ at the treatment interval examined in this review (where analysis not intention-to-treat).
*S Site; Inpatient (= hospital admission), Outpatient (= community), Technique; Clinical (= clinical assessment of symptoms and comfort but may include additional simple daytime monitoring (using pulse oximetry or transcutaneous CO₂ alone or in combination); ABG (= adjustment using PaCO₂ i.e. PaO₂ from arterial sampling (includes arterialis ed ear lobe samples); Overnight monitoring (=use of limited overnight monitoring such as pulse oximetry, transcutaneous CO₂, respiratory polygraphy); PSG (=use of full polysomnography).
*As identified in this review.
*Some studies reported outcomes at multiple time points, the treatment intervals listed here are those that have been used in the analysis and generally represent ‘short-term’ treatment periods.
Table 3  Quality assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias</th>
<th>Study design</th>
<th>Confounders</th>
<th>Blinding</th>
<th>Data collection method</th>
<th>Withdrawals and dropouts</th>
<th>Total 18 = Weakest possible 6 = Strongest possible</th>
<th>Global rating</th>
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<tr>
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<td>Weak</td>
<td>Weak</td>
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<td>Moderate</td>
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<td>Strong</td>
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<td>Moderate</td>
<td>Weak</td>
<td>Weak</td>
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<td>Moderate</td>
<td>Weak</td>
<td>Weak</td>
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<td>Strong</td>
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<td>Weak</td>
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</tbody>
</table>

Total score is the sum of the six component scores where Weak = 3 points, Moderate = 2 points and Strong = 1 point. Global ratings are determined according to the following scheme; no Weak ratings = Strong, 1 Weak rating = Moderate, 2 or more Weak ratings = Weak.

Restrictive thoracic disease

Randomised studies
No randomised controlled trials were identified that reported outcomes according to diagnosis for individuals with RTD.

Prospective cohort studies
We included the study by Ferris et al. in addition to four studies with mixed cohorts that reported outcomes according to diagnostic group in our calculation of composite effect sizes [19,35,42,43]. Additional data was forthcoming for two reports to enable their inclusion in the calculations [19,35].

Fig. 2(b) summarises the composite effect size according to our combined categories for PROs. A consistent beneficial effect of NIPPV on dyspnoea, sleep quality, physical function and health, mental and emotional health and social function was demonstrated across included studies. Somnolence and fatigue also improved in most studies where it was evaluated. There appeared to be a relationship between effect size and study quality with 'weaker' studies tending to report larger effect sizes although it should be noted that all studies evaluating individuals with RTD were rated as weak.

Obesity hypoventilation syndrome

Randomised studies
The review identified one parallel group RCT including individuals with OHS. Borel et al. randomly allocated individuals with 'mild OHS' to treatment with NIPPV or a comparison group that received lifestyle counseling [44]. The study evaluated ambulatory obese individuals (BMI > 30 kg/m²) with a screening daytime arterial blood gas sample to identify those with hypercapnia (initially defined as PaCO₂ ≥ 45 mmHg, however the investigators altered the protocol to include those with PaCO₂ 43–45 mmHg) and invited these individuals to participate. Despite randomisation, the NIPPV group was older (58 ± 11 years vs 54 ± 6 years) and had a higher baseline PaCO₂ (48.0 ± 4.5 mmHg vs 45 ± 3.0 mmHg) than the control group. Pressure-limited NIPPV therapy in spontaneouss-timed (S/T) mode was commenced during an inpatient stay for all those in the NIPPV group. After 1 month of NIPPV there was a greater reduction in daytime PaCO₂, AH1 and severity of overnight disturbances in SpO₂ in the NIPPV group compared with control, however there was no significant difference in daytime somnolence according to the ESS (control mean difference −2.1 (−4.5 to 0.4) vs NIPPV mean difference −3.4 (−6.0 to −0.8)).

Other included studies evaluated the effect of NIPPV on individuals with OHS in comparison to continuous positive airway pressure (CPAP) [34], and average volume assured pressure support (AVAPS) NIPPV [45,46]. While treatment allocation was randomly assigned in these studies (parallel group, and crossover), it was determined to analyse these studies using only the conventional (fixed) NIPPV data as a prospective cohort with repeated measures in order to best address the review question.

Prospective cohort studies
In addition to these three studies [34,45,46], two others with mixed cohorts (previously described) included
Figure 2  Forest plots of composite effect sizes (with 95% confidence intervals) for PROs in studies evaluating the effect of NIPPV in individuals with (a) ALS/MND; (b) RTD and; (c) OHS.
individuals with OHS and reported outcomes specific to diagnosis [19, 35].

Fig. 2(c) summarises the composite effect size according to our combined categories for PROs. There was a consistent beneficial effect of NIPPV on somnolence and fatigue demonstrated across all included studies. Other PRO categories inconsistently improved in association with NIPPV therapy. It should be noted that the study by Storre et al. enrolled those who had ‘failed CPAP therapy’ based on physiological parameters and therefore a partial treatment effect on PROs may have influenced the baseline assessments in this study.

Discussion

This review has demonstrated considerable differences in the manner in which NIPPV influences the health and wellbeing of individuals that require this therapy. Most striking is the finding that of the categories defined in this review, only somnolence and fatigue were demonstrated to consistently improve across studies involving individuals with ALS/MND. Composite effect sizes were generally large but ranged from 0.44 to 1.91. While previous reviews have concluded that NIPPV significantly improves and maintains quality of life for those with ALS/MND [14], our results suggest that the spectrum of benefits from NIPPV is in fact much narrower. The apparent lack of a consistent benefit in other categories defined in this review may be reflection of the rapidly progressive nature of ALS/MND, in which any initial gains in these areas are quickly negated by disease progression, or alternatively this may indeed indicate a lack of benefit of NIPPV on these domains. We speculate that the presence of somnolence and fatigue may identify an individual that is more likely to notice the benefits of NIPPV, and this may have important implications in determining adherence and tolerability with ongoing NIPPV therapy. Regarding survival outcomes, our findings are consistent with those in previous reviews, with the study by Bourke et al. convincingly demonstrating that overall there is prolonged survival associated with NIPPV therapy for those with ALS/MND [29]. For the subgroup with severe bulbar involvement, a survival benefit was not demonstrated in this study, however there were benefits in PRO outcomes associated with NIPPV therapy.

Also notable in our review was the paucity of prospective studies evaluating NIPPV for individuals with DMD, with the study by Raphael et al. remaining the largest prospective study in this population [41]. The excess mortality demonstrated with early NIPPV in this study is not adequately explained by differences in the proportion of left ventricular dysfunction between groups as most of the deaths appeared to be related to retention of tracheobronchial secretions. The authors suggested that the use of NIPPV may have created a false sense of security for this group and thus a less urgent response to deteriorations. It is certainly likely that there were differences between the 17 centres in the management and support of those commencing NIPPV and this may have contributed to the excess mortality. We wonder whether a similar study utilising current NIPPV therapy, community supports and airway clearance techniques would replicate the amount of harm associated with early NIPPV therapy. Despite this negative study for NIPPV therapy in DMD, it remains widely accepted that NIPPV does in fact improve survival in individuals with DMD once hypercapnic respiratory failure develops, and current guideline recommendations are in keeping with this [23, 47]. Indeed there may be a role for earlier institution of NIPPV for those with DMD, with the study reported by Ward et al. demonstrating in a mixed cohort with congenital neuromuscular and chest wall disorders that evidence of nocturnal hypoventilation appears to identify individuals that are at high risk of developing daytime hypercapnia [27]. These individuals warrant at least close clinical assessment and observation, and a low threshold for commencement of NIPPV. Unfortunately, due to its mixed population, this study is limited in its ability to guide specific recommendations for individuals with DMD.

Of the groups included in this review, those with RTD appear to obtain the widest spectrum of benefit in PRO categories after short-term therapy with NIPPV. Dyspnoea, sleep quality, physical function and health, mental and emotional health and social function were demonstrated to improve in all included studies. Somnolence and fatigue also appeared to improve in most studies where it was evaluated. These results for individuals with RTD, who are more likely to have a stable disease process, provide an interesting contrast to those with ALS/MND. However, while the composite effect sizes in these studies were generally large, it did appear that ‘weaker’ studies tended to report larger effect sizes, which suggests that these may overestimate the true magnitude of effect.

Although less consistent than RTD, those with OHS also appear able to benefit across a relatively wide spectrum of PRO categories after commencing NIPPV. Somnolence and fatigue consistently improved in studies involving individuals with OHS and dyspnoea and sleep quality also improved, with the exception of the study by Storre et al. that may have included participants partially treated with CPAP. Mention should be made however, of the study by Borel et al. which did not demonstrate a significant difference in the Epworth Sleepiness Scale after 1 month of NIPPV [44]. This apparent lack of benefit on somnolence may reflect the population studied which had relatively ‘mild’ OHS based on a lower threshold for hypercapnia (≥43 mmHg) and recruitment of ambulatory outpatients from a newspaper advertisement. In contrast, the other studies evaluating individuals with OHS included participants who were more hypercapnic [19, 34, 35, 46] or who had ‘failed’ CPAP therapy [45]. The shorter treatment interval in the study by Borel et al. may also have contributed to the apparent lack of effect. Although a 1 month period of NIPPV therapy is sufficient to alter ABG parameters in those with OHS [48, 49] changes in PROs may require a longer period of acclimatisation to NIPPV.

This review has a number of limitations that require consideration. We have touched on the issues of evaluating non-randomised studies previously and we again highlight the risks of drawing concrete conclusions from these studies due to the likelihood of bias. Overall, the quality of studies in this area was weak, with studies limited predominantly by selection bias, presence of confounders and lack of blinding. In particular, we suspect that interventions such as the method of initial NIPPV
titration, access to 24-h telephone support, use of home visits and provision of airway clearance techniques may have an influence on some PRO measures. Many of these co-interventions are routinely applied during the transition to domiciliary NIPPV therapy, yet the variation in practice demonstrated across the studies included in this review hints at a lack of robust evidence to support their routine use. Their impact on the reported outcomes is therefore unknown but may have been significant and further studies are required to clarify the magnitude of any effect. In addition to study quality, we acknowledge that the exclusion of non-English language articles was not optimal, however, cost and logistical constraints limited our ability to perform translations. Finally, our method of producing composite effect sizes required the review team to make a number of judgements and assumptions regarding the grouping of instruments that we felt measured similar constructs. In calculating our composite effect sizes we used conservative measures of correlation between instruments in addition to the small amount of published data comparing instruments in our study populations. We have provided a detailed description of the process for producing the composite effect sizes in Supplementary File 2 in order that our methods are available for review.

Conclusion

The data regarding the effects of NIPPV on individuals with or at risk of chronic respiratory failure is generally weak. However, there is consistent evidence of benefit for individuals with ALS/MND for both survival and measures of somnolence and fatigue. For those with OHS, NIPPV also appears likely to improve measures of somnolence and fatigue, dyspnoea and sleep quality, while for those with RTD, measures of dyspnoea, sleep quality, physical function and health, mental and emotional health and social function were consistently reported to improve. There was insufficient data to form conclusions regarding DMD, however based on published data, there remains no prospective evidence to support NIPPV therapy for DMD in those without evidence of hypventilation.

This review has identified areas for further research. Previous authors have suggested that further RCTs in this area are required [13], however ethical considerations are likely to be a significant barrier. We would encourage prospective studies examining how the presence of somnolence and fatigue may influence the tolerability and compliance with NIPPV for those with ALS/MND in order to better clarify the significance of these symptoms. There is also a need for more rigorous efforts to prospectively evaluate NIPPV for individuals with DMD in order to better define and refine this therapy. In addition, an examination of the role that co-interventions may play towards improving outcomes for individuals using long-term NIPPV is necessary. Specifically, evaluating the roles of airway clearance techniques, advanced care planning and nocturnal monitoring (including polysomnography) in the provision of NIPPV therapy should be a research priority in this area. Finally, investigators considering the use of PROs in studies involving NIPPV are encouraged to carefully examine the instruments they choose in order to ensure appropriate domains are included that can best identify a treatment effect, if present.

Conflict of interest

All authors contributed to this systematic review and there are no conflicts of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.11.010.

References


8.6 ADDITIONAL DISCUSSION – SYSTEMATIC REVIEW

8.6.1 Choice of patient-reported outcomes for clinical studies of NIPPV

The results of the systematic review indicate that if heterogeneous populations were included in studies of NIPPV, then a relatively broad spectrum of symptoms and other aspects of health would need to be assessed to ensure a treatment effect is not missed if one is present. The heterogeneity of ‘real-world’ populations that use NIPPV (and that are likely to be included in any RCT) suggests that the use of narrow or limited measures may miss effects in some diagnostic groups. Instruments that specifically evaluate somnolence and fatigue should be included in these studies as these were consistent with NIPPV for individuals with ALS/MND, OHS and RTD. These include scales such as the Epworth Sleepiness Scale (ESS), (Johns, 1991) and the Fatigue Severity Scale. (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) Measures of sleep quality may also be valuable although a consistent effect across all populations was not demonstrated. Generic preference-based HRQoL instruments that incorporate an item (or items) relating to sleep may also be preferable given the nocturnal use of NIPPV and the apparent effect on measures related to sleep. Improvements in dyspnoea could not be expected to occur across all groups managed with NIPPV based on these data.

An important additional limitation of the systematic review is that only the symptoms and aspects of health and wellbeing that the original investigators perceived to be important could be evaluated. It is possible that other unmeasured subjective benefits or harms of NIPPV may have been missed. This seems intuitively unlikely but adds further support to the use of both generic and disease-specific instruments in clinical studies of NIPPV. (Guyatt et al., 1993)
8.7 **Generic HRQoL**

While the options for disease-specific instruments are limited, there are a considerable number of generic HRQoL instruments that could be included in longitudinal studies of NIPPV. Some instruments (such as the Short Form Health Survey-36 (SF-36)) have been used in studies evaluating NIPPV, (Bourke et al., 2006; McEvoy et al., 2009; Windisch, 2008) although previous reports have suggested limitations regarding their acceptability in older individuals and those with disability. (Andresen, Gravitt, Aydelotte, & Podgorski, 1999; Fisk et al., 2005; Kersten et al., 1999) A recent study in a cohort of individuals with spinal cord injury (SCI) also suggested that there are considerable differences in the acceptability of these instruments. (Whitehurst et al., 2014)

Most generic preference-based HRQoL instruments incorporate measures of physical function and health, mental and emotional health and social function, however, the emphasis or coverage of these dimensions of health differ. (Richardson, Iezzi, & Khan, 2015) Given that there is a lack of a unifying definition of HRQoL, this is unsurprising. However most of these instruments purport to measure the same construct. Investigators have demonstrated that despite the use of the generic term ‘utility’, in effect each instrument employs a different definition of health. (Richardson, Iezzi, & Maxwell, 2012) The relative coverage of health dimensions also differs, with some instruments more heavily weighted to physical aspects of health, while others provide greater coverage for mental, emotional and social function. (Richardson et al., 2015, 2012) This has been demonstrated to influence the sensitivity of instruments to changes within particular dimensions of health – meaning, for example, that an instrument that contains more content related to physical health will be more sensitive to changes in physical health. (Richardson, Khan, Iezzi, & Maxwell, 2014) Apart from these relative weightings, the way that dimensions of health are measured may also influence the results obtained with these instruments. The descriptive system (the items contained in the questionnaire) has been identified as a major
source of poor agreement between preference-based HRQoL
instruments. (Richardson et al., 2015) The way that items are constructed can
influence the acceptability of an instrument but may also produce results that
may not be an accurate reflection of the individual’s perceived HRQoL. (Andresen
et al., 1999; Fisk et al., 2005; Kersten et al., 1999; Whitehurst et al., 2014) This is
particularly important in populations that include individuals with disability.
Whether instruments allow respondents to incorporate the use of non-human aids in their assessment of health status may be important. (Asada, 2005)
Individuals with disability (for example; poor eyesight, inability to walk, or
hearing impairment) can use non-human aids to assist them (respectively; eye
glasses, wheelchairs, hearing aids). When evaluating HRQoL, certain generic
preference-based instruments explicitly allow respondents to consider their
situation while incorporating the use of these aids, while others do not. (Asada,
2005) This difference, particularly with regard to the evaluation of mobility, may
be an important contributor to the poor agreement between index scores from
different instruments. (Whitehurst, Mittmann, Noonan, Dvorak, & Bryan, 2016)

8.8 Overview

The following manuscript (page 213) details a comparison of index scores
produced from two generic preference-based HRQoL instruments using
responses from the study described in Chapter Seven. Detailed methods (page
218), results (page 221) and discussion (page 223) are included in the manuscript.
Tables (1-3; from page 233), figures (1-3; from page 237), and appendices (1,2; from
page 240) that are referred to in the manuscript are provided. Additional
discussion (page 242) follows the manuscript.
8.9 Manuscript – Framing of Mobility Items - A Source of Poor Agreement Between Preference-Based Health-Related Quality of Life Instruments in a Population of Individuals Receiving Assisted Ventilation

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The final publication is available at Springer via:

https://link.springer.com/article/10.1007%2Fs11136-017-1510-z
Running head  Ventilator assistance and quality of life

Title  Framing of mobility items – a source of poor agreement between preference-based health-related quality of life instruments in a population of individuals receiving assisted ventilation

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Presentations
This work has not been presented at any conferences.

Key Words: AQoL-8D, EQ-5D-5L, Mobility, Quality of Life, Respiratory Insufficiency, Noninvasive Ventilation

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Abstract

**Purpose:** To explore the influence of descriptive differences in items evaluating mobility on index scores generated from two generic preference-based health-related quality of life (HRQoL) instruments.

**Methods:** The study examined cross-sectional data from a postal survey of individuals receiving assisted ventilation in two state/province-wide home mechanical ventilation services, one in British Columbia, Canada and the other in Victoria, Australia. The Assessment of Quality of Life 8-dimension (AQoL-8D) and the EQ-5D-5L were included in the data collection. Graphical illustrations, descriptive statistics and measures of agreement (intragroup correlation coefficients (ICCs) and Bland-Altman plots) were examined using index scores derived from both instruments. Analyses were performed on the full sample as well as subgroups defined according to respondent’s self-reported ability to walk.

**Results:** Of 868 individuals receiving assisted ventilation, 481 (55.4%) completed the questionnaire. Mean index scores were 0.581 (AQoL-8D) and 0.566 (EQ-5D-5L) with ‘moderate’ agreement demonstrated between the two instruments (ICC=0.642). One hundred fifty-nine (33.1%) reported level five (‘I am unable to walk about’) on the EQ-5D-5L Mobility item. The walking status of respondents had a marked influence on the comparability of index scores, with a larger mean difference (0.206) and ‘slight’ agreement (ICC=0.386) observed when the non-ambulant subgroup was evaluated separately.

**Conclusions:** This study provides further evidence that between-measure discrepancies between preference-based HRQoL instruments are related in part to the framing of mobility-related items. Longitudinal studies are necessary to determine the responsiveness of preference-based HRQoL instruments in cohorts that include non-ambulant individuals.
Framing of mobility items – a source of poor agreement between preference-based health-related quality of life instruments in a population of individuals receiving assisted ventilation

Introduction
The measurement of health-related quality of life (HRQoL) is an increasingly important part of clinical and economic evaluation research. Accordingly, the data generated by HRQoL instruments is often a critical determinant of success or failure regarding the evaluation of treatments and interventions. It is therefore imperative that such instruments provide reliable, responsive and empirically valid estimates.[1,2] In the field of economic evaluation, health benefits are often quantified using standardized, generic preference-based measures of HRQoL.[3–6] Preference-based instruments comprise a descriptive system (i.e., the dimensions and items contained within the instrument that define a respondent’s HRQoL as one of a finite number of health states) and a valuation system (i.e., the scoring algorithm that assigns a single index value to each health state in the finite set).[7,8] ‘Generic’ indicates that such HRQoL instruments are not specific to particular age, disease or treatment contexts, comprising domains that (should) make them applicable to patients and the general population.[9,10] Although the range of potential index values differs across preference-based HRQoL instruments, the scores are interpreted on the same scale, where 1 reflects full health and zero indicates a health state equivalent to being dead. Some preference-based HRQoL instruments permit negative values, reflecting health states considered to be worse than dead.

Generic preference-based HRQoL instruments all purport to measure the same underlying construct. However, investigators have demonstrated only moderate agreement, at best, between health state valuations generated with different instruments.[11–16] Sources of disagreement between instruments can relate to variation in the respective descriptive systems and/or variation in the valuation components.[16] Assessing the performance of preference-based HRQoL instruments in...
different patient populations has been suggested as an important step in their evaluation.[17] Head-to-head comparisons provide an opportunity to identify underlying reasons for the discrepancies between instruments, while also providing researchers and policy makers with a clearer understanding of the implications associated with using particular HRQoL instruments.

Mobility is a dimension that has been described and measured inconsistently across different generic HRQoL instruments, and these differences have been highlighted previously as contributing to variations in the performance of these instruments in populations with mobility impairment.[18–21] Specifically, the relevance and applicability of the language contained within mobility-related items and response options has been identified as a key component of instrument acceptability for individuals living with spinal cord injury.[20–23] For example, Whitehurst et al demonstrated that variations in the framing of mobility-related items across four preference-based HRQoL instruments – specifically the reference to an individual’s ability to walk – was a key driver of the differences in index scores generated by the instruments.[20]

The purpose of the current study is to evaluate the comparative performance of two preference-based HRQoL instruments (the Assessment of Quality of Life 8-dimension (AQoL-8D) questionnaire [24] and the 5-level version of the EQ-5D (EQ-5D-5L)[25] in a population of individuals receiving assisted ventilation. This population commonly displays a broad range of underlying pathology (including neuromuscular disorders, chronic obstructive pulmonary disease and obesity-hypoventilation syndrome) and, consequently, demonstrates a range of mobility impairments and frequent use of mobility aids.[26] Examining index scores generated with these two instruments provides an opportunity to (i) consider their comparative performance in a population that comprises a broad range of health states and (ii) contribute to recent literature that explores the influence that the framing of mobility items has on health state valuations.[20]
Methods

Population and data collection

This is a secondary analysis of data from a cross-sectional study evaluating care practices and HRQoL of individuals receiving assisted ventilation, which was conducted using a postal survey. The study included clients of two state/province-wide home ventilation programs; the Provincial Respiratory Outreach Program (British Columbia, Canada) and the Victorian Respiratory Support Service (Victoria, Australia). Both programs support individuals in the community who are receiving assisted ventilation for all or part of the day. Individuals were eligible to participate in the study if they were 18 years or older, were active clients of their respective home ventilation program and could understand written English. Full details of this study have been published elsewhere, along with an exploration of clinical and socioeconomic factors that influence HRQoL in this cohort.[27]

Initial correspondence providing basic information on the study was sent via mail to all clients in February 2013; the study survey and ‘Participant Information and Consent Form’ was subsequently sent via mail in April 2013. Participants were informed that their consent to participate was implied if they provided a response to the survey. Six weeks after the survey was sent, non-responders were contacted by telephone to ascertain their interest in participating. Written responses were returned via a stamped, self-addressed envelope provided with the survey. Alternatively, participants could choose to complete an online version of the survey that was developed by members of the research team using a proprietary online survey provider (Survey Monkey, Palo Alto, CA). Participants were provided remuneration on completion of the survey (equivalent to $15 value in local currency). The study protocol was approved by the University of British Columbia Clinical Research Ethics Board (H12-01479) and the Austin Health Research Ethics Committee (H2012/04850).
The client databases of the two home ventilation providers were used as the primary source of clinical information. Items adapted from the 2000 and 2010 US Census were included in the survey to gather demographic information on participants.[28]

The AQoL-8D is a generic preference-based HRQoL instrument, developed using psychometric methods.[24,29] It comprises 35 items that load onto eight dimensions (Independent Living, Relationships, Mental Health, Coping, Pain, Senses, Self-worth and Happiness).[24] Scoring procedures for the AQoL-8D permit the estimation of an overall single index score, eight separate dimension scores, and scores for physical and mental ‘super dimensions’. [24,30] The AQoL-8D scoring algorithm used in this study (version 14) is the Australian value set (currently the only AQoL-8D value set available), which ranges from 0.090 to 1.000.[31] Two of the 35 items included in the AQoL-8D concern aspects of mobility (item 3 ‘Getting around’ and item 15 ‘Mobility’),[32] with neither item making reference to the respondent’s ability to walk. The wording of these two items, and the respective response options, are described in Appendix 1.

The EQ-5D-5L is the five level version of the original EQ-5D, one of the most widely used instruments for economic evaluations of healthcare and a preferred health status measure of the National Institute for Health and Care Excellence (NICE).[3,33] The EQ-5D-5L comprises five dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression); each dimension is made up of one item that has five levels of response.[25] A number of value sets are available for scoring the EQ-5D-5L. The recently published Canadian value set was used in this study.[34] EQ-5D-5L index scores obtained using the Canadian value set range from -0.148 to 0.949. Sensitivity analyses were conducted using the EQ-5D-5L value set for England to determine if the choice of preference weights influenced the findings.[35]

Although the construction of the AQoL-8D and EQ-5D-5L vary significantly, and the AQoL-8D provides a more comprehensive range of data (e.g., dimension-level scores), it is important to note that the primary purpose of all preference-based HRQoL instruments is to measure and value health status as
a single index value, which allows for the estimation of quality-adjusted life years (QALYs).[7,8] In both the written and online forms of the survey, the instrument order was fixed, with the AQoL-8D instrument coming before the EQ-5D-5L.

**Statistical analysis**

Analyses of AQoL-8D and EQ-5D-5L index scores consisted of graphical illustration of data (frequency distributions and jittered scatterplots), descriptive statistics and agreement (intraclass correlation coefficient (ICC) and Bland-Altman plots).[36] Employing a similar method to that described by Whitehurst et al.,[20] analyses of index scores were performed on the full sample as well as subgroups defined according to respondents self-reported ability to walk. All respondents were classified as either ‘ambulant’ or ‘non-ambulant’ according to their response to the Mobility item of the EQ-5D-5L (i.e., response options one to four = ambulant; response option five = non-ambulant. See Appendix 1).

The jittered scatterplot illustrates individual-level data across the 0-1 index score scale, with the ‘jitter’ procedure adding random noise to the data before plotting to avoid overlapping data points. The subgroup analysis is incorporated into this method of data display through the use of different markers for the ambulant and non-ambulant subgroups. Bland-Altman plots are used to illustrate and quantify agreement between two quantitative measurements (in this case, two measures of preference-based HRQoL). The method involves plotting the difference between paired measurements against the mean of the two measurements.[36] ‘Limits of agreement’ are plotted by using the mean difference ±1.96 standard deviations (of the difference), within which 95% of the plotted data points should lie. For the comparisons explored in this study, smaller mean differences and narrower limits of agreement imply better agreement between the two measures. For the assessment of absolute agreement, single measure ICCs were calculated, based on a two-way mixed analysis of variance model.[37,38] Conservative benchmarks of correlation were used; 0.00 to 0.10
representing virtually no correlation, 0.11-0.40 ‘slight’, 0.41-0.60 ‘fair’, 0.61-0.80 ‘moderate’ and 0.81-1.00 ‘substantial’. Analyses were performed using SPSS v21 (IBM, Armonk, NY) and Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA).

Results
Overall, 868 eligible clients were identified from the respective databases and received the postal survey. Of these, 497 (57.3%) responses were received across both sites. Participants in the study were older on average than non-participants and, at the Australian site, were more likely than non-participants to have an underlying neuromuscular disorder. No other significant differences were identified; further details of the cohort are provided elsewhere. Sixteen responses were incomplete, to the extent that summary measures could not be produced for the HRQoL instruments included in the survey. Characteristics of the remaining 481 (55.4%) participants are reported in Table 1. Mean age was 55.9 years and there was a male predominance. Although there were more respondents from Australia than Canada, response rates at each site were not significantly different. The majority of respondents had an underlying neuromuscular disorder, with lower proportions of obesity hypoventilation syndrome, chronic obstructive pulmonary disease and restrictive thoracic disorders.

Index scores
The distributions of AQoL-8D and EQ-5D-5L index scores are shown in Figure 1 (frequency distributions) and Figure 2 (jittered scatterplot). For the full sample, it is evident that there are notable differences in the range of observed values (i.e., a narrower range of observations for the AQoL-8D (Figure 1a; Figure 2)) and the distribution of responses (AQoL-8D approximating a Normal distribution, whereas the EQ-5D-5L distribution exhibits a negative skew (Figure 1a)). For the EQ-5D-
SL Mobility item, 159 (33.1%) respondents selected the level five response (“I am unable to walk about”), which defined the non-ambulant subgroup. Frequency distributions, by subgroup, were similar for the AQoL-8D (Figures 1b and 1c) but markedly different for the EQ-5D-5L (Normally distributed for the non-ambulant subgroup (Figure 1b); negatively skewed for the ambulant subgroup (Figure 1c)). The jittered scatter plot (Figure 2) provides a clear, visual indication that the EQ-5D-5L index scores are systematically different between the two subgroups; the same observation does not apply to the AQoL-8D index scores. Sensitivity analysis illustrates the same response pattern for EQ-5D-5L responses when using a value set for England (see Appendix 2).

Mean differences between AQoL-8D and EQ-5D-5L index scores were statistically significant in both subgroup analyses, with the AQoL-8D providing a higher mean value for those that were non-ambulant (mean difference = 0.206) but a lower mean value for ambulant respondents (mean difference = -0.079) (Table 2). Health states valued as ‘worse than dead’ were infrequent in both subgroups, with 5 (3.1%) non-ambulant responders and 1 (0.3%) ambulant responder reporting a negative EQ-5D-5L health state value.

Analysis of absolute agreement indicated a ‘moderate’ level of agreement (ICC = 0.642) when analyzed across the full sample, ‘slight’ agreement (ICC = 0.386) for the non-ambulant subgroup and ‘moderate’ agreement (ICC = 0.729) for the ambulant subgroup (see Table 2). Comparison of EQ-5D-5L and AQoL-8D index scores using Bland-Altman plots identified a systematic relationship between the difference in scores (y axis) and the magnitude of scores (x axis) in the full sample (see Figure 3a). Data points were predominantly above the solid horizontal line (the mean difference) at the lower end of the x-axis, which illustrates that a low average of the paired scores is associated with higher AQoL-8D scores compared with the EQ-5D-5L. Nineteen (4.0%) scatter points were outside the limits of agreement in Figure 3a, with 13 above the upper limit. The unequal split above and below the upper and lower limits demonstrates that the disagreement between index scores is not
consistent across the 0-1 scoring range. Similar systematic relationships were more evident among ambulant participants (Figure 3c) compared with non-ambulant participants (Figure 3b).

