Does long-term home non-invasive ventilation, initiated as an outpatient, provide equivalent outcomes compared to non-invasive ventilation initiated as an in-patient in terms of physiological parameters and Health Related Quality of Life in a mixed cohort of patients over a 12-month period?

J K COOPER

PhD 2022

Does long-term home non-invasive ventilation, initiated as an outpatient, provide equivalent outcomes compared to non-invasive ventilation initiated as an in-patient in terms of physiological parameters and Health Related Quality of Life in a mixed cohort of patients over a 12-month period?

JULIE KAREN COOPER

A thesis submitted in partial fulfilment of the requirements of Manchester Metropolitan University for the degree of Doctor of Philosophy

Department of Life Sciences

Manchester Metropolitan University

2022

ABSTRACT

Introduction

Long-term nocturnal home non-invasive ventilation (NIV) has been demonstrated to improve survival, decrease admissions and reduce utilisation of healthcare resources in patients with chronic hypercapnic respiratory failure. Improvements in the management of patients with chronic respiratory disease has increased the number of patients requiring home NIV. In the UK, as in other health systems, initiation of home NIV has historically been via in-patient admission, including an overnight titration study in a specialist centre. However, if it could be demonstrated that initiation of long-term home NIV could be performed safely and effectively in an outpatient setting with outcomes that were not inferior to in-patient initiation, there is potential to reduce the burden on healthcare systems. This hypothesis formed the basis for this study.

Methods

113 patients (in-patient NIV initiation n=92) with a mix of conditions leading to chronic hypercapnic respiratory failure (predominantly COPD and OHVS), commenced on long-term home NIV as either an in-patient or an outpatient, were identified via an NIV database used as part of on-going NIV patient review. Retrospective data for demography, baseline spirometry, initial and subsequent blood gases, ventilator settings exacerbations, hospitalisations, and health-related quality of life (HRQoL) using the Serious Respiratory Insufficiency (SRI) questionnaire was reviewed. Primary outcomes compared were daytime arterial carbon dioxide pressure ($PaCO_2$) reduction after 12 months of NIV, and change in HRQoL measured by the SRI. Secondary outcomes were the impact of home NIV on in-

patient admissions, length of stay and mortality. An investigation of the potential cost savings of outpatient initiation of NIV was also undertaken.

Results

The baseline arterial $PaCO_2$ in the in-patient initiation group was higher (median 9.4kPa, IQR 8.6-11.3) than the outpatient initiation group (median 7.1kPa, IQR 6.8-8.3). Following 12-months of home NIV, there was neither a statistical (p=0.164) nor clinical difference in $PaCO_2$ between the in-patient group (median 5.9kPa, IQR 5.3-6.4) and the outpatient group (median 6.2kPa, IQR 5.7-6.4). The pressure support required by the in-patient group (mean 13.2cmH_2O, SD 3.1) at 12-months was slightly higher than the outpatient group (mean 11.7cmH_2O, SD 3.6), however this difference was not statistically significant (p=0.113).

Compliance, defined as total hours/total days of 'mask on' time measured in hours, was higher for the in-patient group (mean 7.5 hours, SD 2.4 vs. mean 6.1 hours, SD 2.5) but again, this difference was not statistically significant (p=0.059). The baseline SRI scores of the in-patient and outpatient initiation groups were not statistically different (p=0.502) and the difference between the groups (3.4 points) was less than the minimal clinically important difference (MCID), defined as 5 points. The absolute change in the mean SRI score at 12 months was greater than the MCID for both groups (in-patient mean 5.8 points, SD 24.6; outpatient mean 5.7 points, SD 14.1) but below the level of statistical significance (in-patient p=0.345; outpatient p=0.450).

Compared to the outpatient initiation group, the in-patient initiation group had more admissions in the 12 months prior to NIV (p=0.016) as well as more bed days (p=<0.001). Following initiation of NIV, admissions (p=<0.001) and bed days (p=<0.001) were

significantly reduced for the in-patient group; this improvement was observed for the outpatient group. Combined all-cause mortality at 1-year was 15% and there was no statistical difference in mortality between the in-patient and outpatient initiation groups (p=0.523). Based on standard NHS Tariff costs, outpatient initiation of NIV produces a potential cost saving of at least £476 per patient, but this could be as much as £1,018 per patient depending on how costs are calculated.

Conclusions

Based on this single centre observational study, outpatient initiation of long-term home NIV in a mixed patient cohort produces outcomes in $PaCO_2$ and HRQoL that are not inferior to in-patient initiation at 12-months; there appears to be no difference in mortality between the two groups. There is evidence to suggest that single centre studies may provide larger treatment effect estimates than multi-centre trials (Unverzagt, S., et al., 2013) and conclusions drawn from this data must be considered in this context. However, despite the relatively small number of outpatients included in the study, it is reassuring that comparable studies that have drawn similar conclusions do not have significantly larger numbers of patients in their study cohort.

This study supports previous work that demonstrates that, in appropriately selected patients, outpatient initiation appears safe, effective and has the potential to deliver substantial cost benefits without significant reductions in HRQoL. This study provides important information about the “real world” initiation of outpatient NIV in a non-specialist centre. However, these findings can only be applied after careful consideration of the context of this study with an individual’s own situation.

LAY ABSTRACT

There are a number of medical problems such as some long-standing lung diseases or being very, very overweight that can cause patients to be unable to get oxygen in and waste gas (carbon dioxide) out of their body as well as they should. This imbalance is termed respiratory failure. The levels of oxygen and carbon dioxide in the blood are measured using a test called a 'blood gas test' that also identifies if the respiratory failure is causing the patient's blood to become more acidic. If the blood becomes more acidic, it can cause significant health problems for patients.

To reduce the waste gas and increase the oxygen levels in their blood, patients may benefit from a treatment called non-invasive ventilation (NIV). NIV blows air in to the lungs at a higher pressure than room air via a close fitting facemask to help to 'flush out' the waste gas and increase oxygen levels. Patients that are admitted to hospital may require NIV for a short period to improve their blood gas levels, but some patients require NIV more regularly once they are at home. Research has shown that NIV can help patients stay out of hospital and improve how they cope with their breathing problem at home. Traditionally, a specialist NIV team has commenced NIV during an in-patient admission with a stay of a few days whilst the treatment is adjusted. Hospital beds are always in high demand in the UK, so considering other ways of starting NIV treatment may be beneficial. The purpose of this study was to see if starting NIV as an outpatient produced outcomes that were not significantly different from staring NIV as an in-patient, with the potential to reduce the burden on the healthcare system and produce cost savings to the NHS without affecting patient care.

The study compared the outcomes of patients who started on NIV as an in-patient against those who started on NIV as an outpatient over 1-year of treatment. To compare the two groups, we looked at the levels of carbon dioxide in patients' blood before starting NIV, immediately after starting NIV and then at 3 and 12 months after NIV was commenced. The study also looked at the quality of life reported by patients on home NIV using a questionnaire that has been found to be reliable for this group of patients; the questionnaire was called the Serious Respiratory Insufficiency (SRI) questionnaire. The study assessed the costs of staring a patient on NIV as an in-patient compared to the costs for starting NIV as an outpatient. To compare the costs, we use something called NHS National Tariff costs. These are a set of prices and rules used by providers and commissioners of NHS care to deliver the most efficient, cost effective care to patients.

From the data that was obtained during the study period, it does not appear that patients who started NIV as an outpatient had worse blood carbon dioxide levels after 1 year of treatment. The quality of life scores at 12 months for both groups were not significantly different either. This suggests that patients started on NIV as an outpatient have similar outcomes to patients that are started on NIV via the more traditional in-patient route. Using NHS National Tariff costs, the study was able to demonstrate that outpatient NIV initiation produces a potential cost saving of at least £476 per patient, but this could be as much as £1,018 per patient depending on how costs are calculated.

However, for a number of reasons, is not possible to be certain that this study proves that the two groups have similar outcomes. The main reason is the difference in numbers of patients in each group, which makes comparisons between the two groups less reliable. There were 113 patients at the start of the study, of which only 21 (18.5%) had been started

on NIV as an outpatient. Unfortunately, only 67 patients completed the full 12-month study period of NIV treatment resulting in just 15 patients remaining from the initial 21 patients that started NIV as an outpatient. The study looked at patients that had already been started on NIV treatment and followed their progress, rather than finding patients before their treatment had begun. This means that the patients were not selected specifically for the study and there was 'missing' or incomplete data for some patients.

Whilst this study was not able to prove that the two methods for commencing NIV produced similar patient outcomes, it does add to the growing research data that supports the outpatient set up of NIV. The results of this study are similar to other studies that compared in-patient and outpatient set up. The study does demonstrate that significant cost savings are possible using an outpatient set up methodology. Further work is necessary to get a larger number of patients, particularly outpatients so that the data is more reliable.

ACKNOWLEDGEMENTS

First and foremost, I am extremely grateful to my clinical supervisor, Dr Iyad Ismail and to my academic supervisor, Professor Brendan G. Cooper for their invaluable advice, continuous support, and patience during my PhD study. Their extensive knowledge and abundant experience have encouraged me throughout this piece of research.

I would also like to thank Mr Peter Nightingale for his advice and support with the statistical analysis of my study. Special thanks to Mr Richard Glover, for his support with data analysis of the study and for ensuring the Lung Function and Sleep service ran smoothly whilst my attention was elsewhere.

My thanks also to all the members of the Lung Function and Sleep team at Good Hope hospital. It is only with their help and support that I have been able to balance my role as Service Lead with my academic study during a particularly challenging period.

I would also like to express my appreciation for my friends Jackie and Ken, Jane and Glen and my Auntie Wendy and Uncle Allan, who have constantly encouraged me and supported me to complete this – I can see you at weekends now!

Last, but certainly not least, I would like to express my endless gratitude to my husband, Brendan. Without his tremendous understanding, patience and encouragement throughout the entire HSST process, it would have been impossible for me to see it through until the end.

DEDICATION

I would like to dedicate this piece of work to a number of very important people. Firstly and most importantly my husband, Brendan, who believed I could even when I told him I couldn't! Thank you for your patience, persistence and love.

I would also like to dedicate it to my brother, who I lost to suicide 3 years ago. He would have been endlessly amused by the thought of his big sister completing a doctorate!

Finally, I would like to dedicate this to my niece, Harriet, who proves every day that anything is possible if you just try hard enough.

CONTENTS

		PAGE
GLOSSARY		14
LIST OF TABLES		18
LIST OF FIGURES		24
1. INTRODUCTION		24
	1.1 Respiratory failure	25
	1.2 Management of respiratory failure	26
	1.3 Mechanical ventilation of the lung	27
	1.4 Evidence for the use of NIV in the management of AHRF in adults	28
2. LITERATURE REVIEW		
	2.1 Search methodology	31
	2.2 Development of adult home NIV services	32
	2.3 Evidence for the use of home NIV in COPD	32
	2.4 NIV in COPD-OSA overlap syndrome in adults	39
	2.5 Evidence for the use of home NIV in non-COPD in adults	41
	2.6 Modes of ventilatory support	43
	2.7 Patient selection for an adult non –specialist home NIV service	44
	2.8 In-patient versus outpatient initiation of NIV	47
	2.9 Compliance with home NIV	51
	2.10 Health related quality of life	52
	2.11 HRQoL questionnaires in Chronic Respiratory Failure (CRF)	55
	2.12 Minimal Clinically Important Difference	61
	Summary and research questions	63

3. METHODOLOGY

	3.1 Introduction	68
	3.2 Decision to commence long-term nocturnal home NIV	69
	3.3 Study design	72
	3.4 Evidence of stakeholder engagement and patient involvement	73
	3.5 Part A: Quantitative data	76
	3.6 Physiological measurements	77
	3.7 Part B: Quality of life data	81
Research Questions	*3.8 Primary Outcome: Part A*	81
	3.8.1 Secondary Outcomes: Part A	83
	3.9 Primary Outcome: Part B	84
	3.9.1 Secondary Outcomes: Part B	85
	3.10 Time investment and costs	86
	3.11 Study sample size	88
3.12 Study Population	*3.12.1 Inclusion criteria*	88
	3.12.2 Exclusion criteria	89
	3.13 Patient categorisation	90
	3.14 Informed consent and ethical approval	90
	3.15 Data collection procedures	91
	3.16 Data management techniques	92

4. RESULTS

Part A	*4.1 Flow chart for patients in the study*	94
	4.2 Baseline characteristics for the total cohort	95

	4.2.1 Baseline characteristics by clinical diagnosis	96
	4.2.2 Clinical diagnosis confirmed by spirometric data	97
	4.2.3 Patient anthropometric data by route of NIV initiation	99
4.3 Part A Primary Outcome	*4.3.1 $PaCO_2$ First Review Data*	101
	4.3.2 $PaCO_2$ Second Review data	103
	4.3.3 $PaCO_2$ Third Review data	105
4.4 Part A Secondary Outcomes	*4.4.1 Outcome 1: Frequency and length of stay for respiratory related admissions*	108
	4.4.2 Outcome 2: Was poor compliance with NIV associated with re-admission?	110
	4.4.3 Outcome 3: All-Cause Mortality at 12-months following initiation of NIV	111
	4.4.4 Was poor-compliance with NIV associated with death before the end-point of the study?	113
	4.4.5 Outcome 5: Admission free survival at 12 months following initiation of NIV (in-patient versus outpatient NIV initiation)	113
4.5 Part B Primary Outcome:	*4.5.1 SRI scores pre and post initiation of NIV between groups (pooled data)*	115
	4.5.2 SRI scores pre and post initiation of NIV within groups at first review (paired data)	117
	4.5.3 SRI scores pre and post initiation of NIV within groups at second review	118
	4.5.4 SRI scores pre and post initiation of NIV within groups at third review	119
4.6 Part B Secondary Outcomes	*4.6.1 Outcome 1: Are there differences within SRI domain score between groups at First Review compared to Baseline?*	120
	4.6.2 Outcome 1: Comparison of domains of SRI between groups at Second review compared to baseline	122
	4.6.3 Outcome 1: Comparison of SRI domains between groups at third review compared to baseline	125
	4.6.4 Outcome 2: Are there differences in the domains of SRI that are disease specific?	128
	4.6.5 Outcome 3: Are there differences within SRI domain score	129

	over time comparing COPD with OHVS?	
4.7 Cost comparisons	*4.7.1 Equipment costs*	136
	4.7.2 Time taken to initiate NIV	137
	4.7.3 Estimate of procedure costs based on NHS HRG codes	137
	4.7.4 Costs associated with admissions before and after commencing NIV	138
5. DISCUSSION AND CONCLUSION	*5.1 Discussion*	140
	5.2 Critique of the study	152
	5.3 Improvements to the Study Design	160
	5.4 Impact of the Study and Future research	161
	5.5 Conclusion	154
APPENDICES		156
Appendix 1	*Severe Respiratory Insufficiency Questionnaire*	166
Appendix 1a	*Severe Respiratory Insufficiency Questionnaire Scoring guidance*	170
Appendix 2	*Semi-structured interview information sheet*	172
Appendix 3	*Guidelines for the use of Non-Invasive Ventilation (HGS)*	179
Appendix 4	*Outpatient NIV Trial for CHRF in patients requiring non-complex NIV (Good Hope Hospital)*	208
Appendix 5	*Domiciliary NIV Service Proposal Consultant Feedback*	221
Appendix 6	*GHH Home NIV Engagement Meeting Agenda*	224
Appendix 7	*Signed sponsorship letter*	227
Appendix 8	*NIV review (Lung Function and Sleep, Good Hope Hospital)*	228
REFERENCES		235

GLOSSARY

6MWD	6-minute walk distance
AHRF	Acute hypercapnic respiratory failure
AVAPS	Average volume assured pressure support
BE	Base excess (positive number) or base deficit (negative number)
BMI	Body Mass Index
BPM	Beats per minute
BURR	Back up respiratory rate
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRDQ/CRQ	Chronic respiratory disease questionnaire
CRF	Chronic respiratory failure
CWD	Chest wall disease
EPAP	Expiratory Positive Airway Pressure
FEV_1	Forced expiratory volume in the first second of a forced expiratory manoeuvre

FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
GOLD	Global obstructive lung disease
HCO_3	Bicarbonate ions
HOS-AR	Home Oxygen Service – Assessment and Review
HOT-HMV	Home oxygen therapy - home mechanical ventilation
HRG	Healthcare Resource Groups
HRQoL	Health related quality of life
ICU	Intensive Care Unit
IMV	Invasive mechanical ventilation
IPAP	Inspiratory Positive Airway Pressure
IPPV	Intermittent positive pressure ventilation
IV	Invasive ventilation
LOS	Length of stay
LTOT	Long-term oxygen therapy
MCID	Minimal clinically important difference
MRF_{28}	Maugeri Respiratory Failure questionnaire
NHS	National Health Service

NIPPV	Nasal or Non-Invasive Intermittent Positive Pressure Ventilation
NIV	Non-invasive ventilation
NMD	Neuromuscular disease
O_2	Oxygen
OHVS	Obesity Hypoventilation Syndrome
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PCO_2	Partial pressure of carbon dioxide
pH	Logarithm of the reciprocal of hydrogen ion concentration
PEF	Peak expiratory flow
PO_2	Partial pressure of oxygen
POCT	Point of Care Team
PVA	Patient ventilator asynchrony
Q	Perfusion of individual lung units
RCT	Randomised controlled trial
RWE	Real-world evidence
SaO_2	Oxygen saturation in arterial blood