**Mobility-related item-level responses**

Table 3 shows the response patterns to the three mobility-related items (AQoL-8D items 3 and 15, and EQ-5D-5L item 1). Ten (2.1%) participants reported the lowest level of response for the AQoL-8D Mobility item compared with 159 (33.1%) for the corresponding level of response on the EQ-5D-5L Mobility item (Table 3, Panel A). Within the non-ambulant subgroup, over 30% (n=49) reported either “I am very mobile” (level one; AQoL-8D item 15) or “I have no difficulty with mobility” (level two; AQoL-8D item 15). This suggests that the EQ-5D-5L restricts non-ambulant respondents to a response option that indicates extreme mobility impairment even if the respondent perceives no such difficulty. Mobility impairment, as measured by the EQ-5D-5L, appears to be captured more accurately by the AQoL-8D through item 3 (‘Getting Around’); with 49.7% of respondents in the non-ambulant subgroup reporting the lowest level of response (level 6) for this item. Within the ambulant subgroup, 13.7% of respondents also selected the level 6 response for this item, indicating that retaining an ability to walk does not necessarily correspond with an ability to move independently.

**Discussion**

Comparative evaluation of preference-based HRQoL instruments is an important line of research in order to understand the potential reasons for between-measure discrepancies and the associated implications for healthcare decision-making. Through a series of analyses that explored the role of mobility-related items, this study provides further supportive evidence of how differences in the descriptive systems of preference-based HRQoL instruments can influence index scores. In the
overall population of individuals receiving assisted ventilation, there was a small, non-significant mean difference in AQoL-8D and EQ-5D-5L index scores (0.015) and a ‘moderate’ level of agreement (Table 2). By contrast, in the non-ambulant subgroup, the mean difference was considerably larger (0.206) and absolute agreement was classified as ‘slight’. There were clear differences in self-reported mobility ratings using the two instruments, which appeared to be related to whether mobility was evaluated as the ability to walk or, more broadly, as the capacity to be mobile.

The framing of the mobility-related items contained within the AQoL-8D and EQ-5D-5L is different, and appears to be a major factor in the difference in index scores for non-ambulant individuals, as observed previously in a sample of individuals living with spinal cord injury.[20] The EQ-5D-5L evaluates mobility by measuring the ability to perform a behavior (walking) and does not instruct respondents to consider the use of non-human aids in their response. The current analysis suggests that framing a mobility item in this way results in non-ambulant responders being constrained to selecting a more extreme level of mobility impairment than they may perceive.[21,40] In contrast, the AQoL-8D evaluates individuals’ capacity to be mobile and how easily this is achieved independently, and specifically instructs respondents to consider the use of non-human aids (item 15, see Appendix 1).

For the EQ-5D-5L, this constraint on non-ambulant responders imposes a considerable decrement on the achievable index score, i.e., even if all remaining dimensions are answered with the highest level of response (level 1), the EQ-5D-5L index score cannot exceed 0.742 (using the Canadian value set).[34] When performing a similar exercise with the AQoL-8D (i.e., lowest levels of response on the two mobility-related items, and the highest levels for all other items), the corresponding index score is 0.927. The relative sensitivity of the EQ-5D-5L to pain and physical function when compared to other generic preference-based instruments has been described.[13] Evidently, lower ratings on mobility-related items are more heavily ‘penalised’ when using the EQ-5D-5L compared with the AQoL-8D. In part, this is attributable to the relative proportion of mobility-related items within the
respective descriptive systems (i.e., mobility-related items comprise 20% (1 of 5) of the EQ-5D-5L and 6% (2 of 35) of the AQoL-8D). The frequently discordant mobility ratings identified in the current study (see Table 3) suggest that due to the framing of the mobility-related item of the EQ-5D-5L, this penalty is essentially unavoidable for those that are unable to walk, even if they perceive no problems with their mobility.

Previous investigators have demonstrated that differences in the descriptive systems of preference-based HRQoL instruments contribute significantly to the variation in health state valuations.[33,38] Although scale effects and differences in the scoring procedures also contribute, Richardson et al estimated that 66% of the differences between index scores produced from the EQ-5D-5L, SF-6D, HUI-3, 15D and AQoL-8D were attributable to the descriptive systems, concluding that revisions to the valuation systems alone would not reconcile these differences.[33] A number of studies have also suggested that descriptive differences could be due to the fact that some instruments fail to include dimensions of HRQoL that are included in other instruments.[41–43] The results of this study add to this literature, demonstrating that the way in which a dimension of health is described (in the question and/or the response options) is also important.

Including nonhuman aids (e.g., wheelchairs, gait aids, hearing aids or eyeglasses) in the assessment of health status has previously been advocated by Asada, who argued that it was reasonable to include both medical technology and nonhuman aids in health status measures – but that human assistance or accommodating environmental factors should not be included.[44] Results from the current study suggest it may be problematic to evaluate health status (and, consequently, healthcare interventions using economic evaluation) in populations that include non-ambulant individuals with an instrument that does not instruct the respondent to consider the use of nonhuman aids. However, whether or not generic preference-based HRQoL instruments should instruct respondents to consider the use of nonhuman aids is a normative question that requires further research.
The potential difficulties of using HRQoL instruments in populations that include disabled individuals has been highlighted previously.\cite{18,19} Although many HRQoL instruments are intended to be used across populations with various levels of health, the descriptive systems are not typically designed with the direct involvement of disabled individuals.\cite{23} This, combined with the use of ‘value-laden language’ has been considered a barrier to their use in populations that include individuals with disability.\cite{23} The descriptive system of the AQoL-8D has been demonstrated to be acceptable in such a population (spinal cord injury) when compared with other preference-based HRQoL instruments;\cite{21} further work is underway to examine whether the index scores of the AQoL-8D perform ‘better’ than other instruments from a psychometric perspective.\cite{20}

**Implications**

Based on results from the current study, a cautious approach is required regarding the choice of preference-based HRQoL instrument in populations that include non-ambulant individuals. Unless this issue is understood, the use of instruments that presume walking is synonymous with mobility may provide erroneous estimates of health status. This may limit the ability to detect actual changes in health status amongst non-ambulant subpopulations, and may influence the direction and magnitude of change when evaluated across a broader population. Given the widespread use of generic preference-based HRQoL instruments in evaluations of health technology, an understanding of these issues appears crucial to avoid adverse health policy decisions – particularly within groups such as individuals receiving assisted ventilation and others that demonstrate high rates of physical disability.

**Strengths and limitations**
A major strength of this study is that it is the first to compare the performance of two generic preference-based HRQoL instruments in a cohort of individuals using assisted ventilation. The heterogeneity of this clinical population – particularly with regard to mobility impairment – provided an ideal group in which to evaluate the performance of instruments that are specifically designed to measure health status across broad levels of health, including very severe health states.

While the Mobility item of the EQ-5D-5L represents a reasonable, self-reported measure of an individuals’ ability to walk, direct observation of mobility status would have been preferable. This data was not collected in the original study and represents an important limitation of this secondary analysis.[21,40] It is also acknowledged that due to its relative sensitivity to physical function,[13] the EQ-5D-5L could be expected to produce lower index scores in individuals with physical disability in comparison to the AQoL-8D. However, a strength of this study, and other previous work in this area,[20] is the identification that a significant contributor to between-measure discrepancies in such populations is the framing of mobility-related items.

An additional limitation of these analyses is the lack of longitudinal data. Evaluating the responsiveness of these (and other) instruments in populations that include individuals with disability is an important area for further research. Ultimately, differences in the way that instruments measure changes in health status are the greater threat to the validity of QALY-based economic evaluation.

Although participants were instructed to complete the questionnaire themselves, and multiple formats were available to facilitate this, it is possible that some responses were completed by a proxy on behalf of the individual receiving assisted ventilation because of the use of a postal questionnaire. Carers and clinicians have been reported to underestimate the self-reported HRQoL of individuals receiving assisted ventilation and, therefore, this introduces an unknown level of bias into our results.[45,46] In addition, our data collection process was unable to limit the possible influence of order effect bias, with the AQoL-8D routinely administered prior to the EQ-5D-5L.
Finally, the availability of only one value set for the AQoL-8D mandated the use of Australian preference weights for the entire study population (i.e., Canadian AQoL-8D responses were assigned Australian values). Conversely, only a pilot Australian value set is currently available for the EQ-5D-5L,[47] and therefore the recently published Canadian weights were used for the entire population (i.e., Australian EQ-5D-5L responses were assigned Canadian values).[34] The sensitivity analysis (see Appendix 2), using an EQ-5D-5L value set for England, suggests that our findings are unlikely to be influenced by the source of EQ-5D-5L preference weights.[35]

Conclusion
This study provides further evidence that the framing of mobility-related items influences the index scores generated by preference-based HRQoL instruments in populations that include individuals who are unable to walk. The comparison of index scores produced by the AQoL-8D and EQ-5D-5L provides a clear contrast in how respondents answered mobility-related items depending on whether the instrument evaluates the ability to walk or, more broadly, the capacity to be mobile. While the semantic difference between mobility and walking is likely trivial for the able-bodied, it represents a crucial distinction for the non-ambulant. Further research is necessary to determine the responsiveness of preference-based HRQoL instruments in cohorts that include non-ambulant individuals. Our findings suggest a cautious approach is necessary when choosing a preference-based instrument to use in such populations.
Compliance with ethical standards

Funding: LMH received financial support in the form of a Postgraduate Scholarship from the National Health and Medical Research Foundation (Australia).

Conflict of interest: DGTW and SB are members of the EuroQol Group. CFM has been an advisory board member for Pfizer, Boehringer Ingelheim, Astra Zeneca and Novartis, and has received lecture fees from GlaxoSmithKline. MEH has received an unrestricted research grant and travel support from ResMed and an equipment loan from Philips Respironics. LMH, DJB and JDR declare no conflicts of interest.

Ethical approval: All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committees (University of British Columbia Clinical Research Ethics Board (approval H12-01479) and the Austin Health Research Ethics Committee (approval H2012/04850)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.
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**Table 1** - Characteristics of study participants (n=481). Values are numbers (percentages) unless otherwise stated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - mean (SD)</td>
<td>55.9 (15.8)</td>
</tr>
<tr>
<td>Gender - male</td>
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<tr>
<td>Participants from each site (site-specific response rate)</td>
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<tr>
<td>Victoria, Australia</td>
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<td>British Columbia, Canada</td>
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<td>Type of ventilation</td>
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<td>Invasive mechanical ventilation</td>
<td>57 (11.9)</td>
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<tr>
<td>Non-invasive ventilation</td>
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<tr>
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<td>Restrictive thoracic disorder</td>
<td>56 (11.6)</td>
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<td>101 (21.0)</td>
</tr>
<tr>
<td>COPD</td>
<td>34 (7.1)</td>
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<td>Other</td>
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<td>Employed/Self-employed</td>
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</tr>
<tr>
<td>Unemployed</td>
<td>13 (2.7)</td>
</tr>
<tr>
<td>Student</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Retired</td>
<td>202 (42.0)</td>
</tr>
<tr>
<td>Unable to work</td>
<td>167 (34.7)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (3.5)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>199 (41.4)</td>
</tr>
<tr>
<td>Secondary</td>
<td>203 (42.2)</td>
</tr>
<tr>
<td>Primary</td>
<td>57 (11.9)</td>
</tr>
<tr>
<td>No schooling completed</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Household income&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>$100,000+</td>
<td>31 (6.4)</td>
</tr>
<tr>
<td>$40,000-$99,999</td>
<td>145 (30.1)</td>
</tr>
<tr>
<td>$0-$39,999</td>
<td>277 (57.6)</td>
</tr>
<tr>
<td>Housing</td>
<td></td>
</tr>
<tr>
<td>Owner/occupier</td>
<td>274 (57.0)</td>
</tr>
<tr>
<td>Renter</td>
<td>93 (19.3)</td>
</tr>
<tr>
<td>House owned/rented by family/others</td>
<td>84 (17.5)</td>
</tr>
<tr>
<td>Residential care</td>
<td>30 (6.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> *Self-reported household income in local currency (data collected between April and June 2013)*
Invasive mechanical ventilation = assisted ventilation delivered via an invasive artificial airway (such as an endotracheal tube or tracheostomy); non-invasive ventilation = assisted ventilation delivered via a non-invasive interface (such as a mask, mouthpiece or other); neuromuscular disorders includes but is not limited to amyotrophic lateral sclerosis/motor neuron disease, muscular dystrophy, spinal cord injury, post-polio syndrome, and phrenic nerve dysfunction; restrictive thoracic disorder includes but is not limited to congenital and acquired kyphoscoliosis, post-surgical, and post-tuberculous; COPD, chronic obstructive pulmonary disease. Characteristics with mutually exclusive groups do not always sum to 100% due to missing data.
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>IQR</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Mean difference (95% CI; p-value)</th>
<th>ICC</th>
<th>Upper LOA</th>
<th>Lower LOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQoL-8D</td>
<td>0.581</td>
<td>0.208</td>
<td>0.561</td>
<td>0.343</td>
<td>0.997</td>
<td>0.116</td>
<td>0.015 (-0.00 to 0.03; 0.09)</td>
<td>0.642</td>
<td>0.400</td>
<td>-0.370</td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>0.566</td>
<td>0.255</td>
<td>0.569</td>
<td>0.437</td>
<td>0.949</td>
<td>-0.111</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Panel B: non-ambulant subgroup (n=159)

| AQoL-8D    | 0.548  | 0.186  | 0.550  | 0.259  | 0.980   | 0.116   | 0.206 (0.18 to 0.23; <0.001)       | 0.386| 0.477     | -0.065    |
| EQ-5D-5L   | 0.342  | 0.152  | 0.344  | 0.175  | 0.742   | -0.111  |                                  |      |           |           |

Panel C: ambulant subgroup (n=322)

| AQoL-8D    | 0.597  | 0.217  | 0.585  | 0.373  | 0.997   | 0.140   | -0.079 (-0.09 to -0.06; <0.001)    | 0.729| 0.208     | -0.366    |
| EQ-5D-5L   | 0.676  | 0.221  | 0.727  | 0.320  | 0.949   | -0.035  |                                  |      |           |           |

Subgroups were defined according to responses to the EQ-5D-5L Mobility item, with level five responses (“I am unable to walk about”) used to define the non-ambulant subgroup (Panel B).

Mean difference equals AQoL-8D minus EQ-5D-5L

SD, standard deviation; IQR, interquartile range; CI, confidence interval; ICC, intraclass correlation coefficient; LOA, limits of agreement.
Table 3 Patterns of responses across the mobility-related items of the AQoL-8D (items 3 and 15) and EQ-5D-5L (item 1) for the full sample (Panel A), non-ambulant subgroup (Panel B) and ambulant subgroup (Panel C). a Values are numbers (percentages) unless otherwise stated.

<table>
<thead>
<tr>
<th>Item</th>
<th>Panel A: full sample (n=481)</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
<th>Level 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQoL-8D item 3 ('Getting Around')</td>
<td>41 (8.5)</td>
<td>72 (15.0)</td>
<td>104 (21.6)</td>
<td>93 (19.3)</td>
<td>48 (10.0)</td>
<td>123 (25.6)</td>
<td></td>
</tr>
<tr>
<td>AQoL-8D item 15 ('Mobility')</td>
<td>63 (13.1)</td>
<td>57 (11.9)</td>
<td>136 (28.3)</td>
<td>131 (27.2)</td>
<td>84 (17.5)</td>
<td>10 (2.1)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L item 1 ('Mobility')</td>
<td>71 (14.8)</td>
<td>61 (12.7)</td>
<td>108 (22.5)</td>
<td>82 (17.0)</td>
<td>159 (33.1)</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Panel B: non-ambulant subgroup (n=159)</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
<th>Level 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQoL-8D item 3 ('Getting Around')</td>
<td>16 (10.1)</td>
<td>11 (6.9)</td>
<td>21 (13.2)</td>
<td>22 (13.8)</td>
<td>10 (6.3)</td>
<td>79 (49.7)</td>
<td></td>
</tr>
<tr>
<td>AQoL-8D item 15 ('Mobility')</td>
<td>25 (15.7)</td>
<td>24 (15.1)</td>
<td>28 (17.6)</td>
<td>15 (9.4)</td>
<td>57 (35.8)</td>
<td>10 (6.3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Panel C: ambulant subgroup a (n=322)</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
<th>Level 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQoL-8D item 3 ('Getting Around')</td>
<td>25 (7.8)</td>
<td>61 (18.9)</td>
<td>83 (25.8)</td>
<td>71 (22)</td>
<td>38 (11.8)</td>
<td>44 (13.7)</td>
<td></td>
</tr>
<tr>
<td>AQoL-8D item 15 ('Mobility')</td>
<td>38 (11.8)</td>
<td>33 (10.2)</td>
<td>108 (33.5)</td>
<td>116 (36.0)</td>
<td>27 (8.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L item 1 ('Mobility')</td>
<td>71 (22.0)</td>
<td>61 (18.9)</td>
<td>108 (33.5)</td>
<td>82 (25.5)</td>
<td>0 (0.0)*</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

n/a; not applicable

a Subgroups were defined according to responses to the EQ-5D-5L Mobility item, with level five responses ("I am unable to walk about") used to define the non-ambulant subgroup (Panel B). Spearman rank correlations (r_s) for the three mobility-related items: AQoL-8D (item 3) and AQoL-8D (item 15), r_s=0.659; EQ-5D-5L (Mobility) and AQoL-8D (item 3), r_s=0.516; EQ-5D-5L (Mobility) and AQoL-8D (item 15), r_s=0.360.
Figure 1 - Frequency distributions for AQoL-8D and EQ-5D-5L index scores for the full sample (row (a)), and the non-ambulant (row (b)) and ambulant (row (c)) subgroups.
Figure 2 - Jittered scatterplot of individual-level index scores (triangles and crosses) for the AQoL-8D and EQ-5D-5L.

Crosses represent individual-level index scores for respondents who reported the ability to walk (EQ-5D-5L Mobility response levels one to four, n=322); triangles represent individual-level index scores for respondents who reported they were unable to walk (EQ-5D-5L Mobility response level five, n=159). In this figure, the ‘jitter’ procedure adds random noise to the x axis before plotting, which is useful when plotting data that otherwise would result in points plotted on top of each other.
Figure 3 - Bland-Altman plot showing the mean difference between paired AQoL-8D and EQ-5D-5L scores (solid line) and associated 95% limits of agreement (dashed lines), for the full sample (a), and the non-ambulant (b) and ambulant (c) subgroups. The markers represent the difference between scores and the average of the scores for each paired observation.
**Appendix 1 - Wording of mobility-related items in the AQoL-8D and EQ-5D-5L.**

<table>
<thead>
<tr>
<th>Instrument (item number)</th>
<th>Wording of the mobility-related item/dimension and the respective response options</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQoL-8D (3)</td>
<td>Thinking about how easy or difficult it is for you to get around by yourself outside your house (e.g., shopping, visiting):</td>
</tr>
<tr>
<td></td>
<td>RESPONSE OPTIONS</td>
</tr>
<tr>
<td></td>
<td>• Getting around is enjoyable and easy</td>
</tr>
<tr>
<td></td>
<td>• I have no difficulty getting around outside my house</td>
</tr>
<tr>
<td></td>
<td>• A little difficulty</td>
</tr>
<tr>
<td></td>
<td>• Moderate difficulty</td>
</tr>
<tr>
<td></td>
<td>• A lot of difficulty</td>
</tr>
<tr>
<td></td>
<td>• I cannot get around unless somebody is there to help me</td>
</tr>
<tr>
<td>AQoL-8D (15)</td>
<td>Thinking about your mobility, including using any aids or equipment such as wheelchairs, frames, sticks:</td>
</tr>
<tr>
<td></td>
<td>RESPONSE OPTIONS</td>
</tr>
<tr>
<td></td>
<td>• I am very mobile</td>
</tr>
<tr>
<td></td>
<td>• I have no difficulty with mobility</td>
</tr>
<tr>
<td></td>
<td>• I have some difficulty with mobility (for example, going uphill)</td>
</tr>
<tr>
<td></td>
<td>• I have difficulty with mobility. I can go short distance only</td>
</tr>
<tr>
<td></td>
<td>• I have a lot of difficulty with mobility. I need someone to help me</td>
</tr>
<tr>
<td></td>
<td>• I am bedridden</td>
</tr>
<tr>
<td>EQ-5D-5L (1)</td>
<td>Mobility</td>
</tr>
<tr>
<td></td>
<td>RESPONSE OPTIONS</td>
</tr>
<tr>
<td></td>
<td>• I have no problems in walking about</td>
</tr>
<tr>
<td></td>
<td>• I have slight problems in walking about</td>
</tr>
<tr>
<td></td>
<td>• I have moderate problems in walking about</td>
</tr>
<tr>
<td></td>
<td>• I have severe problems in walking about</td>
</tr>
<tr>
<td></td>
<td>• I am unable to walk about</td>
</tr>
</tbody>
</table>
Appendix 2 - Jittered scatterplot of individual-level index scores (triangles and crosses) for the AQoL-8D and two different scoring algorithms for the EQ-5D-5L (Canada and England).

Crosses represent individual-level index scores for respondents who reported the ability to walk (EQ-5D-5L Mobility response levels one to four, n=322); triangles represent individual-level index scores for respondents who reported they were unable to walk (EQ-5D-5L Mobility response level five, n=159). In this figure, the ‘jitter’ procedure adds random noise to the x axis before plotting, which is useful when plotting data that otherwise would result in points plotted on top of each other.
The results presented in the manuscript demonstrate important differences between two preference-based HRQoL instruments that could influence the results of clinical studies involving individuals receiving assisted ventilation. The EQ-5D-5L instrument is an attractive choice for clinical research due to its brevity and preferred status in health technology assessment. However, its performance in this heterogeneous population demonstrates considerable potential limitations. Combining index scores from the EQ-5D-5L from participants who are non-ambulant with those that are ambulant may be problematic. This could also lead to misleading conclusions, even in populations with more homogeneous levels of mobility impairment.

Perhaps in a desire to continue using popular instruments, such as the SF-36 and EQ-5D, investigators have previously attempted to alter or exclude items that were considered to be problematic for individuals with disability. Developing modified formats for these instruments for use in disabled populations is undesirable for a number of reasons. Firstly, such an approach requires a judgement by the investigator that the respondent is sufficiently disabled to warrant use of the modified format. Secondly, it limits the ability to compare data obtained from the standard version with the modified version – as these methods yield values that are ‘corrected’ and ‘uncorrected’ for measures of physical functioning. And thirdly, substitution or exclusion of items for individuals with disability – while retaining the original version for able-bodied participants – could also be perceived as supporting a belief that disability equates to poor health. This belief is not necessarily shared by individuals with disabilities.

Modifying generic preference-based HRQoL instruments is additionally problematic as separate valuation studies would be required. This is due to the
likelihood that the health states described in the modified version may be valued differently in comparison to the original. Previous authors have also suggested that persons with no direct knowledge of a condition are not well positioned to provide a determination of the desirability (or value) of a particular health state if they have no experience of it. (Hays et al., 2002) This suggests problems with the use of community samples that are typically used to value health states described with these instruments. Alternative instruments that consider the health state as an influence on wellbeing may be more acceptable to individuals with disability. (Al-Janabi, Flynn, & Coast, 2012) Such instruments are not widely accepted for use in economic evaluations currently.

In addition to these important issues related to the formulation of these instruments, an important consideration for individual researchers relates to the acceptability of the instrument to participants. Individuals with limited mobility may prefer not to answer questions they deem to be pejorative or even discriminatory – particularly if they feel constrained to a response that does not reflect their own assessment of their circumstances. This has been highlighted previously in a study evaluating individuals with multiple sclerosis. (Fisk et al., 2005) Fisk et al reported that 20% of their participants omitted the mobility item of the SF-36 and 43% omitted the mobility item of the EQ-5D. Both instruments incorporate mobility items that explicitly evaluate the respondent’s ability to walk. Others have described significant limitations in the use of the SF-36 and Nottingham Health Profile in populations with severe levels of disability. (Kersten et al., 1999) High rates of non-completion or missing data are potentially extremely problematic in the interpretation of results. It is unknown whether these issues influenced response rates in the cross-national study described in Chapter Seven.

The analysis described above does not indicate superiority of the AQoL-8D for use in studies involving individuals receiving assisted ventilation. In fact, other generic instruments may perform better. However, the AQoL-8D does
include items and domains of health that on face value may be relevant for users of assisted ventilation. It also allows respondents to incorporate the use of non-human aids. This may have advantages, however its responsiveness to changes in health in this group has not been determined. Instead this analysis has identified potentially significant limitations to the use of the EQ-5D-5L. In studies involving individuals receiving assisted ventilation, where participants may have heterogeneous levels of mobility impairment, the use of the EQ-5D-5L could be problematic. This has broader implications, as the EQ-5D-5L is frequently used for assessments of health technology in Europe and elsewhere. (National Institute for Health and Care Excellence (NICE), 2013) The limitations of this instrument in disabled populations would need to be well understood in order for results to be appropriately interpreted.

This analysis has demonstrated that the two instruments (AQoL-8D and EQ-5D-5L) performed very differently in individuals using assisted ventilation who were unable to walk. A lack of understanding or awareness of how a particular instrument evaluates health status in a given population could influence study outcomes and health policy. This emphasises the conclusion of Asada, who suggested that researchers decide “what they want to measure and ensure they develop [or use] a health measure that reflects their decision”. (Asada, 2005) Careful consideration regarding instrument selection is clearly required in order for results to be meaningful and reliable.

8.11 Conclusion

These analyses have demonstrated that the subjective benefits obtained from NIPPV appear to differ across the diagnostic groups that use this therapy. In addition, it was also confirmed that descriptive differences between two generic preference-based HRQoL instruments contribute to the lack of agreement between the index scores produced.
For determining which dimensions of health are likely to be influenced by the provision of NIPPV therapy, the systematic review confirmed the paucity of studies in this area and their generally low quality. Despite this, it was demonstrated that measures of somnolence and fatigue were the most consistently influenced across studies and across diagnostic groups. Instruments or rating scales that specifically evaluate these symptoms should be included in longitudinal studies of NIPPV in order to identify subjective benefits of treatment if they are present. Measures of sleep quality may also be useful. Other symptoms and health domains were less consistently influenced by NIPPV, possibly limiting their value as outcome measures in heterogeneous populations.

Regarding HRQoL measures, inclusion of a disease-specific instrument should occur as these measures intend to include dimensions of health that are of greatest interest to both users of NIPPV and clinicians. Whether both groups prioritise these dimensions of health with similar weighting is unknown.

For generic preference-based HRQoL measures, poor agreement was demonstrated between the index scores generated for the EQ-5D-5L and the AQoL-8D in those who reported an inability to walk. This is consistent with previous studies that compared the EQ-5D-5L and other preference-based HRQoL instruments in non-ambulant individuals. (Whitehurst et al., 2016) Being constrained to the extreme mobility option of the EQ-5D-5L, despite perceiving no problems or limitations with mobility, represents a considerable limitation of this instrument. If used in populations that include non-ambulant individuals, there is a potential this descriptive format could limit the ability to detect real changes in health status. While not evaluated against a full array of potential alternative instruments, the AQoL-8D demonstrated some attributes that are likely to be preferable in a population with heterogeneous levels of mobility impairment. Specifically; by evaluating the capacity to mobilise rather than the behaviour of walking. Incorporating the use of non-human aids may be advantageous for generic preference-based HRQoL instruments when used in
populations with heterogeneous degrees of disability. The AQoL-8D also includes coverage of sleep in its descriptive system, which, given the results of the systematic review, may also be advantageous.
Chapter 9 – Randomised Controlled Trial Examining the Use of Polysomnography to Titrate Non-Invasive Positive Pressure Ventilation

9.1 Introduction

In Chapter Seven of this thesis, a lack of association between differences in routine respiratory care practices and cross-sectional HRQoL was demonstrated. This lack of association can be considered a hypothesis only. Evaluating specific interventions in randomised controlled trials will allow this to be tested. The use of PSG was one care practice for which there was significant regional discordance. This procedure is associated with significant cost – both in time and resources – and therefore warrants further evaluation.

No controlled trials have been reported that have evaluated the role of PSG in implementing NIPPV. Previous uncontrolled studies have suggested that synchronisation between the ventilator and the user is poor following daytime clinical titration, (Fanfulla et al., 2007) can be improved with setting adjustments, (Fanfulla et al., 2005) and that PSG titration may be an effective means of performing these adjustments. (Adler et al., 2011) Associations have been demonstrated between increased levels of patient-ventilator asynchrony (PVA) and more EEG arousals during sleep, (Crescimanno et al., 2012) less REM sleep and lower sleep efficiency, (Fanfulla et al., 2005) worse nocturnal gas exchange, (Fanfulla et al., 2007) and more intolerance of therapy. (Carlucci, Pisani, et al., 2013) Alternative methods to PSG such as daytime clinical titration are cheaper and simpler to employ and less burdensome on users of NIPPV. However, if the therapy that is instituted is less effective or poorly tolerated, adverse clinical outcomes could result thereby negating any benefit of avoiding PSG.
This chapter reports the results from a single-centre, blinded, parallel group, randomised controlled trial comparing daytime clinical titration (Control) with daytime clinical titration followed by PSG titration (PSG titration).

Demonstrating both physiological and clinical benefits of routine PSG titration would provide support for the use of this practice in centres aiming to deliver high quality care for users of NIPPV.

9.2 **Aim**

The study aim was to determine whether the routine use of PSG to titrate NIPPV is associated with significant physiological and clinical benefits for treatment naïve users.

9.3 **Hypotheses**

The hypotheses tested were;

1. that NIPPV titrated with PSG would be associated with a lower patient-ventilator asynchrony (PVA) index during sleep than NIPPV titrated during daytime clinical titration;

2. that NIPPV titrated with PSG would be associated with a lower EEG arousal index during sleep than NIPPV titrated during daytime clinical titration;

3. that NIPPV titrated with PSG would be associated with greater adherence to therapy and larger improvements in gas exchange, symptoms and HRQoL than NIPPV titrated during daytime clinical titration.
9.4 METHODS

9.4.1 Study design

The study was a single-centre, blinded, parallel group, randomised controlled trial. The study protocol was approved by Austin Health Research Ethics Board (Approval number 05115) and was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR Trial number 365405).

9.4.2 Participants

Participants were recruited from those referred for initiation of long-term domiciliary NIPPV to a state-wide HMV service based in Victoria, Australia. Individuals with, or at risk of, chronic hypercapnic respiratory failure undergoing elective outpatient implementation of NIPPV were invited to participate. The decision to initiate long-term NIPPV was made by the referring specialist clinician on the basis of published guidelines, ([No authors listed], 1999; McKim et al., 2011; Piper et al., 2010) in addition to local protocols.

Individuals over the age of 18 years, who were deemed medically stable and suitable for outpatient implementation of NIPPV, were eligible for inclusion. Exclusion criteria included current inpatient hospitalisation, hypoventilation attributable primarily to sedative/respiratory depressant medications, the use of assisted ventilation in any form (but not including CPAP) for more than one month in the previous 3 months, a lack of proficiency in English, an inability to provide informed consent or a previous documented history of intolerance of NIPPV.
9.4.3 Study procedures

After obtaining informed consent, all participants completed a battery of questionnaires and an arterial blood gas sample was obtained while the participant was breathing room air, at rest, for at least 30 minutes. This occurred prior to NIPPV implementation and represented the baseline measure (Figure 5).

The instruments included in the battery included:

The Pittsburgh Sleep Quality Index (PSQI); a 19-item, self-assessed questionnaire that is reliable and validated to assess sleep quality for individuals with sleep disorders. (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989)

Higher scores represent worse sleep quality.
The Epworth Sleepiness Scale (ESS); a questionnaire containing eight items that evaluates the propensity of subjects to fall asleep in specific situations. (Johns, 1991) Higher values indicate an increased propensity to fall asleep or doze.

The Karolinska Sleepiness Scale (KSS); is a single item, nine-point scale evaluating sleepiness which has been validated against alpha and theta EEG activity and slow eye movement EOG activity. (Åkerstedt & Gillberg, 1990) The scale evaluates sleepiness at a single point in time, requiring respondents to gauge their current level. Higher values indicate increasing subjective sleepiness.

The Fatigue Severity Scale (FSS); a questionnaire containing nine items, each using a 7-point Likert scale to evaluate the affect of fatigue on motivation, exercise, physical functioning, ability to carry out duties related to work, family or social life. Higher values indicate a larger impact of fatigue. (Krupp et al., 1989) The scale also includes a visual-analogue scale for rating fatigue severity where lower ratings indicate more severe fatigue.

The Modified Borg Dyspnoea Scale (MBDS); a scale that provides a reliable determination of dyspnoea. It is simple to administer and is sensitive to change. (Burdon, Juniper, Killian, Hargreave, & Campbell, 1982) Respondents are asked to rate their current level of dyspnoea using a scale from 0 - 10 where higher values indicate worsening severity of dyspnoea.

Side-effects of NIPPV were evaluated using a section of the Calgary Sleep Apnoea Quality of Life Index (SAQLI) instrument. (Flemons & Reimer, 2002) The portion used asks the respondent to rate the three most troubling side-effects experienced with therapy on a 7-point Likert scale according to their severity. The three ratings are combined to provide an overall score out of 21, with higher values indicating more troubling side-effects. In addition, the respondent is asked to offset the severity of side-effects with any benefits obtained from therapy – again on a 7-point Likert scale – with the middle value
(response = four) indicating that side-effects are equivalent with the benefits of therapy.

Disease-specific health-related quality of life (HRQoL) was evaluated with the English translation of the **Severe Respiratory Insufficiency Questionnaire (SRI)**. (Ghosh et al., 2012) This 49-item multidimensional HRQoL instrument was specifically designed for use in individuals receiving assisted ventilation. (Ghosh et al., 2012; Windisch et al., 2003b) It evaluates seven domains of health (respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being, social functioning) and produces a summary scale based on these domain scores. Each domain is scored from 0 - 100, with higher values indicating better HRQoL.

Generic HRQoL was evaluated using the **Assessment of Quality of Life Questionnaire – 8 Dimension (AqoL-8D)**. (Richardson et al., 2013) This 35-item generic preference-based HRQoL instrument incorporates eight dimensions of health (independent living, happiness, mental health, coping, relationships, self worth, pain, senses) and produces a global index score anchored at 0.0 (death) and 1.0 (full health). Both physical and mental ‘superdimensions’ are also calculated. As described in Chapter Eight, the AQoL-8D has attributes that are suited for use in studies involving individuals with heterogeneous levels of mobility impairment.

### 9.4.4 Clinical titration

Following the collection of baseline data, all participants underwent a standard daytime clinical titration of NIPPV according to local procedures. Each of these occurred onsite at a tertiary academic hospital within a modified sleep laboratory located on an inpatient ward. Each clinical titration occurred over a period of at least four hours. The implementation process was performed by one
of two experienced respiratory physiotherapists (LR or CC). These physiotherapists each have greater than five years of experience working with the HMV provider. They are regularly involved in the management of assisted ventilation, have expertise in the details of ventilator and interface technology and considerable experience in both clinical titration and PSG titration of NIPPV.

Each clinical titration included a trial period using NIPPV with settings adjusted to optimise patient comfort, minimise mask leak, achieve adequate minute ventilation (using device derived data), maintain appropriate oxygen saturations (using pulse oximetry via a finger probe) and maximise patient-ventilator synchronisation (based on clinical assessment). Implementation occurred with the participant in their usual sleep position. All participants used the same device (VPAP™ IV ST, ResMed, Bella Vista, Australia) with the exception of participants who required alternative devices due to a specific need for features such as an internal battery, higher pressures than could be delivered with a VPAP™ IV ST, or simpler controls. These individuals received an alternative device (Stellar™ 150 or VPAP S9™ ST-A, ResMed, Bella Vista, Australia). All devices were set to Spontaneous/Timed (S/T) trigger with a minimum starting EPAP of 4cmH₂O and a minimum starting IPAP of 8cmH₂O. All devices were set up with a back-up respiratory rate typically set one to two breaths below the participant’s intrinsic resting awake respiratory rate at the discretion of the physiotherapist. Other device settings (inspiratory time, rise time, trigger and cycle sensitivities) were set at the discretion of the treating physiotherapist with consideration of observed synchronisation and expected respiratory mechanics. Participants were provided the opportunity to doze while using NIPPV and their respiratory parameters (SpO₂, respiratory rate and synchronisation) were observed during sleep where possible. Further adjustments to settings were performed as deemed necessary by the treating physiotherapist.
9.4.5 Acclimatisation period

The acclimatisation period was defined as the day of the initial clinical titration until the day of the intervention (PSG titration or sham PSG titration - see Figure 5). Following the daytime clinical titration described above, all participants were provided with a standardised education session and instructions on the care and use of their device (and masks). A trained nurse employed as part of a dedicated HMV outreach service delivered this education. All were provided access to 24-hour telephone support on return home. A routine phone contact was planned to occur from a member of the outreach team or physiotherapist within the first two weeks of therapy. Further unscheduled contacts were performed as deemed necessary by individual members of the clinical team or at the request of the participant. These included visits to the participant’s homes, where deemed necessary, or contact via phone. Each participant undertook an acclimatisation period of two to three weeks. During this time, further adjustment to settings was performed as deemed necessary by the clinical team (either physiotherapist or outreach team member) to improve tolerance and symptoms.

9.4.6 Randomisation and blinding

Participants were blinded to group allocation. Only the attending sleep scientist on the night of the PSG titration (or sham PSG titration) and those researchers who were required to provide setting recommendations based on the PSG titration study were unblinded to group allocation (MEH, FOD, LR, NS). These individuals were not involved in the collection of outcome measures, scoring and staging of PSG data or subsequent analyses. Those involved in the collection of outcome measures, scoring/staging PSG data or analysis, and in the
support and management of participants in the community were blinded to group allocation.

Randomisation was performed using simple block randomisation with blocks of ten in order to ensure equal numbers in both groups. The blocks were not stratified. The randomisation procedure was performed by a member of the research team who did not have direct contact with participants and who was not involved in their clinical management (DJB). Allocation concealment was ensured through the use of sealed opaque envelopes. Randomisation was performed during the acclimatisation period after the clinical titration process had been completed to ensure that the clinicians performing the clinical titration were not inadvertently made aware of group allocation.

9.4.7 Contacts with healthcare workers

Contacts with healthcare workers were evaluated from entries contained in the centralised clinical database maintained by the HMV provider. All client-healthcare worker interactions provided by the HMV service (visits, phone calls, mask changes, setting adjustments) are routinely recorded in this database as per standard care. The database was interrogated at the conclusion of the study to evaluate the frequency of contact between the participants and staff from the HMV service. In addition, self-reported contacts with healthcare workers were recorded. These included hospital admissions, emergency department presentations, visits or contacts with local medical officers or other healthcare interactions during the study period.
9.4.8 Intervention

At the conclusion of the acclimatisation period (see Figure 5) all participants were randomly allocated to the two arms of the study.

- PSG titration
- Control (sham PSG titration)

9.4.9 PSG titration group

Those allocated to this group underwent an attended in-laboratory overnight PSG with titration of NIPPV settings (and mask adjustments) according to a standardised approach (see Appendix 9.1). Sleep scientists experienced in the titration and interpretation of PSG during NIPPV therapy performed the PSG. Nocturnal data was collected and recorded using the E-series PSG (Compumedics, Abbotsford, Australia) and included electroencephalography (F4/M1, C4/M1, O2/M1), left and right electro-oculography, submental and diaphragm electromyography using surface electrodes, mask pressure, body position sensor, thoracic and abdominal respiratory bands and video recording. Ventilator airflow and leak signals were obtained using a proprietary device (ResMed TX, ResMed, Bella Vista, Australia) with signals calibrated and incorporated with conventional PSG signals. Oxygen saturations were measured continuously with a pulse oximeter with a 2-second signal averaging time (Radical 7, Masimo, Irvine, USA) via a finger probe. Continuous measurement of transcutaneous partial pressure of carbon dioxide (PtcCO₂) was performed using transcutaneous capnography (TCM-4, Radiometer, Copenhagen, Denmark) with the probe heated to 43 degrees. Pre- and post-study arterial blood gases were used for drift and offset correction.
9.4.10 Control group

Those allocated to the Control group underwent a standard attended in-laboratory overnight PSG according to the exact same procedures as the PSG titration group but without changes to NIPPV settings. The attending sleep scientist had clear instructions not to reveal group allocation to participants in either group. A script was provided to assist with answering specific queries from participants in order to avoid inadvertent un-blinding. Sleep scientists were able to provide usual assistance on request from those in the Control group for issues such as difficulties donning or doffing the mask or other minor issues raised during the study. However these interactions could only occur on specific request from the participant. Abnormalities in PSG signals that would normally prompt adjustment to settings or interfaces (low SpO2, sleep fragmentation, excessive leak, poor synchronisation etc.) were not addressed or ameliorated by the sleep scientist.

9.4.11 PSG results

After the overnight PSG was completed, both groups had their PSG reviewed by two members of the research team (from MEH, FOD, LR and NS) who were experienced in the analysis and interpretation of NIPPV studies. Recommended settings were obtained by consensus between the two clinicians (which included at least one sleep physician). NIPPV setting recommendations were written on a standardised form for both groups following the intervention to ensure that group allocation was not inadvertently revealed. A blinded member of the research team (LMH) then programmed the recommended settings for all participants onto individual data cards, SD cards or USB sticks using proprietary software (ResScan™, ResMed, Bella Vista, Australia). These were sent directly to participants in order to update their devices. Confirmation
of the receipt of data cards and correct device settings was performed via telephone.

**9.4.12 Treatment period**

The treatment period was defined as the day after the intervention (either sham PSG titration or PSG titration) until the day of the PSG at study conclusion (see Figure 5). During the treatment period, the clinical management of participants was not influenced by the research study. Clinicians involved in the care of the participants were not restricted or directed in their management. Alterations to settings, masks or the use of additional clinical reviews, home visits or further monitoring was able to occur at clinician discretion. Guidelines are provided for clinicians within the HMV service in order to assist with decision-making regarding these alterations (see Appendix C).

**9.4.13 Final assessment**

At study conclusion (see Figure 5), participants returned for a repeat battery of questionnaires, daytime arterial blood gases and full PSG (using the same procedures as described earlier) on their current ventilator settings. This study was performed with no alterations to NIPPV settings or interfaces during recording. Participants used their most recent NIPPV settings and mask. This may not have reflected the settings recommended at the time of the original PSG titration or clinical titration if subsequently altered by the clinical team. Adherence data was downloaded from the individual machines. Arterial blood gases were again obtained at rest, while breathing room air for at least 30 minutes while off ventilation.
9.4.14 Outcome measures

9.4.15 Primary outcome

The primary outcomes for the study were measures of synchronisation (the PVA index, see below) and sleep disruption (the arousal index, see below) on the final overnight PSG at study conclusion (see Figure 5).

Patient-ventilator asynchrony (PVA) index

A number of different methods for calculating asynchrony indices exist as discussed in Chapter Three of this thesis. Only trigger asynchrony was used to determine the PVA index for this study as this could be identified using conventional PSG signals. The PVA index therefore was calculated as the total number of PVA events during sleep, divided by total sleep time (TST). Separate indices for each of the scored events (ineffective efforts, double-trigger, multiple trigger – see below) were also calculated, again using TST as the denominator.

A single scorer (LMH) performed all PVA scoring manually by inspecting all breaths during each 30-second epoch during overnight recording. Ten randomly selected PSGs were scored twice, at least two weeks apart, in order to determine the intra-rater reliability of the single scorer and scoring rules (see Appendix H). Studies were de-identified and the scorer was blinded to group allocation. PVA scoring was performed without inspection of EEG or other sleep staging information.
The scored PVA events were defined as:

- **Ineffective effort** – the presence of an individual observable respiratory movement (=effort; defined by deviations in the SUM trace of the thoracic and abdominal respiratory bands or by deviations in either the thoracic or abdominal band in the event that one of the signals was un-interpretable) that occurred without an associated mask pressurisation. (Fanfulla et al., 2005) The mask pressure trace therefore was used as the sole determinant of the presence or absence of a ‘ventilator breath’ (Figure 6). The derived flow signal obtained from the ventilator was not used to identify the presence or absence of effort from the user, nor the presence or absence of a ‘ventilator breath’.

![Figure 6 - Schematic representation of the ineffective effort scoring rule; mask pressure refers to measured pressure at the interface during polysomnography; sum trace refers to the additive signal of abdominal and thoracic respiratory bands](image)

Figure 6 - Schematic representation of the ineffective effort scoring rule; mask pressure refers to measured pressure at the interface during polysomnography; sum trace refers to the additive signal of abdominal and thoracic respiratory bands
- **Double trigger event** – this was defined as two consecutive ventilator cycles separated by an expiratory time of less than one second (Figure 7). (Ramsay et al., 2015) Each pair of mask pressurisations was scored as a single event.

![Figure 7 - Schematic representation of the double trigger event scoring rule; each pair of mask pressurisations was scored as a single event; mask pressure refers to measured pressure at the interface during polysomnography; sum trace refers to the additive signal of abdominal and thoracic respiratory bands](image)

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• **Multiple trigger event** – as per double triggering but for sequences >2 ventilator breaths, with each three breath ‘salvo’ was scored as one event (Figure 8). (Vrijsen et al., 2016)

*Figure 8 – Schematic representation of the multiple trigger scoring rule; each group of three breaths was scored as a separate event; mask pressure refers to measured pressure at the interface during polysomnography; sum trace refers to the additive signal of abdominal and thoracic respiratory bands*
Arousal index

The arousal index is equal to the number of EEG arousals observed per hour of TST during PSG recording. (M. Bonnet et al., 1992) An EEG arousal is an abrupt shift in EEG frequency, which may include theta, alpha and/or frequencies greater than 16Hz. (M. Bonnet et al., 1992) A number of rules for scoring EEG arousals have been described by the American Sleep Disorders Association and the reliability of inter-rater reliability of these definitions have been reported. (Loredo, Clausen, Ancoli-Israel, & Dimsdale, 1999) In the current study, PSG data was de-identified and a single experienced sleep scientist, who was unaware of the study hypothesis, scored EEG arousals in all studies in addition to performing sleep staging according to standard criteria. (Iber, Ancoli-Israel, Chesson, & Quan, 2007)

9.4.16 Secondary outcomes

Adherence

Adherence was determined using data from each participant’s device. These were interrogated at the conclusion of the study. Usage on the night of the intervention (sham PSG titration or PSG titration) and on the night of the PSG at study conclusion was not included in adherence calculations. Adherence, defined by average daily use, was compared between the acclimatisation and treatment periods (see Figure 5) to determine if there was an association between group allocation and changes in adherence. Non-adherence was defined as average daily use of <240min. (Mokhlesi et al., 2006; Nickol et al., 2005)
Objective sleep quality

Objective sleep quality was evaluated from data obtained from the PSG at study conclusion. These measures included; TST, percentage rapid eye movement (REM) sleep, slow wave sleep (NREM3), non-rapid eye movement sleep stages one and two (NREM1 and NREM2) and sleep efficiency as well as wake time after sleep onset, sleep latency, and the number of stage transitions and awakenings. (Iber et al., 2007)

Gas exchange

The change in daytime partial pressure of carbon dioxide from arterial blood (PaCO₂) was determined by comparing the baseline measure with that obtained at study conclusion. As described above, both samples were obtained from participants while they were awake, resting, seated and breathing room air without ventilatory support for a minimum of 30 minutes. Nocturnal measures of PtcCO₂ were also compared using the peak and average values during the PSG at study conclusion. The early morning PaCO₂ level measured from an arterial blood gas sample obtained at the conclusion of recording was also evaluated.

Other measures of gas exchange used as secondary outcome measures included those obtained from nocturnal oximetry during the final PSG;

- Oxygen desaturation index (ODI 3% and ODI 4%) – the number of 3% and 4%, respectively, oxygen desaturations per hour of recording time (RT) – both awake and sleep.

- SpO₂ nadir – the lowest value obtained from pulse oximetry during sleep

- Time SpO₂<90% - the amount of time during sleep where SpO₂ is less than 90%
These values were obtained from automated scoring algorithms contained within the Compumedics Profusion PSG™ software (Compumedics, Abbotsford, Australia).

**Patient-reported outcomes**

The change in these measures between baseline (prior to NIPPV therapy) and study conclusion was evaluated. As described above, instruments evaluating sleep quality (PSQI), somnolence (ESS and KSS), fatigue (FSS), dyspnoea (MBDS), side-effects (SAQLI) and HRQoL (generic; AQoL-8D and disease specific; SRI) were used.

**9.4.17 Sample size calculation**

Based on observational data from Fanfulla et al and Adler et al (Adler et al., 2011; Fanfulla et al., 2005) it was estimated that a sample size of n=40 (20 per group) would provide 80% power to detect a 50% difference in both the PVA and arousal indices, and allow up to 15% dropouts.

Due to the heterogeneity of the sample that was expected, we planned a number of subgroup analyses a priori and thus an extended study was anticipated with a sample size of n=110. Planned subgroup analyses included;

1. Individuals with motor neuron disease (MND)
2. Individuals with obesity hypoventilation syndrome (OHS)
3. Individuals with MND and severe bulbar dysfunction
4. Individuals with non-adherence during the acclimatisation period
9.4.18 Statistical evaluation

Statistical calculations were performed using SPSS version 21 (IBM, Armonk, NY) and Excel 2007 (Microsoft, Redmond, WA) software. Graphs were produced using Prism version 6 (GraphPad Software, La Jolla, CA). Between-group comparisons were performed using Pearson’s $\chi^2$ test for proportions, Student’s $t$-test for the comparison of means, and the Mann–Whitney U test for non-normally distributed data. A mixed analysis of variance (ANOVA) was used to explore the interaction between time and group allocation with regard to measures of adherence. A post-hoc exploratory analysis of the relationship between the primary outcome measure and other secondary outcome measures was performed. These relationships were explored first with simple scatter plots and subsequently presented with either Pearson’s or Spearman’s correlation coefficient depending on the linearity of the relationship and the characteristics of the variables (interval or ordinal). The strength of correlations are described; 0.00 to 0.19 as very weak, 0.20 to 0.39 as weak; 0.40-0.59 as moderate; 0.60-0.79 as strong and; 0.80-1.00 as very strong correlation. For all statistical tests, a $p$-value <0.05 was considered statistically significant.
9.5 **Results**

Recruitment for the study commenced in December 2013 and proceeded until December 2015. Over this period, 313 individuals commenced HMV (Figure 9). Of these, 52.1% (n=163) were screened for participation in the study. Those not screened included 45.4% (n=142) who were implemented with NIPPV during an inpatient admission and 1.0% (n=3) who were commenced on long-term IMV (Figure 9).

Of those screened, 31.9% (n=52) were excluded from participating (Figure 9) with the most frequent indication for exclusion being an inability to understand English (n=23). Individuals who were medically unstable (n=10), currently using NIPPV (n=10) or diaphragm pacing (n=2) and previously intolerant of NIPPV (n=3) were also excluded. Of the remaining 111 individuals potentially eligible to participate, 45.9% (n=51) declined, with most citing unwillingness to attend for an additional overnight PSG or difficulty in travel/transport arrangements (Figure 9).

Changes in referral patterns that occurred during the study (predominantly a lack of referrals for individuals with OHS) resulted in insufficient recruitment to allow achievement of the target sample size within a reasonable timeframe. Therefore the study was concluded after the recruitment of n=60 participants.
Figure 9 - CONSORT diagram
The remaining 54.1% (n=60) agreed to participate and after completing their clinical titration were randomly allocated to the two arms of the study (Table 12). Groups were well matched at baseline with regards to age, gender, BMI, diagnosis and respiratory function testing (Table 12). The median daytime PaCO$_2$ was within normal limits for both groups in keeping with a stable outpatient population with the majority of participants having MND as the underlying disease process requiring NIPPV.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=30)</th>
<th>PSG titration (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 (9)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>23:7</td>
<td>20:10</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>29.5 (11.5)</td>
<td>27.3 (6.6)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>1.0 (1.4)</td>
<td>1.37 (1.4)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MND</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>ALSFRS-R score</td>
<td>29.3 (7)</td>
<td>28.0 (7)</td>
</tr>
<tr>
<td>Bulbar (ALSFRS) score</td>
<td>8.7 (3)</td>
<td>7.1 (4)</td>
</tr>
<tr>
<td>Riluzole at enrolment</td>
<td>56%</td>
<td>73%</td>
</tr>
<tr>
<td>NMD</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>RTD</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>OHS</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>COPD/OSA</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>55 (14)</td>
<td>54 (15)</td>
</tr>
<tr>
<td>MIP (cmH$_2$O)</td>
<td>30 (23-54)</td>
<td>28 (22-33)</td>
</tr>
<tr>
<td>Daytime PaCO$_2$ (mmHg)</td>
<td>43 (39-48)</td>
<td>45 (38-51)</td>
</tr>
</tbody>
</table>

MND=motor neuron disease, ALSFRS=amyotrophic lateral sclerosis functional rating scale, NMD=neuromuscular disorder, RTD=restrictive thoracic disorder, OHS=obesity hypoventilation syndrome, COPD/OSA=chronic obstructive pulmonary disease with obstructive sleep apnoea, BMI=body mass index, FVC=forced vital capacity, MIP=maximum inspiratory pressure, PaCO$_2$=arterial partial pressure of carbon dioxide.
9.5.1 Ventilator and settings

Most participants (n=55) were implemented with a VPAP™ IV ST. One participant who lived remotely required a device with an internal battery and was implemented with a Stellar™ 150, while four others who demonstrated difficulties with the machine interface due to visual impairment and poor hand function, or, who required higher pressures, were implemented with the VPAP S9™ ST-A. Two participants preferred a nasal mask while the remainder used an oro-nasal mask. There were no changes in interface type during the study period.

There were no significant differences in the baseline NIPPV settings between groups (Table 13, p>0.05 for all parameters; independent samples t-test).
Table 13 – Initial ventilator settings prescribed after daytime clinical titration; according to group allocation*

<table>
<thead>
<tr>
<th>Group</th>
<th>n=</th>
<th>PS (cmH&lt;sub&gt;2&lt;/sub&gt;O)</th>
<th>EPAP (cmH&lt;sub&gt;2&lt;/sub&gt;O)</th>
<th>RR (breaths/min)</th>
<th>Trigger</th>
<th>Cycle</th>
<th>Ti min (seconds)</th>
<th>Ti max (seconds)</th>
<th>Rise time (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>6.5 (2)</td>
<td>7.6 (3)</td>
<td>13.1 (2)</td>
<td>Med</td>
<td>Med</td>
<td>1.1 (0.1)</td>
<td>1.6 (0.2)</td>
<td>0.37 (0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range</td>
<td>4-12</td>
<td>4-18</td>
<td>Low-High</td>
<td>Low-High</td>
<td>0.9-1.3</td>
<td>1.4-2.0</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>PSG titration</td>
<td>30</td>
<td>6.7 (2)</td>
<td>6.5 (2)</td>
<td>13.5 (2)</td>
<td>Med</td>
<td>Med</td>
<td>1.1 (0.1)</td>
<td>1.7 (0.1)</td>
<td>0.39 (0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range</td>
<td>5-13</td>
<td>4-12</td>
<td>Low-High</td>
<td>Low-Med</td>
<td>0.9-1.3</td>
<td>1.4-2.0</td>
<td>0.3-0.5</td>
</tr>
</tbody>
</table>

*p*-value >0.05 for all parameters; independent samples t-test.

PS=pressure support, EPAP=expiratory positive airway pressure, RR=respiratory rate, Trigger=Trigger sensitivity (Range: Very Low to Very High), Cycle=Cycle sensitivity (Range: Very Low to Very High), Ti min=minimum inspiratory time, Ti max=maximum inspiratory time.
9.5.2 Adherence during acclimatisation

There was no difference between groups in the time between the initial referral for NIPPV and subsequent implementation (mean (SD) interval in days; Control 24.9 (17) vs. PSG titration 20.4 (15); \( p=0.317 \)). There was also no difference in the length of the acclimatisation period (mean (SD) in days; Control 20.1 (8) vs. PSG titration 20.4 (5); \( p=0.832 \)) or length of the treatment period (mean (SD) in days; Control 53.6 (8) vs. PSG titration 54.3 (13); \( p=0.812 \)).

During the acclimatisation period, the average daily use in both groups was over 240 minutes (Table 14). There was no significant difference between groups in the average daily use, percentage days with zero use, percentage days with <240 minutes use or in the proportion who were non-adherent during the acclimatisation period (\( p \)-value all >0.05, see Table 14).

| Table 14 - Adherence during acclimatisation period according to group allocation* |
|---|---|---|---|---|
| Group | Average use\(^a\) | Days with zero use | Days with <240min use | Non-adherent\(^b\) |
| | Mean (SD) | | | n= |
| Control\(^c\) (n=28) | 305 (185) | 15% | 25% | 9 (30%) |
| PSG titration\(^c\) (n=28) | 291 (197) | 14% | 30% | 12 (40%) |

\(^*\) \( p \)-value >0.05 for all parameters; independent samples t-test, Pearson \( \chi^2 \) for proportions

\(^a\) Average daily use (minutes) during the acclimatisation period

\(^b\) Non-adherence defined as average use <240min per 24-hour period

\(^c\) Adherence data not available for drop-outs (n=2), deceased (n=1) and one (n=1) participant in Control group due to a malfunctioning data card
Table 15 - Alterations to the baseline settings in the PSG titration group (n=30)

<table>
<thead>
<tr>
<th>Alterations</th>
<th>Mean (cmH₂O)</th>
<th>Range (cmH₂O)</th>
<th>Mean (breaths/min)</th>
<th>Range (breaths/min)</th>
<th>Mean (seconds)</th>
<th>Range (seconds)</th>
<th>Mean (seconds)</th>
<th>Range (seconds)</th>
<th>Mean (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS</td>
<td>0.6</td>
<td>(-2.0 to 6.0)</td>
<td>1.4</td>
<td>(-4.0 to 8.0)</td>
<td>0.5</td>
<td>(6.0 to 0.0)</td>
<td>0.0</td>
<td>(-0.2 to 0.2)</td>
<td>0.0</td>
</tr>
<tr>
<td>EPAP</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>RR</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Trigger</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Cycle</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Ti min</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Ti max</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Rise time</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td></td>
<td>0.0</td>
</tr>
</tbody>
</table>

Prescribed alterations n= (%)

- PS=pressure support, EPAP=expiratory positive airway pressure, RR=respiratory rate, Trigger=Trigger sensitivity, Cycle=Cycle sensitivity, Ti min=minimum inspiratory time, Ti max=maximum inspiratory time
9.5.3  PSG titration and alterations to settings

Following PSG titration, recommendations were made for adjustment in at least one ventilator parameter in 96.7% (n=29) of the PSG titration group. The most frequently altered parameters were the expiratory positive airway pressure (EPAP) and pressure support (PS) levels (Table 15).

Recommended changes were small on average, however at an individual level were more substantial (for example; EPAP range -4.0 to +8.0cmH2O; Table 15). For PS, EPAP and respiratory rate, changes on average tended to represent an increase over those set during the clinical titration (Table 15). Changes to inspiratory time and rise time settings tended to be small in magnitude and were less frequent than changes to pressure settings. Recommendations to alter trigger and cycle sensitivities were also infrequent (Table 15).

9.5.4  Dropouts, deaths and failure to complete the protocol.

Only individuals with MND dropped out of the study (n=2) with both allocated to the PSG titration group (Figure 9). One participant with MND (n=1) in the Control group was deceased during the treatment period due to the development of a lower respiratory tract infection. An additional three participants with MND in each arm of the study were unwilling to return for the final PSG. These individuals provided data (questionnaire responses, daytime arterial blood gases) but were unable to be included in the analysis of the primary outcome.
9.5.5 Primary outcome

Patient-ventilator asynchrony (PVA) index

The PVA index was significantly different between the two groups on the PSG at study conclusion. Those in the PSG titration group had a lower median PVA index than the Control group (Table 16 and Figure 10, \( p=0.046 \), independent samples Mann Whitney U test). The PVA index for both groups was non-normally distributed with a positive skew (Figure 10). The difference in the PVA index was primarily attributable to differences in the frequency of ineffective efforts (see Table 16 and Figure 11), with double trigger and multiple trigger events occurring with similar frequency across both groups.

Table 16 - Patient-ventilator asynchrony events (by type) per hour of total sleep time; PSG titration compared with Control; data are presented as median (interquartile range)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Control (n=25)</th>
<th>PSG titration (n=25)</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA index (total events per hour TST)</td>
<td>41.0 (28-182)</td>
<td>25.7 (12-68)</td>
<td>0.046</td>
</tr>
<tr>
<td>Ineffective efforts (per hour TST)</td>
<td>26.4 (15-107)</td>
<td>13.6 (5-37)</td>
<td>0.040</td>
</tr>
<tr>
<td>Double trigger (per hour TST)</td>
<td>5.5 (3-33)</td>
<td>5.6 (2-11)</td>
<td>0.594</td>
</tr>
<tr>
<td>Multiple trigger (per hour TST)</td>
<td>0.5 (0-4)</td>
<td>0.5 (0-2)</td>
<td>0.576</td>
</tr>
</tbody>
</table>

* \( p \)-value from independent samples Mann Whitney U test
* (n=1) participant in the Control group had malfunction in mask pressure trace and therefore no PVA events were obtained
Figure 10 - Patient-ventilator asynchrony events per hour of total sleep time during PSG at study conclusion; PSG titration compared with Control; markers represent individual data points, horizontal lines indicate the median value for each group.
1) Ineffective efforts

2) Double trigger events

3) Multiple trigger events

Figure 11 - Patient-ventilator asynchrony events by subtype; PSG titration compared with Control; 1) ineffective efforts per hour total sleep time; 2) double trigger events per hour total sleep time; 3) multiple trigger events per hour total sleep time; markers (hollow circles) represent individual data points, horizontal lines represent the median value for each group.
Arousal index

There was no significant difference between the two groups in the arousal index on the PSG at study conclusion. The median arousal index was 14.6/hour for the Control group and 11.4/hour in the PSG titration group ($p=0.26$; independent samples Mann Whitney U test, see Figure 12 and Table 17).