SAQLI	Calgary Sleep Apnoea quality of life index
SF_{36}	Short form survey instrument 36
SGRQ	St. George's Respiratory Questionnaire
SO_2	Oxygen saturation
SpO_2	Arterial oxygen saturation estimated by pulse oximetry
SRI	Serious respiratory insufficiency questionnaire
$\dot{V}$	Ventilation of the lung
Weqas	Wales External Quality Assessment Service

LIST OF TABLES

	TITLE	Page
Table 1	Consensus clinical indicators for home NIV use in COPD (taken from Cheung et al., 2010)	48
Table 2	WHO domains of quality of life (Adapted from World Health Organisation WHOQOL-100.2)	55
Table 3	Summary of papers for validation of translated SRI	60
Table 4	Summary of papers for validation of SRI in a range of clinical conditions	61
Table 5	NIV patient database data collection	78
Table 6	Baseline characteristics for the total cohort (N=113)	97
Table 7	Baseline characteristics by confirmed clinical diagnosis	98
Table 8	Spirometric data by route of NIV initiation for the combined cohort data	99
Table 9	Spirometric data by clinical diagnosis for the combined cohort data	100
Table 10	Patient anthropometric data by method of NIV initiation	102
Table 11	$PaCO_2$ at first review following NIV initiation	104
Table 12	$PaCO_2$ at second review following NIV initiation	106
Table 13	$PaCO_2$ at third review following NIV initiation	108
Table 14	Admissions and bed days pre and post initiation of NIV between groups (in-patient vs. outpatient)	111
Table 15	Admissions and bed days pre and post initiation of NIV	112

	within groups (in-patient and outpatient)	
Table 16	Mortality at 1-year (in-patient initiation vs. outpatient initiation of NIV)	113
Table 17	Admission free survival at 1-year (in-patient initiation vs. outpatient initiation of NIV)	116
Table 18	SRI summative score comparison pre and post initiation of NIV between groups (in-patient versus outpatient)	117
Table 19	Baseline summary SRI versus first review summary SRI Score within groups (in-patient and outpatient)	119
Table 20	Baseline summary SRI versus second review summary SRI Score within groups (in-patient and outpatient)	120
Table 21	Baseline summary SRI versus third review summary SRI Score within groups (in-patient and outpatient)	121
Table 22	Comparison of baseline and first review SRI domains for in-patient NIV initiation	122
Table 23	Comparison of baseline and first review SRI domains for outpatient NIV initiation	122
Table 24	Comparison of the absolute change in SRI domain scores between in-patient and outpatients NIV initiation groups from baseline to first review	124
Table 25	Comparison of baseline and second review SRI domains for in-patient NIV initiation	125
Table 26	Comparison of baseline and second review SRI domains	125

	for outpatient NIV initiation	
Table 27	Comparison of the absolute change in SRI domain scores between in-patient and outpatients NIV initiation groups from baseline to second review	126
Table 28	Comparison of baseline and third review SRI domains in in-patients	127
Table 29	Comparison of baseline and third review SRI domains in in-patients	127
Table 30	Comparison of absolute change in SRI domain scores between in-patient and outpatients NIV initiation groups from baseline to third review	129
Table 31	Comparison of baseline SRI domain scores in COPD and OHVS	130
Table 32	Comparison of baseline and first review SRI domain data in OHVS	131
Table 33	Comparison of baseline and first review SRI domain data in COPD	132
Table 34	Comparison of absolute change in SRI domain score between OHVS and COPD from baseline to first review	132
Table 35	Comparison of baseline and second review SRI domains in OHVS	134
Table 36	Comparison of baseline and second review SRI domains in COPD	134

Table 37	Comparison of absolute change in SRI domain score between OHVS and COPD from baseline to second review	134
Table 38	Comparison of baseline and third review SRI domain score in OHVS	136
Table 39	Comparison of baseline and third review SRI domain score in COPD	136
Table 40	Comparison of the absolute change in SRI domain score between OHVS and COPD from baseline to third review	136
Table 41	In-patient NIV initiation versus outpatient NIV equipment costs	138
Table 42	Time required for initiation of NIV (in-patient versus outpatient)	139
Table 43	Comparison of in-patient and outpatient NIV costs based on HRG tariff	140
Table 44	Cost of NIV 1-year pre and post NIV initiation (in-patient versus outpatient initiation)	141
Table 45	Baseline SRI reported in HRQoL studies in home NIV	147
Table 46	Number of subjects in outpatient versus in-patient NIV initiation comparison studies	158

LIST OF FIGURES

	TITLE	Page
Figure 1	Respiratory failure; failure of the lung or the pump	26
Figure 2	Figure 2: Children in iron lungs during a polio outbreak in the US in the 1950s	29
Figure 3	Total hospital beds per 1,000 inhabitants in Europe	66
Figure 4	Flow chart for study participants (physiological data)	96
Figure 5	Change in daytime $PaCO_2$ values for in-patient NIV initiation group	109
Figure 6	Change in daytime $PaCO_2$ values for outpatient NIV initiation group	109
Figure 7	Kaplan-Meir Survival curve at 1-year (in-patient initiation vs. outpatient initiation of NIV)	114
Figure 8	Kaplan-Meir admission free survival curve at 1-year (in-patient initiation vs. outpatient initiation of NIV)	116
Figure 9	Change in SRI over 12 months for in-patient and outpatient NIV initiation	118
Figure 10	Absolute change in SRI domain score from baseline to first review for in-patient and outpatient NIV initiation	123

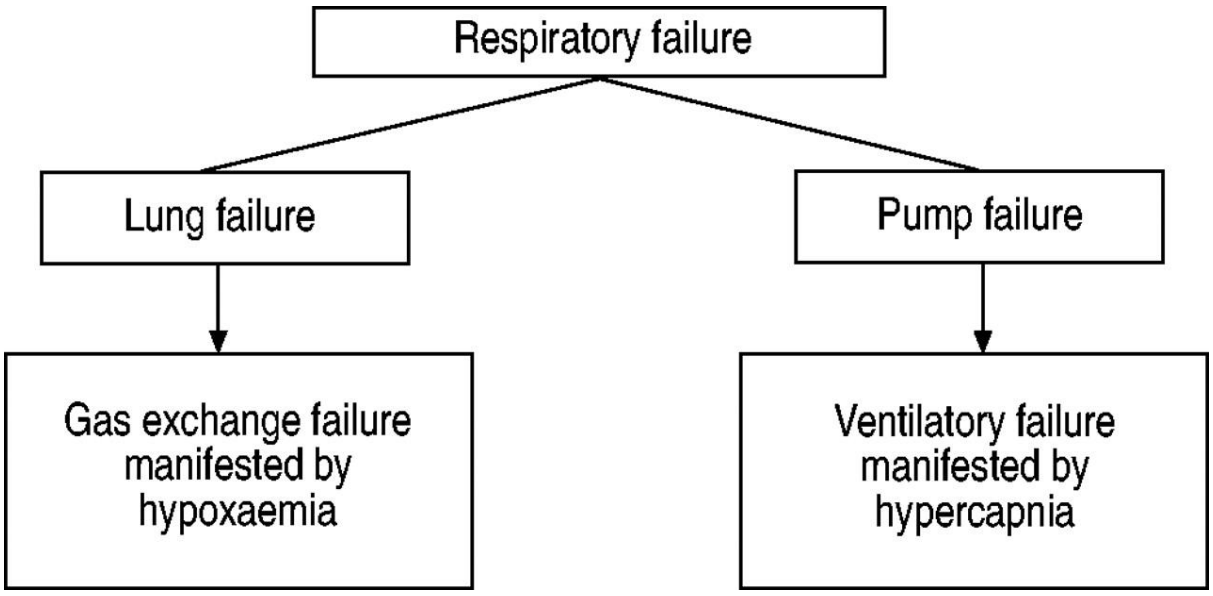
Figure 11	Absolute change in SRI domain score from baseline to second review up for in-patient and outpatient NIV initiation	126
Figure 12	Absolute change in SRI domain score from baseline to third review up for in-patient and outpatient NIV initiation	128
Figure 13	Absolute change in SRI domain score from baseline to first follow up in patients with COPD and OHVS	133
Figure 14	Absolute change in SRI domain score from baseline to second review in patients with COPD and OHVS	135
Figure 15	Absolute change in SRI domain score from baseline to third review in patients with COPD and OHVS	137
Figure 16	Hierarchy of evidence for questions about the effectiveness of an intervention or treatment (Taken from Akobeng, A.K., 2005)	154

1. INTRODUCTION

The respiratory system may be broadly considered as two parts: the lung and the pump that ventilates the lungs (Palange, P. and Rohde, G. eds., 2019). The principle function of the lung is to facilitate the exchange of the respiratory gases, oxygen (O_2) and carbon dioxide (CO_2); this is contingent on appropriate matching of ventilation of the lung ($\dot{V}$) and perfusion (Q) of individual lung units. The pump consists of the chest wall and respiratory muscles, the respiratory controllers in the central nervous system (CNS) and the pathways that connect the central controllers with the respiratory muscles via the spinal and peripheral nerves (Roussos, C. and Koutsoukou, A., 2003).

When respiratory failure occurs, the respiratory system fails in one or both of its gas exchange functions i.e. oxygenation of and/or elimination of carbon dioxide from mixed venous blood.

Figure 1: *Respiratory failure; failure of the lung or the pump. Taken from Roussos, C. and Koutsoukou, A., 2003.*



1.1. Respiratory Failure

The diagnosis of respiratory failure is not clinical, but based on arterial blood gas assessment. Hypoxaemic respiratory failure (Type I) is characterized by an arterial partial pressure of oxygen (PaO_2) lower than 8.0kPa with a normal or low arterial carbon dioxide partial pressure ($PaCO_2$). Hypoxaemic respiratory failure represents a failure of the lung (Figure 1) and is the most common form of respiratory failure. It can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units. Failure of the pump (Figure 1) results in alveolar hypoventilation and hypercapnia (hypercapnic or Type II respiratory failure) and is defined as $PaCO_2$ > 6.0kPa. Common causes include drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (e.g. chronic obstructive pulmonary disease [COPD]). Hypoxaemia when breathing room air is seen frequently in patients with hypercapnic respiratory failure. The increase in arterial CO_2 directly influences the blood pH (logarithm of inverse concentration of H+) according to the following equation:

$$\mathbf{CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow {}^{-}HCO_3 + H^{+}}$$ (Raherison, C. and Girodet, P.O., 2009)

Thus, the consequence of hypercapnia due to failure of the pump mainly consists in increase of H^+ concentration and development of respiratory acidosis. From the Henderson-Hasselbach equation, which describes the relationship between pH, bicarbonate ion concentration ($^{-}$HCO3), and partial pressure of CO_2:

$$\mathbf{pH = 6.1 + \log {}^{-}HCO_3 / 0.03pCO_2}$$ (Bach, P.B., et al., 2001)

It is clear that the pH is strictly determined by the bicarbonate/pCO_2 ratio, rather than their individual values; a change in either the bicarbonate (metabolic) or the pCO_2 (respiratory)

will directly affect pH and activate compensatory mechanisms. The extent of these compensatory changes are for the most part dependent on that of the primary alteration and, from the acid base equation described earlier, can be predicted (Bruno, C.M. and Valenti, M., 2012).

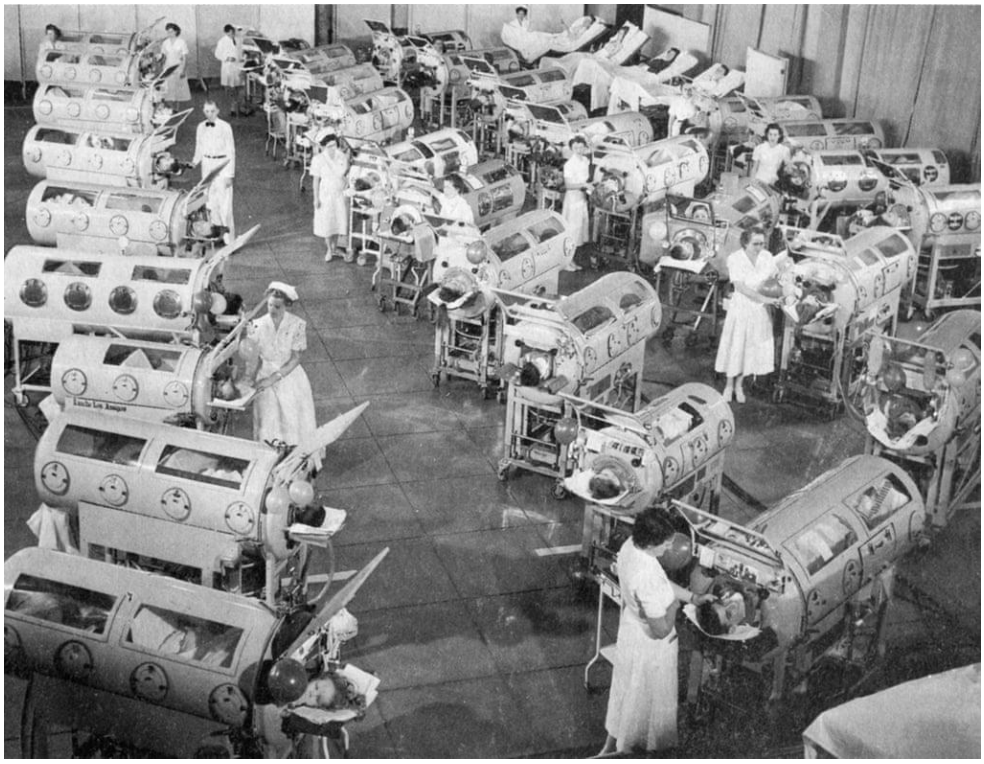
1.2. Management of Respiratory Failure

Respiratory failure is classified according to its onset, course and duration into acute, chronic, and acute on top of chronic respiratory failure; the clinical presentation and management differs significantly between each type. Acute respiratory failure of either type may be immediately life threatening and management will depend on its cause, severity, and the likely benefits and complications of possible interventions. The first objective in the management of respiratory failure is to reverse and/or prevent tissue hypoxia. This is achieved by the provision of supplemental oxygen to increase the PaO_2. For patients with hypoxic respiratory failure, this requires the titration of fraction of inspired oxygen (FiO_2) to achieve an improvement in PaO_2; for those patients with hypercapnic failure this is more challenging for the reasons described earlier. Hypercapnia unaccompanied by hypoxemia is generally well tolerated and probably is not a threat to organ function unless accompanied by severe acidosis (Kaynar, A.M. and Sharma, S., 2011). However, coexistent hypercapnia and respiratory acidosis that is either acute or chronic will need to be managed. In acute hypercapnic respiratory failure, this may be achieved by correcting the underlying cause or providing ventilatory assistance. In chronic hypercapnic respiratory failure, nocturnal ventilatory support may be required in conjunction with supplemental oxygen to correct hypoxaemia (Hardinge, M., et al., 2015).

1.3. Mechanical Ventilation of the Lung

Mechanical ventilation is not a new concept and reference to the use of positive pressure to ventilate the lungs was first described in the mid-16th century (Vesalius, 1998). The 'modern era' of mechanical ventilation can be traced back to the poliomyelitis epidemics of the mid-20th century, which resulted in large numbers of patients requiring mechanical ventilatory support (Figure 1). Initially, this was delivered via negative-pressure ventilation ('iron lung') but despite this, patient mortality remained high.

Figure 2: Children in iron lungs during a polio outbreak in the US in the 1950s (taken from https://www.theguardian.com/society/2020/may/26/last-iron-lung-paul-alexander-polio-coronavirus)



It was recognized that these devices were insufficient for ventilation of severe cases, particularly with respect to elimination of carbon dioxide, and positive pressure ventilation by tracheostomy was developed (Engström, C.G., 1954). Its initial application for long-term

use in the home was for hypoventilation due to paralysis of central origin, neuromuscular diseases, and spinal and chest wall deformities. Increased understanding of pulmonary gas exchange and the widespread use of arterial blood gas sampling and analysis led to its use in a range of patients with hypercapnic ventilatory failure (defined by a PaO_2 of <8 kPa and a $PaCO_2$ of >6 kPa [BTS, 2002]). However, due to the many complications associated with invasive mechanical ventilation (IMV) (Zwillich, C.W. et al, 1974; Pierson, D.J., 1990; Slutsky, A.S., 2005; Tremblay, L.N. and Slutsky, A.S., 2006), there was a resurgence of interest in less invasive and potentially less harmful techniques to provide ventilatory support.

1.4 Evidence for use of NIV in the Management of AHRF in adults

The application of non-invasive ventilation was studied in the late 1940's (Motley, H.L. and Werko, L., 1947), but only became widespread following the work by Sullivan et al (1981). This was initially with nasal Continuous Positive Airway Pressure (CPAP) to treat obstructive sleep apnoea (OSA), and subsequently the successful use of intermittent positive pressure ventilation (IPPV) via a nasal mask in five patients with respiratory muscle weakness (Ellis E.L., et al, 1987). This demonstrated that NIV could be used successfully in the intensive care setting to ventilate patients with respiratory insufficiency, without the complications associated with the use of IMV. The term IPPV became known as Nasal or Non-Invasive Intermittent Positive Pressure ventilation (NIPPV) and finally as NIV. Subsequent studies demonstrated that NIV produced similar physiological improvements to those observed when using IMV (Meduri et al., 1989); it was more effective than standard care (Brochard, L. et al., 1990) and was successful in avoiding intubation (Chevrolet, J.C. et al., 1991).