Other objective measures of sleep quality (which were secondary outcome measures) were also not significantly different between the two groups (Table 17).

<table>
<thead>
<tr>
<th>Objective measure</th>
<th>Control (n=26)</th>
<th>PSG titration (n=25)</th>
<th>$p$-value$^#$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arousal index (arousals per hour TST)</td>
<td>14.6 (11-19)</td>
<td>11.4 (9-19)</td>
<td>0.258</td>
</tr>
<tr>
<td>Total sleep time (TST) (minutes)</td>
<td>289 (220-346)</td>
<td>274 (227-336)</td>
<td>0.821</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>69 (51-77)</td>
<td>63 (53-76)</td>
<td>0.910</td>
</tr>
<tr>
<td>Sleep latency (minutes)</td>
<td>18.5 (7-33)</td>
<td>20.0 (11-47)</td>
<td>0.429</td>
</tr>
<tr>
<td>Wake after sleep onset (minutes)</td>
<td>119 (85-153)</td>
<td>123 (94-172)</td>
<td>0.480</td>
</tr>
<tr>
<td>Awakenings (number)</td>
<td>29.5 (22-38)</td>
<td>29.0 (23-37)</td>
<td>0.910</td>
</tr>
<tr>
<td>Stage transitions (number)</td>
<td>185 (122-233)</td>
<td>174 (138-207)</td>
<td>0.843</td>
</tr>
<tr>
<td>Rapid eye movement (REM) sleep (%)</td>
<td>16 (11-21)</td>
<td>16 (11-21)</td>
<td>0.720</td>
</tr>
<tr>
<td>Slow wave sleep (NREM3) (%)</td>
<td>39 (23-59)</td>
<td>30 (25-41)</td>
<td>0.486</td>
</tr>
<tr>
<td>NREM1 and NREM2 (%)</td>
<td>44 (27-62)</td>
<td>52 (39-62)</td>
<td>0.356</td>
</tr>
</tbody>
</table>

$^\#$ $p$-value from independent samples Mann Whitney U test
Figure 12 - Electroencephalographic arousals per hour of total sleep time during PSG at study conclusion; PSG titration compared with Control; markers (hollow circles) indicate individual data points, horizontal lines indicate the median value for each group.
9.5.6 Secondary outcomes

Adherence to therapy

Average daily use increased for the PSG titration group when comparing the acclimatisation period to the treatment period (Figure 13). There was no significant change observed for the Control group over these two time periods.
Figure 13 - Average daily use during acclimatisation and treatment periods; according to group (Control and PSG titration); markers (hollow circles) represent individual data points connected for each participant; solid horizontal lines indicate group means; the dashed horizontal lines indicate the 240-minute threshold for adherence; $p$-values from related samples $t$-test
A mixed analysis of variance (ANOVA) tested the interaction between group (PSG titration, Control) and time period (acclimatisation, treatment) with regard to average daily use. Average daily use was not significantly related to time period ($F[1,54] = 3.91, p=0.053, \eta=0.068$) The interaction between group and time period was also not statistically significant ($F[1,54] = 2.952, p=0.091, \eta=0.052$). There was no significant between-group difference in the change in average daily use between acclimatisation and treatment periods ($p=0.09$; independent samples $t$-test, Table 18).

<table>
<thead>
<tr>
<th>Table 18 - Mean difference in average daily use between the acclimatisation period and the treatment period according to group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>PSG titration</td>
</tr>
</tbody>
</table>

*Adherence data not available for one participant in Control group due to malfunctioning data card
# Between group $p$-value from independent samples $t$-test

An increase in average daily use during enrolment in the study may have represented increased use in those that had already achieved adequate adherence (>240min average daily use). (Mokhlesi et al., 2006; Nickol et al., 2005). An exploratory analysis to test this hypothesis was performed by categorising users according to their average daily use during the acclimatisation period (see Figure 5). As described in the methods section in this chapter, those with non-adherence during the acclimatisation were identified $a priori$ as a subgroup of interest.
A total of 21 individuals demonstrated non-adherence (<240 min average daily use) during the acclimatisation period with n=9 in the Control group and n=12 in the PSG titration group (see Table 14).

Again, a mixed ANOVA was performed for those with non-adherence during acclimatisation. This tested the interaction between group (PSG titration, Control) and time period (acclimatisation, treatment) with regard to average daily use. Average daily use was not significantly related to time period (F[1,19] = 2.918, p = 0.104, η = 0.133). The interaction between group and time period was statistically significant however (F[1,19] = 7.941, p = 0.011, η = 0.295). For those who were categorised as non-adherent during the acclimatisation period, the mean increase in average daily use was 95 minutes in the PSG titration group, compared with a mean decrease of 23 minutes in the Control group (Table 19; Panel B). This difference was statistically significant both within- and between-groups (see Figure 14 and Table 19; Panel B).
In contrast, average daily use did not change for either group in those categorised as adherent during the acclimatisation period (see Table 19; Panel A). This suggests that any supportive effect of PSG titration on average daily use was most marked in those with non-adherence during the acclimatisation period.
Table 19 - Mean difference in daily use according to categorical adherence during the acclimatisation period; mean difference refers to the average daily use during treatment period minus the average daily use during the acclimatisation period

<table>
<thead>
<tr>
<th></th>
<th>n=</th>
<th>Mean difference (minutes)</th>
<th>95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel A: Adherent\textsuperscript{a} during acclimatisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>19</td>
<td>16</td>
<td>-31 to 64</td>
<td>0.93</td>
</tr>
<tr>
<td>PSG titration</td>
<td>16</td>
<td>19</td>
<td>-42 to 81</td>
<td></td>
</tr>
<tr>
<td>Panel B: Non-adherent\textsuperscript{a} during acclimatisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>-23</td>
<td>-86 to 39</td>
<td>0.01</td>
</tr>
<tr>
<td>PSG titration</td>
<td>12</td>
<td>95*</td>
<td>29 to 161</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Adherence defined as average use ≥240min per 24hr period; non-adherence defined as average use <240min per 24hr period

\# Between group p-value from independent samples t-test

* Within group p-value <0.05 from related samples t-test

Gas exchange

Daytime PaCO\textsubscript{2} was lower in both groups following the implementation of NIPPV with a mean difference (baseline minus final) in PaCO\textsubscript{2} of 3mmHg (PSG titration (n=28); 3.07mmHg, Control (n=25); 3.25mmHg, Figure 15). There was no significant between-group difference in the change in PaCO\textsubscript{2} (p=0.92, from independent samples t-test).
Figure 15 - Daytime PaCO₂ values at the beginning of the study (Baseline) compared with study conclusion (Final); PSG titration compared with Control; markers (hollow circles) represent individual data points linked for each participant; the filled square markers represent median values, dashed horizontal lines indicate PaCO₂=40mmHg.
Nocturnal measures of gas exchange obtained from the PSG at study conclusion also did not demonstrate significant between-group differences (Table 20).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control (n=26)</th>
<th>PSG titration (n=25)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time spent with SpO₂&lt;90% (%RT)</td>
<td>0.1 (0.0 to 0.8)</td>
<td>0.0 (0.0 to 2.6)</td>
<td>0.317</td>
</tr>
<tr>
<td>SpO₂ nadir</td>
<td>88.0 (86 to 90)</td>
<td>89.0 (86 to 92)</td>
<td>0.261</td>
</tr>
<tr>
<td>ODI 3% (RT)</td>
<td>2.4 (0.7 to 5.0)</td>
<td>0.7 (0.0 to 6.0)</td>
<td>0.631</td>
</tr>
<tr>
<td>ODI 4% (RT)</td>
<td>0.4 (0 to 1.5)</td>
<td>0.0 (0.0 to 2.8)</td>
<td>0.699</td>
</tr>
<tr>
<td>Average PtcCO₂</td>
<td>47 (43 to 50)</td>
<td>46 (41 to 49)</td>
<td>0.254</td>
</tr>
<tr>
<td>Peak PtcCO₂</td>
<td>50 (47 to 54)</td>
<td>49 (43 to 53)</td>
<td>0.221</td>
</tr>
<tr>
<td>Morning PaCO₂</td>
<td>44 (38 to 46)</td>
<td>42 (38 to 46)</td>
<td>0.522</td>
</tr>
<tr>
<td>% TST with leak&gt;24L/min</td>
<td>0.0 (0 to 25)</td>
<td>0.0 (0 to 16)</td>
<td>0.602</td>
</tr>
</tbody>
</table>

*p-value from independent samples Mann Whitney U test
ODI=oxygen desaturation index, PtcCO₂=partial pressure of transcutaneous carbon dioxide, RT=recording time, SpO₂=oxygen saturation from pulse oximetry

Subjective outcomes

Significant symptomatic improvements were demonstrated in both groups in sleep quality (PSQI, see Table 21). Only the PSG titration group demonstrated a significant change in somnolence (ESS, see Table 21). There were no between-group differences in these measures, however, and no significant changes within-or between-groups in ratings of dyspnoea, fatigue or side-effects related to NIPPV.
Table 21 - Subjective outcome measures for both the Control and PSG titration groups; mean difference represents the final measure (at study conclusion) minus the baseline measure (prior to commencing NIPPV); with the exception of the FSS VAS, negative values indicate an improvement within the measure.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>PSG titration</th>
<th></th>
<th>p-value#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=</td>
<td>Mean difference (SD)</td>
<td>n=</td>
<td>Mean difference (SD)</td>
<td>p-value#</td>
</tr>
<tr>
<td>PSQI</td>
<td>29</td>
<td>-2.1 (3.9)*</td>
<td>28</td>
<td>-1.4 (3.0)*</td>
<td>0.486</td>
</tr>
<tr>
<td>ESS</td>
<td>29</td>
<td>-1.3 (5.0)</td>
<td>28</td>
<td>-1.9 (3.8)*</td>
<td>0.619</td>
</tr>
<tr>
<td>KSS</td>
<td>29</td>
<td>-0.4 (1.7)</td>
<td>28</td>
<td>-1.1 (2.5)</td>
<td>0.201</td>
</tr>
<tr>
<td>FSS</td>
<td>29</td>
<td>-3.7 (17.1)</td>
<td>28</td>
<td>-1.3 (11.4)</td>
<td>0.522</td>
</tr>
<tr>
<td>FSS VAS</td>
<td>29</td>
<td>0.5 (2.7)</td>
<td>27</td>
<td>0.6 (2.1)</td>
<td>0.781</td>
</tr>
<tr>
<td>MBDS</td>
<td>28</td>
<td>0.2 (2.2)</td>
<td>28</td>
<td>0.3 (1.6)</td>
<td>0.836</td>
</tr>
<tr>
<td></td>
<td>n=</td>
<td>Mean (SD)</td>
<td>n=</td>
<td>Mean (SD)</td>
<td>p-value#</td>
</tr>
<tr>
<td>SAQLI side-effectsb</td>
<td>28</td>
<td>10.6 (4.5)</td>
<td>28</td>
<td>11.1 (4.4)</td>
<td>0.652</td>
</tr>
<tr>
<td>SAQLI SE vs. benefitsc</td>
<td>28</td>
<td>2.7 (1.5)</td>
<td>28</td>
<td>2.6 (1.2)</td>
<td>0.766</td>
</tr>
<tr>
<td>Healthcare contactsd</td>
<td>29</td>
<td>2.6 (1.9)</td>
<td>28</td>
<td>2.7 (2.9)</td>
<td>0.888</td>
</tr>
<tr>
<td>Database contacts</td>
<td>30</td>
<td>3.2 (2.6)</td>
<td>30</td>
<td>4.2 (4.8)</td>
<td>0.321</td>
</tr>
</tbody>
</table>

* Within group p<0.05; related samples t-test
# Between group p-value from independent samples t-test
a Responses to the KSS were not adequately matched for time-of-day for the majority of participants
b Scored as the sum of ratings (on a 7-point Likert scale) for each of the most troubling side-effects. Lower scores therefore represent less troubling side-effects.
c Scored on a 7-point Likert scale where the middle value (=4) represents a balance between side-effects and benefits. Scores <4 therefore indicate that the benefits of therapy outweigh the side-effects
d Sum of self-reported contacts with healthcare workers
PSQI=Pittsburgh Sleep Quality Index, ESS=Epworth Sleepiness Scale, KSS=Karolinska Sleepiness Scale, FSS=Fatigue Severity Scale, FSS VAS=Fatigue Severity Scale Visual Analogue Scale, MBDS=Modified Borg Dyspnoea Score, SAQLI=Sleep Apnoea Quality of Life Questionnaire
Contacts with healthcare workers (both self-reported and those obtained from clinical database) were also not significantly different (Table 21). Most of the self-reported healthcare contacts were described as being unrelated to NIPPV therapy, although this anecdotal observation was unable to be objectively verified.
Health-related quality of life (HRQoL)

For the disease-specific HRQoL measure there were within-group changes in domains of the SRI – with the PSG titration group demonstrating a significant improvement in the Attendant Symptoms and Sleep domain (see Table 22). This domain predominantly includes items which evaluate aspects of sleep quality. (Hannan et al., 2014) There was also a significant deterioration in the Social Relationships domain observed in the Control group, which reached statistical significance in the between-group comparison (Table 22). Neither of these differences in the domain scores resulted in an overall difference in disease-specific HRQoL using the Summary Scale of the SRI (Table 22).

Table 22 - Change in the domain scores of the Severe Respiratory Insufficiency questionnaire; mean difference indicates the final measure (at study conclusion) minus the baseline measure (prior to commencing NIPPV); positive values represent an improvement in the respective domain

<table>
<thead>
<tr>
<th>SRI Domains^a</th>
<th>Control (n=29)</th>
<th>PSG titration (n=28)</th>
<th>p-value#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (SD)</td>
<td>Mean difference (SD)</td>
<td></td>
</tr>
<tr>
<td>Summary Scale</td>
<td>0.3 (11)</td>
<td>1.7 (9)</td>
<td>0.612</td>
</tr>
<tr>
<td>Respiratory Complaints</td>
<td>4.1 (20)</td>
<td>2.4 (19)</td>
<td>0.735</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>-2.4 (15)</td>
<td>0.0 (18)</td>
<td>0.587</td>
</tr>
<tr>
<td>Attendant Symptoms and Sleep</td>
<td>5.2 (18)</td>
<td>7.9 (13)*</td>
<td>0.513</td>
</tr>
<tr>
<td>Social Relationships</td>
<td>-7.6 (14)*</td>
<td>0.7 (12)</td>
<td>0.022</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.2 (21)</td>
<td>3.1 (18)</td>
<td>0.834</td>
</tr>
<tr>
<td>Psychological Well-Being</td>
<td>-1.6 (13)</td>
<td>0.8 (10)</td>
<td>0.432</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>0.5 (16)</td>
<td>-3.0 (18)</td>
<td>0.455</td>
</tr>
</tbody>
</table>

* Within group p<0.05; related samples t-test
# Between group p-value from independent samples t-test
^a Domains of the SRI are scored from 0-100
Results using the generic preference-based HRQoL instrument (AQoL-8D) demonstrated no significant difference between- or within-group in the index score (Table 23). There were also no significant between-group or within-group changes in any of the dimension scores produced with this instrument.

### Table 23 - Change in the index score, dimension scores and superdimension scores of the Assessment of Quality of Life Instrument (AQoL-8D); mean difference indicates the final measure (at study conclusion) minus the baseline measure (prior to commencing NIPPV); positive values represent an improvement in the respective measure

<table>
<thead>
<tr>
<th>AQoL-8D Dimensions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Control (n=29)</th>
<th>PSG titration (n=28)</th>
<th>p-value&lt;sup&gt;#&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (SD)*</td>
<td>Mean difference (SD)*</td>
<td></td>
</tr>
<tr>
<td>Index score</td>
<td>-0.002 (0.10)</td>
<td>0.000 (0.10)</td>
<td>0.961</td>
</tr>
<tr>
<td>Independent Living</td>
<td>-0.027 (0.08)</td>
<td>-0.029 (0.10)</td>
<td>0.932</td>
</tr>
<tr>
<td>Happiness</td>
<td>-0.039 (0.12)</td>
<td>-0.018 (0.10)</td>
<td>0.460</td>
</tr>
<tr>
<td>Mental Health</td>
<td>0.015 (0.11)</td>
<td>0.026 (0.09)</td>
<td>0.677</td>
</tr>
<tr>
<td>Coping</td>
<td>-0.015 (0.13)</td>
<td>0.024 (0.15)</td>
<td>0.293</td>
</tr>
<tr>
<td>Relationships</td>
<td>-0.008 (0.11)</td>
<td>0.001 (0.10)</td>
<td>0.739</td>
</tr>
<tr>
<td>Self Worth</td>
<td>-0.016 (0.10)</td>
<td>-0.009 (0.10)</td>
<td>0.794</td>
</tr>
<tr>
<td>Pain</td>
<td>0.062 (0.17)</td>
<td>-0.024 (0.23)</td>
<td>0.111</td>
</tr>
<tr>
<td>Senses</td>
<td>-0.002 (0.07)</td>
<td>-0.018 (0.10)</td>
<td>0.484</td>
</tr>
<tr>
<td>Mental Superdimension</td>
<td>-0.005 (0.10)</td>
<td>0.005 (0.11)</td>
<td>0.732</td>
</tr>
<tr>
<td>Physical Superdimension</td>
<td>0.010 (0.08)</td>
<td>-0.029 (0.13)</td>
<td>0.181</td>
</tr>
</tbody>
</table>

* All within group comparisons p>0.05; related samples t-test
# Between group p-value from independent samples t-test
<sup>a</sup> Index scores and dimension scores range from 0.0 to 1.0
9.5.7 Relationship between PVA and adherence

A post-hoc exploratory analysis was performed in order to examine relationships between adherence to therapy during the treatment period and PVA, with other outcome measures assessed at study conclusion (data are presented in Appendix I). There was no evidence of a monotonic relationship between PVA on the PSG at study conclusion and PSQI, ESS or summary measures of HRQoL obtained at this time (Appendix I; Table I9). There was however a weak relationship between the PVA index and arousals ($r_s=0.304$, $p=0.034$) and moderate correlations between PVA and the oxygen desaturation index (both 3% and 4%) and percentage time with $\text{SpO}_2<90\%$ ($r_s=0.528$, $r_s=0.450$ and $r_s=0.475$ respectively, all $p<0.05$; Appendix I; Table I9 and Figure I3).

In contrast, average daily use during the treatment period was negatively correlated with PSQI ($r_s=-0.446$), ESS ($r_s=-0.311$) and the rating of side-effects to benefits ($r_s=-0.526$) reflecting weak to moderate correlations between increasing use and lower scores on these rating scales (Appendix I; Tables I9). A weak correlation was also observed between the AQoL-8D index score at the conclusion to the study and average daily use during the treatment period (Appendix I; Tables I9 and Figure I4).

9.5.8 Subgroup analyses

Subgroup analyses that were planned a priori were limited due to insufficient recruitment as mentioned above. This was most marked for individuals with OHS who were infrequently referred for elective implementation of NIPPV during the study period.
Individuals with motor neuron disease (MND)

As presented previously, 66.7% of participants in the study had an underlying diagnosis of MND (Table 12 with further clinical characteristics provided in Appendix I; Table I1). Between-group comparisons for those with MND revealed a significant difference in the severity of daytime somnolence at enrolment (according to the ESS) but no other significant differences (Appendix I, Table I1).

For the primary outcome, there was no significant difference in PVA index (or specific PVA events) when only those with MND were analysed (Appendix I; Table I2 and Figure I1). There was also no significant difference in the arousal index (Appendix I; Figure I2 and Table I3).

Secondary outcomes for individuals with MND were similar between groups, with the exception of nocturnal measures of gas exchange (SpO₂ nadir, peak PtCO₂), which appeared to favour the PSG titration group (Appendix I; Table I4). These apparent benefits did not translate into differences in daytime PaCO₂ or morning PaCO₂ (Appendix I; Table I4) Subjective measures (symptoms, side-effects and HRQoL) were also not significantly different between the two groups (Appendix I; Tables I5, I6 and I7). Rates of non-adherence amongst individuals with MND were similar between the two groups during the acclimatisation period (Appendix I, Table I8) however there was a significant difference in the rate of non-adherence during the treatment period that favoured the PSG titration group (15% (PSG titration) vs. 56% (Control), \( p=0.024 \); Pearson’s \( \chi^2 \) for proportions).
Individuals with obesity hypoventilation syndrome (OHS)

Individuals with OHS were not recruited in sufficient numbers to analyse as a subgroup (Table 12). Only three individuals with this diagnosis were recruited to the study and all were allocated to the Control group.

Individuals with MND with severe bulbar symptoms

Bulbar dysfunction was rated using the bulbar subscale of the ALSFRS-R. Individuals with a bulbar subscale score of ≥6 were categorised as severe. This assessment was made at the time of enrolment and prior to commencing NIPPV and was made without reference to the MND clinical phenotype.(Talman, Forbes, & Mathers, 2009) This assessment therefore did not necessarily identify individuals with bulbar-onset MND as it may have included individuals with a non-bulbar onset phenotype of MND who had developed severe bulbar symptoms prior to requiring NIPPV therapy.

Only 14 participants had severe bulbar symptoms at the time of enrolment with five in the Control group and nine in the PSG titration group (Appendix I; Table I1). Based on this lack of recruitment, analyses of this subgroup were not performed.
9.6 DISCUSSION

This is the first randomised controlled trial to directly compare PSG titration with clinical titration of NIPPV. A number of significant findings were identified which specifically address the hypotheses stated earlier in this chapter. Firstly, PSG titration was associated with a lower PVA index compared to daytime clinical titration alone. Despite this, there did not appear to be an association between PSG titration and reduced sleep disruption, as EEG arousals were not different between the two groups. There did appear to be an influence on adherence from PSG titration although this effect was limited to those with non-adherence during the acclimatisation period. Other secondary outcomes (gas exchange, symptoms or measures of HRQoL) did not suggest an advantage with PSG titration in this short-term study.

These results have demonstrated that routine PSG titration is associated with improved synchronisation between ventilator and user. This finding is novel, as the only previous report that suggested an influence of PSG titration on PVA was from an uncontrolled, un-blinded, observational study. (Adler et al., 2011) No previous blinded, parallel group studies have demonstrated this effect of PSG titration, although anecdotally this is one of the primary purposes – and previously theoretical benefits – of PSG titration. (Berry, 2010; Hannan et al., 2015) The influence of PSG titration on synchronisation appears to be mediated primarily through a reduction in ineffective efforts, although the relative infrequency of double trigger and multiple trigger events across the two groups may mean that this study was underpowered to detect a difference in these forms of PVA. This predominance of ineffective efforts in comparison to other forms of PVA has been noted previously. (Ramsay et al., 2015; Vrijsen et al., 2016)

Based on the previous studies by Fanfulla et al. (Fanfulla et al., 2007, 2005) it is understood that PVA events may be common when settings are determined clinically in awake individuals (even when they are stable and well established on therapy) and that if identified, changing ventilator parameters can reduce their
Fanfulla et al also demonstrated that after reducing PVA, measures of sleep quality improved dramatically. What remained unclear from this short-term physiological data was how to adjust ventilator settings. Fanfulla et al proposed that the use of PSG would be a reasonable alternative to the method described in their report (which required the insertion of an oesophageal balloon catheter in order to target transdiaphragmatic pressure swings). The current study therefore extends these findings by demonstrating an effective, clinically feasible and acceptable method to reduce PVA. The question remains however, how clinically valuable and desirable are lower levels of PVA?

To address this aspect, it is worth considering the second hypothesis. This was not proven, in that routine PSG titration was not associated with fewer EEG arousals during sleep. Despite the demonstrated improvement in synchronisation, there was no difference between groups in the arousal index, TST or sleep efficiency. A number of explanations are possible for this observation.

The first is that indeed there is no effect mediated on sleep disruption by performing routine PSG to titrate NIPPV. This implies that one of the primary assumptions regarding the benefits of performing PSG to titrate ventilator settings is false. This is in contrast to previous studies that have reported a (marked) reduction in sleep disruption following adjustment of settings in order to improve PVA. Other observational studies have demonstrated associations between increased PVA and increased arousals from sleep. The findings in this current study differ from these short-term, or cross-sectional, studies in that the purpose was to evaluate the effectiveness of the intervention (routine PSG) in improving both PVA and sleep disruption rather than determining if one led to the other. Arguably, the short-term, repeated measures study design described by Fanfulla et al supports the contention that inappropriate NIPPV settings do lead to both PVA and sleep...
disruption. The current results instead suggest a lack of effect on sleep disruption from the routine use of PSG titration.

There are possibilities other than the null hypothesis that explain this finding. It is possible the study was underpowered to detect a difference in the arousal index. The sample size calculation was performed based on the results reported by Fanfulla et al and this may have been erroneous. (Fanfulla et al., 2005) As stated previously, the clinical titration described by Fanfulla et al is not in accordance with clinical practice at the centre in which the current study was performed. (Fanfulla et al., 2005) Fanfulla described setting the pressure support level to “the maximal tolerated inspiratory pressure support able to reduce awake PaCO$_2$ by more than 5%”. (Fanfulla et al., 2005) Such an approach differs to that used in the current study where tolerability and effectiveness of ventilation were more equally balanced. The approach in the current study is therefore more akin to that used within sleep laboratories (with CPAP therapy) where the ‘lowest effective pressure’ is preferred. (Ficker, Wiest, Lehnert, Wiest, & Hahn, 1998) This difference in approach is reflected by the observation that the average pressure support used in the current study following clinical titration (6.6cmH$_2$O) was dramatically lower than that used by Fanfulla et al (14.3cmH$_2$O). The current study also used a Spontaneous/Timed trigger and a higher EPAP (7.0cmH$_2$O compared to 2.2cmH$_2$O) than that described by Fanfulla et al. Therefore it is speculated that the arousal index reported by Fanfulla et al at baseline (mean of 29.9/hour TST) was in part attributable to clinical titrations that produced high levels of pressure support, low levels of EPAP, and the use of a purely Spontaneous trigger. An error in the sample size calculation is therefore possible considering the large reduction in the arousal index reported by Fanfulla et al (to mean 16/hour TST). In hindsight, this effect size would be difficult to achieve without an elevated baseline level. Although there may be important clinical differences between the two study populations that may explain these differences in the frequency of arousals during sleep, these comparisons are not possible as only limited details are provided regarding the population included in the study
by Fanfulla et al. (Fanfulla et al., 2005) Participants were described as having “miscellaneous neuromuscular disorders” and were previously established on NIPPV. The reported respiratory function testing suggests that they may have been more restricted (mean vital capacity 39% predicted) but with less respiratory muscle weakness (mean maximal inspiratory pressure 41cmH$_2$O) than those enrolled in the current study (see Table 12). (Fanfulla et al., 2005) The participants in the current study were treatment naïve, had predominantly MND and could reasonably be expected (on average) to have had relatively normal respiratory compliance, airway resistance and minimal upper airway obstruction. This could have meant that clinical titrations were simpler. The resulting NIPPV settings may have been less likely to produce sleep disruption, than in individuals with more deranged respiratory mechanics.

Another aspect that requires discussion is the comparatively low arousal index for both groups in the current study. These were low in comparison to those reported in normal populations, (M. H. Bonnet & Arand, 2007) and in previous studies in individuals using nocturnal NIPPV. ( Adler et al., 2011; Contal, Adler, et al., 2013; Fanfulla et al., 2005; Vrijsen et al., 2016) Arousal scoring is known to have relatively poor inter-rater reliability. (Loredo et al., 1999) It is unknown therefore whether the low arousal index reflects a bias of the experienced sleep scientist who performed these analyses or a truly lower level of sleep disruption than demonstrated in previous studies of individuals using NIPPV. (Berlowitz et al., 2006; Contal, Adler, et al., 2013; Fanfulla et al., 2005; Vrijsen et al., 2016) It is also possible that the clinical titration strategy used, which prescribed lower pressures than in previous reports, could have resulted in less sleep disruption within the Control group – even in the presence of PVA.

An additional source of error which may have contributed to an apparent lack of effect of PSG titration on sleep disruption is that the two groups may not have had the same arousal index and other objective sleep measures at baseline. A baseline PSG (with the initial settings prescribed during daytime clinical
titration) was not performed and therefore it is uncertain if this was the case. Whether multiple nights of monitoring (including home-based PSG monitoring) would have provided additional supportive evidence regarding the effect of PSG titration on sleep quality is uncertain. Vrijsen et al have reported that multiple nights of PSG monitoring and “meticulous” titration did not reduce the frequency of PVA in their observational cohort of individuals with MND. (Vrijsen et al., 2016) They also reported a lack of influence of PVA on sleep quality. However, this study did not include a control arm and therefore it is uncertain if PVA would have been more frequent and sleep quality poorer if no PSG titration was performed at all. (Vrijsen et al., 2016)

Broader inclusion criteria, particularly the inclusion of more medically unstable participants with greater derangements at baseline in sleep quality, gas exchange and symptoms, may also have provided increased confidence of a true lack of effect of PSG titration of NIPPV on sleep disruption.

The final contributing factor to discuss regarding this negative finding on sleep disruption is the possibility that any effect of PSG titration was blunted by the expertise of the physiotherapists who performed the clinical titration. The approach to the clinical titration of NIPPV within the service has been discussed, however it is important to consider the influence that expertise may have had on the lack of sleep disruption and comparatively low levels of PVA in both groups. Only experienced, specialised respiratory physiotherapists are able to perform implementation of NIPPV independently at the institution in which the study was conducted. As the CONSORT diagram (Figure 9) demonstrates, over 300 new users were implemented with long-term HMV by the two physiotherapists over the two-year duration of the study. This reflects an enormous caseload in which both the science and the art of implementation of NIPPV could be learned and refined. In addition, both have over five years of experience with the service, regularly review and analyse PSG studies during NIPPV, are involved in case discussions and clinical audit as well as participating directly in research studies.
in this area. This provides them with extensive exposure to the clinical and technical issues that must be navigated to successfully perform clinical titration. It is likely that this produces a very high degree of expertise that few others would possess. It is therefore likely that both the amount of sleep disruption and PVA produced with clinical titration alone was lower in the current study than it would have been if non-experts had implemented NIPPV. Experience with NIPPV has been shown to be associated with clinical success when this therapy is used in the acute setting. (Lopez-Campos et al., 2006) The somewhat idiosyncratic array of difficulties that can be experienced by users suggests that clinician expertise is likely to be supportive. (Dunn, 2013) It is suspected therefore that better clinical titrations would limit the ability of PSG titration to provide an additive benefit, thereby mitigating its effect. It is hypothesised that in centres where caseload and therefore expertise are considerably less, clinical titration could be less effective, thereby producing more PVA and sleep disruption than demonstrated here. It is also possible that the performance, interpretation and review of NIPPV therapy with PSG could itself improve the effectiveness of clinical titrations. This question was not addressed in the current study and this possible effect is therefore speculative only.

The final hypothesis tested in the current study was not proven, as although routine PSG was associated with a trend towards increased average daily use, it was not associated with significant differences in gas exchange, symptoms or HRQoL.

The possible supportive effect of PSG titration on average daily use does warrant further discussion. The exploratory analysis presented suggests this effect was mediated primarily by increasing average daily use within those with non-adherence (<240min averaged daily use) during the acclimatisation period. The mean increase in average daily use of 95 minutes is large and probably of clinical importance. Those with non-adherence during the acclimatisation period may represent individuals experiencing difficulty transitioning to the use
of assisted ventilation. Longer-term adherence to positive pressure therapy has been shown to be associated with early adherence – particularly in the case of CPAP. (Budhiraja et al., 2007; Weaver & Grunstein, 2008) The apparent effect of PSG titration to shift users towards adequate adherence, suggests a potentially important clinical effect of this intervention, but also an easily identifiable cohort of users in which to apply it. The subgroup analysis of individuals with MND suggests this group in particular could benefit from PSG titration in order to improve adherence although it is acknowledged that clinical heterogeneity within this disorder is considerable, and this limits the strength of any conclusions.

Any link between the change in average daily use and measures of sleep disruption or PVA is unable to be made based on data from this study. Therefore the mechanism as to why average daily use increased in the PSG titration group is uncertain. Again the lack of baseline PSG measures prior to the intervention represents a limitation in study design, as this may have revealed a systematic effect. Alternatively, there may be other unmeasured parameters through which PSG titration may support adherence. It is also possible that it may act idiosyncratically for a given individual. Because PSG titration provides a multifactorial assessment, it is able to both detect and remedy numerous problems that may not have been observed during daytime clinical titration. Issues as varied as anxiety, mask discomfort, excessive leak, poor synchronisation, impaired gas exchange or reduced sleep quality, among others, could be addressed. Improvements could therefore be achieved for an individual in any or all of these. A systematic effect may therefore be difficult to detect in a study that is evaluating group mean behaviour.

While this finding of a possible supportive effect on average daily use may be important, it raises questions as to why the reduction in PVA and improvement in adherence did not translate to significant differences in symptoms and HRQoL? The only between-group difference demonstrated was in
the Social Relationships domain of the SRI although this may represent a chance finding. Given the lack of difference in summary measures of HRQoL (AQoL-8D index score or SRI Summary Scale) and symptom scores, it can be concluded that any gains associated with PSG titration, were small or offset by decrements in other aspects of health. It is also possible that the time period used in the study (ten weeks between enrolment and study conclusion) was too short. Given that over 66.7% of the participants had MND, a disorder generally associated with inexorable decline, the finding that summary measures of HRQoL were not worse suggests that both groups probably obtained a relative benefit in HRQoL following the commencement of NIPPV. (Bourke et al., 2006) While an alternative explanation for the lack of change in these measures is that the NIPPV delivered in this study produced no significant effect on HRQoL, this possibility is felt to be unlikely. More plausible is the possibility that the clinical stability of participants at enrolment selected a group with less likelihood of obtaining an acute change in HRQoL with NIPPV. The lack of change in HRQoL over this short timeframe is therefore encouraging but would be considered more clinically relevant if persistent over a longer period. Given that over 50% of the Control group who had MND were non-adherent with therapy during the treatment period, it is hypothesised that a longer period of observation may also have been more appropriate in order to detect any divergence in HRQoL and symptom measures that could be attributable to non-adherence. It could be expected that a titration strategy associated with lower levels of adherence would be associated with greater morbidity and mortality over time, especially for those with MND. (Bourke et al., 2006; Butz et al., 2003)

Overall, there were essentially no subjective benefits demonstrated with the routine use of PSG titration of NIPPV compared with daytime clinical titration alone during the ten-week study period. It remains uncertain if the benefits would be larger over a longer timeframe, in more acutely unwell or diverse populations or in clinical scenarios where expert clinical titration was not available. Routine use of PSG titration is not unequivocally indicated for stable
outpatients that are treatment naïve based on the results of this study. Such an approach is unlikely to prove cost-effective based on these data, as many users appear to be able to be adequately managed with clinical titration alone. For those who demonstrated adequate adherence during the acclimatisation period, further increases in adherence were not achieved although four individuals in the Control group did deteriorate from adherent to non-adherent (see Figure 13). Whether this reflected a temporary reduction in use or may have important clinical impacts in the longer term is unknown. Whether alternative clinical evaluations may suffice in adherent users, while PSG is reserved for those with poor adherence, lack of subjective benefits, or abnormalities on simpler investigations (for example; nocturnal oximetry or arterial blood gases) is unknown. Based on these results, forgoing PSG titration in individuals who are demonstrating adequate adherence is unlikely to compromise safety given the effectiveness of clinical titration performed by expert clinicians for the Control group. This may particularly be relevant for individuals with MND or NMD who could experience greater challenges in attending for PSG.

The ability to generalise these findings to other clinical settings or HMV providers with different levels of experience and expertise is questionable. In higher acuity populations, for example in cohorts where unplanned hospital or ICU admissions may be more likely, or in centres where experienced respiratory physiotherapists are not available, routine PSG titration may confer advantages over clinical titration alone. Significant uncertainty therefore remains and an abandonment of routine PSG titration could not be justified on these results. It is therefore not possible to determine whether this practice should form a benchmark for high quality care for individuals receiving assisted ventilation.
9.7 Conclusion

In this medically stable outpatient cohort of treatment naïve individuals with predominantly MND and other stable or slowly progressive NMD, titration of NIPPV during PSG was associated with improved synchronisation but not reduced sleep disruption. The clinical benefits of this intervention appeared limited to a supportive influence on adherence – which was significant only in those with early non-adherence. This finding may be the most compelling, with this group representing both a therapeutic challenge, and an opportunity. Other effects on HRQoL and symptoms were not identified but may have been muted by the medical stability of the cohort and the relatively short follow-up period. The expertise of the clinicians performing clinical titration may have been a factor in the relatively low rates of both PVA and EEG arousals in comparison to previous studies. It is unclear whether the expertise gained by performing and analysing PSG titrations assists in enhancing this expertise, however it is possible that clinical titrations that prioritise comfort and tolerance could produce less sleep disruption despite the presence of PVA.

The association between PSG titration and lower PVA is novel but alone does not represent conclusive evidence of the benefits of routine PSG titration. The trend towards an effect on adherence is more clinically important however the mechanism of this effect remains uncertain based on these data. It is hypothesised that the benefits of routine PSG titration on adherence may be multifactorial and that how this effect is mediated could be dependent on the idiosyncrasies of the user. Whether other simpler or cheaper measures could produce a similar effect is unknown. Further research should evaluate important clinical outcome measures over a longer time period, in addition to the use of broader inclusion criteria. A multi-centre study would allow further exploration of the influence that clinician expertise has on the effectiveness of clinical titration.
Section 4 – Synthesis

Chapter 10 – Discussion

10.1 INTRODUCTION

There is substantial variation in the care provided to individuals receiving assisted ventilation. In part, this reflects the variable level of evidence for HMV amongst the heterogeneous range of conditions in which it is used. Identifying and defining high quality care for users of HMV is extremely difficult. Clinicians and researchers in this area have tended to operate in regional ‘silos’, with a lack of consistency in expert opinion and hence considerable variation in practice.

In this thesis, two large, regional HMV providers from countries with similar healthcare systems, economies and demographics have been shown to provide very different approaches to care. These differences were not associated with the HRQoL of users, however, with physical function, employment and household income demonstrating stronger associations. Significant differences were also demonstrated in the proportions of individuals receiving assisted ventilation with underlying COPD, OHS and NMD, (Hannan et al., 2016) with this finding consistent with previous regional comparison studies. (Garner et al., 2013; Lloyd-Owen et al., 2005) The subjective benefits that can be obtained from NIPPV have also been described for different diagnostic groups, with these findings, in addition to the limitations identified with certain generic HRQoL measures, highlighting some of the challenges of evaluating quality of care in this area.

The subsequent research study described in Chapter Nine, attempted to determine the role of routine PSG titration. This is a care practice used frequently in Australian HMV centres, but infrequently elsewhere. (Garner et al.,
It was hypothesised that routine PSG titration would demonstrate advantages over clinical titration alone. Although measures of patient-ventilator asynchrony (PVA) were lower in the PSG titration group, sleep disruption was not different and other secondary outcomes were similar between groups. There was a trend towards improved adherence in the PSG titration group however this did not translate into measurable clinical differences within the timeframe evaluated. There were clearly limitations in the study design, which may explain these relatively modest findings, and these have been discussed.

The primary aim of this thesis was to determine whether the routine application of PSG titration of NIPPV represents high quality care for a provider of HMV. This aim has been addressed but not unequivocally answered. The results presented provide a considerable basis for future research to identify and deliver high quality of care for individuals receiving assisted ventilation. The following discussion outlines the potential of longitudinal observational studies as part of ongoing cross-national collaboration between HMV providers to address gaps in knowledge. Consistent disease definitions, data collection and reporting will be crucial for these results to be interpretable and to build consensus among experts. Further randomised controlled trials are also required and examples of specific gaps in the evidence are discussed below. There is sufficient pilot data presented here to justify a multi-centre study evaluating the use of routine PSG titration in comparison with clinical titration, although careful study design and planning will be critical.

The aim of this chapter is therefore to place the findings presented thus far in this thesis in context, and to describe future research efforts that should be undertaken to improve the quality of care for individuals receiving assisted ventilation.
10.2 DIFERENCES IN CARE PRACTICES AND GAPS IN KNOWLEDGE

The results presented in this thesis have confirmed the hypothesis that there is regional variation in practice regarding the care of users of HMV. The demonstration that two centrally managed HMV providers in countries with broadly similar economies, demographics and healthcare funding have developed models that deliver such different care practices perhaps is not surprising based on anecdotal reports and previous comparison studies. (Garner et al., 2013; Lloyd-Owen et al., 2005; Rabkin et al., 2012) In fact it would be expected that even greater differences could have been identified if other developed countries such as Germany or Japan were included in this comparison. (Rabkin et al., 2012; Windisch et al., 2010) There are clearly large gaps in the evidence, variations in healthcare funding, differences in incentives for particular interventions or therapies and, presumably, firm philosophical preference for certain approaches. These combine to produce care that is very different. Variation in practice is not unique to HMV however. As an example, the management of congestive heart failure has previously been shown to vary significantly between institutions within the United States, (Fonarow, Yancy, & Heywood, 2005) and in Europe. (Komajda et al., 2003) This is in spite of agreed indicators of quality of care and numerous consensus guidelines. (Ponikowski et al., 2008; Yancy et al., 2013) Identifying benchmarks and achieving a broad consensus amongst experts will therefore not guarantee the delivery of high quality care in all places and at all times; but they are clearly essential first steps if this is to be an aspiration.

As previously outlined in Chapter Five, to be able to provide benchmarks for quality of care, evidence must be known, or if it is lacking, consensus between experts must be reached. Currently, consensus between experts in HMV appears limited essentially on a geographical basis. Comparison between guideline documents and consensus statements regarding HMV from Germany, Canada and Australia provides some indication of this. (McKim et al., 2011; Piper et al., 2010; Windisch et al., 2010) Cross-national comparison studies have provided
further supportive evidence. (Garner et al., 2013; Hannan et al., 2016; Lloyd-Owen et al., 2005) This therefore represents a significant barrier to the identification of high quality care. The persistence of what appear to be regional ‘silos’ – where care practices are based primarily on local data, clinician preferences and established dogma – appears to support the notion that care should be considered high quality provided local experts decide that it is. This would suggest a degree of medical paternalism that has long since departed other areas of medicine. How can shared decision-making between users and clinicians occur when experts can’t agree on what high quality care looks like?

10.2.1 Cross-national evaluations broaden perspectives

Comparisons between healthcare providers, such as the study presented in Chapter Seven, provide valuable insights into how others deliver care. Descriptive studies such as this allow a greater focus on aspects of care that are different and enable the drivers of these differences to be considered. The cross-sectional design used has important limitations, however, that can lead to erroneous conclusions. Many of these have been discussed previously. It should be re-emphasised that the potential for responder bias, particularly the possibility that those with better HRQoL may have been more likely to respond to such a study, could significantly alter the conclusions that can be drawn. This would seem more likely to be problematic in a population of users of HMV, where considerable heterogeneity exists with regard to physical function and potentially HRQoL. Obtaining additional qualitative data may have provided clarity regarding barriers to responding to the survey and allowed further exploration of the potential for bias in the overall responses. Semi-structured interviews in a random subset from the two populations may also have allowed the identification of additional themes and concerns from users of HMV that could have
contributed to further refinement of the questionnaire. This may also have provided additional context to the findings and generated additional hypotheses.

The cross-sectional design used also failed to account for mortality within the two services. This is clearly an important measure of both safety and effectiveness of the HMV delivered. Attempts to speculate on the influence of mortality on the results obtained are difficult. It is possible that the use of IMV in the Canadian service may have skewed the population towards relatively more users with NMD and MND. If true, this did not influence measures of HRQoL across the two sites. It is speculated that a more restrictive policy towards IMV within the Australian service could mean fewer long-term users of HMV with NMD or MND, with this possibility supported by not confirmed by the data presented (see Chapter Seven; Table 7). Deceased users are therefore unaccounted for in the cross-sectional analysis presented and any difference in mortality rates between the two services is unknown. For longitudinal analyses, those users who are deceased would be assigned an index score (using an instrument such as the AQoL-8D) of 0.00 (=death). This, in addition to ensuring those with severe levels of physical disability or other barriers to completion of these instruments are able to provide responses, would allow more complete comparisons of HRQoL between the two sites.

10.2.2 Sharing longitudinal observational data may help to define quality care

Despite these limitations, cross-national collaboration can lead to improvements in the quality of care. (Horbar, Plsek, Schriefer, & Leahy, 2006; Levy et al., 2010) Data-sharing collaboratives that allow longitudinal observation of outcomes and comparisons between centres are described in a number of circumstances. These include registers evaluating outcomes from congenital cardiac surgery, (Jacobs et al., 2005; Shahian et al., 2013) neonatal intensive care units, (Horbar et al., 2006) severe sepsis, (Levy et al., 2010) tracheostomy
use, (Enamandram et al., 2014) and surgery with hip joint prostheses. (Malchau, Herberts, Eisler, Garellick, & Söderman, 2002) These collaboratives are particularly suited to circumstances where there are gaps in knowledge, heterogeneity of clinical populations and difficulty with conducting multi-centre RCTs due to feasibility, practicality or cost. (Enamandram et al., 2014) Such an approach allows practice to be scrutinised and high quality care identified and used as benchmarks against which others can be compared. An example of such an approach is described by Enamandram et al who reported on the Global Tracheostomy Collaborative. (Enamandram et al., 2014) This group aims to “provide the foundation necessary to translate data and knowledge into local quality change by opening lines of communication, disseminating high quality information and sharing best practices, supported by clinical data”. (Enamandram et al., 2014) Similar to the population managed with HMV, those managed with tracheostomy often experience considerable morbidity and mortality. (Das et al., 2012; Halum et al., 2012) The bulk of literature regarding tracheostomy care is also similar to HMV in that it “focuses on single-institution interventions with a paucity of widely generalizable evidence”. (Enamandram et al., 2014) The parallels between tracheostomy use and HMV continue with regard to the difficulty of performing RCTs, the clinical heterogeneity of the underlying disease states and the wide variety in clinical approaches. The development of data sharing collaboratives between HMV providers therefore provides a similar potential to identify high performing centres from observational clinical data and translate it into effective quality improvement strategies in lower performing centres.

Evidence confirming the benefits of quality improvement collaboratives is relatively limited, however, and there are considerable barriers to their implementation. One of the main criticisms of this approach is the relative lack of robust patient-level outcome data. (Nadeem, Olin, Hill, Hoagwood, & Horwitz, 2013) This would be absolutely crucial to the success of this approach were it to be considered by HMV providers. The centrally administered HMV services
described in Chapters Six and Seven already demonstrate a number of features (including administrative support, shared goals for improvement, team-based care, interdisciplinary teams, physician leadership and data collection for quality assurance) that would suggest they are structurally likely to deliver high quality care. (Bradley et al., 2001; Shortell et al., 2007) The important clinical questions in this area would therefore predominantly be answered with patient-level data from these organisations, rather than provider-level data. That is not to suggest that examining the organisations themselves would not be important, however simply describing and refining the structure of these organisations, although potentially beneficial for smaller, decentralised or less established providers, would not be sufficient to provide useful clinical benchmarks that could allow the measurement and improvement of quality of care.

The results presented in Chapter Eight of this thesis provide preliminary evidence regarding patient-level data that would be valuable to collect. Clearly physiological data, hospital admissions and mortality are required, and this must be accurate and consistent across sites. This will require uniform disease definitions and data collection methods. (Richesson, Shereff, & Andrews, 2010) There is potential for the incorporation of novel data collection methods (including that obtained by remotely accessing ventilators) that could reduce administrative burden. Patient-reported outcomes must include measures that are acceptable and important to users, which respond to real changes in health, are meaningful for clinicians and that can account for mortality to avoid the potential of attrition bias. It could be argued that regardless of the development of a collaborative, these should in some way be incorporated into routine clinical care for HMV providers. Such an approach would allow internal benchmarking aside from the potential advantages of comparisons with other organisations.

The data presented in Chapter Eight suggest the inclusion of a generic preference-based HRQoL instrument such as the AQoL-8D may be appropriate alongside other measures. Others have evaluated HRQoL instruments using
both qualitative assessments, (Whitehurst et al., 2014) and quantitative assessments, (Richardson et al., 2015, 2014; Whitehurst et al., 2016) These studies, and the results presented in Chapter Eight, suggest that the AQoL-8D may have advantages for use in populations of individuals receiving assisted ventilation. One limitation of the instrument relates to it size (35-items), as this could pose an excessive burden on users of HMV and those administering the data collection. Longitudinal data collection would require responses to the instrument on multiple occasions. Further qualitative and quantitative studies may identify alternative instruments that are preferable to the AQoL-8D or even that abbreviated versions (the AQOL-6D or 4D) perform similarly but with less burden. These analyses should include the SRI, as in its current 49-item format; the burden of collecting both disease-specific and generic HRQoL measures would be considerable.

The inclusion of other measures should also be carefully considered. Measures of somnolence and fatigue were improved in studies evaluating treatment naïve users of NIPPV who had OHS, RTD and MND. (Hannan et al., 2014) Sleep quality (where evaluated) also improved in most studies, (Hannan et al., 2014) as well as in the RCT presented in Chapter Nine. However, it is uncertain in what format these aspects of health should be measured. Although not evaluated in this thesis, there may be similar limitations regarding the use of established instruments (such as the PSQI, ESS and FSS), to those identified with the EQ-5D-5L in individuals receiving assisted ventilation. A lack of response might therefore reflect a true lack of effect of NIPPV for an individual, or alternatively could instead represent an intrinsic problem with the measurement properties of the instrument itself. It is possible that this could provide an additional explanation for the inconsistency between studies included in the systematic review for some aspects of health. (Hannan et al., 2014) It is speculated that there may be other methods of measuring these symptoms that prove simpler and more robust in longitudinal assessments. Specifically, it is possible
that simple rating scales could perform equally well and this could greatly simplify data collection if used across multiple sites and in multiple languages.

Further work is therefore required to determine whether there are particular advantages of using the disease-specific SRI in longitudinal data collection. In particular, it is uncertain if combining a generic preference-based HRQoL instrument with simple rating scales of symptoms may produce similar performance with fewer burdens. Again, qualitative data obtained from interviews with individuals receiving assisted ventilation could provide valuable insights into this issue. These data would supplement the findings presented in Chapter Eight and ensure that aspects of health that are used as benchmarks for quality of care are prioritised by users and not just clinicians. (Van der Waal et al., 1996)

A final consideration regarding longitudinal measures relates to whether measures of wellbeing or QoL (rather than narrower measures of HRQoL) might be more relevant to users of HMV. These provide the ability to consider health status as an influence over wellbeing rather than the only determinant of a positive outcome. (Al-Janabi et al., 2012) Such instruments evaluate aspects including security, autonomy, and enjoyment and could provide complementary data to the more traditional measures of health status. In longitudinal assessments, these could assist in determining whether the health, technology or social interventions employed by HMV providers impact on a person's “capability to do and be the things that are deemed valuable in their life”. (Al-Janabi et al., 2012) This could avoid erroneous conclusions regarding a lack of efficacy for interventions that do not influence traditional measures of health status but that do support wellbeing and QoL.
10.2.3 Randomised controlled trials are still required

Despite these justifications for the use of cross-national data sharing collaboratives and longitudinal observational studies, there remains an urgent need for further randomised controlled trials to attempt to answer important clinical questions within this field. One question for which there remains considerable debate is the use of long-term NIPPV for individuals with stable hypercapnic COPD. As discussed previously in this thesis, there are now two RCTs that suggest a survival benefit could be obtained in this group although only the most recent study suggested an advantage with regard to HRQoL. (Köhnlein et al., 2014; McEvoy et al., 2009) There were considerable differences between these two studies, both with regard to the intervention (‘high-intensity’ NIPPV) but also the inclusion criteria. (Köhnlein et al., 2014; McEvoy et al., 2009) The study by Köhnlein probably included individuals with co-existent COPD and OSA and the conclusions regarding HRQoL and adherence are less robust due to missing data. (Köhnlein et al., 2014) Regardless, findings from these studies provide support for an international multi-centre RCT. This should occur without industry involvement in order to ensure confidence in the findings. (Bekelman, Li, & Gross, 2003) It will be critical to apply a consistent intervention to a well-characterised cohort of individuals with COPD. Ideally, such a study should specifically identify those with co-existent COPD and OSA and attempt to determine whether NIPPV provides advantages in this group over CPAP. Despite limited available evidence, observational data suggests that CPAP could modify the prognosis of those with COPD and OSA. (Marin et al., 2010) It will be imperative that this simpler and cheaper positive pressure therapy also be evaluated. Results from such a study would ensure that specific benefits and advantages of NIPPV are identified if they are present, and thus, allow the findings to be translated more effectively and consistently into clinical practice.
Other interventions currently used routinely for HMV users also require scrutiny in RCTs. Specifically, the use of routine lung inflations in the absence of respiratory infections or excessive secretions (either manual inflation or with proprietary mechanical devices) should be evaluated. Again, in this area it appears that practice and opinion has outpaced the available evidence. While the use of assisted cough techniques are essentially standard care during acute deteriorations due to respiratory infections in individuals with NMD, the evidence for their routine use is not strong. Some authors have suggested that such an approach could be beneficial in maintaining lung function, however these retrospective data are not compelling evidence to support widespread routine domiciliary use.\cite{Katz2016, McKim2012}

While capital costs for manual inflation devices are relatively low, carer and user training is required in order for therapy to be delivered effectively, increasing the burden on HMV providers. Proprietary mechanical devices are considerably more expensive and do not appear to confer any advantage, at least with regards to peak cough flow, to justify their additional cost.\cite{Toussaint2016}

Clinical equipoise exists for an RCT examining routine lung inflations in individuals with NMD in Australia, as this practice does not yet represent standard care in HMV centres based there.\cite{Hannan2016} The results of such a study would provide clarification of the role of this intervention.

While these examples identify clinical questions in which RCTs are required, other areas of debate will almost certainly not be subjected to this method of scrutiny. In particular there are considerable ethical barriers to performing studies to evaluate long-term IMV for those with progressive NMD. There is clearly difference in practice in this area,\cite{Hannan2016, Rabkin2012} and there may be considerable resistance to change. Such an intervention may therefore be better evaluated in longitudinal observational comparison studies. Other, aspects of care delivered by HMV providers are also not well suited to examination in RCTs. Administrative structures, dedicated outreach services, 24-hour telephone support and the influence of expert
inpatient medical services (for ventilation management and weaning) are also more suited to evaluation in longitudinal comparisons. With sufficient coordination and planning, such comparisons could allow the identification of high performing services so that their approach to care could be emulated.

10.2.4 Measuring quality of care may remain difficult

Because HMV uses a non-implanted medical device without a need for drug therapy, in most settings there are fewer regulatory barriers to its use and therefore comparatively less incentive to prove efficacy or effectiveness. Arguably, device manufacturers benefit more from the absence of these data than do users. (Stafford, Wagner, & Lavori, 2009) Unfortunately, without cooperation and collaboration to allow international multi-centre RCTs, along with well-designed observational studies, it is likely that identifying and defining high quality care for HMV will remain difficult. This represents a challenge to individuals receiving assisted ventilation, their carers, as well as clinicians, researchers and policymakers. Such studies would evaluate clinically relevant alternative interventions, include diverse populations, recruit from heterogeneous practice settings and collect data on a broad range of outcomes. (Tunis, Stryer, & Clancy, 2003) Other areas within healthcare have benefited from such a combination of approaches that fall within a comparative effectiveness research definition. (Concato, Peduzzi, Huang, O’Leary, & Kupersmith, 2010; Lauer, 2009) Combining conventional RCTs with practical clinical trials, observational data collection and clinical audit have provided a wealth of evidence to guide recommendations for clinicians managing cardiovascular disease. (Concato, Lawler, et al., 2010; Concato, Peduzzi, et al., 2010; Lauer, 2009) These therefore represent well-established pathways to achieve the sort of consensus and practice improvement that is required for HMV.
It was anticipated that the results from the RCT presented in Chapter Nine would provide compelling evidence of the superiority of PSG titration over clinical titration alone. In fact, modest benefits were identified through the routine application of this intervention, with these limited to the measure of synchronisation between the user and the device (PVA index) and to an apparent supportive effect on adherence. Some of the reasons for this have been explored in Chapter Nine. It is worth revisiting the limitations in the study design, but also the limitations in the physiological measures available for nocturnal monitoring in clinical practice, in order to place these findings in context.

10.3.1 Limitations in study design

As previously discussed, the study may well have been underpowered to detect a difference in sleep disruption, as previous studies in this area which demonstrated large benefits from adjustments to ‘usual’ NIPPV settings were likely to have produced these primarily due to the use of comparatively aggressive clinical titrations. Reflecting standard clinical practice at the centre in which the current study was conducted, comfort, adherence and synchronisation were prioritised. The daytime PaCO$_2$ of these medically stable participants also tended to be within the normal range, which suggests that large acute improvements in gas exchange were neither likely nor desirable. This may have meant that settings used in the control group were less likely to produce sleep disruption and thus muted some of the benefit of PSG titration. This, combined with the relative clinical stability of this outpatient population was likely a factor in the limited benefits demonstrated with PSG titration over clinical titration alone. Additionally, the time interval over which these were evaluated may have
been a limitation. Although there was a trend overall to differences in adherence between the two groups, the treatment period may have been too short for this to manifest into a divergence in symptom control or HRQoL measures. Although still considered an important part of the study design (in order to control for any placebo effect from PSG titration) the use of the sham PSG may too have provided inadvertent effects. Contact with an experienced clinician (sleep scientist) during nocturnal monitoring may itself be beneficial in terms of reassurance, expectation management or self-efficacy.

10.3.2 Limitations of physiological measures

The PVA index was a primary outcome measure for the study and this was evaluated using scoring rules adapted from previous reports from Fanfulla et al, Ramsay et al and Vrijsen et al. There are other alternative scoring methods described and it is unknown whether the results reported here would be different if an alternative method were chosen. A review of the literature suggests similar themes between scoring methods, and none of the alternative methods have been compared directly. Ramsay et al has described a reliance on parasternal EMG for event detection and reported measures of inter-rater reliability from brief recordings scored by two assessors (ICC 0.94 for ineffective efforts). (Ramsay et al., 2015) However their technique was not applied to all of their nocturnal recordings, with only 12 minutes scored out of every 60 minutes recorded. Additionally, the initial 60 minutes and sections with movement artefact were discarded. Due to the absence of sleep measurement, it is also uncertain how much of their data was scored while users were awake. (Ramsay et al., 2015) Similarly, Fanfulla et al also analysed only segments of their nocturnal recordings, however these sections were defined according to sleep stage. (Fanfulla et al., 2005) Others have described analysis of entire nocturnal recordings but consistency in the events measured and the scoring criteria used is lacking. (Adler
et al., 2011; Atkeson et al., 2011; Caldarelli et al., 2013; Crescimanno et al., 2011; Guo et al., 2007; Vrijsen et al., 2016)

The major limitation in any currently available scoring method is the limited ability to accurately identify inspiration, as it is this event that allows the identification of ineffective efforts. Ideally, the gold standard measure would be negative deflections in oesophageal pressure and/or diaphragm EMG from an oesophageal catheter. These were considered impractical in a voluntary clinical study of this kind due to the potential difficulty of tolerating catheter insertion. (Chervin et al., 2003) Once inserted, these also have the potential to disturb sleep. (Chervin & Aldrich, 1997) Non-invasive measures of inspiratory effort (surface EMG or respiratory movements) are less accurate but more acceptable to patients. (Luo et al., 2009) Pulse-transit time, while seemingly reliable in determining if inspiratory effort is present, (Contal, Carnevale, et al., 2013) has not been shown to be useful for identifying its onset. Sternal notch pressure monitoring may be suitable for this purpose, (Meslier et al., 2002) although its performance during NIPPV has not been evaluated. As a result, it was determined that scoring rules utilising only mask trace and respiratory movements (measured with respiratory bands) were the most appropriate measures for this study. It was also determined that although surface diaphragm EMG signal and parasternal EMG are utilised in clinical practice, that these signals should not be used to score PVA events due to the inconsistency with these signals both within and between recordings. Consequently, PVA event scoring was extremely labour intensive and in the absence of automated measures, is unlikely to form part of routine clinical evaluations. More likely, it will remain a qualitative assessment that is made by clinicians during PSG, rather than a quantitative measure. Future studies considering PVA should determine whether alternative measures of inspiratory effort could improve PVA event detection. Those that could be incorporated into automated scoring algorithms would allow PVA to be more easily quantified. These physiological studies should, where possible, use oesophageal pressure or diaphragm EMG measured
with an oesophageal catheter as the gold standard against which other inspiratory effort measures are compared. (Vandenbussche, Overeem, van Dijk, Jan Simons, & Pevernagie, 2015)

10.3.3 Adherence and PSG titration

Adherence to NIPPV has been shown to be associated with survival, (Aboussouan et al., 2001; Bourke et al., 2003; Kleopa et al., 1999) and duration of HRQoL benefit (measured with the SF-36 mental component score), (Bourke et al., 2003) in individuals with MND. Data presented in Chapter Nine demonstrated that average daily usage during the treatment period was correlated with better sleep quality, lower ratings of daytime somnolence, better HRQoL (using the AQoL-8D index score) and higher ratings of benefits (vs. side-effects) of NIPPV (see Appendix I, Table I9). These findings do not prove causation as improvements in sleep quality, somnolence, HRQoL and side-effects could conceivably encourage greater usage. Nevertheless, non-adherent users from both groups had on average more 3% oxygen desaturations, more time with SpO₂ less than 90% and a trend to more ineffective efforts on the final sleep study, suggesting less adequate control of nocturnal gas exchange and synchronisation than those able to achieve more than 240-minutes of average daily usage (see Appendix I, Table I10). It is uncertain if more effective NIPPV would support greater adherence, however this remains a possibility.