There were early concerns that NIV was more time-consuming than IMV (Chevrolet, J.C. et al., 1991), but subsequent studies concluded that NIV was neither more expensive nor time-

consuming and after the first few days of ventilation, NIV was significantly less time-consuming in the ITU setting (Nava, S. et al., 1997). Wood K.A., et al. (1998) concluded that NIV applied in the emergency department demonstrated a greater utilization of respiratory care services on 'Day 1' when compared to IMV, but not beyond.

These early applications of NIV (Wood, K.A. et al, 1998; Chevrolet, J.C. et al., 1991) used relatively low ventilatory pressure (IPAP <10cmH_2O) and variable usage from 60 minutes, four times daily (Foglio, C. et al., 1992) to periods of 3 to 88 hours (Meduri, G.U. et al., 1989). Brochard et al. (1990) applied NIV for 7.6 hours/day (±3.9 hours) and demonstrated that it could can obviate the need for IMV; continuous use of NIV in the first 24 hours in AHRF, rather than short 'bursts', produced more favourable outcomes and was further supported by the 1993 study from Bott, J. et al.

Subsequent work (Conway, J.H. et al., 1993; Celikel, T. et al., 1998) demonstrated that NIV, with the addition of supplemental oxygen, could successfully correct severe hypoxaemia without increasing hypercapnia in patients with AHRF. Studies examining the efficacy of NIV during AHRF within the ICU setting (Brochard L., et al., 1995; Kramer N., et al., 1995; Antonelli M., et al., 1998; Celikel T., et al., 1998) demonstrated its efficacy in reducing the need for intubation and in-hospital mortality associated with severe exacerbations of COPD. Conway et al. (1993) and Plant et al. (2000) demonstrated that early use of NIV for patients with AHRF due to COPD, leads to more rapid improvement of physiological variables and, more importantly, NIV was delivered on a medical ward as opposed to the traditional ITU setting. A Cochrane Review (Lightowler J.V., et al., 2003) demonstrated the benefit of NIV as first line intervention, in addition to normal medical care, for the management of AHRF secondary to an acute exacerbation of COPD.

Research into the utilisation and effectiveness of long-term home NIV has increased exponentially; use of long-term home NIV has been shown to improve outcomes in chronic respiratory failure due to a number of clinical conditions (McKim, D.A., et al., 2011; MacIntyre, E.J., et al., 2016; Windisch, W., et al., and Guideline Commission, 2018).

The research to support the use of long-term NIV in COPD has historically been equivocal. However, with the introduction of 'high intensity NIV', which can be described as non-invasive ventilation utilising higher inspiratory pressures and a higher back up respiratory rate (BURR), clinically important improvements have been demonstrated in COPD (Köhnlein T., et al., 2014; Ergan, B., et al., 2019). Importantly, these improvements in physiological parameters, principally $PaCO_2$, have been made without the loss of health related quality of life (Windisch, W., et al., 2005; Dreher, M., et al., 2011; Duiverman, M.L., et al., 2011).

Given the evidence for the success of long-term home NIV in improving survival, reducing admissions and utilisation of healthcare resources, combined with the expected increase in patients requiring home NIV in the UK (Snell, N., Set al., 2016), it is important to look at the capacity to deliver this service. In the UK, as in other health systems, initiation of home NIV has historically been performed with an in-patient admission, including an overnight titration study in a specialist NIV centre (Suh, E.S., et al., 2019). However, if initiation of long-term home NIV could be performed safely and effectively in appropriately selected patients in an outpatient setting and produce equivalent outcomes to in-patient initiation, it may have the potential to reduce the burden on the healthcare system and produce cost savings to the NHS. This hypothesis forms the basis for this study.

2 LITERATURE REVIEW

2.1 METHODOLOGY

The literature review has been structured to:

1. Establish the evidence to support the use of non-invasive ventilation (NIV) in stable ventilatory failure. Consideration for home NIV is determined by the clinical presentation of the patient; evidence to support its use in specific, clinically appropriate patient groups is presented.
2. Present the current literature on the impact of NIV (acute and home) on patient reported health related quality of life (HRQoL).
3. Compare the outcomes of initiating home NIV in an outpatient setting versus elective in-patient admission in terms of safety, effectiveness and HRQoL.
4. Develop the research questions for the study.

Published articles were located by searching general computerised indexes in the health science disciplines (MEDLINE; PubMed; CINAHL), high quality electronic databases (NHS Evidence Search; TRIP database; Cochrane library) and common search engines (Google; Google Scholar). The reference lists of identified articles were reviewed for relevant papers and multiple key words were used as follows: *Non-invasive ventilation; adult(s); Guidelines; Respiratory failure; Acute hypercapnic respiratory Intermittent positive pressure ventilation; Nasal /Non-invasive intermittent positive pressure ventilation; failure; Chronic hypercapnic respiratory failure; COPD; Neuromuscular disorders; Chest wall disorders; Obesity*

hypoventilation/obesity hypoventilation syndrome; Obstructive Sleep Apnoea/Obstructive Sleep Apnoea Syndrome; Supplemental oxygen therapy; service delivery; models.

Boolean operators were used to combine the keywords in database searches to both broaden and focus the search results as required.

2.2 Development of Adult home NIV Services

In light of the benefits observed with acute NIV, the impact of long-term NIV in chronic stable COPD was investigated. The 'cost and consequences' analysis of 13 COPD patients on home NIV by Tuggey et al. (2003) concluded that, in selected patients with recurrent admissions with acidotic exacerbations of COPD, NIV was effective at reducing further admissions, reducing utilisation of primary care resources and thus minimised associated costs. Despite the economic arguments to support the use of home NIV (Tuggey J.M., 2003; Elliott M.W., 2009; Dretzke J., 2015), the clinical evidence for its use was contradictory, and the conclusions drawn from the research evidence were often inconsistent. The Eurovent survey (Lloyd-Owen S.J., et al, 2005), a Europe wide study of 483 NIV centres, concluded that despite conflicting evidence of a long-term benefit for ventilation in COPD patients, NIV was being used widely in this group of patients.

2.3 Evidence for the use of Home NIV in COPD

Historically, home NIV had been used to manage patients with chronic hypercapnia due to neuromuscular disorders. However, the success of NIV in COPD patients with AHRF led to researchers investigating the potential benefits of its long-term use in those patients with persistent hypercapnia following recovery from an acute exacerbation. Janssens et al. (2003) described major changes in patient selection for NIV between 1992 and 2000, with a

marked increase in the use of NIV for COPD and obesity hypoventilation syndrome (OHVS). However, evidence of benefit for its longer-term use in COPD remained ambiguous.

Meecham Jones et al. (1995) demonstrated that in 14 patients with chronic respiratory failure due to COPD, receiving NIV in addition to LTOT improved daytime blood gases, nocturnal $PaCO_2$ and reported improved HRQoL compared to patients receiving LTOT only at 3 months. A similar study by Casanova et al. (2000), with 52 randomised patients and increased study duration, found an improvement in hospital admissions at 3 months, and an improvement in Borg dyspnoea rating at 6 months. However, beyond that, they concluded that NIV '*does not affect the natural course of the disease and is of marginal benefit in outpatients with severe COPD who are in stable condition'*. In contrast, a similar multi-centre study of 90 stable COPD patients over a 2-year period demonstrated comparable findings in terms of survival and hospital admissions, but noted the duration of hospital admissions was shorter. Improvements in carbon dioxide retention, dyspnoea and HRQoL led them to conclude that there were some improvements with use of home NIV (Clini E., et al., 2002). The randomised controlled trial (RCT) of 105 consecutive patients with acute hypoxemic respiratory failure admitted to the ICU by Ferrer et al. (2003) found NIV in a clinically mixed group of patients to be independently associated with decreased risks of intubation and 90-day mortality, when compared to high concentration oxygen therapy. However, it is important to note that patients with hypercapnia, defined as a $PaCO_2$ >6kPa (45mmHg) for this study, were excluded and thus the conclusions drawn cannot necessarily be applied to a hypercapnic COPD patient cohort.

The observational study of 140 patients with severe persistent hypercapnic COPD ($PaCO_2$ 60.1 ± 9.2mmHg; 8kPa + 1.22kPa) treated with NIV at high inspiratory pressure levels and

showing high adherence to therapy by Budweiser et al. (2007), demonstrated that long-term survival was significantly higher than in non-ventilated patients. Of interest is the finding that patients displaying more severe disease, according to known risk factors, seemed to benefit most from long-term NIV. The multicentre RCT of LTOT and NIV versus LTOT alone in 144 patients by McEvoy et al. (2009), which followed the patient cohort for up to 5 years, supported the findings of Budweiser et al (2007). It is of note that McEvoy (2009) observed that this improvement in survival appeared to be at the cost of worsening HRQoL when measured using the St. George's Respiratory Questionnaire (SGRQ).

The negative effect on HRQoL reported is in contrast to the earlier study by Clini et al. (2002) of 122 stable hypercapnic COPD patients who reported an improvement in HRQoL in favour of NPPV+LTOT when using the Maugeri Respiratory Failure Questionnaire (MRF_{28}). A small study by Ali and Kabir (2007) of 17 patients with mixed disease causing hypercapnic respiratory failure, also found that community-based NIV significantly improved HRQoL including dyspnoea, fatigue, mastery and emotional function using the Chronic Respiratory Disease Questionnaire (CRDQ or CRQ), as well as arterial blood gases. It is of note that the cohort within this study was biased towards patients with neuromuscular or chest wall disease, which may contribute to the reported outcomes.

Whilst studies have demonstrated improvements with NIV in stable COPD using a range of outcomes, a meta-analysis (4 trials) of 3 months of NIV in patients with stable COPD indicated that it did not improve lung function, gas exchange, or sleep efficiency. A statistically significant improvement was found in 6-minute walk distance (6MWD), but the authors did not conclude that NIV was beneficial (Wijkstra P.J., et al., 2003). An update of this systematic review (Struik F.M. et al., 2013), which included 3 further studies, concluded

that home NIV used for at least three months, in hypercapnic patients with stable COPD, had no consistent clinically or statistically significant effect on gas exchange, exercise tolerance, HRQoL, lung function, respiratory muscle strength or sleep efficiency. Whilst the conclusions drawn are disappointing, the differences seen in the studies may be due to methodological factors including variations in ventilator setting, study endpoints, non-heterogeneous study populations and relatively small study numbers. Crimi et al. (2016) concluded that, due to the lack of conclusive data from RCT's, the use of NIV in stable COPD '*still relies on empirical and subjective decisions, and this may eventually lead to under or over-prescription of chronic ventilator support*'.

Despite a historic lack of consensus and large-scale controlled clinical trial data for the use of home NIV in COPD, accumulating evidence for its benefit is becoming incorporated into clinical practice guidelines (Nava and Ergan, 2013). The RESCUE trial (REspiratory Support in COPD after acUte Exacerbation) was an attempt to provide clarity on the effectiveness of NIV in COPD patients with prolonged hypercapnia following ventilatory support for acute respiratory failure. It was a multicentre, prospective, randomised controlled study designed to assess the impact of home NIV in addition to standard care on admission-free survival in patients who remained hypercapnic 48 hours after cessation of acute NIV (Struik, F.M., et al., 2014). 201 patients with severe COPD were recruited (mean FEV_1 26% predicted; mean $PaCO_2$ 7.7 kPa) and received moderate pressure support (IPAP 19 cmH_2O; EPAP 4 cmH_2O). The study found there was no difference between the intervention group and standard treatment group in the primary outcome, which was time to readmission or death. The study did demonstrate a significant treatment effect in the intervention arm in terms of reduction in $PaCO_2$. However, this was matched by a similar reduction in $PaCO_2$ in the

control arm and served to emphasise the importance of ensuring that the target population is selected to be the one most likely to benefit from the intervention. The initiation of long-term NIV in COPD patients in the early phase of a recovery from an acute exacerbation in this study failed to fully consider and adjust for the transient hypercapnia observed post acutely following a life-threatening exacerbation.

Thus, the literature to this point provided limited data to support the clinical and cost effectiveness of NIV in patients with COPD. However, Murphy and Hart (2014) suggested that the failure of NIV to enhance the clinical outcome in COPD patients with chronic respiratory failure should be considered as either a consequence of:

1. inappropriate target population selection
2. failure to deliver the intervention effectively
3. inappropriate primary outcome selection
4. failure of the intervention itself

More recent studies have suggested that the previous poor outcomes observed may be attributed to the use of NIV pressures that fail to adequately reduce hypercapnia; the use of high-intensity ventilation (a combination of higher IPAP and BURR) have demonstrated promising results. In the RCT by Köhnlein et al. (2014), 195 stable hypercapnic COPD patients were recruited and randomly assigned to the NIV group (n=102) or to the control group (n=93). The control group received optimised COPD therapy without NIV, but NIV was allowed temporarily in the case of an acute exacerbation with an increase in $PaCO_2$ to >10kPa (74 mmHg). In the NIV group, the NIV settings were aimed to decrease baseline $PaCO_2$ by ≥ 20% or achieve $PaCO_2$ < 6·5 kPa (48·1 mmHg), with a mean inspiratory pressure (IPAP) of 22cmH_2O used to achieve this. This study provides evidence that in chronic

hypercapnic COPD patients, the addition of NIV targeted to greatly reduce hypercapnia, when compared to standard treatment, improves overall survival, exercise capacity, and HRQoL (using Short Form Survey Instrument [SF-36]) over 1 year in patients with COPD compared with optimised COPD treatment without NIV. The findings of this study were in contrast to those of McEvoy et al. (2009) in that there was a significant improvement in blood gases, primarily the values of $PaCO_2$ without a decline in HRQoL. It should be noted that different tools were used to measure HRQoL in these studies and it has been demonstrated that the values from different HRQoL tools cannot be used interchangeably (Buss, A.S. and Silva, L.M., 2009; Swigris, J.J., et al., 2010); it is therefore not possible to compare directly the outcomes observed in HRQoL in these two studies. In addition, another group of investigators in another country have yet to replicate the survival outcomes with NIV observed in this study and there remain conflicting data, even from subsequent studies (Struik, F.M., et al., 2014).

2.3.1 Effect of NIV on the Cardiovascular System in COPD

It has been demonstrated that mechanical ventilation can affect cardiac output; the nature of the haemodynamic side effects depend upon the cardiac and respiratory status of the patient, the mode of ventilatory support and the ventilatory parameters chosen. In general, NIV reduces right ventricular and left ventricular preload and improves left ventricular afterload (Duke, G.J., 1999). These effects are enhanced especially if it is applied with higher inspiratory and/or expiratory positive airway pressures (Cournand, A., et al., 1947; Lukácsovits, J., et al., 2012; Esquinas, A.M., et al., 2013; Duiverman, M.L et al., 2016). However, in an analysis of 11 severe stable COPD patients, comparing cardiac and pulmonary effects of 6 weeks of low-intensity NIV and 6 weeks of high-intensity NIV, NIV per

se did not have an overall adverse effect on cardiac performance (Duiverman M.L., et al., 2016). Indeed, it may have a positive effect on HRQoL measures (using the Serious Respiratory Insufficiency Questionnaire [SRI]) with no significant change in sleep quality as measured by the Calgary Sleep Apnoea Quality of Life Index (SAQLI) (Weir M., et al., 2015).

2.3.2 NIV COMBINED WITH OXYGEN THERAPY IN COPD

The 'HOT-HMV' trial (Murphy P.B., et al., 2017) was a multi-centre RCT investigating the effect of home NIV with oxygen therapy, compared to oxygen therapy alone on hospital re-admission or death. It examined a cohort of 116 patients (59 randomized to home oxygen alone; 57 to home oxygen plus home NIV) with persistent hypercapnia ($PaCO_2$ >53mmHg; 7kPa), 2 to 4 weeks after resolution of respiratory acidosis. The study established that adding high intensity home NIV to home oxygen therapy (HOT) produced a 51% reduction in the risk of hospital readmission or death compared to the HOT only arm within the 12 months of the study. This study provides the necessary evidence to support the argument that home NIV should be adopted more widely as part of the management of severe COPD patients. The results also suggest that patients with severe COPD should be screened for suitability for home NIV therapy within 2-4 weeks following a hospitalisation requiring acute NIV, with the potential to reduce costs associated with hospital admissions (Vogelmeier C.F. et al., 2017).

2.3.3 CURRENT GUIDELINE FOR USE OF NIV IN COPD

Despite the increasing body of research now available, there remains disagreement in the recommendations for the use of NIV in COPD. The 2018 Global Initiative for Obstructive Lung Disease (GOLD) report considered that there was '*inadequate evidence of long-term*

benefit for patients with stable severe COPD' to warrant routine use of NIV (Mirza, S., et al., 2018). In contrast, the 2019 European Respiratory Society Guidelines suggest that long-term home NIV be used for patients with chronic stable hypercapnic COPD, and in those with COPD and persistent hypercapnia after a life-threatening episode of acute hypercapnic respiratory failure requiring NIV, and that NIV be titrated to normalise or reduce $PaCO_2$ levels (Ergan, B., et al., 2019).

2.4 NIV IN COPD-OSA OVERLAP SYNDROME

COPD and Obstructive Sleep Apnoea (OSA) are both highly prevalent, with 4.5% of the UK population aged over 40 diagnosed with COPD (British Lung Foundation, 2018) and 1.5 million adults with OSA (Rejón-Parrilla, J.C., et al., 2014). Given their prevalence, it is therefore likely that both conditions will occur together (overlap syndrome) based on chance association alone. Flenley (1985) first described the COPD-OSA overlap syndrome and defined it as a synergistic relationship between OSA and COPD.

Historically, typical phenotypes of COPD were described as '*pink puffers*' and '*blue bloaters*' (Filley, G.F., et al 1968; Netter, F.H., 1979) based on their physical presentation, with predominantly emphysema (pink puffers) and predominantly bronchitis (blue bloaters) as the two extreme phenotypes. The increased lung volumes and low body mass index (BMI) associated with the predominant emphysema phenotype protects against OSA, whereas the higher likelihood of peripheral oedema and increased BMI associated with the predominant chronic bronchitis phenotype promotes OSA (McNicholas, W.T., 2017). For a number of reasons, patients with COPD-OSA overlap syndrome may have a worse prognosis compared with patients with only one of those diseases. Studies have demonstrated that COPD is associated with oxygen desaturation during sleep, the level of which may exceed that

associated with maximum exercise (Mulloy, E. and McNicholas, W.T., 1996); a central element of OSA is intermittent nocturnal oxygen desaturation associated with apnoeas and hypopneas (Budin, C.E., et al., 2019). During sleep, patients with combined COPD and OSA suffer from more frequent episodes of oxygen desaturation and more total sleep time with hypoxaemia and hypercapnia than patients with OSA alone (Chaouat, A.R.I., et al., 1995).

Treatment with continuous positive airway pressure (CPAP) improves pulmonary function and gas exchange in patients with COPD-OSA overlap (de Miguel, J., et al., 2002; Mansfield, D. and Naughton, M.T., 1999). Marin et al. (2010) demonstrated that patients with COPD-OSA overlap treated with long-term CPAP and followed for a median of 9.4 years had a survival similar to patients with COPD alone, whereas overlap patients not treated with CPAP had a higher mortality (relative risk, 1.79; 95% confidence interval, 1.16-2.77) and were more likely to suffer a severe COPD exacerbation leading to hospitalization (relative risk, 1.70; 95% confidence interval, 1.21-2.38) versus the COPD-only group. The 2010 study by Machado M.L. et al. similarly demonstrated increased survival in patients with COPD-OSA overlap and hypoxaemia treated with CPAP when compared to patients who declined CPAP therapy. In patients with predominant OSA, standard CPAP is the preferred option, either set in the continuous or auto-adjusting pressure mode. However, where COPD is the dominant component, non-invasive ventilation (NIV) in the form of bi-level positive airway pressure (BIPAP) may be more appropriate (McNicholas, W.T., 2017).

2.5 Evidence for the use of Home NIV in Non-COPD in Adults

2.5.1 Neuromuscular and chest wall disorders

Prior to its introduction to manage respiratory failure in COPD, most published reports of sustained clinical use of NIV was centred on patients with neuromuscular disease (Kerby G.R., et al., 1987; Ellis E.R., et al., 1987; Hill N.S. and Braman S.S., 1999; DiMarco A.F. and Renston J.P., 1999; Mehta S. and Hill N.S., 2001). Neuromuscular and chest wall disorders are individually uncommon, but together form an important group of conditions that can lead to chronic ventilatory failure (Shneerson J.M. and Simonds A.K., 2002). Due to the progressive nature of many neuromuscular diseases and their associated complications, it is recommended that they be managed as part of a specialist multi-disciplinary team (Farrero E., et al., 2013). In the UK, patients who require assisted ventilation for >14 hours during a 24 hour period and are at risk of significant clinical harm if ventilation is interrupted are managed within the NHS Specialised Commissioning Framework (NHS England, 2013/14). This patient group falls outside the remit of a non-specialist outpatient home NIV service, and are therefore excluded from further discussion within the scope of this research study.

2.5.2 Obesity Hypoventilation Syndrome

The World Health Organisation's definition of obesity is a Body Mass Index (BMI) greater than or equal to 30kg/m^2. In 2014/15, there were 6,032 Finished Consultant Episodes (FCE's) in NHS hospitals with a primary diagnosis of obesity; obesity prevalence has increased from 15% in 1993 to 26% in 2014. The prevalence of Obesity Hypoventilation Syndrome (OHVS) in adults is unknown, but it has been estimated to be 0.3–0.4% (Mokhlesi B., 2010). OHVS is characterised by obesity and chronic hypercapnic respiratory failure in the absence of other

causative clinical conditions e.g. neuromuscular, metabolic, lung or chest wall disease (Mokhlesi B., et al., 2008). It frequently co-exists with OSA, which is also associated with obesity. The study by Masa et al. (2015) reported that 73% of patients with OHVS also had OSA, but the symptoms and cardiovascular consequences of OHVS are worse than those in patients with OSA (Kessler R., et al, 2001).

The recommended therapy for OSA is CPAP (NICE, 2008) and research has focussed on whether CPAP or NIV is the more appropriate management strategy for patients with OHVS and OSA. Pieper et al. (2007) found CPAP and NIV to be equally effective in improving daytime hypercapnia in patients with OHVS without severe nocturnal hypoxaemia; an RCT from Howard et al. (2014) comparing NIV with CPAP for initial treatment of OHVS found no difference in treatment failure, sleepiness or HRQoL at 3 months between treatment groups. In contrast, a large multicentre RCT by Masa et al. (2015) comparing NIV, CPAP, and lifestyle modification over a 2-month period in patients with OHVS but without OSA concluded that NIV yielded better respiratory functional improvements than CPAP. It was observed that there was a tendency towards lower healthcare resource utilisation in the NIV group. Despite the higher initial cost of NIV, reduction in healthcare resource use would be attractive to both commissioners of service and to service providers.

Given the characteristics of obesity-associated hypoventilation, there has been interest in to the effects of different modes of ventilation (‘volume assured’ ventilation versus ‘pressure support’ ventilation). Whilst the use of volume assured ventilation has demonstrated improvements in nocturnal and daytime blood gases (Storre J.H., et al., 2006; Murphy P.B., et al., 2012), there were no significant changes in the other clinical and HRQoL outcomes

reported; this suggests that there is no significant additional benefit provided by this mode of ventilatory support in OHVS patients.

In a similar approach to that currently used to characterise COPD, Pépin et al. (2016) described OHVS in terms of phenotypes, which may also guide their management:

- Patients with marked desaturation, hypercapnia, and worsening hypoventilation in REM sleep.
- Patients with predominant OSA
- Patients with OHVS and chronic lung disease such as COPD, termed 'overlap' patients

CPAP may be sufficient in those with predominant OSA, whereas NIV is almost always required in those with hypercapnia, or in individuals for whom CPAP fails; this would therefore include those patients with OHVS/COPD overlap (Simonds A.K., 2016).

The primary goal of treatment for OHVS has been to correct sleep-related breathing abnormalities, thus reversing chronic respiratory failure. More recent studies have demonstrated that a more holistic management approach, with focus weight loss as well as physiological parameters, demonstrates improved reduction in body mass index (BMI), exercise capacity and HRQoL (Mandal S., et al, 2018) reinforcing the importance of weight reduction in conjunction with NIV in the management of this patient cohort.

2.6 Modes of Ventilatory Support

NIV is most commonly delivered using a bi-level positive airway pressure support modality. In its simplest terms, it referrers to the intermittent delivery of positive pressure during the

patients breathing cycle; the higher positive pressure delivered during inspiration is termed 'inspiratory positive airway pressure' (IPAP) and the lower pressure delivered during the expiratory phase is termed 'expiratory positive airway pressure' (EPAP). The difference between these two pressures is the amount of 'pressure support' that is being delivered to the patient and serves to increase tidal volume and hence minute ventilation.

The most frequent mode of NIV delivery is using a fixed pressure support mode, where the clinician sets the upper and lower pressure limit; there is disagreement about which ventilator set-up is preferable. Some studies have found that a 'high-pressure' approach that uses a lower backup rate (6 breaths/min) works as well as the 'high-intensity' high BURR approach (Murphy, P.B., et al., 2012), whilst others have advocated for different modes of ventilation than the usual pressure support and PEEP approach.

Average volume-assured pressure support (AVAPS-AE), which adjusts pressure support to maintain target average ventilation over several breaths, is a relatively recent mode of non-invasive positive pressure ventilation. A retrospective cohort study from Coughlin et al. (2015) of a QI initiative using AVAPS-AE in conjunction with medication reconciliation, appropriate oxygen therapy initiation and patient education, demonstrated a significant improvement in readmission rates. The proportion of patients who were readmitted on two or more occasions decreased from 100% (397 of 397) in the year prior to initiation of intervention to 2.2% (9 of 397) in the following year ($\chi 2 = 758$, $p < 0.0001$).

2.7 Patient Selection for an Adult Non-Specialist Home NIV Service

The continuing improvements in the medical management of many chronic respiratory and extra-pulmonary diseases, and the rising levels of obesity, are likely to be contributing

factors to the growth in home NIV use (Bwika J., et al., 2013). Therefore, it is essential that patients considered for home NIV be selected with care and rigour to optimise patient outcomes, maintain patient safety and manage service expenditure. However, it is not enough to consider only the clinical suitability of patients for home NIV, it is also essential to consider suitability in terms of treatment tolerance and the support required for the patient to be able to use NIV successfully.

Data from the Eurovent survey (Lloyd-Owen S.J., et al., 2005) indicates that only 56% of hospitals initiating home ventilation assessed whether patients or caregivers cleaned and operated the ventilatory equipment correctly after discharge from hospital. An editorial by Simonds (2006) emphasises the importance of effective education of patients, families, and carers to use home NIV confidently, with the provision of a clear plan of action should a problem arise.

2.7.1 Patient Selection in COPD

From the literature, there are no universally accepted indications for commencing home NIV in COPD patients. The Eurovent survey (Lloyd-Owen S.J. et al., 2005) indicated that decisions about when and how to start NIV in patients with COPD are highly dependent on local guidelines and each physician's current clinical practice. In the UK, home NIV for patients with COPD is considered on health economic grounds if a patient has had three hospital admissions with AHRF (Tuggey J.M. et al., 2003). The NICE COPD guideline (NICE, 2010) states that '*adequately treated patients with chronic hypercapnic respiratory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on LTOT should be referred to a specialist centre for consideration of long-term NIV*'. The guidance for invasive and non-invasive NIV from

Germany is more specific, recommending long-term NIV when $PaCO_2$ is >6.66kPa during the day, or >7.33kPa at night (Windisch, W. et al., 2010).

Consensus guidelines developed almost 20 years ago (Goldberg, A., 1999 are still in widespread use and summarised in Table 1:

Table 1: Consensus clinical indicators for home NIV use in COPD (taken from Cheung et al., 2010)

Disease Documentation	Before considering a COPD patient for NIV, a physician with skills and experience in NIV must establish and document an appropriate diagnosis on the basis of history, physical examination, and results of diagnostic tests, and assure optimal management of COPD with such treatments as bronchodilators, oxygen when indicated, and optimal management of other underlying disorders (such as performing a multi-channel sleep study to exclude associated sleep apnoea if clinically indicated) The most common obstructive lung diseases would include chronic bronchitis, emphysema, bronchiectasis, and cystic fibrosis.
Indications for Usage	**Symptoms** (fatigue, dyspnoea, morning headache, etc.) **AND** **Physiological criteria** (one of the following): a) $PaCO_2 \geq 7.33$kPa b) $PaCO_2$ 6.66 – 7.20kPa and nocturnal desaturation (oxygen saturation by pulse oximeter ≤88% for 5 continuous minutes while receiving oxygen therapy ≥2 L/min) c) $PaCO_2$ 6.66 – 7.20kPa and hospitalisation related to recurrent

(≥2 in a 12-month period) episodes of hypercapnic respiratory failure.

2.7.2 Patient Selection in OHVS

There are a number of historic cohort studies of patients with OHVS that demonstrate that the use of NIV improves blood gases (Masa J.F., et al, 2001; Heinemann F., et al, 2007; Budweiser S., et al., 2007). When initiated early, there is growing evidence to suggest that NIV is effective in reducing ITU requirements, general health care resources (Berg G., et al., 2001) as well as improving survival (Budweiser S., et al., 2007). However, screening for OHVS is often delayed until after an episode of AHRF (Quint J.K., et al., 2007).

It is clear that simply correcting $PaCO_2$ is not enough. Work by Manuel et al. (2015) has suggested that the diagnostic criteria in OHVS for NIV use base excess rather than arterial carbon dioxide, with normocapnic patients with a base excess ≥2 mmol/L being considered as having an early obesity-related nocturnal hypoventilation and thus be considered for NIV. It is therefore suggested that patients with BMI >30kgm^2 are screened with blood gases and overnight oximetry as a minimum.

2.8 In-patient versus Outpatient initiation of NIV

Traditionally, initiation of home NIV has been as part of either an acute or elective in-patient admission. In-hospital initiation of NIV has undoubted advantages, the obvious one being the presence of a team of trained experts able to resolve any medical or technical problems that may arise, and the ability to titrate pressures whilst monitoring physiological parameters. However, admission to hospital has clear cost implications for the healthcare

purchaser/provider (Plant, P.K., et al., 2003). Non-acute hospital admissions are often inconvenient for the patient, beds may be unavailable, there is a risk of nosocomial infections particularly with the current concerns around COVID 19, and patients and families inevitably lose time off work or study (Rodger, M.A., et al., 2003).

In keeping with NHS England's current healthcare policy of providing high quality and cost-effective care in the community (England, N.H.S., 2019), the numbers of people receiving and services delivering home NIV are increasing (Lloyd-Owen, S.J., 2005; Fletcher, S.V., Ewles, S. and Wilkinson, J.E., 2012; Mandal, S., et al., 2013). Initiation of home NIV has historically been performed with an in-patient admission, including an overnight titration study within the UK National Health Service and other healthcare systems (Suh, E.S., et al., 2019). However, more recent studies have demonstrated that NIV can be set up safely in the outpatient setting or in the patients' home, and the effectiveness of NIV treatment can be monitored in the community (Bertella, E., et al., 2017).

A prospective, observational study of a mixed cohort of 16 patients divided into two groups (outpatient protocol n=9; standard in-hospital initiation with an elective admission n=7) demonstrated that at 3 months, the effectiveness of ventilation and the number of hours of ventilation was equivalent in all groups. This was irrespective of the route of NIV initiation (Luján, M., et al., 2007). A retrospective review of 22 patients undergoing clinic NIV initiation over 12-months by Newnham, M., et al. (2014) similarly demonstrated that in selected patients, clinic NIV initiation was a viable alternative to in-patient initiation. Both studies also demonstrated considerable cost savings for outpatient initiation compared to in-patient initiation.

A randomised trial of 28 stable neuromuscular and chest wall disease patients with nocturnal hypoventilation demonstrated that outpatient initiation of NIV is feasible, with equivalent outcome in the outpatient and the in-patient groups (Chatwin, M., et al., 2008). A larger study of 77 patients with neuromuscular disease (39 in-patient set up, 38 home set up) demonstrated that not only was home set up of NIV feasible, it was as effective for gas exchange and quality of life as hospital initiation and produced significant reduction in healthcare costs (Hazenberg, A., et al., 2014).

Whilst these results are important for patients with neuromuscular and chest wall disease, it is important that the data is not simply extrapolated and applied to the COPD patient cohort, as has often happened with NIV. The study by Criner, G.J., et al. (1999) demonstrated success rates in terms of gas exchange, functional status, and respiratory mechanics following NIV initiation of 80% in restrictive disorders (NMD & chest wall disease) and only 50% in COPD. Patients with neuromuscular disease are a significantly different population from COPD; they are generally younger, are more familiar with medical equipment, often have excellent support in place and have less comorbidity, all of which favour successful home initiation of NIV.

The study by Tai, C., et al. (2018) retrospectively examined patient records of arterial blood gas results, compliance, air leak and frequency of exacerbations resulting in hospital admissions in 39 patients with COPD who had been set up on home NIV (24 in-patient set up, 15 outpatient set up). The study found similar clinical outcomes in the outpatient group compared to those set up as in-patients. The study also demonstrated a significant cost benefit (at least £759 per patient compared to in-patient setup), which is important when considering the management of an increasing number of hypercapnic COPD patients.

Similarly Duiverman et al. (2020) in a study of 67 stable hypercapnic COPD patients that were randomised to initiation of NIV in the hospital or at home using telemedicine, found that home NIV initiation was non-inferior to in-hospital initiation, was preferred by the patients (64 of 67) and reduced costs by over 50%. Schwarz, S.B., et al. (2018) demonstrated that stable COPD patients, established on NIV, could be effectively monitored in an outpatient setting without the need for in-patient visits to assess control.