In spite of the relatively high proportion of non-adherence across both arms (39.3% overall), the stable outpatient population included in the study manifested very few adverse events overall. Self-reported hospital admissions and emergency department presentations were rare and even total contacts with healthcare workers were surprisingly low for both groups. Again, study duration may have been too short for differences in these to become apparent in those with non-adherence to NIPPV.
Based on the data presented in Chapter Nine, it is reasonable to speculate that PSG titration could act to shift non-adherent individuals above a four-hour threshold of average daily usage if they have failed to achieve this with clinical titration alone. It should be stated that in such a heterogeneous population, it is difficult to exclude individual clinical factors that may have contributed to this trend. And, if PSG titration alone was the mediator of the effect, it remains uncertain from these data as to the mechanism through which it was achieved. On one level, the data could be interpreted to suggest that lower levels of PVA were the mechanism although this remains speculation. It is unknown whether very high levels of PVA were present at baseline in those who were non-adherent (as this was not measured) and whether PSG titration acted to reduce these levels. It is theoretically possible that increased adherence itself could have reduced PVA, through a mechanism where the user’s neural respiratory activity is entrained to the rhythm of the ventilator. (Simon et al., 2000) While there were correlations between PVA and other nocturnal measures, including oximetry and leak levels (see Appendix I, Table I9), these measures were not significantly different between groups. This suggests that no other systematic effect was achieved through routine PSG titration – although again this finding has the previously stated limitation that baseline parameters prior to the PSG titration are unknown.

Therefore, all of the criteria for causation have not been established with these data. It can be concluded that PSG titration was associated with less PVA and a trend to improved adherence but not that less PVA resulted in improved adherence. It is conceivable that PVA events may represent the ‘final common pathway’ for problems that can be observed and ameliorated during PSG. They may therefore represent a marker of the effect of PSG titration, rather than an explicit mediator of improved adherence.

The question remains as to whether adherence represents a useful clinical marker to identify those not benefiting from NIPPV. The data presented here
were not intended to answer this question. However, if the dose effect of NIPPV previously reported is accurate (Mokhlesi et al., 2006; Nickol et al., 2005) it is very likely that across a population, inability to achieve a minimum level of adherence is a reasonable surrogate for a lack of effectiveness. These data suggest that PSG titration could improve adherence in those unable to achieve the four-hour threshold of average daily use. They also clearly demonstrate that PSG titration alone is insufficient to guarantee adherence. There was still a large proportion in the PSG titration group that demonstrated non-adherence at study conclusion. Again the population included in this study (stable outpatients with predominantly MND and NMD) provides some context for this. In a cohort with more clinical instability, adherence rates and the influence of PSG titration on both short- and long-term clinical outcomes could be very different.

10.3.4 Further study evaluating PSG titration

A multi-centre RCT evaluating routine PSG titration is justified based on these pilot data. In particular, the apparent trend towards differences in adherence could translate into important clinical differences over a longer period of observation. It may be valuable to enrol only individuals with MND or NMD in order to limit, where possible, the heterogeneity of the population. Minimisation should be used to ensure equivalent numbers of individuals with MND in both groups as over a longer time period it would be expected that this group would have higher mortality than individuals with stable or slowly progressive NMD. (Altman & Bland, 2005) Balancing the clinical phenotype of individuals with MND would also be important. (Berlowitz et al., 2016; Talman et al., 2009) The use of minimisation could also ensure that early adherence was similar between both groups. Consideration should be given to non-inclusion of those with OHS due to the poor recruitment demonstrated in the study described in Chapter Nine. This lower than anticipated recruitment may reflect
the increasing evidence of a lack of superiority of NIPPV over CPAP in this group, or it may have been a purely local effect. (Masa et al., 2015; Piper et al., 2008) Broader inclusion criteria should allow the inclusion of hospital inpatients at the time they are implemented onto NIPPV if they are willing to consent to the study interventions. Careful consideration is required in the study design regarding the control intervention. As discussed in the thesis, many of the studies that have compared titration methods have delivered settings that could be considered overly aggressive. One potential option to remove the influence of expertise on the settings chosen during clinical titration would be to utilise the ‘intelligent’ titration systems incorporated in modern devices. (Jaye et al., 2009; Kelly et al., 2014) Although the evidence supporting this technology is limited, it has been suggested to provide equivalent therapy to that determined by expert clinical titration. (Kelly et al., 2014) Its use would remove some of the potential influence that the clinical approach to titration in the control arm could have on outcomes. Therefore, it is proposed that both groups in the study should undergo clinical titration with the aid of an auto-titrating device and only the intervention group return for PSG titration. Clinicians would still be involved in the education of users as well as the selection and fitting of interfaces. Conducting the study across multiple sites would allow the influence of this expertise to be considered in the analysis.

The primary outcome in this study should not be a physiological or subjective measure. Instead it is proposed that tracheostomy-free survival be the primary outcome measure. Other secondary outcome measures should include hospital admissions, sleep and nocturnal gas exchange measures (obtained pre- and post- intervention using portable home-based PSG) as well as adherence, arterial blood gases, HRQoL (both generic and disease-specific) and symptom ratings at three-monthly intervals. Sub-studies could specifically address some of the questions outlined above regarding subjective outcome measures. If sternal-notch pressure monitoring or parasternal EMG can be sufficiently refined for
whole-of-night recording and scoring, they should be incorporated in PSG titrations and portable studies.

Results from this proposed study would clarify the role of routine PSG titration of NIPPV for individuals with NMD and ALS/MND.

10.4 Conclusion

The care delivered to individuals receiving assisted ventilation is very different between similarly resourced HMV providers. Longitudinal observation, improved collaboration and data sharing would provide an effective means of identifying high quality care. Building consensus between experts should allow best practice to be defined and delivered more consistently. Careful consideration of subjective measures and HRQoL instruments for longitudinal use is required to ensure outcomes that are meaningful for both users and clinicians are collected. Instruments such as the AQoL-8D that evaluate capacity instead of behaviour, may perform better in this context. For specific areas of discordant practice; such as the use of NIPPV for individuals with COPD and prescription of routine lung-volume recruitment in NMD, further multi-centre randomised studies are required.

A single-centre RCT evaluating routine PSG titration of NIPPV in stable treatment naïve outpatients with predominantly NMD and MND demonstrated an association between PSG titration and less PVA as well as a trend towards better adherence – but no other clear advantages over clinical titration alone. This intervention has therefore not been confirmed as representing high quality care for users of HMV, although larger, longer-term, multi-centre studies with broader inclusion criteria are required to better clarify its role.

These findings suggest that defining high quality care will remain challenging for HMV providers. As the prevalence of HMV continues to increase,
demands on these services may grow considerably. Ongoing scrutiny of the care delivered by HMV providers is essential to ensure the sustainability of these organisations and to ensure individuals receiving assisted ventilation can be managed safely and successfully in the community.
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Appendix A - Case report: Altering ventilator inspiratory time can reduce autocycling during sleep.

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Images in Sleep Medicine

Altering ventilator inspiratory time can reduce autocycling during sleep

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A R T I C L E   I N F O

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1. Introduction to the case

We report on a 51-year-old man with chronic respiratory failure due to motor neuron disease (amyotrophic lateral sclerosis) referred for overnight polysomnography (PSG) to optimise nocturnal non-invasive positive pressure ventilation (NIPPV).

NIPPV was delivered with a full-face mask and ResMed (San Diego, CA) VPAP™ IV ST in spontaneous/timed mode with the following initial settings: inspiratory pressure = 11 cm H₂O, expiratory pressure = 5 cm H₂O and respiratory rate = 12 breaths/min. The trigger and cycle sensitivity were ‘medium’. The minimum inspiratory time (Tmin) was 1.0 s and the maximum inspiratory time (Tmax) was 1.6 s.

After sleep onset, frequent episodes of rapid delivery of ventilator breaths occurring in excess of the back-up respiratory rate and without evidence of coordinated patient efforts were observed (Fig. 1a). Increasing Tmin to 1.4 s was effective in suppressing these events; however, they reoccurred following a reduction in Tmin back to 1.0 s. Subsequently, an increase in Tmin to 1.2 s effectively controlled events (Fig. 1b).

2. Image analysis

Following the increase in Tmin, Fig. 1b demonstrates improved patient-ventilator synchrony with coordination between respiratory movements and device-delivered breaths.

3. Discussion

Autocycling (or rapid cycling) is a form of patient-ventilator asynchrony (PVA) that can be recognised by the rapid delivery of multiple cycles of ventilator breaths above the preset backup respiratory rate and without evidence of patient effort [1]. The phenomenon appears similar to auto-triggering, but it is differentiated by the presence of multiple consecutive breaths.

In flow-triggered ventilators, autocycling and auto-triggering are believed to arise due to the presence of disturbances in flow that can occur from random noise, water in the circuit, excessive leak or cardiogenic oscillations [1–3]. Previous authors have described an increased propensity for random noise to trigger the ventilator in users with both low respiratory drive and low breathing frequency and when dynamic hyperinflation is absent [4]. In these circumstances, there is a more prolonged period of zero patient flow during expiration, therefore possibly making the system more vulnerable to triggering from flow signals not due to inspiratory efforts [4]. Increasing Tmin while maintaining the same respiratory rate should shorten the duration of zero patient flow that the device needs to maintain during expiration. Theoretically, this reduces the likelihood of auto-triggering and autocycling occurring.

When autocycling during NIPPV is observed in our sleep laboratory, our practice is to ensure that the mask and tubing are free from condensation, that unintentional leak is minimised and that appropriate trigger and cycle sensitivities are set. If events persist, we will trial an increase in Tmin.

Although PVA has been associated with poorer nocturnal gas exchange [5], reductions in total sleep time and percentage rapid eye
Fig. 1. (a) and (b) are representative images from the polysomnographic recording obtained. Both demonstrate a 5-min page of NREM 3 sleep (with the inset representing a 30-s magnified view) before (a) and after (b) adjustment of Tami. Abbreviations: ECG, Electrocardiogram; EMGsub, Submental electromyogram; EOG, Electrooculogram; EEG-C4-M1 and O2-M1, Electroencephalogram; SpO2, Pulse oximetry; PtcCO2, Transcutaneous partial pressure carbon dioxide; Pmask, Mask pressure; Flow, Device flow signal; Thor, Thoracic respiratory band; Abdo, Abdominal respiratory band; Leak, Device leak signal; Pos, Position sensor; EMGlimb, Limb electromyogram.
movement (%REM) sleep as well as more frequent arousals [6]. longitudinal studies confirming the clinical significance of autocycling and other forms of PVA during NIPPV are awaited. This case, however, demonstrates that a systematic approach to the adjustment of ventilator parameters can be successful in reducing the frequency of this type of event.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.05.009.

References

Appendix B - Medical inclusion criteria for Provincial Respiratory Outreach Program*

**PROP Medical Criteria**

Home ventilation should be considered for patients that meet the following medical criteria:

- Neuromuscular disorders or chest wall restriction who have documented hypercapnia (PCO2 at rest on room air >45 mm Hg)

- The patient should be stable and be on optimal management for any reversible component of any associated pulmonary disease

- Patients with a normal PCO2 (in the range of 40-45 mm Hg) may be considered if any of the following criteria are present:

  1. Cor Pulmonale
  2. Nocturnal hypoventilation (as documented by elevations in nocturnal CO2 levels (TCCO2) and associated morning symptoms
  3. Severe supine dyspnea (e.g. Diaphragmatic paralysis)
  4. Symptoms of alveolar hypoventilation

- Patients with central alveolar hypoventilation also qualify in the presence of normal neuromuscular function but abnormal ventilatory control.

- Home ventilation is not indicated in patients with chronic hypercapnea secondary to either chronic obstructive lung disease or interstitial lung disease.

Appendix C - Victorian Respiratory Support guideline for ventilator setting changes in the community
VRSS CLINICAL GUIDELINE

Guideline for ventilator setting changes in the community

Staff this document applies to:
VRSS Outreach staff, VRSS Medical Staff and VRSS Physiotherapists

Related Austin Health policies, procedures or guidelines:
- Implementing Non-Invasive Ventilation for the treatment of Chronic Hypercapnic Ventilatory Failure

Purpose:
The Victorian Respiratory Support Service (VRSS) based at Austin Health is responsible for the implementation of positive pressure ventilation and long term care of patients requiring long term ventilation (either invasive or non-invasive ventilation) for chronic hypercapnic ventilatory failure throughout the state of Victoria.

VRSS patients in the community may require ventilator setting changes:
- To improve patient comfort on ventilation
- To improve sleep quality or compliance
- To address clinical symptoms of progressive ventilatory failure or an abnormal arterial blood gas (ABG)

This guideline provides a resource to guide staff in changing ventilator settings in the community so the patient will have improved comfort, usage compliance and ventilation is optimised.

Clinical Alert:
- If the patient is acutely unwell, they should be instructed to present to the emergency department at Austin Health or nearest hospital, and VRSS Registrar should be notified.
- It is recommended that clinicians:
  - Consider changes to respiratory rate, inspiratory time or trigger sensitivity in order to improve comfort before making alterations to pressure or volume settings
  - Only change settings within 10% of prescribed settings on any single occasion

- This guideline does not replace clinical decision making

Procedure:
Prior to making ventilator setting changes, consider the following:
- The underlying disease process
- Is the patient reporting infective signs such as increased cough, increased sputum production or fevers? If so, consider referring to GP, VRSS Clinic or emergency department
- Is the patient reporting new or changed symptoms? (e.g. increased dyspnoea, sleepiness, headaches)
- Use the most recent sleep study report for recommendations
- Check mask setup and fit. Check that the circuit is assembled correctly

Disclaimer: This Document has been developed for Austin Health use and has been specifically designed for Austin Health circumstances. Printed versions can only be considered up-to-date for a period of one month from the printing date after which, the latest version should be downloaded from the hub.
### BILEVEL or PRESSURE CYCLED VENTILATION

<table>
<thead>
<tr>
<th>Patient’s reported symptoms</th>
<th>Possible changes to make (trial in consecutive order)</th>
</tr>
</thead>
</table>
| Pressure too low OR “Not enough air” | ▪ Decrease ramp time / disable ramp function  
▪ Decrease rise time (or Slope) (i.e. shorter rise time)  
▪ Increase both EPAP & IPAP (or PEEP & PS) by 1-2 cmH20  
▪ Increase Ti min (by 0.1ms) |
| Pressure too high OR “Too much air” | ▪ Increase ramp time / enable ramp function  
▪ Increase rise time or slope (i.e. longer rise time)  
▪ Reduce IPAP (or PS) by 1-2cmH20 (consider also reducing EPAP or PEEP) |
| Aerophagia | ▪ Take Mintec 30 min before bed  
▪ Increase ramp time / enable ramp function  
▪ Increase Rise time/slope (i.e. longer Rise time)  
▪ Reduce rate (by 1-2 bpm) |
| Breath rate too slow OR “Ventilator going too slow” OR “Not getting a breath” | ▪ Increase rate by 1-2 bpm  
▪ Increase trigger sensitivity (i.e. Higher trigger sensitivity) |
| Breath rate too fast OR “Ventilator going too fast” “Too many breaths” | ▪ Decrease rate by 1-2 bpm  
▪ Decrease trigger sensitivity (i.e. Lower trigger sensitivity)  
▪ Decrease cycle sensitivity (i.e. Lower cycle sensitivity) |

### VOLUME CYCLED VENTILATION

<table>
<thead>
<tr>
<th>Patient’s reported symptom</th>
<th>Possible changes to make (trial in consecutive order)</th>
</tr>
</thead>
</table>
| “Not enough air” “Need bigger breaths” | ▪ Change flow (Astral, VSiII) or slope (VS Ultra)  
▪ Change trigger to higher sensitivity  
▪ Increase TV by 50ml |
| Breath rate too slow OR “Not getting a breath” | ▪ Increase RR by 1-2 bpm  
▪ Increase trigger to higher sensitivity |
| Breath rate too fast OR “Ventilator going too fast” “Too many breaths” | ▪ Reduce RR by 1-2 bpm  
▪ Decrease trigger to lower sensitivity  
▪ Change to lower cycle/expiration sensitivity |
| Aerophagia | ▪ Take Mintec capsule 30 min before bed.  
▪ Change slope or flow  
▪ Increase Ti by 0.1-0.2 ms  
▪ Reduce rate by 1-2 bpm |
| Low pressure alarm (not related to circuit leak) | ▪ Mouthpiece or leak speech: check mouthpiece setting ON  
▪ Assess minimum PIP: Ensure LP alarm is set to 2-3 cmH2O below min PIP.  
**Alert:** If LP alarm threshold is set too low, it may not detect or delay detection of disconnection from the ventilator |
| High pressure alarm (not resolved by suction or related to aerophagia) | ▪ Assess maximum PIP: Ensure HP alarm is set to 3-5 cmH2O above max PIP.  
**Alert:** Ongoing HP alarms may indicate a new pathology (e.g. chest infection, pneumothorax) and requires clinical review |

**Disclaimer:** This Document has been developed for Austin Health use and has been specifically designed for Austin Health circumstances. Printed versions can only be considered up-to-date for a period of one month from the printing date after which, the latest version should be downloaded from the hub.
**Post - Procedure**

- Document changes on Resmed Database
- Email DL VRSS Outreach and VRSS Physiotherapists if appropriate: re patient details and changes made

- Follow up arrangements:
  - VRSS Outreach follow up within 4 weeks: for changes in breath delivery (e.g. RR, Rise time, Ti) or IPAP/EPAP of < 2 cmH2O
  - VRSS clinic review within 4 weeks: If 2 or more changes are made; changes of more than 10% are made to any parameters; or there is no improvement in symptoms or compliance

- If unsure about the appropriate course of action discuss with a senior clinician (e.g. VRSS Outreach Co-ordinator, VRSS Physiotherapist or VRSS medical staff on ward service) – for example more severe symptoms of dyspnoea or drowsiness or symptoms that fail to resolve

**Communication Strategy:**

DL Respiratory medicine  
VRSS registrar/resident handbook

**Author/Contributors:**

Current Authors: Sharon Sibenaler and Caroline Chao (May 2016) in consultation with A/Prof Mark Howard and Dr Liam Hannan

Original Author and Date: Sharon Sibenaler, Nicole Sheers, Dr Mark Howard in consultation with Anne Duncan, Gavin Fahey, Tim Walsh, Chris Smith, Dr David Berlowitz (2009)

**Authorised/Endorsed by:**

A/Prof Mark Howard

**Primary Person/Department Responsible for Document:**

Caroline Chao (VRSS Physiotherapist)
Appendix D - Questionnaire
Study Questionnaire

If you have decided that you would like to participate in this study, PLEASE SKIP QUESTION 1 and continue over the page

If you have decided NOT to participate in this study, please answer Question 1 and send all parts of the survey back to us in the enclosed envelope.

1. You have chosen NOT to participate in this voluntary study. Please select your reason for NOT participating from the list below:

   I don’t have time to complete the study
   I am physically unable to complete a written or online survey
   I am not able to read English well enough to complete the survey
   I’m concerned about confidentiality/privacy issues
   I no longer use a ventilator/BIPAP/bilevel/VPAP
   I don’t want to be a part of this research project
   Other (please explain) ________________________________

PLEASE SEND ALL PARTS OF THE SURVEY BACK TO US IN THE ENCLOSED ENVELOPE

Returning the survey to us will ensure we do not contact you again regarding this project. Thank you very much for your time and assistance with this.
Thank you for your participation. Please try to answer all questions where possible. Some questions will require you to estimate and therefore exact answers are not required.

If you would prefer to complete the questionnaire online simply type the following URL into your browser address bar: www.surveymonkey.com/hmv-study

Once you begin the online survey you will need your unique subject number that can be found on the cover letter attached to this questionnaire. Please enter this accurately as this is the only way we can accurately identify that you have completed the online version in order for us to process the payment of $15 that we will pay to all participants who complete the survey.

If you have any questions or concerns please contact the research team using the contact details on the cover letter.

2. How old are you? ___

3. Gender
   Male
   Female

4. What is the size of the town or city you live in/near?
   Village/township (population less than 250 people)
   Small town (250-5,000 people)
   Large town (5,000-30,000 people)
   Small city (30,000-100,000 people)
   Large city (greater than 100,000 people)

5. Employment status – are you currently...?
   Employed for wages
   Self-employed
   Out of work and looking for work
   Out of work but not currently looking for work
   A homemaker
   A student
   Retired
   Unable to work
   Other (please explain) ___________________________

6. Where do you live?
   A house/apartment/mobile home that I rent
   A house/apartment/mobile home that I own
   A house/apartment/mobile home that my family own or rent
   A low level care facility (ie hostel, supported accommodation)
   A high level care facility (ie nursing home, hospital)
   Other (please describe) ________________

7. Think back to when you first started using a device/machine to assist with breathing. What illness led to you needing this device?
   Emphysema/COPD or asthma
   Cystic fibrosis
   Bronchiectasis
   Muscular dystrophy
   ALS or motor neurone disease
   Spinal injury
   Sleep apnea
   Obesity
   Chest wall stiffness/post-polio or Scoliosis
   Unsure
   Other (please describe) ____________

8. How long have you been using a device/machine to assist with breathing? (ie ventilator or BIPAP or VPAP or bilevel)
   Less than 3 months
   4-12 months
   1-2 years
   3-5 years
   More than 5 years (please estimate in whole years) ___

9. Do you have a tracheostomy?
   (a surgical opening in your windpipe where a tube may sit to allow you to attach your ventilator and/or remove secretions)
   Yes
   No
   Unsure

10. What do you use to connect yourself to your device/machine? (select all the options that you have used in the past month)
    Face mask (covers both mouth and nose)
    Nose/nasal mask (covers only the nose)
    Mouthpiece
    Tracheostomy
    Diaphragm pacemaker/pacing box
    Iron lung or ventilator belt
    Unsure

11. On average, how many hours per day do you use your device/machine (ventilator/BIPAP/VPAP/bilevel)?
    24 hours
    16-23 hours
    12-15 hours
    7-11 hours
    4-6 hours
    Less than 4 hours

12. Over the last month, how many times did you go without using your device/machine for an entire 24 hour period?
    No times
    1-3 days
    4-6 days
    7-10 days
    More than 10 days (please estimate in whole days) ___
13. Think back to the VERY FIRST time you were set-up with a device/machine (ventilator/BIPAP/bilevel/VFAP). Where were you?

- At hospital
- At home
- At an outpatient/medical clinic
- Unsure/can’t remember

14. If you chose “At hospital”, what type of hospital admission was it?

- Emergency/acute admission
- Non-emergency/elective admission
- Unsure

15. Please estimate how long it took you to notice benefits from when you first started using the device/machine

- Immediate
- Within 24 hours
- Within 2 to 7 days
- After 1 week but before 4 weeks
- After 4 weeks but before 3 months
- After 3 months
- I haven’t noticed any benefit from the device
- Other (please explain) __________________________

16. Please estimate how long it took you to feel confident using your device from when you first started using the device/machine

- Immediate
- Within 24 hours
- Within 2 to 7 days
- After 1 week but before 4 weeks
- After 4 weeks but before 3 months
- After 3 months
- I haven’t noticed any benefit from the device
- Other (please explain) __________________________

17. Approximately how many times have you been admitted to hospital in the last 12 months?

0  4  More than 6 admissions
1  5  (please estimate) _____
2  6  

18. On the table below, please mark the approximate number of times you have been in contact (phone, email, letter) with your family doctor, specialist and outreach team (that help with your device/machine) in the last 12 months

<table>
<thead>
<tr>
<th></th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>More than 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family doctor/GP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory specialist/Respirologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outreach support staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>368</td>
<td></td>
</tr>
</tbody>
</table>

19. What is the highest level of school or degree that you have completed? (If currently enrolled, mark the previous grade or highest degree received)

- No schooling completed
- Junior/primary schooling completed
- High school completed (or high school equivalent)
- Associate degree/TAFE qualification/Diploma
- University degree (ie Bachelor)
- Professional degree or Masters degree (ie LLB)
- Doctorate degree – (ie PhD)

20. Please estimate your TOTAL annual HOUSEHOLD income (from all sources)

- Less than $40,000
- $40,000 - $59,999
- $60,000 - $79,999
- $80,000 - $99,999
- $100,000 - $129,999
- $130,000 - $160,000
- More than $160,000

21. How do you feel you are supported in the community by your hospital/health service/respiratory team?

- I feel very well supported
- I feel well supported
- I feel supported
- I feel poorly supported
- I feel very poorly supported
- I don’t have an opinion on this/I’d rather not say
- Other (please describe) __________________________

22. Have you ever had an overnight sleep study (in a sleep laboratory) while you were using your device?

- Yes
- Unsure
- No

23. If you answered “Yes” to Question 22, in your opinion, how would you describe the experience of the sleep study in the sleep laboratory? (please tick all that apply)

- Helpful
- Unhelpful
- Not stressful
- Stressful
- Necessary
- Unnecessary
- Convenient
- Inconvenient
- Other (please describe) __________________________
Please tick the MOST appropriate box that describes how much help you require for the daily activities listed below (please tick ONLY ONE box for each activity)

24. BATHING
You bathe yourself independently or only need help to wash a single part of your body (such as your back or other hard to reach area)

OR
You need help with bathing more than one part of your body, getting in or out of the tub/shower or you require total bathing (from your carer or another person)

25. DRESSING
You get clothes from closets/cupboards/drawers and put them on without assistance. You may need help tying your shoes.

OR
You need help with dressing or you need to be completely dressed (by your carer or another person)

26. TOILEETING
You go to the toilet, get yourself on and off, rearrange your clothes and clean yourself without any help

OR
You need help getting to and from the toilet, cleaning yourself or you use a commode or bedpan

27. TRANSFERRING or MOVING FROM BED TO CHAIR
You move in and out of a bed or chair without any help from anyone else (but you may use a stick/frame or other aid to help you)

OR
You need help moving from bed to chair or need someone to lift (including with a hoist) you to enable you to move about

28. CONTINENCE
You never have accidents with urination (urine) or defecation (faeces)

OR
You are sometimes or always incontinent of bladder or bowel

29. FEEDING
You get food from the plate to your mouth without help (someone else may do your cooking/shopping and meal preparation)

OR
You need some or complete help with feeding or you are fed with a tube via your nose or stomach

31. If you have a chest infection, which of the following techniques do you use to help you clear your secretions/mucus? (choose all that apply)

Breath stacking or inflating the chest with my machine/device
Breath stacking or inflating the chest with a bag & mask/mouthpiece
Percussion on the chest (done by another person)
Coughing with the help of another person who pushes on my abdomen or chest
Cough assist machine (also called a mechanical insufflator-exsufflator)
Suction catheter (myself or another person)
I don’t use ANY specific technique to help clear secretions
I use another method (please describe)

32. Which of the following techniques do you perform Regularly (ie most days of the week, even when you are well)? (choose all that apply)

Breath stacking or inflating the chest with my machine/device
Breath stacking or inflating the chest with a bag & mask/mouthpiece
Percussion on the chest (done by another person)
Coughing with the help of another person who pushes on my stomach or chest
Cough assist machine (also called a mechanical insufflator-exsufflator)
Suction catheter (myself or another person)
I don’t use ANY specific technique to help clear secretions
I use another method (please describe)

33. Have you ever been taught how to clear secretions from your chest using your device/machine, a bag & mask/mouthpiece, a cough assist machine or another person (pushing on your chest/stomach)?
Please select a statement that best applies to you.

No, I have not been taught how to do this but I think it would be helpful
No, I have not been taught how to do this but I don’t think it would be helpful
Yes, I have been taught how to do this and it was helpful
Yes, I have been taught how to do this but it was unhelpful
Unsure/I don’t remember
I don’t have an opinion for this question

30. Thinking about your own life and personal circumstances, how satisfied are you with your life as a whole? (mark the appropriate position on the scale opposite →)

<table>
<thead>
<tr>
<th>Completely dissatisfied</th>
<th>Completely satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
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<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

34. Thinking about your own life and personal circumstances, how do you rate your overall quality of life? (mark the appropriate position on the scale below)

| Terrible | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Excellent | 10 |

35. Some patients that use a device/machine or who have a chronic illness choose to complete an Advanced Care Plan. This is a document that patients complete with their doctor, family members and other important people. It is intended to help patients understand their illness and treatment options better. It also lets patients communicate their values, beliefs and their own goals of medical care. Some patients also nominate a substitute decision maker who can ensure they are cared for according to their wishes in situations where they cannot communicate. An Advanced Care Plan is DIFFERENT to a ‘resuscitation plan’ or an ‘advanced directive’ however it can include your own instructions/preferences regarding what care you would want in the event you needed resuscitation.

Do you currently have an Advanced Care Plan?

Yes – please skip the next question and go on to Question 37

No

Unsure

36. If you answered ‘No’ or ‘Unsure’ to Question 35, please choose the statement that best represents your views regarding advanced care plans (Please choose only one option)

I don’t want to complete an Advanced Care Plan
I would like to complete an Advanced Care Plan
I’m interested in Advanced Care Plans but I would like to learn more before deciding if they are suitable for me
I don’t want to complete an Advanced Care Plan because I’m worried I won’t get the same medical care from my doctor
I don’t want to complete an Advanced Care Plan because my family and/or doctor are already aware of my wishes
None of the above
Other (please describe) __________________________

37. Do you currently have a PRIMARY CARER or carers (for example friend, partner or a family member) who is the main person(s) that assists you at home?

Yes

No

If you answered ‘No’ to Question 37 (ie you don’t have a specific carer) – PLEASE SKIP QUESTIONS 38 AND 39 and continue to complete the rest of the survey

If you answered ‘Yes’ to Question 37 (ie you do have a specific carer) – PLEASE COMPLETE QUESTIONS 38 AND 39 before completing the rest of the survey

38. How would you rate your PRIMARY CARER’S quality-of-life? (mark the appropriate position on the scale below) – if you have more than one primary carer please provide a combined rating of their quality-of-life

| Terrible | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Excellent | 10 |

39. If your primary carer(s) developed the same medical condition that has led you to need a ventilator, would you recommend they use one?