As previously described, patients with COPD frequently present with other co-morbid conditions. Patients with COPD–OSA overlap syndrome have a greater incidence of chronic respiratory failure compared with patients with OSA alone. Guidelines recommend the use of full polysomnography (PSG), accompanied by waveform analysis and retrospective NIV modification the following day to direct NIV titration and reduce patient-ventilator asynchrony [PVA] (Kushida, C.A., et al., 2005; Chediak, A., et al., 2010). If this guideline were to be followed rigidly, it would make outpatient initiation of NIV problematic in this group of patients, as full polysomnography is technically demanding, requiring highly skilled staff to perform the analysis and necessitates an overnight admission with all of the associated costs. A recent study of 14 patients with COPD–OSA overlap syndrome ($PaCO_2$ >6 kPa; BMI >30 kg/m^2) by Patout et al. (2019) found that the change in daytime $PaCO_2$ at 3 months in patients initiated using limited monitoring and nurse-led titration was comparable with patients titrated during an in-patient admission using polysomnography. A similar but larger study of 60 patients with predominantly neuromuscular disorders produced similar outcomes (Hannan, L.M., et al., 2019), reporting no differences in nocturnal gas exchange or overall measures of HRQoL. They noted that NIV titrated with PSG was associated with less PVA, but not less sleep disruption when compared with therapy titrated during the daytime

alone. The literature has indicated that outpatient NIV setup in OHVS, using an auto-titrating device, has similar cost as an inpatient setup using nurse-led overnight titration NIV. Importantly, there was no difference in clinical effectiveness or safety between inpatient and outpatient setup (Murphy, P.B., et al., 2019).

2.9 Compliance with Home NIV

There are a number of studies that suggest that lower NIV usage is associated with poorer outcomes. It was demonstrated by Funk, G.C., et al. (2011) that withdrawal of NIV causes clinical worsening in a cohort of 26 COPD patients with chronic hypercapnic respiratory failure. A retrospective analysis of 20 COPD patients demonstrated that long-term home NIV used for at least 4 hours per day was effective in reducing recurrent AHRF and readmissions in a highly select group of patients with severe, unstable COPD and frequent AHRF (Ankjærgaard, K.L., et al., 2016). A systematic review and individual patient data meta-analysis of stable COPD patients using home NIV found a significant drop in $PaCO_2$ at 3 months in patients who used ventilation on average for more than 5 hours per night compared to those who used it for less than 5 hours per night (Struik, F.M., 2014). The European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD acknowledge the adverse effect of poor adherence to NIV and recommend that patients should aim to use NIV for 5 hours a day (Ergan, B., et al., 2019). A more recent study of 1,210 patients on home NIV with a range of conditions including NMD, CWD, COPD, OHS and overlap syndrome showed that less than 4 hours NIV usage per day was associated with worse survival (Schwarz, E.I., et al., 2020). Furthermore, the study also indicated that interrupted patterns of ventilation or an overall decreased use might indicate inappropriate settings, adverse effects or patient discomfort. Conversely, in patients with

COPD, increasing use of their NIV over time may also reduce deterioration in their overall health and potentially predict exacerbations (Blouet, S., et al., 2018; Borel, J.C., et al., 2015). It is therefore reasonable to conclude that 'daily use' or compliance monitoring from ventilator hardware seems to be of clinical use, and a minimum of 5 hours NIV usage over a 24 period is recommended to achieve a significant reduction in $PaCO_2$ and improve patient outcomes.

It has been suggested that initiation of NIV as an outpatient procedure may reduce overall compliance when compared to an in-patient set up. In a study of 7 patients, Strumpf, et al. (1991), recorded poor compliance with ventilation in up to 70% of patients with COPD who received NIV after receiving minimal instructions at the health centre where the prescription was made. In contrast, Meecham Jones et al. (1995) recorded poor compliance in only 22% of their 14 patients initiated on NIV as an in-patient; Luján et al. (2007) concluded from their study of 16 patients that that the model of initiation used does not influence the patient's level of compliance. A larger and more recent retrospective analysis of 94 home NIV patients (57 OHVS; 37 COPD) by Ramalho, et al. (2019) demonstrated poorer adherence to NIV in the patients with COPD, suggesting that adherence to NIV may be more intrinsically related to the patients' disease rather than where NIV was initiated.

2.10 Health Related Quality of Life

Research has demonstrated that patients with chronic respiratory failure have poor survival (Postma, D.S., et al., 1979; Celli, B.R., et al. 2008); in patients with severe COPD, a 5-year mortality of 70–100% was reported (Sahn, S.A., et al. 1980). Survival rates are difficult to improve once this group of patients have developed respiratory insufficiency. Despite treatment with long-term oxygen or NIV, median survival remains at approximately 3 years

(Chailleux, E., 1996). Although survival rates appear difficult to improve, interventions such as NIV may have the potential to improve HRQoL (Nishiyama, O., et al, 2005; Carone, M., et al., 2007). Indeed, data from the *Quality of Life Evaluation and Survival Study* (Carone, M., et al.,2016) suggests that Health Status assessment can detect a worsening in health better than functional parameters, and that it is a better predictor of mortality than functional parameters such as FEV_1 and exercise performance (Carone, M., et al., 2001).

In 1948, the World Health Organisation (WHO) defined health as '*a state of complete physical, mental and social well-being, and not merely the absence of disease*' (World Health Organization, 2014). This definition suggests that quality of life encompasses several key areas, or 'domains' and is summarised in Table 2.

Table 2: WHO domains of QoL (Adapted from World Health Organisation WHOQOL-100.2)

Domain	Items incorporated within the domains
1. Physical health	○ Energy and fatigue ○ Pain and discomfort ○ Sleep and rest
2. Psychological health	○ Body image and appearance ○ Negative feelings ○ Positive feelings ○ Self-esteem ○ Thinking, learning, memory, and concentration
3. Level of independence	○ Mobility ○ Activities of daily living ○ Dependence on medicines and medical aids ○ Work capacity
4. Social relationships	○ Personal relationships ○ Social support

(HRQoL)	○ Sexual activity
5. Environment	○ Financial resources ○ Freedom, physical safety and security ○ Health and social care: accessibility and quality ○ Home environment ○ Opportunities for acquiring new information and skills ○ Participation in and opportunities for recreation and leisure ○ Physical environment (pollution, noise, traffic, climate) ○ Transport
6. Personal values and beliefs	○ Religion ○ Spirituality ○ Personal beliefs

Health can be considered in terms of a person's body structure and function and the presence or absence of disease or signs (health status); their symptoms and what they can and cannot do i.e. the extent to which the condition affects the person's normal life (quality of life). Quality of life may be expressed as a measure of the difference between the hopes and expectations of the individual and the individual's present experience (Fayers, P.M. and Machin, D., 2013). HRQoL is primarily concerned with those factors that fall within the spheres of influence of health care providers and health care systems.

Evaluation of HRQoL has become steadily more crucial in research and health care practice in order to evaluate the human and financial costs and benefits of modern medical techniques (Testa, M.A. and Simonson, D.C., 1996). During the last two decades, a number of generic and disease-specific questionnaires have been developed to assess HRQoL in

disease (Fayers, P.M. and Machin, D., 2015). In the main, generic questionnaires are not specific to any particular disease and allow comparisons of HRQoL to be made between patients with different diseases or patients without disease. One of the most widely evaluated generic health measures is the Medical Outcomes Study 36-item Short-Form Health Survey Questionnaire (SF-36), accounting for 10% of all published reports before 2000 (Garratt, A.M. et al, 1993). The SF-36 is commonly used in the UK to provide an indication of the health status of particular populations to assist with service planning, and to measure the impact (in terms of health gains) of clinical and social interventions (Burholt, V. and Nash, P., 2011).

Condition or disease specific questionnaires are designed to measure how a specific disease affects HRQoL in a particular patient population. The choice of instrument depends on the approach of the study, and it is important to use instruments that are both reproducible and valid for the condition being investigated (Guyatt, G.H., et al 1989). Many of the common HRQoL tools used for patients with respiratory disease are well validated in chronic respiratory failure due to COPD; patients with chronic respiratory failure due to other diseases or causes may also report some of the same respiratory complaints as COPD patients. However, they might report a heavier burden of symptoms and other kinds of disease related problems, especially in the advanced stages of disease.

2.11 HRQoL Questionnaires in Chronic Respiratory Failure (CRF)

From the research and current guidelines, non-invasive ventilation is indicated in patients with chronic, severe respiratory insufficiency of different causes. However, not only the underlying disease, but also the intervention itself can have a deep impact on the patients'

quality of life. HRQoL is an important outcome factor in patients with chronic, non-curable disorders. This is particularly pertinent to patients with severely advanced chronic respiratory failure who receive home NIV and in whom life expectancy is considerably reduced (Huttmann S.E. et al., 2015).

The generic HRQoL questionnaire most widely studied and used is the SF-36 (Ware Jr, J.E. and Sherbourne, C.D., 1992). The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale that assesses eight health concepts/domains:

1. limitations in physical activities because of health problems
2. limitations in social activities because of physical or emotional problems
3. limitations in usual role activities because of physical health problems
4. bodily pain
5. general mental health (psychological distress and well-being)
6. limitations in usual role activities because of emotional problems
7. vitality (energy and fatigue)
8. general health perceptions

Despite its extensive use prior to the year 2000, studies that are more recent have demonstrated that, compared to disease specific HRQoL tools, the SF-36 lacks discriminative capacity and is not an appropriate instrument for determining the affective state of COPD patients (Buss, A.S. and Silva, L.M., 2009).

The St. George's Respiratory Questionnaire (SGRQ) has become one of the most widely used instruments for assessing HRQoL in respiratory patients since its development in 1991 (Jones, P.W., at al. 1991). It is a standardised, self-completed questionnaire for measuring

impaired health and perceived well-being ('quality of life') in airways disease (Jones, P.W., Quirk, F.H. and Baveystock, C.M., 1991) and is well validated for use in patients with COPD and asthma (Guyatt, G.H., et al., 1987; Jones, P.W., et al., 1991) but not for patients with chronic respiratory failure receiving NIV. The specificity of the SGRQ for airway disease may mean that it fails to address a number of factors that are important for the daily life of patients receiving home mechanical ventilation; this leads to an incomplete assessment of HRQoL in these patients (Windisch, W., et al. 2003). Therefore, an instrument with more relevant 'domains' may be more appropriate when assessing HRQoL in home NIV patients.

The Maugeri Respiratory Failure Questionnaire (MRF_{28}) was the first instrument designed to identify a core set of items that may characterize impaired health in chronic respiratory failure (CRF), since none of the questionnaires previously used to measure impaired health in patients with CRF were developed for use specifically in such patients (Carone M., et al., 1999). Its 28 items are grouped around three specific factors:

- *Daily activity*, associated with disability in daily life due to breathlessness
- *Cognitive function*, related to impaired cognitive function
- *Invalidity*, related to the experience of social isolation or dependency on others.

The MRF_{28} total and subscale scores range from 0% (best health status) to 100% (poorest health status) (Carone, M., et al., 1999). From a practical perspective for research, the MRF_{28} may be more attractive than other HRQoL questionnaires, as it is self-administered, contains only 28 items and takes approximately 10 minutes for patients to complete (Duiverman, M.L., et al., 2008).

More recently, the Serious Respiratory Insufficiency (SRI) questionnaire, originally produced in German, was developed as a specific HRQoL measurement tool for patients with chronic

respiratory failure receiving HMV to identify relevant domains of HRQoL in this patient group (Windisch, W., et al., 2003). It measures diversified health impairments more multi-dimensionally and discriminatively, with greater balance in patients receiving NIV. Subsequently, the SRI has been translated and validated for a number of different languages; the key papers are summarised in Table 3.

Table 3: *Summary of papers validating the translated SRI*

Author	Study type	Patients	SRI Summary Score for home ventilation patients
Gosh et al. 2012	English SRI validation	152 stable NIV and IV patients	55.9 ± 18.9 (all patients) 43.1 ± 17.3 (COPD) 61.9 ± 16.1 (RCWD) 58.8 ± 20.3 (NMD) 53.4 ± 18.8 (OHVS) 53.5 ± 19.7 (miscellaneous)
Markussen et al. 2015	Norwegian SRI validation	127 stable NIV and IV patients	55.8 ± 18.4 (all patients) 61.0 ± 14.7 (NMD) 43.2 ± 19.0 (COPD) 58.4 ± 18.3 (OHVS) 55.8 ± 18.4 (RCWD)
Chen et al. 2017	Chinese SRI validation	149 stable NIV patients	52.93 ± 15.11
Oga et al. 2017	Japanese SRI validation	56 stable NIV patients	56.0 ± 15.3 (all patients) 56.6 ± 14.7 (COPD) 55.5 ± 16.4 (Tb)
Ribeiro et al. 2017	Portuguese SRI validation	93 stable NIV and IV patients	56.6 ± 15.7 (all patients) 57.0 ± 16.5 (COPD)

			55.6 ± 15.1 (OHVS) 62.0 ± 12.6 (RCWD) 50.2 ± 16.2 (COPD+OSA) 59.4 ± 19.2 (NMD) 46.0 ± 13.3 (miscellaneous
Valko et al. 2020	Hungarian SRI validation	104 stable NIV and IV patients	66.8 ± 15.1 (NIV) 58.2 ± 13.6 (IV)

(NIV – Non Invasive Ventilation; IV – Invasive ventilation)

The SRI has been validated in a number of specific clinical conditions requiring NIV including COPD, restrictive thoracic disorders, neuromuscular disorders, and OHVS as well as mixed clinical cohorts (see Table 4). However, whilst it is self-administered, the SRI contains significantly more items than the 28 items of the MRF_{28} (49 items) and thus takes approximately 20 minutes to complete rather than 10 minutes reported for the MRF_{28}.

Table 4: *Summary of papers for validation of SRI in a range of clinical conditions*

Author	Study type	Patients	SRI Summary Score for home ventilation patients
Storre et al. 2006	High intensity vs. target volume NIV	10 COPD patients with established HMV	59.3 ± 14.8 vs. 62.4 ± 18.9
Budweiser, 2007	Prognostic value of HRQL	231 stable IV and IV patients	61.2 ± 17.7 (all patients) 52.2 ± 15.6 (COPD) 66.2 ± 17.2 (RCWD)

			55.3 ± 9.2 (NMD) 71.3 ± 15.7 (OHVS/OL)
Windisch, 2008	SRI validation in COPD	162 COPD patients with established NIV	52 ± 17
Murphy, 2012	High intensity vs. high pressure NIV	7 COPD with established HMV	57 ± 11 vs. 69 ± 16
Huttmann et al. 2015	HRQL of invasively ventilated HMV patients	32 IV patients	53 ± 16 (all patients) 58 ± 16 (NMD)
Walterspracher, 2016	SRI for LOT COPD patients	COPD patients with established NIV	42 53.2 ± 18.6
Arellano-Maric et al. 2020	NIV vs. CPAP	42 OHVS patients with established NIV	61.2 ± 16 vs. 65.3 ± 14

Research suggests that the SRI is able to detect the influence of bicarbonate levels from arterial blood gases on physical functioning and social activities (Duiverman, M.L., et al., 2008). This is in line with a previous study, which demonstrated a high correlation between a reduction in bicarbonate level following establishment of home NIV and an increase in the SRI summary scale (Windisch, W., et al., 2006).

The comparative review of the MRF_{28} compared to the SRI (Duiverman, M.L. et al., 2008) concluded that both instruments were reliable and valid questionnaires in COPD patients with chronic hypercapnic respiratory failure, but emphasise different aspects of HRQoL.

While the emphasis in the MRF_{28} questionnaire is on activities of daily living, the SRI questionnaire, like the CRQ, is more related to anxiety and depression. Thus, to include the most extensive measurement of health-related quality of life in COPD patients with chronic hypercapnic respiratory failure, Duiverman, et al., (2008) recommended using the SRI. The systematic review and individual patient data meta-analysis by Struik at al., (2013) demonstrated that the SRI performed slightly better than the Clinical COPD Questionnaire (CCQ), CRQ and, MRF_{28} Questionnaire, which renders it the preferred questionnaire for scoring HRQL in patients with very severe COPD.

More recently, an association between SRI score and mortality in patients treated with long-term NIV has been demonstrated (Markussen, H., et al., 2019), with higher SRI sum scores associated with a lower mortality risk even after adjustment for age, education, hours a day on NIV, time since initiation of NIV, disease category and comorbidity (HR 0.98, 95% CI: 0.96-0.99). Thus, the use of HRQoL measurements should be considered an essential part of the holistic care of home NIV patients and the SRI is the tool of choice when assessing patients that use long-term non-invasive ventilation.

2.12 Minimal Clinically Important Difference

A minimal clinically important difference (MCID) is an important concept used to determine whether a medical intervention improves perceived outcomes in patients. Prior to the introduction of this concept in 1989, studies focused primarily on statistical significance (Jaeschke, R., Singer, J. and Guyatt, G.H., 1989). Whilst reporting the mean effect of an intervention may demonstrate a statistical difference, it does not necessarily inform clinicians or policy makers whether the patient will perceive these differences as important to them. During the 20th century, patient centred care became a focus of healthcare

systems, with its potential benefits in terms of patient satisfaction and perceived quality of care (McMillan, S.S., et al., 2013). Thus, identifying the difference that a patient feels is important may have an impact in terms of their satisfaction with treatment or therapy; it can also serve as a benchmark of what constitutes a meaningful effect of an intervention. There are several definitions of the MCID that correspond to the perspective of those who are evaluating it. For example, Jaeschke et al. (1989) defines MCID as '*the smallest difference in a score in a domain of interest that patients perceive as beneficial and that would mandate, in the absence of side effects, a change in the patient's management*'. Meltzer, E.O., et al. (2016) defines it as '*a statistical model that attempts to define the smallest change in a treatment outcome that a patient would identify as important'*.

However, as Jones (2002) described, there are difficulties and complexities associated with methods to determine the MCID. Since there is no "gold standard" for measuring health status, the subjective evaluation of "clinically significant" becomes important for health status (Jaeschke, R., et al., 1989). Health status measures may be compared or anchored to other clinical changes or results, which is thus termed anchor-based interpretation. The 'anchor' may be the patient's perception of the difference relative to their memories, or the clinician's perception. The reliability of patient judgement of their health remains problematic, and the relevant anchor judged clinically significant, may differ within different patient groups. In addition, there is substantial data showing that the patients' perspective and the clinicians' perspective usually differ (Hajiro, T. and Nishimura, K., 2002).