Yes

Not sure

No

Other (please describe) __________
### Table E1 (from online supplement) - Comparison of responders and non-responders at the Australian and Canadian sites

<table>
<thead>
<tr>
<th></th>
<th>Australia Responders</th>
<th>Australia Non-responders</th>
<th>Canada Responders</th>
<th>Canada Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n= 284</td>
<td>218</td>
<td>211</td>
<td>153</td>
</tr>
<tr>
<td>Age</td>
<td>mean (SD)</td>
<td>56.3 (15.0)</td>
<td>52.4 (16.4)*</td>
<td>56.0 (16.9)</td>
</tr>
<tr>
<td>Gender</td>
<td>% male</td>
<td>55.6%</td>
<td>58.7%</td>
<td>58.3%</td>
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<tr>
<td>Diagnosis</td>
<td>ALS/MND</td>
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<td>10.1%</td>
<td>15.6%</td>
</tr>
<tr>
<td></td>
<td>NMD</td>
<td>37.0%</td>
<td>27.5%*</td>
<td>62.6%</td>
</tr>
<tr>
<td></td>
<td>RTD</td>
<td>12.0%</td>
<td>8.7%</td>
<td>10.9%</td>
</tr>
<tr>
<td></td>
<td>OHS</td>
<td>31.0%</td>
<td>39.0%</td>
<td>8.1%</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>10.9%</td>
<td>10.6%</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2.8%</td>
<td>4.1%</td>
<td>0.0%</td>
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<tr>
<td>Usage</td>
<td>nocturnal only</td>
<td>91.9%</td>
<td>89.9%</td>
<td>75.8%</td>
</tr>
<tr>
<td></td>
<td>&gt;nocturnal</td>
<td>8.1%</td>
<td>10.1%</td>
<td>23.7%</td>
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<tr>
<td>HMV type</td>
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<td>97.5%</td>
<td>95.0%</td>
<td>75.8%</td>
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<td></td>
<td>IMV</td>
<td>2.5%</td>
<td>5.0%</td>
<td>24.2%</td>
</tr>
</tbody>
</table>

*p<0.05; independent samples t-test
*P<0.05; Pearson’s χ² for proportions

Australia = Victorian Respiratory Support Service, Victoria, Australia, Canada = Provincial Respiratory Outreach Program, British Columbia, Canada, ALS/MND = Amyotrophic lateral sclerosis/Motor neuron disease, NMD = Neuromuscular disease, RTD = Restrictive thoracic disease, OHS = Obesity hypoventilation syndrome, COPD = Chronic obstructive pulmonary disease, HMV = Home mechanical ventilation, NIPPV = Non-invasive ventilation, IMV = Invasive mechanical ventilation
Table E2 (from online supplement) - Demographics and socioeconomic attributes of participants receiving assisted ventilation at the Australian and Canadian sites; values represent number (%) except where indicated

<table>
<thead>
<tr>
<th></th>
<th>Australia (n=284)</th>
<th>Canada (n=211)</th>
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<tbody>
<tr>
<td><strong>Household income</strong></td>
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<tr>
<td>&gt;160K</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>130-160K</td>
<td>4</td>
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<td>100-130K</td>
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<td>80-100K</td>
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<td>9</td>
</tr>
<tr>
<td>60-80K</td>
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<tr>
<td>40-60K</td>
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<tr>
<td>&lt;40K</td>
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<td><strong>Highest level of education completed</strong></td>
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<tr>
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<tr>
<td>Diploma</td>
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<tr>
<td>Secondary</td>
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<td>Primary</td>
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<td>No response</td>
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<td><strong>Size of location of residence</strong></td>
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<td>Small city</td>
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<td>Home-maker</td>
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<td>7</td>
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<td>Unable to work</td>
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<td>Pension</td>
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<td>113</td>
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<td>Renting</td>
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</tr>
<tr>
<td>Lives in house owned by family</td>
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<td>41</td>
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<tr>
<td>LLC/supported accommodation</td>
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<td>12</td>
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<tr>
<td>HLC facility</td>
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<tr>
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<td>1</td>
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<tr>
<td><strong>Katz ADL scale</strong></td>
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</tr>
<tr>
<td>6</td>
<td>127</td>
<td>64</td>
</tr>
<tr>
<td>3-5</td>
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</tr>
<tr>
<td>0-2</td>
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<td>98</td>
</tr>
<tr>
<td>No response</td>
<td>0</td>
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</tr>
</tbody>
</table>

_Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, Income=Annual household income_
(K= x $1000), Education=Highest level of schooling completed, Population=Estimated population where the individual resides, Employment=Current employment/occupational status, DSP=Disability support pension, Housing=Current housing situation/circumstance, LLC/supported=Low Level Care facility or supported accommodation, HLC=High Level Care facility or nursing home, ADL=Activity of Daily Living
## Table E3 (from online supplement) - Summary statistics for Severe Respiratory Insufficiency Summary Scale (SRI-SS) for participants at both sites

<table>
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<tr>
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<th>Australia</th>
<th></th>
<th>Canada</th>
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<td></td>
<td>n=</td>
<td>Median</td>
<td>IQR</td>
<td>n=</td>
</tr>
<tr>
<td>Overall</td>
<td>279</td>
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</tr>
<tr>
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<td>Male</td>
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<td>Female</td>
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<tr>
<td>Diagnosis</td>
<td></td>
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</tr>
<tr>
<td>ALS/MND</td>
<td>18</td>
<td>48.8</td>
<td>20.6</td>
<td>33</td>
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<tr>
<td>NMD</td>
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<td>58.9</td>
<td>23.3</td>
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<tr>
<td>RTD</td>
<td>34</td>
<td>60.8</td>
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<td>23</td>
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<tr>
<td>OHS</td>
<td>86</td>
<td>61.3</td>
<td>30.6</td>
<td>17</td>
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<tr>
<td>COPD</td>
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<td>56.9</td>
<td>29.9</td>
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<tr>
<td>Other</td>
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<td>57.5</td>
<td>6.5</td>
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*Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, IQR=interquartile range, ALS/MND=Amyotrophic lateral sclerosis/Motor neuron disease, NMD=Neuromuscular disease, RTD=Restrictive thoracic disease, OHS=Obesity hypoventilation syndrome, COPD=Chronic obstructive pulmonary disease, HMV=Home mechanical ventilation, NIPPV=Non-invasive positive pressure ventilation, IMV=Invasive mechanical ventilation*
Table E4 (from online supplement) – Comparison of domain scores of the Severe Respiratory Insufficiency instrument according to site

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<tr>
<th>n=</th>
<th>RC</th>
<th>PF</th>
<th>AS</th>
<th>SR</th>
<th>AX</th>
<th>WB</th>
<th>SF</th>
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<tr>
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<td>56.3</td>
<td>45.8</td>
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<td>71.0</td>
<td>60.1</td>
<td>63.2</td>
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<tr>
<td></td>
<td></td>
<td>(31.8)</td>
<td>(37.5)</td>
<td>(18.8)</td>
<td>(19.5)</td>
<td>(25.1)</td>
<td>(19.9)</td>
</tr>
<tr>
<td>Canada</td>
<td>210</td>
<td>62.5</td>
<td>41.7</td>
<td>56.8</td>
<td>70.5</td>
<td>61.6</td>
<td>64.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(28.1)</td>
<td>(33.3)</td>
<td>(18.2)</td>
<td>(18.8)</td>
<td>(23.4)</td>
<td>(19.7)</td>
</tr>
</tbody>
</table>

p=0.68  p=0.01  p=0.11  p=0.71  p=0.49  p=0.27  p=0.93

Data are median (interquartile range);
p-value from independent samples Mann Whitney U test;
Australia=Victorian Respiratory Support Service, Victoria, Australia, Canada=Provincial Respiratory Outreach Program, British Columbia, Canada, RC=Respiratory Complaints, Canada, PF=Physical Function, AS=Attendant symptoms and Sleep, SR=Social Relationships, AX=Anxiety, WB=Psychological Well-being, SF=Social Functioning
Dependent variable: AQoL-8D index score

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates/factors</th>
<th>p-value</th>
<th>Adjusted r-squared</th>
<th>EMM</th>
</tr>
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<td>1</td>
<td>age</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>gender</td>
<td>0.25</td>
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<tr>
<td></td>
<td>LFP</td>
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<td>4.3%</td>
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<tr>
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<td>labour force participation: yes</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>model 1 (+ Katz ADL scale)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>0.63</td>
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<td></td>
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<td>0.58</td>
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<td>Katz ADL scale:</td>
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<td>0-2</td>
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<td>age</td>
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<tr>
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<td>Katz ADL scale</td>
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<td>13.6%</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Katz ADL scale</td>
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<tr>
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<td>diagnosis</td>
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<tr>
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<tr>
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<tr>
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<td>age</td>
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<tr>
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<td>Katz ADL scale</td>
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<td>7</td>
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<tr>
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<tr>
<td>8</td>
<td>model 7 (+ site)</td>
<td>0.72</td>
<td>43.6%</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>Australia</td>
<td>0.65</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>model 7 (+ HH income &gt;60K)</td>
<td>0.002</td>
<td>43.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>age</td>
<td>0.002</td>
<td></td>
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<td>gender</td>
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<td>HH income &gt;60K:</td>
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<tr>
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<td>&lt;0.001</td>
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</tr>
<tr>
<td>employed</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HH income &gt;60K</td>
<td>0.01 44.8%</td>
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</table>

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<thead>
<tr>
<th>10 model 9 (+ admissions in last 12M)</th>
<th>admissions in last 12M</th>
</tr>
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<tbody>
<tr>
<td>age</td>
<td>0.003</td>
</tr>
<tr>
<td>gender</td>
<td>0.96</td>
</tr>
<tr>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>diagnosis</td>
<td>0.39</td>
</tr>
<tr>
<td>SRI-PF</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>employed</td>
<td>0.04</td>
</tr>
<tr>
<td>HH income &gt;60K</td>
<td>0.005 6 or more 0.64</td>
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</table>

<table>
<thead>
<tr>
<th>11 model 9 (- gender)</th>
<th>diagnosis:</th>
</tr>
</thead>
<tbody>
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<td>0.002</td>
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<tr>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>diagnosis</td>
<td>0.40</td>
</tr>
<tr>
<td>SRI-PF</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>employed</td>
<td>0.03</td>
</tr>
<tr>
<td>HH income &gt;60K</td>
<td>0.009 44.9%</td>
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</table>

<table>
<thead>
<tr>
<th>12 model 11 (- diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
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<tr>
<td>SRI-PF</td>
</tr>
<tr>
<td>employed</td>
</tr>
<tr>
<td>HH income &gt;60K</td>
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</tbody>
</table>

Figure E1 (from online supplement) - Multivariable regression – model construction for AQoL-8D index score

EMM=Estimated marginal means, LFP=Labour force participation (Employed/Self-employed/Unemployed), ADL=Activities of daily living, ALS/MND=Amyotrophic lateral sclerosis/Motor neuron disease, NMD=Neuromuscular disorders RTD= Restrictive thoracic disorders, OHS=Obesity hypoventilation syndrome, COPD=Chronic obstructive pulmonary disease, SRI-PF=Severe Respiratory Insufficiency-Physical Function scale, HH income=Household income, Employed=Employed/Self-employed (for wages)
### Table 1: Regression Analysis for LFP and Katz ADL Scale

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates/factors</th>
<th>p-value</th>
<th>Adjusted r-squared</th>
<th>EMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>age</td>
<td>0.95</td>
<td>4.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LFP</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>model 1 (+ Katz ADL scale)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>age</td>
<td>0.57</td>
<td></td>
<td>69.2</td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>0.56</td>
<td></td>
<td>58.7</td>
</tr>
<tr>
<td></td>
<td>LFP</td>
<td>&lt;0.001</td>
<td></td>
<td>60.0</td>
</tr>
<tr>
<td></td>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>model 2 (+ diagnosis)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age</td>
<td>0.97</td>
<td></td>
<td>ALS/MND 56.7</td>
</tr>
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<td>gender</td>
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<td></td>
<td>NMD 63.0</td>
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<tr>
<td></td>
<td>LFP</td>
<td>&lt;0.001</td>
<td></td>
<td>RTD 64.6</td>
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<tr>
<td></td>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
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<td>OHS 63.2</td>
</tr>
<tr>
<td></td>
<td>diagnosis</td>
<td>0.12</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Other 66.6</td>
</tr>
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<td>4</td>
<td>model 3 (– age, gender)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LFP</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
<td>13.6%</td>
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<td></td>
<td>diagnosis</td>
<td>0.10</td>
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</tr>
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<td>5</td>
<td>model 3 (+ SRI-PF)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Katz ADL scale</td>
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<tr>
<td></td>
<td>diagnosis</td>
<td>0.23</td>
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<td>61.6%</td>
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</tr>
<tr>
<td>6</td>
<td>model 5 (- LFP)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diagnosis</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SRI-PF</td>
<td>&lt;0.001</td>
<td>61.5%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>model 6 (+ employed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age</td>
<td>0.04</td>
<td></td>
<td>yes 63.8</td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>0.92</td>
<td></td>
<td>no 60.0</td>
</tr>
<tr>
<td></td>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diagnosis</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SRI-PF</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>employed</td>
<td>0.01</td>
<td>61.9%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>model 7 (+ site)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>site</td>
<td>0.88</td>
<td>61.8%</td>
<td>BC 62.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VIC 61.8</td>
</tr>
<tr>
<td>9</td>
<td>model 7 (+ HH income &gt;60K)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age</td>
<td>0.03</td>
<td></td>
<td>yes 63.9</td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>0.49</td>
<td></td>
<td>no 61.1</td>
</tr>
<tr>
<td></td>
<td>Katz ADL scale</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnosis</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRI-PF</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>employed</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HH income &gt;60K</td>
<td>0.02 62.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10 model 9 (+ admissions in last 12M) admissions in last 12M:
- age 0.02 0 64.0
- gender 0.63 1 61.9
- Katz ADL scale <0.001 2 59.9
- diagnosis 0.63 3 73.8
- SRI-PF <0.001 4 61.6
- employed 0.049 5 60.3
- HH income >60K 0.02 6 or more 63.1
- admission in last 12M 0.06 63.0%

11 model 9 (- gender) diagnosis:
- age 0.03 ALS 63.2
- Katz ADL scale <0.001 NMD 62.6
- diagnosis 0.605 RTD 62.2
- SRI-PF <0.001 OHS 60.7
- employed 0.04 COPD 60.8
- HH income >60K 0.02 62.1% Other 65.5

12 model 11 (- diagnosis)
- age 0.03
- Katz ADL scale <0.001
- SRI-PF <0.001
- employed 0.049
- HH income >60K 0.01 62.3%

Figure E2 (from online supplement) - Multivariable regression – model construction for SRI-Summary Scale

EMM=Estimated marginal means, LFP=Labour force participation (Employed/Self-employed/Unemployed), ADL=Activities of daily living, ALS/MND=Amyotrophic lateral sclerosis/Motor neuron disease, NMD=Neuromuscular disorders RTD=Restrictive thoracic disorders, OHS=Obesity hypoventilation syndrome, COPD=Chronic obstructive pulmonary disease, SRI-PF=Severe Respiratory Insufficiency-Physical Function scale, HH income=Household income, Employed=Employed/Self-employed (for wages)
Appendix F - Supplementary Files (Hannan et al., 2014)

Supplementary File 1 - Search Strategy

Medline (1946 – Nov 2012), EMBASE, EBM reviews
1. Respiratory Insufficiency/ or Respiration, Artificial/ or Intermittent Positive-Pressure
   Ventilation/ or Positive-Pressure Respiration/
2. Ventilators, Mechanical/
3. 1 or 2 (73931 records)
4. (noninvasive or non-invasive or non invasive or niv or bipap or bilevel or nippv or hmv or vai
   or domiciliary).mp. [mp=title, abstract, original title, name of substance word, subject heading
   word, protocol supplementary concept, rare disease supplementary concept, unique
   identifier]
5. 3 and 4 (4035 records)
6. spinal curvatures/ or kyphosis/ or scoliosis/
7. kyphosis.mp.
8. kyphoses.mp.
9. (idiopathic adj3 kypho*).mp. [mp=title, abstract, original title, name of substance word,
   subject heading word, protocol supplementary concept, rare disease supplementary concept,
   unique identifier]
10. thorax/ or thoracic wall/
11. kyphoscoliosis.mp.
14. or/6-13 (36917 records)
15. poliomyelitis/ or poliomyelitis, bulbar/ or postpoliomyelitis syndrome/
16. (polio$ adj3 syndrome).mp. [mp=title, abstract, original title, name of substance word,
   subject heading word, protocol supplementary concept, rare disease supplementary concept,
   unique identifier]
17. (pps or post polio syndrome or polio syndrome or post poliomyelitis syndrome or
   poliomyelitis or postpolio syndrome).mp. [mp=title, abstract, original title, name of substance
   word, subject heading word, protocol supplementary concept, rare disease supplementary
   concept, unique identifier]
18. or/15-17 (22635 records)
19. muscular dystrophies/ or muscular dystrophy, duchenne/
20. duchenne.mp.
21. dystrophin.mp.
22. muscular dystr$.mp.
23. or/19-22 (24706 records)
24. Obesity hypoventilation syndrome/
25. (obesity hypoventilation or ohs or Pickwick$ syndrome).mp.
26. Hypoventilation/
27. (obesity adj3 hypoventilation).mp. [mp=title, abstract, original title, name of substance
   word, subject heading word, protocol supplementary concept, rare disease supplementary
   concept, unique identifier]
28. or/24-27 (2994 records)
29. amyotrophic lateral sclerosis/
30. (amyotrophic lateral sclerosis or lou gehrig$ or als or motor neuron$ or mnd).mp.
31. or/29-30 (83961 records)
32. 14 or 18 or 23 or 28 or 31 (169033 records)
CINAHL
Obesity hypoventilation
MH “Pickwickian Syndrome” OR obesity hypoventilation OR hypoventilation
(414 records)
Amyotrophic lateral sclerosis
MH “Amyotrophic Lateral Sclerosis” OR “amyotrophic lateral sclerosis” OR motor neuron*
disease
(1827 records)
Duchenne muscular dystrophy
MH “Duchenne Muscular Dystrophy” OR MH “Muscular Dystrophy” OR dystrophin OR muscular dystr*
(1314 records)
Kyphoscoliosis
MH “Kyphosis” OR “kyphosis” OR MH “Spinal Curvatures” OR MH “Scoliosis, Idiopathic, Adolescent” OR MH “Scoliosis” OR Poliomyelitis OR post polio syndrome
(4523 records)
NIV
MH “Positive Pressure Ventilation” OR MH “Positive-Pressure Respiration, Intrinsic” OR MH “Intermittent Positive Pressure Breathing” OR MH “Pressure Support Ventilation” OR MH “Intermittent Positive Pressure Ventilation” OR non-invasive ventilation OR nippv OR niv OR bilevel OR bipap OR vai OR hmv
(1919 records)
Combined search (NIV + diagnostic groups) (159 records)

Centre for Reviews and Dissemination
“positive pressure respiration”
03/12/2012 = 75 results

Grey literature
Manual searching of Proceedings First – “non-invasive” or “ventilation” – 0 results
Manual searching of Papers First – “non-invasive” or “ventilation” – 7 results
ProQuest Dissertations and Theses (PQDT) – manual scanning of results using search terms (“obesity” OR “duchenne muscular dystrophy” OR “amyotrophic lateral sclerosis” OR “kyphoscoliosis”) AND (“noninvasive ventilation” OR “non-invasive ventilation” OR “non invasive ventilation”) – 22 results (none relevant)
Supplementary File 2 - Generation of composite effect sizes

Introduction
Due to the large number of patient-reported outcomes (PROs) in the identified studies (Figure 1), we determined that the use of composite effect sizes would improve the ability to perform a qualitative synthesis. A meta-analysis with pooled effects sizes (across studies) was not performed due to the heterogeneous populations and interventions in the review, and the significant number of non-randomised studies.

Figure 1 - Description of Patient-Reported Outcomes (PROs) reported in included studies

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>8-item questionnaire that measures the propensity of subjects to fall asleep. Subjects are asked to rate their usual chances of dozing (falling asleep) in 8 different situations according to a 4-point scale (0-3) with higher values indicating an increased propensity to fall asleep.(1)</td>
</tr>
<tr>
<td>Stanford Sleepiness Scale</td>
<td>Single item assessment that evaluates the ‘degree of sleepiness’ at a given point in time. The instrument determines sleepiness at the time the instrument is used according to a 7-point scale, with higher values indicating increasing sleepiness (or reduced alertness).(2)</td>
</tr>
<tr>
<td>Von Zerssen Mood Scale</td>
<td>28-item instrument developed to evaluate ‘well-being’ and frequently used to provide serial evaluations of mood. Higher scores indicate increased discontent and dysphoria.(3,4)</td>
</tr>
<tr>
<td>Beck’s Depression Inventory</td>
<td>21-item self-report instrument used to measure the severity of depression with items rated on a 4-point scale according to intensity (from 0-3).(5) Higher scores indicate increasing severity of depression.(5)</td>
</tr>
<tr>
<td>Fatigue scale</td>
<td>13-item questionnaire evaluating different aspects of fatigue. Respondents score each item (representing a symptom of fatigue) from 0-2 which represent ‘same as usual’,</td>
</tr>
</tbody>
</table>
‘worse’ and ‘much worse than usual’ respectively. Higher scores indicate worsening fatigue and results can be divided into ‘mental’ and ‘physical’ fatigue domains.

(modified) Borg Dyspnea Scale

Single item linear scale of dyspnea originally based on perceived exertion and used most frequently during exercise testing. Original scale modified to a 10-point scale and asks the subject to rate the current level of dyspnea with higher scores indicating increased perceived dyspnea.

Medical Research Council Dyspnea Score

Single item 5-point scale (1-5) that quantifies the disability associated with breathlessness by identifying that breathlessness occurs when it should not. Higher scores indicate increased disability due to breathlessness.

Fatigue Severity Score

9-item questionnaire using a 7-point Likert scale to evaluate the affect of fatigue on motivation, exercise, physical functioning, carrying out duties, interfering with work, family or social life with higher values indicating a larger impact of fatigue.

Sadoul Dyspnea Scale

Single item linear 5-point scale (1-5) evaluating dyspnea with higher scores indicating worsening severity of dyspnea.

Visual Analogue Scale (VAS) – Fatigue, Sleep quality, Sleep comfort, Morning headache, Diurnal drowsiness, Dyspnea, Physical activity

Single item linear scale (typically 100mm and scored 0-10 or 1-100) that may be oriented horizontally or vertically. The ends of the scale are defined as the extreme limits of the parameter to be measured however the orientation of the scale can be variably applied (for example a higher value may imply either an improvement or a deterioration in the measured variable and this is defined by the investigator). VAS are more sensitive to small changes than are simple descriptive ordinal scales (which use ratings such as mild, moderate, severe etc) and may be as valid, reliable and responsive as multi-item scales.

Hospital Anxiety and Depression Scale

14-item instrument (7-items related to anxiety, 7-items related to depression) using a 4 point Likert scale (0-3) yielding a score out of 21 that aims to detect emotional
disorder in subjects and also produces a valid measure of severity. Higher scores indicate a higher likelihood and/or greater severity of the emotional disorder.

**Pittsburgh Sleep Quality Index**

19-item instrument that are scored using a 4-point Likert scale (0-3) and measures sleep disturbance and usual sleep habits during the prior month only. 7 domains (subscales) of sleep difficulties can be derived; sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. Higher scores indicate worsening sleep quality.

**Medical Outcomes Study Short Form Health Survey (SF-36)**

36-item instrument that uses varying scaling methods and measures (generic) health-related quality of life. The instrument produces 8 domains (subscales) including; 1) vitality, energy or fatigue; 2) role limitations due to physical health problems; 3) role limitations due to emotional health problems; 4) physical functioning; 5) general health perceptions; 6) bodily pain; 7) general mental health; 8) social functioning. Two component (summary) scores (physical and mental) can also be generated. The standard instrument asks subjects to answer questions as they pertain to the way he or she felt or acted during the past 4 weeks however a shorter version exists which asks for a 1 week recall period. Responses are converted to a scale from 0-100 for each subscale and for both component scores, with higher values indicating better quality of life.

**McGill Quality of Life Questionnaire**

17-item instrument that measures generic health-related quality but has been most extensively evaluated in the palliative care setting. The instrument produces 5 domain scores; physical well-being, physical symptoms, psychological, existential and support, and an overall score can be generated by calculating the mean of the 5 subscales. Higher scores are associated with improved health-related quality of life.

**Severe Respiratory Insufficiency Questionnaire**

49-item, disease specific health-related quality of life instrument that was specifically designed for use by individuals with respiratory failure receiving mechanical ventilation. The instrument uses a 5-point Likert scale and produces 7 subscales (domains) and a summary scale, all of which are scored from 0-100, with higher scores indicating better health-related quality of life. The domains include; respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being and social functioning. The instrument was initially
developed in German but has been translated to other languages including Spanish and English. (19–21)

**Calgary Sleep Apnea Quality of Life Index**

The original version of this instrument is a 35-item questionnaire which measures 4 domains (daily functioning, social interactions, emotional functioning and symptoms) as well as 5th domain (with 5 additional items) to capture adverse consequences of therapy (treatment related symptoms). (22) A shorter (18-item) version has also been developed with similar evaluative properties. (23) Items are scored on a 7-point Likert scale (1 to 7) with lower scores indicating greater impairment. Domain scores are calculated by dividing the total score by the number of questions answered for that domain, providing a range of 1-7 for each domain. The overall score is the overall mean of the 4 domains (minus the 5th domain if treatment has commenced), with higher scores indicating better health-related quality of life.

**Chronic Respiratory Disease Questionnaire**

20-item interviewer-administered disease specific instrument that aims to measure both physical and emotional aspects of chronic respiratory disease. The instrument measures 4 domains (subscales); dyspnoea, fatigue, emotion and mastery. (24,25) Each item is scored according to a 7-point Likert scale and produces a total score and subscores for the 4 domains, with higher scores indicating better health-related quality of life. (24,25)

**Methods**

We undertook a method of producing composite effect sizes as described in the Cochrane Handbook of Systematic Reviews and reported in the study by Busse et al. (26,27)

Two reviewers (LMH and YWC) independently grouped PROs in to 6 discreet categories; dyspnoea, sleep quality, somnolence and fatigue, mental and emotional health, social functioning, and physical function and health (Table 1). Reviewers examined all included PROs (Figure 1) and assessed instruments/subscales for their face validity according to our combined categories. Where correlations between instruments had previously been reported, these were used to guide decisions related to groupings. (19,20,28–35) The review group met to discuss the combined categories and discrepancies were resolved by consensus.
<table>
<thead>
<tr>
<th>Combined category</th>
<th>PRO instrument or subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>SRI – Respiratory complaints</td>
</tr>
<tr>
<td></td>
<td>VAS – Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Sadoul – Dyspnea</td>
</tr>
<tr>
<td></td>
<td>MRC Dyspnea Scale</td>
</tr>
<tr>
<td></td>
<td>Borg Dyspnea Scale</td>
</tr>
<tr>
<td></td>
<td>CRDQ – Dyspnea</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>PSQI</td>
</tr>
<tr>
<td></td>
<td>VAS – Sleep quality</td>
</tr>
<tr>
<td></td>
<td>VAS – Sleep comfort</td>
</tr>
<tr>
<td></td>
<td>SRI – Attendant symptoms and sleep</td>
</tr>
<tr>
<td>Somnolence and fatigue</td>
<td>VAS – Diurnal drowsiness</td>
</tr>
<tr>
<td></td>
<td>VAS – Fatigue</td>
</tr>
<tr>
<td></td>
<td>FSS</td>
</tr>
<tr>
<td></td>
<td>CRDQ - Fatigue</td>
</tr>
<tr>
<td></td>
<td>SF-36 – Vitality</td>
</tr>
<tr>
<td></td>
<td>ESS</td>
</tr>
<tr>
<td>Physical function and health</td>
<td>SRI – Physical functioning</td>
</tr>
<tr>
<td></td>
<td>SF-36 – Physical functioning</td>
</tr>
<tr>
<td></td>
<td>SF-36 – Role physical</td>
</tr>
<tr>
<td></td>
<td>SF-36 – General health</td>
</tr>
<tr>
<td></td>
<td>VAS – Physical activity</td>
</tr>
<tr>
<td>Mental and emotional health</td>
<td>SRI – Psychological well being</td>
</tr>
<tr>
<td></td>
<td>SRI – Anxiety</td>
</tr>
<tr>
<td></td>
<td>HADS – Depression</td>
</tr>
<tr>
<td></td>
<td>HADS – Anxiety</td>
</tr>
<tr>
<td></td>
<td>HADS – Combined</td>
</tr>
<tr>
<td></td>
<td>CRDQ – Emotional</td>
</tr>
<tr>
<td></td>
<td>SF-36 – Mental health</td>
</tr>
<tr>
<td></td>
<td>SF-36 – Role emotional</td>
</tr>
<tr>
<td></td>
<td>CRDQ – Mastery</td>
</tr>
<tr>
<td>Social function</td>
<td>SRI – Social functioning</td>
</tr>
<tr>
<td></td>
<td>SRI – Social relationships</td>
</tr>
<tr>
<td></td>
<td>SF-36 – Social functioning</td>
</tr>
</tbody>
</table>

SRI – Severe Respiratory Insufficiency Questionnaire, SF-36 – Medical Outcomes Study Short Form Health Survey, SAQLI – Calgary Sleep Apnea Quality of Life Index, PSQI – Pittsburgh Sleep Quality Index, ESS – Epworth Sleepiness Scale, FSS – Fatigue Severity Scale, CRDQ – Chronic Respiratory Disease Questionnaire, HADS – Hospital Anxiety Depression Score, MRC – Medical Research Council, McGill – McGill Quality of Life Questionnaire, VAS – Visual Analogue Scale
Not all instruments or domains were assigned to our categories, either because no suitable category existed or due to studies failing to report repeated measures data (mean, SD for baseline and post-treatment) for the instruments in question. Unassigned instruments and domains are detailed in Table 2.

**Table 2 – Unassigned PRO instruments and domains**

| SAQLI – Overall
| McGill – Overall
| SRI – Summary scale
| SF-36 – Bodily pain
| VAS – Morning headache
| Fatigue scale*
| Beck’s depression inventory*
| von Zersen mood scale* |

*Studies using these tools did not present repeated measures data (mean, SD) and therefore these instruments were not assigned
SRI – Severe Respiratory Insufficiency Questionnaire, SF-36 – Medical Outcomes Study Short Form Health Survey, SAQLI – Calgary Sleep Apnea Quality of Life Index, McGill – McGill Quality of Life Questionnaire, VAS – Visual Analogue Scale

**Composite effect size**

Effect size for a given instrument (i) was determined

\[
ES_i = \frac{(mean_{post} - mean_{pre})}{SD_{change}}
\]

Composite effect size (CES) for instruments (ES₁ and ES₂) is

\[
CES = \frac{ES_1 + ES_2}{2}
\]

The 95% confidence interval of the CES is
\((SD_{CES})^2 = \text{variance of the composite effect size}\)
\(r_{1,2} = \text{correlation between instrument 1 and instrument 2}\)
\(n = \text{number of participants}\)

\[
(SD_{CES})^2 = \frac{(2 + 2r_{1,2})}{4n}
\]

\(\text{CES +/- 1.96} \times SD_{CES}\)

We elected to use a conservative estimate of correlations between instruments \((r=0.5)\) as there were limited reports comparing instruments in similar groups of individuals to our diagnostic groups that had reported \(r\) values.(19,20)

Calculations and forest plots were formulated using GraphPad Prism version 6.0 (San Diego, CA).