The minimal effect that would be meaningful to patients is termed the MCID; the minimal difference that reflects a true improvement (or deterioration) in an outcome is the minimally important difference (MID). There are no standard or universally accepted ways

for defining or determining the MCID for HRQoL questionnaires. However, different approaches for evaluating the MCID for HRQoL have reached similar conclusions. Thus, a score of 0.5 for the CRQ (Jaeschke, R., et al., 1989) and Asthma Quality of Life Questionnaire [AQLQ] (Juniper, E.F., et al., 1994), a score of 4 for the SGRQ (Jones, P.W. and Bosh, T.K., 1997) and a score of 6 points (using distribution based method) for the SRI (Kort, J., et al., 2018) were recommended as the interim standards for the clinical thresholds. More recently Raveling, T., et al. (2020) estimated that of change of between 4.5 - 6.2 points in SRI in patients with severe COPD who use long-term NIV was important, and therefore it was suggested a MCID of approximately 5 points is the cut-off point for a change in SRI to be clinically relevant.

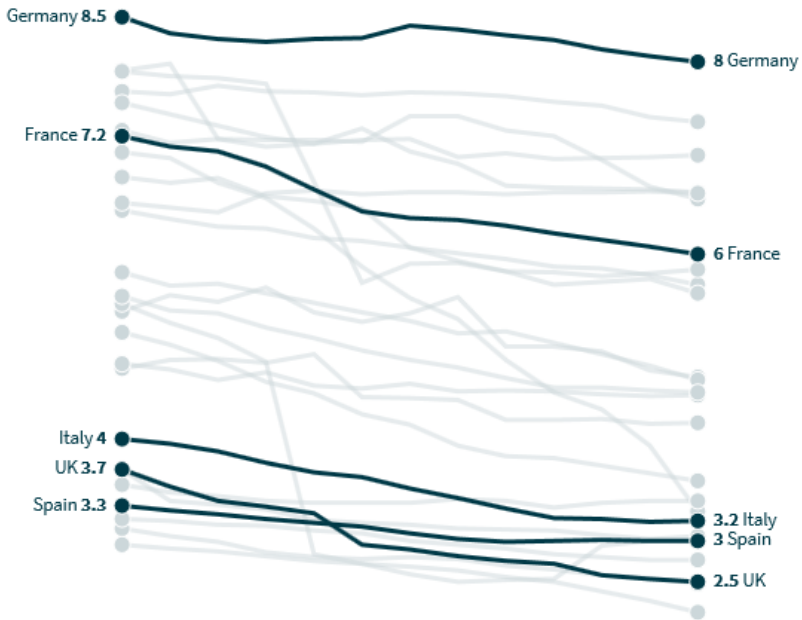
SUMMARY AND RESEARCH QUESTIONS

As medical care continues to advance, it becomes possible to prolong the survival of patients with chronic respiratory diseases until the very advanced stages of their natural history. It therefore becomes inevitable that the number of unavoidable acute in-patient admission for AHRF will also increase (Wilt, T.J., et al., 2007). The benefit of NIV has been demonstrated as first line intervention, in addition to normal medical care, for the management of AHRF secondary to an acute exacerbation of COPD (Lightowler J.V., et al., 2003). Historically, home NIV had been used to manage patients with chronic hypercapnia due to neuromuscular disorders. However, the success of NIV in COPD patients with AHRF led its long-term use in those patients with persistent hypercapnia following recovery from the acute exacerbation including patients with COPD and obesity hypoventilation syndrome (Janssens, J.P., et al. 2003). There remains disagreement about the evidence of long-term

benefit for patients with stable severe COPD (Mirza, S., et al., 2018; Ergan, B., et al., 2019), but with the introduction of high-intensity NIV, more consistent improvements have been demonstrated in patients with COPD.

It has been suggested that the initiation of NIV in patients with advanced COPD requires a high amount of motivation and cooperation from the patient and the therapy team and can therefore take well up to 2 weeks on the hospital ward before stable treatment conditions are achieved (Windisch, W., et al., 2018). However, there is also mounting evidence that hospitals in the UK are struggling: between 1987/88 and 2019/20, the total number of NHS hospital beds fell by 53 per cent – from 299,400 to 141,000 and as demonstrated in Figure 3, the UK has fewer hospital beds than most comparable countries (Ewbank, L., et al., 2017).

Figure 3: *Total hospital beds per 1,000 inhabitants in Europe (Taken from: NHS hospital bed numbers: past, present, future. Ewbank, L., et al., 2017)*



Given the continuing reduction in total number of NHS hospital beds, the initiation of long-term home NIV in an outpatient setting would potentially alleviate a proportion of the burden on the UK healthcare system. There is also literature to suggest that outpatient initiation may be effective and safe in appropriately selected patients (Duiverman, M.L., et al., 2020). Thus, the primary aim of the quantitative aspect of this research was to demonstrate that that initiation of long-term nocturnal home NIV via elective outpatient set up produces equivalent improvements in daytime $PaCO_2$ to those following NIV initiation as an acute in-patient admission over a 12-month period of treatment with NIV.

The literature indicates that patients who develop Type II respiratory failure due to an exacerbation of COPD and who then require non-invasive ventilation have a poor prognosis after they are discharged from hospital (Niewoehner, D.E., 2006; McGhan, R., et al., 2007; Suissa, S., et al., 2012. Titlestad, I.L., et al., 2013). Chu et al. (2004) found that, within the first year following discharge, more than 60% of patients who developed Type II respiratory failure due to an exacerbation of COPD are re-admitted, and more than 25% are deceased. Secondary analysis of the landmark 'HOT-HMV' trial (Murphy, P.B., et al., 2016) demonstrated that, in those patients that remain hypercapnic following an acute exacerbation of COPD, initiation of long-term home NIV delayed and reduced hospital admissions. This was in contrast to the 'RESCUE' trial (Struik, F.M., et al., 2014), which did not show any improvement in time to readmission or death by adding NIV. Thus, a secondary aim of the study was to assess the impact of the introduction of NIV on the frequency and length of stay (LOS) of respiratory related admissions based on the number of admissions and bed days in the previous 12 months versus the number of admissions and bed days in the 12 months following the introduction of NIV.

The research literature demonstrates that there is an association between NIV compliance and patient outcomes, particularly readmissions. A pilot study of treatment compliance in home non-invasive ventilation by Cheng, L., et al. (2011) found a correlation between the number of adverse event and lower percentage of days with home NIV use ≥ 4 hours/day in a mixed cohort of 65 patients. Thus, a further outcome of interest for the study was to identify if there were any associations between compliance and non-compliance with NIV with subsequent respiratory related admissions and mortality for a mixed cohort of patients. A review of a mixed cohort of 120 patients over 4 years found that patients with poorer compliance had worse outcomes (Ansari, Z., et al., 2014). They also reported a mortality rate of 30.8%, with mean duration between initiation of home NIV and death of 7.63 months. Chu, C.M., et al. (2004) reported 1-year mortality 49.1% for COPD patients having survived an AHRF and treated with NIV, which is significantly higher than the 20% reported by Ankjærgaard, K.L., et al.(2016). The study by Chu, C.M., et al. (2004) also found that 79.9% of patients had been re-admitted to hospital one year after discharge. Therefore, it was of interest to compare all-cause mortality and admission free survival in this mixed cohort with that from previous studies.

It is important with any intervention to consider not only the impact on physiological parameters and disease outcomes, but also patients feel and how satisfied they are with treatment. There is a growing recognition of the importance of understanding the impact of healthcare interventions on patients' lives rather than just on their bodies (Addington-Hall, J. and Kalra, L., 2001). Assessment of HRQoL has become steadily more important in order to evaluate the true costs and benefits of treatment modalities in patients with chronic disease. This is particularly true for patients with long-term home NIV and severe objective

limitations in daily living (Windisch, W. and Criee, C.P., 2006). Whilst clinicians often consider the most important outcome as the improvement in $PaCO_2$, patients usually care most about their quality of life (QoL), might care about survival (with good QoL), but usually do not care about $PaCO_2$ changes (Duiverman, M.L., 2018)

This research therefore also aimed to assess the impact of long-term nocturnal domiciliary NIV on the patients quality of life using a validated quality of life tool, the SRI questionnaire, which been specifically designed for assessing the effects of long-term home NIV on HRQoL. The primary aim of the quality of life aspect of this research was to demonstrate that that initiation of long-term nocturnal home NIV via elective outpatient set up produces equivalent improvements in HRQoL outcomes (based on summary SRI score) when compared to initiation as an acute in-patient admission over a 12-month period of treatment with NIV.

3 METHODOLOGY

3.1 INTRODUCTION

The purpose of this chapter is to describe the research methodology used for this study of the relationship between physiological parameters and quality of life in a cohort of patients treated with long-term home nocturnal non-invasive ventilation (NIV). The aim of the research was to examine a group of patients over a 12-month period that had previously presented to a district general hospital (Good Hope Hospital, Sutton Coldfield, UK) with decompensated Type II respiratory failure requiring management with long-term nocturnal home NIV.

The study aimed to provide a body of evidence to support the delivery of long-term nocturnal home NIV by a non-specialist NIV service and, via that service, demonstrate the efficacy and safety of outpatient initiation of NIV when compared to a more traditional in-patient initiation, using quantitative data and quality of life data. Comparison was made between patients that were established on long-term nocturnal home NIV during an acute in-patient admission and patients that were established on long-term nocturnal home NIV electively via an outpatient service.

The primary objective of the study was to establish if patients commenced on long-term nocturnal home NIV as an elective outpatient had equivalent outcomes in physiological variables when compared to patients commenced on long-term nocturnal home NIV as an in-patient during an acute admission with decompensated Type II respiratory failure. Secondary outcomes assessed the impact of long-term nocturnal home NIV on the

frequency and duration of respiratory related admissions and time to death following initiation of NIV.

The study also examined the effect of long-term nocturnal home NIV on the self-reported quality of life using the SRI questionnaire and scoring matrix (Appendix 1 and Appendix 1a), a validated tool for assessing quality of life in patients on long-term NIV. Comparison was made between patients that were established on long-term nocturnal home NIV during an acute in-patient admission and patients that were established on long-term nocturnal home NIV electively via an outpatient service. To identify any meaningful differences in quality of life that were linked to a specific clinical condition, the patient cohort was subdivided by clinical condition for sub-analysis.

Within the C1 Innovation Proposal was the requirement to demonstrate the potential for an on-going cost-benefit analysis of the proposed innovation; this study built on this requirement by providing analysis of comparative costs of in-patient versus outpatient initiation of long-term nocturnal home NIV and use of healthcare resources following initiation of long-term nocturnal home NIV.

3.2 Decision to Commence Nocturnal Long-Term Home NIV

The decision to commence nocturnal long-term home NIV was made on a case-by-case basis using clinical evidence, and in accordance with local clinical guidelines and the NHS Birmingham and Solihull and NHS Sandwell and West Birmingham Clinical Commissioning Group '*Policy for use of domiciliary Non-Invasive Ventilation, Version 1.0*' (NHS Birmingham and Solihull CCG & NHS Sandwell and West Birmingham CCG. 2020). Patients that had rapidly progressive neuromuscular disease or who required home NIV for >14 hours per 24

hour period fell outside the scope of the non-specialist NIV service provided at Good Hope hospital and were not included in this study cohort. The care of this group of patients was transferred to the local Tertiary Complex Sleep and Ventilation service at Birmingham Heartlands Hospital for on-going ventilatory management and support.

The indications for long-term nocturnal home NIV via the non-specialist service were evidence of chronic hypercapnia, demonstrated by an awake, non-acute, stable $PaCO_2$ level > 6.5kPa and a confirmed clinical diagnosis of one of the following:

- COPD with:
    - Evidence of recurrent admissions with decompensated hypercapnic respiratory failure requiring acute NIV (>2 in a 12 month period)

      OR

    - Difficulty weaning / unable to tolerate weaning from acute NIV
- OHVS indicated by:
    - BMI > 30 kg/m^2
    - Exclusion of other causes of hypoventilation
    - Polysomnography revealing sleep hypoventilation with nocturnal hypercapnia with or without obstructive apnoea/hypopnoea events
- Chest wall disease:
    - Diagnosed via physical examination and confirmed with radiological findings.
- Neuromuscular and neurological weakness with:
    - FVC<50% predicted or FVC <1L
    - Maximal inspiratory pressures (MIP)< 60cmH2O

- nocturnal symptoms of hypoventilation including sleep disruption, and headache upon awakening

Patients that commenced long-term home nocturnal NIV during an acute admission were set up with either a Stellar™ 150 ventilator or a Lumis™ 150 VPAP ST ventilator (ResMed Inc., San Diego, California, USA). NIV was initiated by a member of the NIV Physiotherapy Team on a dedicated respiratory ward, with a Respiratory Consultant clinically responsible for the patient and the decision to treat with long-term NIV.

Patients where NIV was begun as an outpatient were set up with a Lumis™ 150 VPAP ST. NIV was initiated by a specialist NIV respiratory and sleep scientist in an outpatient clinical room, with a couch and appropriate resuscitation facilities. A Respiratory Consultant remained clinically responsible for the patient and the decision to treat on the day of initiation, following clinical assessment of the patient. Patients that were commenced on NIV as an outpatient were identified from an outpatient home oxygen assessment and review (HOS-AR) clinic or following a respiratory sleep study, and after discussion at an NIV multidisciplinary team (MDT) meeting

The patient interface was selected on an individual basis and decisions about the interface were based on patient comfort, fit and tolerance. The interfaces used by patients in this study were: ResMed AirFit™ F20 full face mask (ResMed Inc., San Diego, California, USA); Fisher & Paykel Simplus™ full face mask (Auckland, New Zealand) and Philips Amara View™ hybrid face mask (Koninklijke Philips N.V, Amsterdam, Netherlands). Nasal masks were not used for patients in this study.

3.3 STUDY DESIGN

The initial study design was a two-part study; Part A, which assessed quantitative physiological variables and Part B, which assessed self-reported quality of life using the SRI questionnaire and a qualitative assessment of the perceptions and feelings of NIV users and their carers using semi-structured face to face interviews. Part A and Part B used an observational, longitudinal, retrospective study methodology in addition to semi-structured interviews for the qualitative data.

Patients established on long-term nocturnal home NIV as an in-patient followed the pathway and protocol specified in Appendix 3 (Guidelines for the use of Non-Invasive Ventilation (HGS)); they were commenced on home NIV during an admission with decompensated Type II respiratory failure. Patients established on home NIV as an outpatient followed the Standard Operating Procedure described in Appendix 4 (Outpatient NIV Trial for chronic hypercapnic respiratory failure in patients requiring non-complex NIV (Good Hope Hospital)).

During the period when the semi-structured interviews were planned to take place, the study was paused due to COVID 19 pandemic. Within the sponsoring Trust, all outpatient clinical work and research activity was ceased; clinicians were redeployed to support the in-patient workload and access to patients was severely restricted. Under COVID 19 guidelines, the majority of patients included within this study were deemed clinically vulnerable and as such were required to remain at home. Following re-evaluation of the study with my clinical supervisor in the light of the COVID 19 pandemic, it was regretfully decided to withdraw the semi-structured interview component from the study, as it was unlikely I would be able to obtain adequate data to be meaningful. For the purposes of this submission, I have included

a copy of the proposed semi-structured interview instruction sheet (Appendix 2), which had been submitted to, reviewed and amended by a qualified social scientist. It was planned to perform thematic analysis of the data using the NVivo 12 analysis package (QSR International, Melbourne, Australia) to explore the perceptions, feelings and experiences of home NIV patients and their carers.

3.3.1 Methodological Considerations

The aim of the study was observe the effect of a specific outcome; in this case, the introduction of NIV in the same cohort, by means of repeated measures, over a defined period. Thus, a longitudinal methodology was considered the most appropriate. On reflection, a prospective study design would have enabled the primary variables of interest to be more clearly defined at the outset and avoided the risks associated with missing variables. However, the unpredictability of the number of patients initiated on to domiciliary NIV as an outpatient in the time that was available for data collection made a prospective methodology impractical, with a significant risk of insufficient data to support the study hypothesis. A retrospective longitudinal study design allowed the use of an existing data set created for the management of the long-term home NIV patient cohort as the primary data source. It also was advantageous in terms of planning, initiating, and following a prospective cohort, not to mention less costly and time consuming.

3.4 Evidence of Stakeholder Engagement and Patient Involvement

The aim of this study was to provide evidence to support the efficacy and safety of long-term nocturnal home NIV initiated as an outpatient compared to that initiated as an inpatient; the inpatient route was already well established within the organisation. As part

of the development of a new clinical service, it is vital to involve key stakeholders in its development from the outset. The overarching goal of stakeholder engagement in medical research is to generate evidence that is more relevant and useful to those making real-world health care decisions, with the hope that this will increase the dissemination and uptake of research findings in clinical practice (Basch, E., et al., 2012). Recognition of the value and importance of integrating stakeholder engagement into comparative effectiveness research (CER) and patient-centred outcomes research (PCOR) to improve health care delivery continues to grow (Barger, S et al., 2019). Patients may enhance CER and PCOR by providing experiential knowledge to a research question or study design, informing data collection and analysis, reviewing and interpreting results, and improving translation and dissemination of key findings (Ciccarella, A., et al., 2018; Domecq, J.P., et al., 2014; Mullins, C.D., et al., 2012). Patient and public involvement (PPI) is now so well embedded that it is a funding requirement by the National Institute for Health Research (NIHR) and other funders that applicants provide information on how PPI has and will continue to inform the proposed research (Hayes, H., Buckland, S. and Tarpey, M., 2012).

Prior to commencing the study, a stakeholder group was created to inform the development of the service that would subsequently form the basis of this research. The stakeholder group comprised of the following groups:

- the Respiratory Consultants at Good Hope site who would support delivery of NIV
- Patients that use NIV and their caregivers
- Local General Practitioners (GP's) and Clinical Commissioning Groups (CCG's)
- Community based teams involved in supporting patients with complex health conditions.

- Local Home Oxygen Services - Assessment & Review (HOSAR)
- Acute NIV Physiotherapists
- Respiratory Clinical Scientists/Physiologists

A Respiratory Consultant with appropriate NIV experience was identified as the lead physician for the proposed NIV service at GHH. The opinions from the four respiratory consultants based at Good Hope site about the proposed service were obtained via a brief questionnaire; their feedback is summarised in Appendix 5.

A stakeholder engagement meeting was held in September 2017 to obtain input from key stakeholders not included in the cross-site group. The minutes from this meeting are included as Appendix 6, with the key points as follows:

- Patient representatives were positive about the proposed domiciliary NIV service closer to their locality and the benefits this would potentially offer.
- Representatives of local GP's and Community based teams were supportive but expressed some concerns in terms of supporting this complex cohort of patients in the community. It was agreed there would be additional education and training for healthcare professionals involved in the care of domiciliary NIV patients. Reassurances were provided that the GHH Trust clinicians would retain clinical responsibility for the patients from an NIV perspective.
- The CCG were unable to send representation to the meeting, but indicated via the Trust Clinical Commissioning team that they would support and financially reimburse a service that met the NIV Service Specification (NHS England, 2013/14) for domiciliary NIV.

A cross site working group consisting of the HEFT NIV Lead Consultant, GHH Consultant NIV Lead, HEFT Therapies Manager, NIV Lead Physiotherapist (BHH), NIV Lead Physiotherapist (GHH), Respiratory Clinical Service Lead (GHH), Respiratory Divisional Manager and Respiratory Group Support Manager was established to assess feasibility and ensure service standardisation and patient safety were maintained across the Trust. A pathway and documentation for the proposed service was developed and agreed with input from all working group members (Appendix 4).

3.5 PART A: QUANTITATIVE DATA

Part A of the study was an observational, longitudinal retrospective review of patients managed with long-term nocturnal home NIV initiated at Good Hope Hospital as either an in-patient or an outpatient. Data was recorded on a local database created for the on-going management of the long-term home NIV patient cohort and is summarised below in Table 5:

Table 5: NIV patient database standard data collection

Outcome	Measurement
Clinical	**Anthropometric:** Age; sex; BMI; clinical diagnosis **Treatment data:** Date of commencement; in-patient or outpatient set up; date NIV ceased if <12 months; days to 1st admission post NIV; days on NIV until death/first admission; number of admissions pre NIV; number of admissions post NIV; respiratory bed days pre NIV; respiratory bed days post NIV; using long-term oxygen therapy (LTOT)
Physiological (baseline; 1st review; 2nd review;	**Blood gases:** $PaCO_2$;pH; PaO_2; HCO_3; BE $\pm$ FiO_2 **NIV data:** IPAP; EPAP; mode; compliance

3rd review)	**Baseline spirometry**: FVC; FEV_1; FEV_1/FVC
Quality of life (baseline; 1st review; 2nd review; 3rd review)	**SRI (total and domains):** respiratory; physical functioning; sleep quality; social functioning; feelings of fear; mental health; social functioning

The study was registered with and sponsored by the research board at University Hospitals Birmingham NHS Foundation Trust (Reference number 20190055STU; 18/04/2019); the sponsorship letter is included as Appendix 7. Reporting of the study followed guidelines for observational studies using routinely collected health data.

Part A examined the relationship between use of long-term nocturnal home NIV and its impact of physiological parameters comparing initiation as an in-patient versus initiation as an outpatient.

3.6 Physiological Measurements

The primary outcome measure of Part A of the study was change in daytime $PaCO_2$ measured by blood gases, during spontaneous breathing. Other standard blood gas parameters (pH; PaO_2; HCO_3; Base excess) were recorded at each review but the data was not reported in this study due to the changes in prescribed oxygen FiO_2 that occurred during the study period. The data is available for review within the NIV database.

3.6.1 Blood gas sampling

$PaCO_2$ was measured using either arterial (via radial artery puncture) or arterialised capillary (via earlobe puncture) blood gas analysis taken at least 2 hours after cessation of nocturnal NIV. It has been shown that arterialised capillary blood sampling is less invasive than arterial

blood gas sampling (Fajac, I., et al., 1998) and less painful (Hajiseyedjavady, H., et al., 2012). A range of healthcare staff can perform it after minimal training (Higgins, C., 2008), it produces minimal discomfort to the patient (Dar, K., et al., 1995; Crawford, A., 2004) and very small sample volumes are required (approximately 60µL of blood).

Arterial blood gas sampling was performed in accordance with the AARC (American Association for Respiratory Care. 1992) clinical practice guideline; local anaesthesia was not routinely used for radial artery sampling in accordance with local Standard Operating Procedures. Arterialised capillary blood gas sampling was performed in accordance CLSI document GP42-A6 (Clinical and Laboratory Standards Institute, 2008). Arterialisation of capillary blood gas samples was achieved by the application of a rubefacient cream containing the active ingredients methyl salicylate and menthol (Deep Heat Max Strength, The Mentholatum Company Limited, East Kilbride, Scotland) for a minimum of 10 minutes prior to skin puncture. Arterial samples were collected using 3mL pre-filled heparinized single-use disposable syringes with a 23G x 1inch safety needle (BD Preset™ Eclipse™ Arterial Blood Collection Syringe. Becton, Dickinson and Company, Plymouth, UK); arterialised capillary samples were collected using 150ul, 1.90 x 100mm heparinized single-use disposable plastic capillary tubes (Protech Medical Limited, Glossop, UK). Patient blood gas samples were processed within <5 minutes for arterial samples and <2 minutes for capillary blood gas samples.

3.6.2 BLOOD GAS ANALYSIS

Blood gas samples were analysed using the Cobas b123 POC blood gas system or the Cobas b221 blood gas system (F. Hoffmann-La Roche Ltd, Basel, Switzerland). All analysers were calibrated, maintained and operated according to their manufacturer's instructions and

were included in an external quality control programme (Weqas POCT Blood Gas EQA programme). Arterial and arterialised capillary blood gas samples were performed by healthcare professionals that had successfully completed a competency based training program in blood gas sampling. Blood gas samples were analysed by healthcare professionals that had successfully completed a competency based training program in use of the Cobas b123 or Cobas b221 blood gas analyser.

3.6.3 SPIROMETRIC MEASUREMENTS

Baseline spirometry was performed to confirm clinical diagnosis; spirometric values (Forced Vital Capacity (FVC); Forced Expiratory Volume in the first second (FEV_1); FEV_1/FVC) were recorded. Spirometry was performed using the nSpire HDpft 1000 portable spirometer (nSpire Health Inc., Longmont, CO 80501, USA) and data was downloaded and stored using nSight™ Software V6.2 (nSpire Health Inc., Longmont, CO 80501, USA). Spirometry was performed in accordance to ERS/ATS guidelines (Miller, M.R., et al., 2005) by healthcare professionals that had completed an accredited certification program. Clinically significant airflow limitation was defined as an FEV_1/FVC below the lower limit of normal (LLN), which represents the lower 5% of test results from a healthy, non-smoking population. Use of a fixed ratio to define airflow limitation, traditionally 0.70, was avoided in this study as it may underestimate airflow limitation in younger individuals (Cerveri, I., et al., 2008) and overestimate airflow limitation in older individuals (Swanney, M.P., et al., 2008).

Patients receiving long-term oxygen therapy had been formally assessed by a member of the specialist Home Oxygen Assessment Service (HOS-AR). Home oxygen was prescribed in accordance with BTS Quality Standards for home oxygen use in adults (Suntharalingam, J., et al., 2017).

The physiological data set formed part of the routine review of long-term nocturnal home NIV patients at Good Hope Hospital; no additional data was recorded other than that collected as part of the routine care and management of the patient cohort. The standard operating procedure for each NIV outpatient review is documented in Appendix 8.

3.6.4 COMPLIANCE DATA

Each Stellar™ 150 ventilator or Lumis™ 150 VPAP ST ventilator (ResMed Inc., San Diego, California, USA) has an internal memory that collects patient treatment data. This includes information on mask fit (leak data), usage hours and the time of day that the unit was used. At each patient visit, the data was downloaded to the ResScan™ patient management system either via direct link or a USB stick. The ResScan™ patient management system consists of the ResScan software, ResScan Data Card, ResLink™, and ResScan Serial and USB Adapters. Remote monitoring software was available, but was not used during this study as the Stellar™ 150 ventilator was not compatible without an appropriate modem and adequate numbers of these were not available at the time of the study.

Patient compliance was reported as 'mask on' hours rather than 'device on' hours to measure true patient usage; the 'average' daily usage was recorded rather than the 'median' usage. The average daily usage is caculated as '*total hours/total days'*, wheras the median usage is calculated as '*hours per day/used days'*. Average daily usage was selected for the study as it more closely true patient usage; use of the median values minimises the impact of 'non-used' days and was therefore rejected. From the research literature and for the purposes of this study, patients that used NIV every day for ≥5 hours/day were classified as 'compliant'; patients who used NIV irregularly and <5 hours/day were classified as 'non-compliant'.

3.7 PART B: QUALITY OF LIFE DATA

Part B examined the relationship between use of long-term nocturnal home NIV and its impact of quality of life as recorded using the SRI questionnaire (and specific domains within the tool). Patients initiated on long-term nocturnal home NIV either as an acute in-patient admission or as an elective outpatient set up were asked to complete a baseline SRI questionnaire and to complete repeat SRI questionnaires at subsequent reviews at approximately 3, 6 and 12 months after initiation of home nocturnal NIV. Subsequent SRI values were compared with baseline SRI in patients commenced on long-term nocturnal home NIV, comparing set up as an acute admission versus as an elective outpatient. The quality of life data set using the SRI formed part of the routine review of long-term nocturnal home NIV patients at Good Hope Hospital; no additional data was recorded other than that collected as part of the routine care and management of the patient cohort.

3.8 PRIMARY OUTCOME: PART A

The primary outcome of Part A of this study was to assess if there was a statistically significant difference in daytime $PaCO_2$ measured by blood gases during spontaneous breathing after approximately 6/52, and subsequently 6 and 12 months of long-term nocturnal home NIV compared with baseline $PaCO_2$ in a cohort of patients, comparing set up as an acute in-patient admission versus as an elective outpatient. Statistical significance provides an indication of the reliability of the study results, but may not reflect the clinical relevance or importance. The clinical significance of the difference in the change in daytime $PaCO_2$ may therefore more closely reflect its impact on clinical practice.

In order to establish whether elective outpatient initiation of home NIV is equivalent to in-patient initiation, it is helpful to make an estimate of the difference in the effect between

the outpatient and in-patient NIV set up that would be clinically relevant. This methodological approach is termed a non-inferiority study and is routinely used in randomised controlled trials to assess an established treatment or medicine against a new or alternative treatment. Whilst not routinely used in observational, longitudinal, retrospective studies, an estimate of clinically acceptable non-inferiority was considered helpful in assessing a clinically relevant difference in effectiveness between the two routes of NIV initiation, in addition to the statistical significance. A true estimate of non-inferiority cannot be made without an estimate of the statistical power required to detect non-inferiority. This study was not randomised nor controlled and the two groups in the study were not matched, therefore accurate calculation of non-inferiority between the groups cannot be made. However, using evidence from previous studies, an estimate of the difference in $PaCO_2$ that would be clinically relevant was assigned.

Previous studies of the impact of NIV have suggested that a change in $PaCO_2$ > 0.45kPa demonstrates clinically relevant benefits in sleep quality and sleep time (Meecham Jones, D.J., et al., 1995), 6-minute walk distance and dyspnoea measured by the Transition Dyspnoea Index (Diaz, O., et al., 2005) and health related quality of life (Meecham Jones, D.J., et al., 1995, Duiverman, M.L., et al., 2008; Duiverman, M.L., et al., 2011). Therefore, if a difference of $\leq$0.4kPa in $PaCO_2$ between in-patient and outpatient NIV initiation was observed at 12 months, it would be unlikely to defer any clinically relevant benefit and thus would not be considered clinically significant.

The null hypothesis stated that over a 12-month period of treatment with NIV, initiation of long-term nocturnal home NIV via elective outpatient set up produces improvements in

daytime $PaCO_2$ that are equivalent to those observed following initiation as an acute in-patient admission.

3.8.1 Secondary Outcomes: Part A

The secondary outcome for the quality of life component of the study assessed the impact of the introduction of NIV on the frequency and length of stay (LOS) for respiratory related admissions. This was based on the number of admissions and bed days in the previous 12 months versus the number of admissions and bed days in the 12 months following the introduction of NIV. Bed days are defined as a day during which a person is confined to a bed and in which the patient stays overnight in a hospital. The NIV usage data, which was recorded at each visit, was analysed to ascertain any association between compliance and non-compliance with domiciliary NIV and subsequent respiratory related in-patient admissions. The mean hours of 'mask on' on rather than 'device on' time were recorded in the NIV database to ensure that true 'treatment effect' could be assessed.

To assess the potential impact of NIV on patient admissions, the admission free survival at 12 months post NIV was calculated for the combined patient cohort and the in-patient versus outpatient NIV initiation groups. Admission free survival was defined as patients who were not re-admitted and/or did not die within 12 months of starting NIV.

Changes to the home NIV treatment based on the physiological parameters recorded were documented on the NIV database that was used within the study. The study was retrospective and did not influence treatment or management of NIV patients during the data collection period.

3.9 PRIMARY OUTCOME: PART B

Part B of the study used a validated health related quality of life tool, the SRI Questionnaire, which was specifically developed for use with patients with chronic respiratory failure receiving home mechanical ventilation.

The primary outcome of Part B was to assess if there was a statistically significant difference in the summary SRI score (calculated over the 7 SRI domains) after approximately 6/52, and subsequently 6 and 12 months of long-term nocturnal home NIV comparing in-patient NIV initiation with outpatient NIV initiation. As stated, statistical significance does not necessarily equate to clinical significance. A minimal clinically important difference (MCID) is an important concept used to determine whether a medical intervention improves perceived outcomes in patients. The research literature has suggested that for patients with severe COPD and CHRF who use long-term NIV, a MCID of between 5 and 7 points (Kort, J., et al., 2018) and more recently, 5 points is clinically significant (Raveling, T., et al., 2020). No values for MCID in other clinical conditions producing CHRF requiring long-term NIV were available in the literature at the time of the study. Therefore, in addition to statistical analysis of the data, a MCID of 5 points in the SRI score (calculated over the 7 SRI domains and for each domain) irrespective of the clinical condition of the patient was considered clinically significant. Baseline SRI Score was compared to SRI score after approximately 6/52, 6 and 12 months of long-term nocturnal home NIV, comparing in-patient NIV initiation with outpatient NIV initiation patient groups.

The null hypothesis stated that over a 12-month period of treatment with NIV, initiation of long-term nocturnal home NIV via elective outpatient set up produces equivalent

improvements in HRQoL outcomes (based on summary SRI score) to initiation as an acute in-patient admission

3.9.1 Secondary Outcomes: Part B

For the secondary outcomes of Part B, the individual SRI domain scores for in-patient and outpatient NIV initiation groups were compared over the 12-month review period to identify any statistically significant changes within each domain. The individual SRI domains are stated as:

- Respiratory complaints
- Physical Function
- Sleep quality
- Social relationships
- Anxiety
- Psychological well-being
- Social functioning

To assess if there are statistically significant differences in the domains of SRI that are disease specific, the patient cohort were grouped as defined in Section 3.13:

- Chronic Obstructive Pulmonary Disease (COPD)
- Obesity Hypoventilation Syndrome (OHVS)
- Chest wall disease (CWD)
- Slowly progressive neuromuscular disease (NMD)

For each clinical sub-group, the domain specific SRI scores were compared within groups and between groups at baseline to identify similarities and differences. This analysis was repeated to identify similarities and differences:

a. between baseline to first review
b. between baseline to second review
c. between baseline to third review

The absolute change in domain specific SRI was compared to identify differences in the magnitude of any SRI domain score changes within each clinical sub group at each follow up interval. In addition to statistical analysis of the data, a MCID of 5 points in the SRI score for each domain, irrespective of the clinical condition of the patient, was considered clinically significant.

3.10 Time Investment and Costs

A comparison of the costs of initiating long-term home NIV as an in-patient and as an outpatient was made. Device and consumable cost were identified for each group, and from this, a mean cost per patient was calculated. The time taken for in-patient compared to outpatient initiation of long-term home NIV was estimated. Prior to being sent home with an NIV machine, the patient was assessed to ensure they were competent to independently fit the NIV mask and headgear correctly and operate the NIV machine; the patients in both groups were provided with identical patient information packs to support NIV use at home.