**Limitations**

We are aware that our method is limited by a lack of reported correlations between instruments that allow confirmation that instruments included in our combined categories are actually measuring similar constructs. To address this, two reviewers independently assessed face validity and reported correlations in order to guide our decisions, and we used conservative estimates of correlations in our calculations in order to address the uncertainty inherent in our assumptions.

**References**


Supplementary File 3 – Excluded studies

Reason for exclusion: Review article, editorial, case report (n = 21)


Reason for exclusion: Retrospective design (n = 19)


**Reason for exclusion: Outcomes not measured or reported (n = 47)**


Reason for exclusion: Non-English language (n = 32)


Reason for exclusion: No abstract or fulltext available (n = 6)


2. Leger P. Noninvasive Positive-Pressure Ventilation at Home. RESPIRATORY CARE Number: VOL 39; NUMBER 5 ISSN: 0730-8418.

3. Soudon P. Tracheal versus noninvasive mechanical ventilation in neuromuscular patients: experience and evaluation. MONALDI ARCHIVES FOR CHEST DISEASE Number: VOL 50; NUMBER 3 ISSN: 0022-0643.
4. Quality of Life Evaluation of Patients With Noninvasive and Invasive Home Mechanical Ventilation. CHEST -CHICAGO- Number: 2000; VOL 118; NO 4; SUPPL ISSN: 0012-3692.

5. Effect of Noninvasive Positive Pressure Ventilation (NPPV) on Quality of Life. CHEST -CHICAGO- Number: 2000; VOL 118; NO 4; SUPPL ISSN: 0012-3692.


Reason for exclusion: Letter to the editor (n = 2)


Reason for exclusion: Irrelevant population or intervention (n = 15)


Reason for exclusion: Cross-sectional design or inadequate design (n = 15)


Reason for exclusion: Data included elsewhere (n = 3)


Appendix G - PSG titration advice/guidelines

Oxygen should not be added during this study as SpO$_2$ and PtcCO$_2$ are parameters that will be measured. However, following the overnight titration, supplemental oxygen may be added for home use if SpO$_2$ remains <88% for a third of the night or in the presence of hypoxia related sequelae.

Bilevel-S/T Titration

- Commence the subject on EPAP and IPAP 2cmH$_2$O lower than that determined during the daytime trial. Leave the device in S/T mode and the rate and other settings as determined during the daytime trial
- Carefully observe the interaction of the following respiratory channels when titrating
  - Chest wall and abdominal bands
  - Airflow signal
  - Mask/machine pressure
  - Leak
- Increase EPAP in 1cmH$_2$O increments in the presence of frank obstructive events. A trial of increased EPAP should also be undertaken if inspiratory efforts do not consistently trigger to IPAP in the absence of a significant leak
- Maintain an IPAP-EPAP difference as set during the day
- Hypoventilation should be looked for and primarily addressed through an increase in IPAP (and hence pressure support). Hypoventilation is a rise of 10mmHg in PtcCO$_2$ above awake, supine resting baseline.*
- Before altering settings (especially EPAP for ineffective efforts or IPAP due to hypoapnoeas/low baseline SpO$_2$), check for leak and correct first. If no leak is apparent then the following strategies could be considered.
- Increase IPAP to eliminate hypoventilation. An increase in IPAP can also be trialled to minimize non-obstructive hypopnoeas, flow limitation or improve SpO$_2$. 

*Hypoventilation is a rise of 10mmHg in PtcCO$_2$ above awake, supine resting baseline.
• If signs of partial obstruction persist (e.g., flattened airflow contour signal), trial an increase in EPAP while maintaining pressure support level.

• The respiratory rate and timing settings should remain set as during the day. The exception to this is where significant device-patient dysynchrony is observed. Should this be apparent, all attention should be given to eliminating leak first and then all possible pressure changes should be made. If dysynchrony persists after all these changes, an increase or decrease in respiratory rate of up to 4 above or below the daytime rate can be trialled.

*If PtcCO$_2$ is suspected during the study, re-apply electrode / check zero reading in room air / re-calibrate electrode, as required. Otherwise assume reading to be correct and titrate accordingly. (After the study, a drift and offset correction can then be applied using ABG results).
Appendix H - Intra-rater reliability for patient-ventilator asynchrony events

In order to determine the reliability of PVA event scoring, intra-rater reliability was evaluated. Ten PSGs were randomly selected and scored twice by the same scorer (LMH). The two scoring procedures were performed not less than two weeks apart for each study. The summary values from the ten PSGs are detailed below (Table H1). Intra-rater reliability was determined using a two-way mixed intraclass correlation coefficient (Table H2). Based on these results, the reliability of the scoring rules and the ability of them to be applied consistently by a single expert scorer was determined to be adequate. Given the labour-intensive nature of the scoring process, it was determined that the PVA index used would be unlikely to be useful in clinical practice and therefore an evaluation of the inter-rater reliability of the scoring rules was not performed.

Table H1 – Patient-ventilator asynchrony events (per hour total sleep time) from ten overnight polysomnographic recordings from users of nocturnal NIPPV; results reflect repeat scoring performed by a single scorer on two occasions at least two weeks apart

<table>
<thead>
<tr>
<th></th>
<th>Ineffective efforts/TST</th>
<th>Double triggers/TST</th>
<th>Multiple triggers/TST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score 1</td>
<td>Score 2</td>
<td>Score 1</td>
</tr>
<tr>
<td>PSG1</td>
<td>4.7</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td>PSG2</td>
<td>35.9</td>
<td>36.1</td>
<td>1.0</td>
</tr>
<tr>
<td>PSG3</td>
<td>24.5</td>
<td>25.0</td>
<td>10.1</td>
</tr>
<tr>
<td>PSG4</td>
<td>2.3</td>
<td>1.8</td>
<td>10.8</td>
</tr>
<tr>
<td>PSG5</td>
<td>9.1</td>
<td>9.3</td>
<td>2.6</td>
</tr>
<tr>
<td>PSG6</td>
<td>9.8</td>
<td>15.3</td>
<td>1.1</td>
</tr>
<tr>
<td>PSG7</td>
<td>9.5</td>
<td>12.9</td>
<td>21.0</td>
</tr>
<tr>
<td>PSG8</td>
<td>43.4</td>
<td>38.3</td>
<td>8.0</td>
</tr>
<tr>
<td>PSG9</td>
<td>33.5</td>
<td>28.3</td>
<td>19.6</td>
</tr>
<tr>
<td>PSG10</td>
<td>33.2</td>
<td>24.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>
Table H2 – Intraclass correlation coefficient for patient-ventilator asynchrony events identified on polysomnography; results obtained from repeat scoring of ten overnight recordings with scoring on two occasions by a single scorer at least two weeks apart

<table>
<thead>
<tr>
<th>PVA type</th>
<th>ICC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineffective efforts/TST</td>
<td>0.955</td>
</tr>
<tr>
<td>Double triggers/TST</td>
<td>0.999</td>
</tr>
<tr>
<td>Multiple triggers/TST</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Single-measures Intraclass correlation coefficient (two-way mixed) for absolute agreement
Appendix I - Subgroup analyses

Motor neuron disease

Table I – Baseline characteristics for the subgroup with motor neuron disease according to group allocation; values represent mean (SD) unless otherwise stated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=18)</th>
<th>PSG titration (n=22)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 (8)</td>
<td>64 (10)</td>
<td>0.115</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>13:5</td>
<td>16:6</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 (5)</td>
<td>26.2 (5)</td>
<td>0.380</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>58.8 (14)</td>
<td>56.6 (14)</td>
<td>0.635</td>
</tr>
<tr>
<td>MIPa</td>
<td>28 (11)</td>
<td>29 (9)</td>
<td>0.701</td>
</tr>
<tr>
<td>SNIPb</td>
<td>35 (12)</td>
<td>32 (11)</td>
<td>0.369</td>
</tr>
<tr>
<td>Daytime PaCO₂ (baseline)</td>
<td>42.7 (7)</td>
<td>44.0 (8)</td>
<td>0.591</td>
</tr>
<tr>
<td>Orthopnoea scorec</td>
<td>2.7 (1)</td>
<td>2.8 (1)</td>
<td>0.862</td>
</tr>
<tr>
<td>Severe bulbar dysfunctiond</td>
<td>28%</td>
<td>41%</td>
<td>0.594*</td>
</tr>
<tr>
<td>PSQI (baseline)</td>
<td>9.2 (5)</td>
<td>7.7 (4)</td>
<td>0.301</td>
</tr>
<tr>
<td>ESS (baseline)</td>
<td>10.2 (5)</td>
<td>7.3 (4)</td>
<td>0.035</td>
</tr>
<tr>
<td>KSS (baseline)e</td>
<td>4.3 (2)</td>
<td>4.3 (2)</td>
<td>0.994</td>
</tr>
<tr>
<td>FSS (baseline)</td>
<td>47.3 (13)</td>
<td>43.9 (11)</td>
<td>0.384</td>
</tr>
<tr>
<td>MBDS (baseline)</td>
<td>1.8 (2)</td>
<td>1.8 (1)</td>
<td>0.935</td>
</tr>
<tr>
<td>SRI-SS (baseline)</td>
<td>53.1 (12)</td>
<td>59.7 (12)</td>
<td>0.088</td>
</tr>
<tr>
<td>AQtQoL-8D index (baseline)</td>
<td>0.52 (0.2)</td>
<td>0.61 (0.2)</td>
<td>0.119</td>
</tr>
</tbody>
</table>

* p-value from independent samples t-test
# p-value from Pearson’s χ² for proportions
a missing data for (n=2) in both Control and PSG titration groups
b missing data for (n=1) in PSG titration group and (n=2) in Control group
c From the orthopnoea item in the ALSFRS-R
d Defined as bulbar subscale score ≤6 from ALSFRS-R
e Responses to the KSS were not adequately matched for time-of-day for the majority of participants

MIP=maximal inspiratory pressure, SNIP=sniff nasal inspiratory pressure, PSQI=Pittsburgh Sleep Quality Index, ESS=Epworth Sleepiness Scale, KSS=Karolinska Sleepiness Scale, FSS=Fatigue Severity Scale, MBDS=Modified Borg Dyspnea Scale, SRI-SS=Severe Respiratory Insufficiency Questionnaire Summary Scale, AQtQoL-8D=Assessment of Quality of Life-8 Dimension index score
**Table I2** – Patient-ventilator asynchrony events (by type) per hour of total sleep time for individuals with motor neuron disease; PSG titration compared with Control; data are presented as median (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PSG titration</th>
<th>p-value #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=14)</td>
<td>(n=17)</td>
<td></td>
</tr>
<tr>
<td>PVA index (total events per hour TST)</td>
<td>30.8 (15-112)</td>
<td>22.5 (10-47)</td>
<td>0.399</td>
</tr>
<tr>
<td>Ineffective efforts (per hour TST)</td>
<td>16.9 (6-29)</td>
<td>10.1 (4-30)</td>
<td>0.336</td>
</tr>
<tr>
<td>Double trigger (per hour TST)</td>
<td>4.9 (3-44)</td>
<td>4.6 (2-8)</td>
<td>0.518</td>
</tr>
<tr>
<td>Multiple trigger (per hour TST)</td>
<td>0.5 (0-8)</td>
<td>0.4 (0-1)</td>
<td>0.518</td>
</tr>
</tbody>
</table>

\# p-value from independent samples Mann Whitney U test
PVA=patient-ventilator asynchrony, TST=total sleep time

**Figure I1** – Patient-ventilator asynchrony events per hour of total sleep time during PSG at study conclusion for individuals with motor neuron disease; PSG titration compared with Control; markers (hollow circles) indicate individual data points; horizontal lines indicate the median value for the group
Figure 12 – Electroencephalographic arousals per hour of total sleep time during PSG at study conclusion for individuals with motor neuron disease; PSG titration compared with Control; markers (hollow circles) indicate individual data points; horizontal lines indicate the median value for the group.
Table I3 – Objective measures of sleep obtained during PSG at study conclusion for individuals with motor neuron disease; PSG titration compared with Control; values indicate median (interquartile range) unless stated

| Measure                                      | Control (n=14)   | PSG titration (n=17) | p-value#
|----------------------------------------------|------------------|----------------------|---------
| Arousal index (arousals per hour TST)        | 13.7 (9-18)      | 10.9 (9-19)          | 0.739   |
| Total sleep time (TST) (minutes)             | 273 (204-310)    | 274 (231-329)        | 0.653   |
| Sleep efficiency (%)                         | 63 (45-72)       | 62 (54-72)           | 0.984   |
| Sleep latency (minutes)                      | 23 (12-65)       | 22 (15-47)           | 0.891   |
| Wake after sleep onset (minutes)             | 127 (78-153)     | 160 (108-172)        | 0.077   |
| Awakenings (number)                          | 30 (23-39)       | 29 (23-33)           | 0.799   |
| Stage transitions (number)                   | 174 (110-212)    | 183 (136-212)        | 0.653   |
| Rapid eye movement (REM) sleep (%)           | 16 (11-21)       | 16 (8-20)            | 0.444   |
| Slow wave sleep (NREM3) (%)                  | 38 (23-58)       | 28 (22-38)           | 0.356   |
| NREM1 and NREM2 (%)                          | 39 (27-62)       | 54 (47-62)           | 0.215   |

# p-value from independent samples Mann Whitney U test
REM=Rapid eye movement sleep, NREM=Non-rapid eye movement sleep, TST=total sleep time

Table I4 – Measures of nocturnal gas exchange during PSG at study conclusion for individuals with motor neuron disease; PSG titration compared with Control; values indicate median (interquartile range) unless stated

| Measure                              | Control (n=14) | PSG titration (n=17) | p-value#
|--------------------------------------|----------------|----------------------|---------
| Time spent with SpO₂ <90% (TST)      | 0.1 (0.0 to 0.8) | 0.0 (0.0 to 2.6)    | 0.071   |
| SpO₂ nadir (TST)                     | 89 (86 to 90)   | 91 (86 to 92)        | 0.048   |
| ODI 3% (RT)                          | 3.0 (2 to 4)    | 2.0 (1 to 4)         | 0.246   |
| ODI 4% (RT)                          | 1.2 (0 to 2)    | 0.5 (0 to 1)         | 0.421   |
| Average PtcCO₂                        | 46 (43 to 50)   | 42 (40 to 47)        | 0.059   |
| Peak PtcCO₂                          | 49 (47 to 54)   | 45 (42 to 50)        | 0.036   |
| Morning PaCO₂<sup>a</sup>            | 38 (37 to 45)   | 40 (37 to 45)        | 0.999   |

# p-value from independent samples Mann Whitney U test
<sup>a</sup> Morning arterial blood gas was unable to be obtained from (n=1) in the Control group
TST=total sleep time, ODI=oxygen desaturation index, PtcCO₂=partial pressure of carbon dioxide (transcutaneous), PaCO₂=partial pressure of carbon dioxide (arterial), RT=recording time, SpO₂=oxygen saturation from pulse oximetry
Table I5 – Subjective outcome measures for individuals with motor neuron disease; Control group compared with PSG titration; mean difference represents final measure (at study conclusion) minus the baseline measure (prior to commencing NIPPV); with the exception of the MBDS and the FSS VAS, negative values indicate an improvement within the measure

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PSG titration</th>
<th>p-value*#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference</td>
<td>Mean difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(SD) (n=16)</td>
<td>(SD) (n=19)</td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td>-2.3 (3.9)*</td>
<td>-1.5 (2.5)*</td>
<td>0.459</td>
</tr>
<tr>
<td>ESS</td>
<td>-1.5 (4.9)</td>
<td>-0.8 (3.1)</td>
<td>0.641</td>
</tr>
<tr>
<td>KSSa</td>
<td>-3.9 (17.7)</td>
<td>-0.7 (12.1)</td>
<td>0.502</td>
</tr>
<tr>
<td>FSS</td>
<td>-3.9 (17.7)</td>
<td>-0.7 (12.1)</td>
<td>0.502</td>
</tr>
<tr>
<td>FSS VAS</td>
<td>0.4 (3.1)</td>
<td>0.0 (1.6)</td>
<td>0.651</td>
</tr>
<tr>
<td>MBDS</td>
<td>0.5 (2.4)</td>
<td>-0.1 (1.5)</td>
<td>0.406</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>p-value#</td>
</tr>
<tr>
<td></td>
<td>(n=16)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>SAQLI side-effectsb</td>
<td>11.1 (4)</td>
<td>10.0 (4)</td>
<td>0.554</td>
</tr>
<tr>
<td>SAQLI SE vs. benefitsc</td>
<td>2.7 (2)</td>
<td>2.2 (1)</td>
<td>0.411</td>
</tr>
<tr>
<td>Healthcare contacts</td>
<td>2.8 (2)</td>
<td>2.8 (3)</td>
<td>0.970</td>
</tr>
<tr>
<td>Database contacts</td>
<td>4.1 (3)</td>
<td>3.8 (5)</td>
<td>0.906</td>
</tr>
</tbody>
</table>

* Within group p<0.05; related samples t-test
# Between group p-value from independent samples t-test
a Responses to the KSS were not adequately matched for time-of-day for the majority of participants
b Scored as the sum of ratings (on a 7-point Likert scale) for each of the most troubling side-effects. Lower scores therefore represent less troubling side-effects.
c Scored on a 7-point Likert scale where the middle value (=4) represents a balance between side-effects and benefits. Scores <4 therefore indicate that the benefits of therapy outweigh the side-effects.

PSQI=Pittsburgh Sleep Quality Index, ESS=Epworth Sleepiness Scale, KSS=Karolinska Sleepiness Scale, FSS=Fatigue Severity Scale, FSS VAS=Fatigue Severity Scale Visual Analogue Scale, MBDS=Modified Borg Dyspnoea Score, SAQLI=Sleep Apnoea Quality of Life, Healthcare contacts=self-reported contact with healthcare workers, Database contacts=entries in the centralised database maintained by the HMV provider.
Table 16 – Change in the domain scores of the Severe Respiratory Insufficiency questionnaire for individuals with motor neuron disease; Control group compared with PSG titration group; mean difference indicates the final measure (at study conclusion) minus the baseline measure (prior to commencing NIPPV); positive values represent an improvement in the respective domain

<table>
<thead>
<tr>
<th>SRI Domains</th>
<th>Control (n=17)</th>
<th>PSG titration (n=20)</th>
<th>p-value&lt;sup&gt;#&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (SD)</td>
<td>Mean difference (SD)</td>
<td></td>
</tr>
<tr>
<td>Summary Scale</td>
<td>-1.4 (13)</td>
<td>2.5 (9)</td>
<td>0.284</td>
</tr>
<tr>
<td>Respiratory Complaints</td>
<td>1.7 (20)</td>
<td>6.7 (18)</td>
<td>0.433</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>-6.1 (16)</td>
<td>-0.4 (18)</td>
<td>0.313</td>
</tr>
<tr>
<td>Attendant Symptoms and Sleep</td>
<td>3.8 (18)</td>
<td>10 (13)*</td>
<td>0.237</td>
</tr>
<tr>
<td>Social Relationships</td>
<td>-8.6 (17)</td>
<td>-1.0 (13)</td>
<td>0.129</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.0 (24)</td>
<td>5.6 (15)</td>
<td>0.470</td>
</tr>
<tr>
<td>Psychological Well-Being</td>
<td>-1.3 (16)</td>
<td>0.5 (11)</td>
<td>0.687</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>-0.6 (17)</td>
<td>-3.8 (19)</td>
<td>0.610</td>
</tr>
</tbody>
</table>

<sup>*</sup> Within group <i>p</i>&lt;0.05; related samples <i>t</i>-test
<sup>#</sup> Between group <i>p</i>-value from independent samples <i>t</i>-test
<sup>a</sup>Domains of the SRI are scored from 0-100
Table I7 – Change in the index score, dimension scores and superdimension scores of the Assessment of Quality of Life Instrument (AQoL-8D) for individuals with motor neuron disease; Control group compared to PSG titration group; mean difference indicates the final measure (at study conclusion) minus the baseline measure (prior to commencing NIPPV); positive values represent an improvement in the respective measure.

<table>
<thead>
<tr>
<th>AQoL-8D Dimensions&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Control (n=17)</th>
<th>PSG titration (n=20)</th>
<th>p-value&lt;sup&gt;#&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index score</td>
<td>-0.002 (0.12)</td>
<td>-0.018 (0.11)</td>
<td>0.682</td>
</tr>
<tr>
<td>Independent Living</td>
<td>-0.026 (0.06)</td>
<td>-0.047 (0.11)</td>
<td>0.482</td>
</tr>
<tr>
<td>Happiness</td>
<td>-0.055 (0.14)</td>
<td>-0.016 (0.11)</td>
<td>0.348</td>
</tr>
<tr>
<td>Mental Health</td>
<td>0.020 (0.11)</td>
<td>0.025 (0.10)</td>
<td>0.898</td>
</tr>
<tr>
<td>Coping</td>
<td>-0.024 (0.15)</td>
<td>-0.003 (0.13)</td>
<td>0.650</td>
</tr>
<tr>
<td>Relationships</td>
<td>0.020 (0.12)</td>
<td>0.004 (0.13)</td>
<td>0.662</td>
</tr>
<tr>
<td>Self Worth</td>
<td>-0.044 (0.11)</td>
<td>-0.021 (0.09)</td>
<td>0.483</td>
</tr>
<tr>
<td>Pain</td>
<td>0.050 (0.19)</td>
<td>-0.055 (0.23)</td>
<td>0.149</td>
</tr>
<tr>
<td>Senses</td>
<td>-0.004 (0.06)</td>
<td>-0.027 (0.08)</td>
<td>0.350</td>
</tr>
<tr>
<td>Mental Superdimension</td>
<td>0.002 (0.11)</td>
<td>-0.003 (0.13)</td>
<td>0.904</td>
</tr>
<tr>
<td>Physical Superdimension</td>
<td>0.004 (0.09)</td>
<td>-0.056 (0.13)</td>
<td>0.131</td>
</tr>
</tbody>
</table>

* All within group comparisons p>0.05; related samples t-test
# Between group p-value from independent samples t-test
<sup>a</sup>Index scores and dimension scores range from 0.0 to 1.0

Table I8 – Categorical non-adherence<sup>a</sup> during the acclimatisation and treatment period for individuals with motor neuron disease; Control group compared with PSG titration group

<table>
<thead>
<tr>
<th></th>
<th>Acclimisation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=16)</td>
<td>7 (39%)</td>
<td>9 (56%)*</td>
</tr>
<tr>
<td>PSG titration (n=20)</td>
<td>6 (30%)</td>
<td>3 (15%)*</td>
</tr>
</tbody>
</table>

<sup>a</sup>Non-adherence defined as average daily use <240 minutes per day
<sup>*p<0.05, Pearson’s χ² for proportions</sup>
Table I9 - Correlation matrix for adherence (during the treatment period) and PVA, with subjective measures, gas exchange and other parameters measured during nocturnal PSG; figures represent Spearman correlation coefficients with significant correlations (\( p < 0.05 \)) indicated in bold text

<table>
<thead>
<tr>
<th></th>
<th>Subjective measures</th>
<th>PVA and arousals</th>
<th>Gas exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adherence</td>
<td>PSQI</td>
<td>ESS</td>
</tr>
<tr>
<td>Adherence</td>
<td>1</td>
<td>-0.446</td>
<td>-0.311</td>
</tr>
<tr>
<td>PVA</td>
<td>-0.260</td>
<td>0.167</td>
<td>0.240</td>
</tr>
</tbody>
</table>

Adherence=average daily use during the treatment period, PSQI = Pittsburgh Sleep Quality Index at study conclusion (higher values indicate worse subjective sleep quality), ESS=Epworth Sleepiness Scale at study conclusion (higher values indicate worse daytime somnolence), SE=Side-effect ratings adapted from the Sleep Apnea Quality of Life scale (higher scores indicate more troublesome side-effects), SEvB=Self-reported weighting of side-effects with benefits adapted from the Sleep Apnea Quality of Life scale (higher scores indicate that side-effects outweigh benefits), SRI=Severe Respiratory Insufficiency questionnaire Summary Scale at study conclusion (higher ratings indicate better disease-specific HRQoL ratings), AQoL=Assessment of Quality of Life-8D index score (higher values indicate better generic HRQoL ratings), PVA=patient-ventilator asynchrony index on PSG at study conclusion (events per hour TST), IE=ineffective efforts on PSG at study conclusion (events per hour TST), DT=double trigger events on PSG at study conclusion (events per hour TST), MT=multiple trigger events on PSG at study conclusion (events per hour TST), AI=EEG arousal index (events per hour TST) on PSG at study conclusion, %Leak=percentage time (RT) with device leak signal >24L/min during PSG at study conclusion, ODI3=oxygen desaturation of 3% or more per hour RT during PSG at study conclusion, ODI4=oxygen desaturation of 4% or more per hour RT during PSG at study conclusion, T<90%=percentage time (TST) with oxygen saturation less than 90% during PSG at study conclusion, ΔCO\(_2\)=difference in daytime PaCO\(_2\) from baseline, CO\(_2\)=daytime PaCO\(_2\) at study conclusion.
Figure I3 – Scatter plot for patient-ventilator asynchrony index (PVA), 3% oxygen desaturation index (ODI3), percentage TST with SpO₂<90% (T<90%) and percentage time (RT) with device leak >24L/min (%Leak) during the final PSG at study conclusion; markers represent individual data points for both the PSG titration group and the Control group.
Figure I4 – Scatter plot for adherence (Adherence; average daily use during the treatment period), subjective sleep quality (PSQI; Pittsburgh Sleep Quality Index at study conclusion), daytime somnolence (ESS; Epworth Sleepiness Scale at study conclusion), disease-specific HRQoL (SRI-SS; SRI-Summary Scale at study conclusion), generic HRQoL (AQoL-8D; AQoL-8D index score at study conclusion), side-effects (SE; side-effect rating adapted from the SAQLI) and side-effects vs benefits (SEvB; adapted from the SAQLI); markers represent individual data points for both the PSG titration group and the Control group.
Table I10 – Exploratory comparison of outcome measures at study conclusion according to categorical adherence during the treatment period (defined as >240 minutes average daily use); populations represent both Control and PSG titration groups combined; values represent mean (SD) or median (interquartile range) as appropriate

<table>
<thead>
<tr>
<th>Measure</th>
<th>Non-adherent (n=16)</th>
<th>Adherent (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>9.0 (6-13)</td>
<td>4.0 (3-7)**</td>
</tr>
<tr>
<td>ΔPSQI</td>
<td>-1.2 (3)</td>
<td>-1.9 (4)</td>
</tr>
<tr>
<td>ESS</td>
<td>10.0 (5-12)</td>
<td>4.0 (3-10)*</td>
</tr>
<tr>
<td>ΔESS</td>
<td>-1.8 (5)</td>
<td>-2.0 (5)</td>
</tr>
<tr>
<td>AQoL</td>
<td>0.56 (0.4-0.7)</td>
<td>0.68 (0.5-0.8)*</td>
</tr>
<tr>
<td>ΔAQoL</td>
<td>0.02 (0.1)</td>
<td>0.0 (0.1)</td>
</tr>
<tr>
<td>SRI</td>
<td>59.0 (45-65)</td>
<td>62.8 (53-73)</td>
</tr>
<tr>
<td>ΔSRI</td>
<td>-3.0 (9)</td>
<td>2.9 (12)</td>
</tr>
<tr>
<td>SE</td>
<td>13 (9-16)</td>
<td>11 (5-13)</td>
</tr>
<tr>
<td>SEvB</td>
<td>3.0 (2-4)</td>
<td>2.0 (1-3)**</td>
</tr>
<tr>
<td>Contact</td>
<td>3.5 (3)</td>
<td>3.4 (4)</td>
</tr>
<tr>
<td>AI</td>
<td>14.6 (12-22)</td>
<td>11.3 (9-18)</td>
</tr>
<tr>
<td>PVA</td>
<td>64.3 (30-190)</td>
<td>26.9 (11-92)</td>
</tr>
<tr>
<td>IE</td>
<td>31.4 (18-148)</td>
<td>14.2 (6-35)*</td>
</tr>
<tr>
<td>DT</td>
<td>8.8 (5-60)</td>
<td>4.7 (2-11)</td>
</tr>
<tr>
<td>MT</td>
<td>0.7 (0-2)</td>
<td>0.5 (0-4)</td>
</tr>
<tr>
<td>ODI3</td>
<td>6.4 (3-11)</td>
<td>2.9 (2-5)**</td>
</tr>
<tr>
<td>ODI4</td>
<td>2.1 (1-4)</td>
<td>0.9 (0-2)*</td>
</tr>
<tr>
<td>T&lt;90%</td>
<td>1.8 (0-6)</td>
<td>0.0 (0-0)**</td>
</tr>
<tr>
<td>%Leak</td>
<td>10.9 (0-36)</td>
<td>0 (0-19)</td>
</tr>
<tr>
<td>CO₂</td>
<td>40.3 (36-46)</td>
<td>40.3 (36-45)</td>
</tr>
<tr>
<td>ΔCO₂</td>
<td>3.4 (7.4)</td>
<td>3.6 (5.8)</td>
</tr>
</tbody>
</table>

**p<0.05; independent samples Mann-Whitney U test
*p<0.10; independent samples Mann-Whitney U test
Avg. use=average daily use during the treatment period, PSQI = Pittsburgh Sleep Quality Index at study conclusion (higher values indicate worse subjective sleep quality), ESS=Epworth Sleepiness Scale at study conclusion (higher values indicate worse daytime somnolence), SE=Side-effect ratings adapted from the Sleep Apnea Quality of Life scale (higher scores indicate more troublesome side-effects), SEvB=Self-reported weighting of side-effects with benefits adapted from the Sleep Apnea Quality of Life scale (higher scores indicate that side-effects outweigh benefits), SRI=Severe Respiratory Insufficiency questionnaire Summary Scale at study conclusion.
conclusion (higher ratings indicate better disease-specific HRQoL ratings),
AQoL=Assessment of Quality of Life-8D index score (higher values indicate better
generic HRQoL ratings), PVA=patient-ventilator asynchrony index on PSG at study
conclusion (events per hour TST), IE=ineffective efforts on PSG at study conclusion
(events per hour TST), DT=double trigger events on PSG at study conclusion (events
per hour TST), MT=multiple trigger events on PSG at study conclusion (events per
hour TST), AI=EEG arousal index (events per hour TST) on PSG at study conclusion,
%Leak=percentage time (RT) with device leak signal >24L/min during PSG at study
conclusion, ODI3=oxygen desaturation of 3% or more per hour RT during PSG at study
conclusion, ODI4=oxygen desaturation of 4% or more per hour RT during PSG at study
conclusion, T<90%=percentage time (TST) with oxygen saturation less than 90%
during PSG at study conclusion, ΔCO₂=difference in daytime PaCO₂ from baseline,
CO₂=daytime PaCO₂ at study conclusion.
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Hannan, Liam Michael

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