This was a retrospective study, therefore an accurate calculation of the true procedure costs per patient was not possible as it was not achievable to calculate the number of hours of healthcare professional time utilised for an in-patient initiation per patient. An analysis using procedure costs based on clinical coding was rejected due to the errors associated

with retrospective analysis of NHS Healthcare Resource Groups (HRG) codes, which may have been inaccurately completed and include additional scores for individual complexity and co-morbidity (cc) that are not relevant to this study. HRG codes consist of patient events that have been judged to consume a similar level of resource and are assigned using the software application HRG4+ Grouper (NHS Digital).

To reduce bias from complex, unrelated healthcare issues during an in-patient admission, unrelated to the initiation of home NIV, the HRG code DZ37A (Non-Invasive Ventilation Support Assessment, 19 years and over) was selected to represent the procedure cost for both in-patient and outpatient initiation. The 'Combined day case / ordinary elective spell' tariff was used as most elective prices are for the average of day-case and ordinary elective-case costs.

Comparisons were made between:

- Equipment costs
    - Device
    - Consumables
- Initiation period cost
    - In-patient NIV spell costs calculated using HRG code DZ37A as a 'Combined day case / ordinary elective spell' versus a 'Non-elective spell'
    - Outpatient initiation
        - Calculated using DZ37A as both 'outpatient procedure' and 'Combined day case / ordinary elective spell'

Home NIV patients all followed the same pathway, therefore the follow up period costs were not calculated but were stated.

The data from frequency and duration of respiratory related admissions following initiation of home nocturnal NIV compared to the 12-month period prior to initiation of NIV were included in the overall cost analysis. The calculated cost included adjustment for long stay payments, where the length of stay of the in-patient spell exceeded a specified trim point. A trim point is defined as the upper quartile length of stay for the HRG plus 1.5 times the inter-quartile range of length of stay. For elective admissions, a trim point of 5 days was used and for non-elective admissions a trim point of 14 days; a long stay payment attracted a payments of £246 per day.

3.11 Study Sample Size

The study cohort was taken from a database of sequential patients commenced on home nocturnal NIV at Good Hope Hospital. The study sample size was limited by the size of the patient population receiving long-term home non-invasive ventilation via the Good Hope NIV service over the study period.

At each patient review, the available data was collected in a database that was created in 2016; the available data in the database was reviewed and analysed over a 9-month period from 18/04/2019 to 31/12/2019 and initially consisted of 113 patients (see Results). There was subsequent attrition of patients and data points during the study period.

3.12 Study Population

3.12.1 Inclusion Criteria

1) Evidence of Type II respiratory failure requiring the use of long-term home nocturnal NIV

2) Commenced on long-term nocturnal home NIV via the Good Hope NIV service, either:
    a) Following an acute admission requiring NIV
    b) Or as an elective outpatient NIV set up in accordance with Trust NIV policy.
3) Age > 18 years
4) Patient can read and comprehend written and verbal English

3.12.2 Exclusion Criteria

1. Inclusion criteria not met.
2. Persistent hypercapnic respiratory acidosis defined as pH <7.30
3. Rapidly progressive neuromuscular disease
4. Significant bulbar weakness
5. History of, or current spontaneous pneumothorax
6. Uncontrolled cardiac failure or arrhythmia
7. Pregnancy
8. Failure to tolerate NIV during initiation or if required to treat acute decompensation
9. Patient is not compliant with prescribed NIV
10. Patient unable to fit and remove mask independently, unless a waking carer was in place
11. Psychiatric disease necessitating antipsychotic medication, on-going treatment for drug or alcohol addiction, persons of no fixed abode post discharge
12. Requirement for ventilatory support for >14 hours/day

3.13 Patient Categorisation

For the purposes of analysis, patients were categorised in to the following clinical groups based on spirometric values, blood gas values and anthropometric data:

1) COPD defined as:
    a) Reduced FEV_1/FVC ratio, such that FEV_1/FVC is less than the lower limit of normal (LLN), measured following administration of bronchodilator medication.
2) OHVS defined as:
    a) The presence of daytime alveolar hypoventilation (awake, sea level, arterial $PaCO_2$>6kPa) among patients with BMI ≥30 kgm^2 in the absence of other causes of hypoventilation.
3) Chest wall disease defined as:
    a) Disease or deformities that affect the rib cage (thoracic spine, ribs, sternum) and abdomen confirmed by radiological examination.
4) Slowly progressive neuromuscular disease defined as:
    a) Diseases that affect any part of the nerve and muscle producing weakness, particularly affecting the diaphragm, rib cage muscles and the abdominal muscles.

3.14 Informed Consent Procedures and Ethical approval

Both Part A and Part B used an observational, longitudinal retrospective methodology using data that was collected as part of routine review of the patient cohort. All data used within the study was fully anonymised and there was no patient identifiable information. The submission does not report on primary research. All data analysed within the study were collected as part of routine diagnosis and management of the cohort. Patients were

diagnosed, treated and managed according to national guidelines and local Clinical Guidelines. Testing blood gasses and recording all other variables included in the analysis were essential for confirming diagnosis, monitoring disease and managing patients. The measurements are made for each patient as part of routine care and are in no way an add-on for the purposes of research. The study does not report on the use of experimental or new protocols; the protocol that was evaluated was the agreed Trust protocol.

Therefore, based on this information and following review by the UHB Trust Research Department, informed patient consent was not required for this study. The study was registered with, and sponsored by the research board at University Hospitals Birmingham NHS Foundation Trust (Reference number 20190055STU; 18/04/2019).

3.15 Data Collection Procedures

Following the decision to treat with long-term nocturnal home NIV, the patient's baseline anthropometric, physiological, quality of life score and NIV treatment data were added to the NIV patient database. Patient reviews in the Good Hope NIV outpatient clinic were scheduled for 6 weeks, sixth, and twelfth month after the initiation of NIV. If the patient had an infective exacerbation within 6 weeks of a scheduled appointment, the appointment was re-booked and the review was performed 6 weeks after the event.

At each follow up visit, the patient received a physical examination by a member of the respiratory team. Arterial or arterialised capillary blood gases and spirometry were measured with patient consent, and the compliance data (hours used) and the settings of the ventilator were downloaded in order to assess the effectiveness of NIV treatment, quality of mask fit and patient compliance. Throughout the study, patients underwent

adjustments in NIV masks or ventilator settings as needed in order to maintain patient–ventilator synchrony and optimize gas exchange and functional status. Additional measurements routinely recorded included the number of hospital admissions, number of in-hospital days and number of deaths during the follow-up period of 1 year.

Patients were asked to complete the English version of the SRI Questionnaire. If the patient was unable to complete this on his or her own, the SRI was completed with support from the clinician performing the review. Support consisted of the items being read aloud and answers were marked according to patient's response. To maintain objectivity, all of the registered senior healthcare scientists (4 team members in total) randomly performed the patient reviews and subsequent SRI questionnaires. Relatives and carers were excluded from answering or completing SRI questionnaires on behalf of the patient; translators were not required as all patients had English as their first language and there were no visually impaired patients. Patients could decline to complete the SRI at each visit.

3.16 Data Management Techniques

Data was analysed with IBM SPSS 26.0 Statistics software package (IBM, Armonk, New York, USA). Prior to statistical analysis, data was tested for normality distribution using the Shapiro-Wilk and Kolmogorov-Smirnov non-parametric tests. Categorical variables were presented as frequency (%); continuous variables were shown as mean ± standard deviation (S.D.), with ranges in parentheses (if normally distributed) or median (interquartile range) if not normally distributed unless otherwise mentioned

Comparisons between two groups were performed with independent (students) sample t-tests, comparisons among three or more groups were performed with one-way analysis of

variance (ANOVA) using an appropriate post-hoc test (Bonferroni) where the data were parametric.

For non-parametric data, Mann Whitney U (unpaired) and Wilcoxon signed rank test (paired) tests were used. A two-sided p-value < 0.05 was considered statistically significant.

Comparison of survival times and admission free survival times for in-patient versus outpatient groups following initiation of NIV was made using the Mantel–Haenszel log-rank test and Kaplan-Meir survival curves. The Pearson Chi-Square Test of Association was used to look for associations between NIV usage and outcomes.

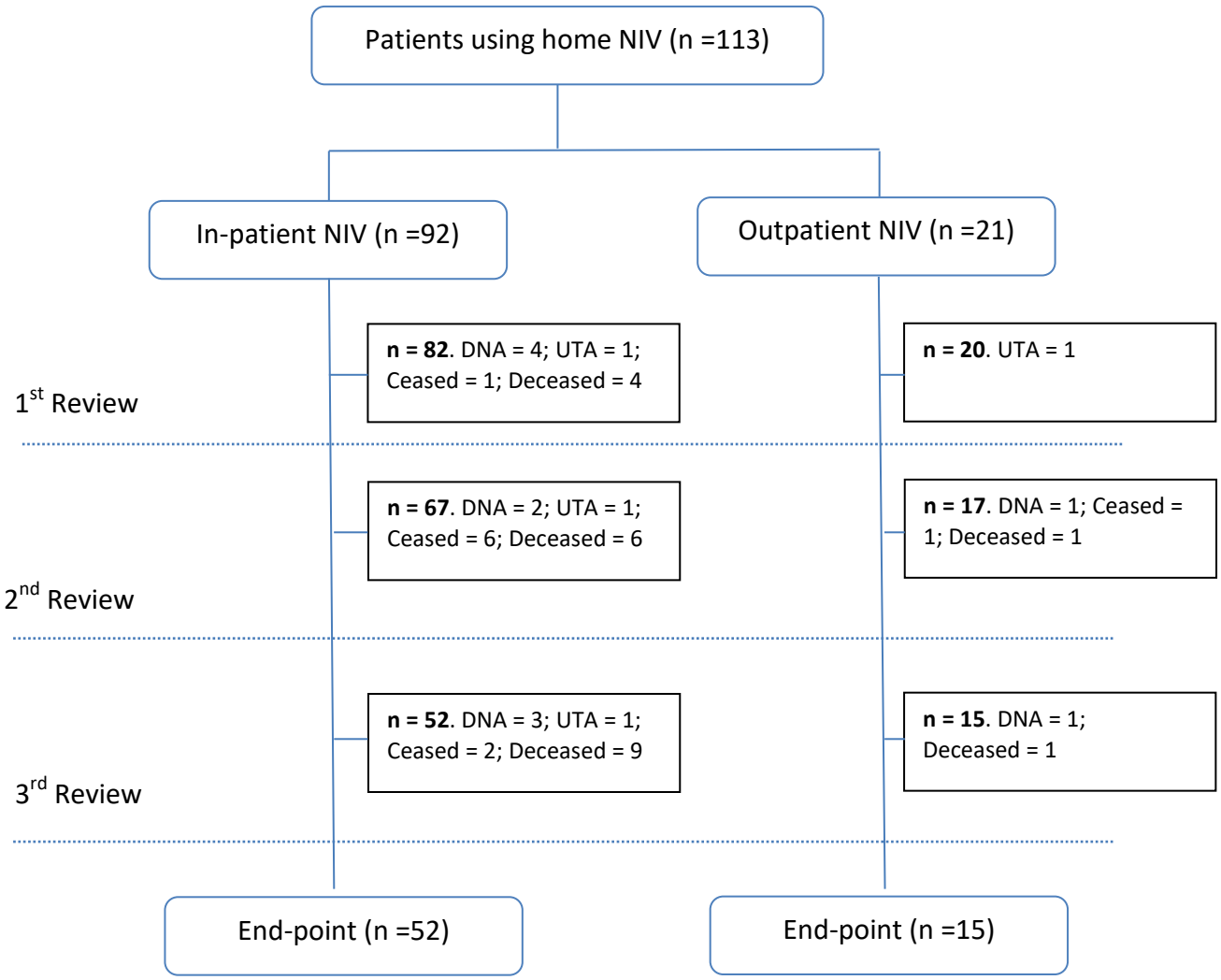
4 RESULTS

PART A: QUANTITATIVE DATA

4.1 FLOW CHART FOR PATIENTS IN THE STUDY (PART A)

The flow chart for the study participants is shown in Figure 4. 113 patients were active on the NIV database and were confirmed to be receiving long-term home NIV via the Good Hope service.

Figure 4: *Flow chart for study participants*



The attrition rate for the in-patient cohort at 12 months (56.53%) is significantly higher than that seen in the outpatient NIV initiation group (28.27%). This may reflect that this group had a lower initial health status.

4.2 Baseline Characteristics for the Study Cohort (Part A)

The baseline characteristics for the total study cohort (n = 113) are shown in Table 6. This represented the data for all patients that were using long-term nocturnal home NIV and were actively being followed up by the Good Hope NIV Service during the study period.

Table 6: *Baseline characteristics for the total cohort (N=113)*

Primary Diagnosis	Chronic Obstructive Pulmonary Disease (COPD)	61 [54.0%]
	Obesity hypoventilation (OHVS)	37 [32.7%]
	Chest wall disease (CWD)	10 [8.8%]
	Neuromuscular disease (NMD)	5 [4.4%]
Male sex		49 [43.4%]
Body Mass Index (kg/m^2)		34.5 (24.2 - 43.2)
Age (years)		68 (60 - 75)
Pre-NIV $PaCO_2$ (kPa)		9.5 (8.2 – 11.2)
On Long Term Oxygen therapy		48 (42.5%)
In-patient set up		92 (81.4%)

Units shown in brackets. Categorical variables shown as frequency (%); continuous variables shown as median (IQR).

The largest clinical clusters within the study cohort were patients with COPD, followed by OHVS; there were a very small number of patients with CWD and slowly progressive NMD

within the study cohort. This observation is unsurprising, as the service was commenced as a non-specialist NIV service for patients requiring home NIV for < 14 hours/day. The patient group was elderly (mean age 68 years (60 – 75)), approximately equally distributed between males and females (male n = 49 (43.4%)) and with an elevated BMI (BMI = 34.5kg/m^2 (24.2 - 43.2)), which would categorise them as clinically obese (Purnell, 2018). From the BMI, there were few patients with overt cachexia despite the number of patients clinically diagnosed as having severe COPD. As would be expected, significant hypercapnia was observed (mean $PaCO_2$ = 9.5kPa (8.2 – 11.2)), with almost half of the cohort (42.47%) currently prescribed long-term oxygen therapy; the majority of the patients in the study were established on NIV during an acute in-patient admission (n = 92 (81.4%)).

4.2.1 BASELINE CHARACTERISTICS BY CLINICAL DIAGNOSIS

Analysis of the anthropometric data of the study cohort by clinical diagnosis, as stated by the referring clinician on the NIV 'Decision to Treat' document, is summarised in Table 7.

Table 7: *Baseline characteristics of the whole cohort by confirmed clinical diagnosis*

Diagnosis	**COPD** (n=61)	**OHVS** (n=37)	**CWD** (n=10)	**NMD** (n=5)
Male sex	27 (44.3%)	16 (43.2%)	3 (30%)	3 (60.0%)
BMI (kg/m^2)	25.7 (19.8, 34.2)	48.6 (40.0, 51.4)	26.0 (5.4)	35.1 (10.3)
Age (years)	69 (9)	63 (13)	66 (13)	63 (12)
Pre-NIV $PaCO_2$ (kPa)	10.1 (8.4, 11.5)	9.2 (2.0)	11.1 (4.1)	9.9 (3.8)
On LTOT	32 (52.5%)	9 (24.3%)	5 (50.0%)	2 (40.0%)
In-patient set up	52 (85.2%)	29 (78.4%)	7 (70.0%)	4 (80.0%)

Continuous variables shown as mean ± SD (if normally distributed) or median (IQR) if not normally distributed.

There were small numbers of patients with CWD (n = 10) and NMD (n = 5); the limited number of patients with these clinical conditions in the study cohort influenced subsequent analysis of the data by clinical diagnosis. For the largest clinical disease groups (COPD and OHVS), there were similar numbers of male and female patients; CWD patients were predominantly female and NMD patients predominantly male, but the numbers of patients in each group were too small for this to be considered significant in any way. Patients with OHVS unsurprisingly had the highest BMI (mean BMI 48.6 kg/m^2 (40.0, 51.4)), were less hypercapnic (mean pre NIV $PaCO_2$: 9.2 kPa (2.0)) and were prescribed LTOT less frequently than the other clinical sub groups.

4.2.2 CLINICAL DIAGNOSIS CONFIRMED BY SPIROMETRIC DATA

In addition to the clinical diagnosis recorded in the NIV 'Decision to Treat' document, spirometric data, where available, was used to confirm the primary diagnosis (n=95). The spirometric data is summarised by route of NIV initiation (Table 8) and by clinical diagnosis (Table 9). For n = 18 patients, spirometry was either not requested by the referring clinician or the patient was unable to produce spirometry results that met ATS/ERS standards (Miller, M.R., et al., 2005) and values were not reported.

Table 8: *Spirometric data by route of NIV initiation for the combined cohort data*

	Inpatient (n=77)	**Outpatient** (n=18)	**p value**
FVC (L)	1.64 (1.07, 2.31)	1.79 (1.45, 2.08)	0.473
FVC predicted (%)	48.6%0 (39.0, 63.0)	52.3 (14.6)	0.729

FVC (Z-score)	-3.22 (1.12)	-3.21 (1.14)	0.976
FEV_1 (L)	0.79 (0.55, 1.26)	0.86 (0.63, 1.28)	0.635
FEV_1 predicted (%)	34.2 (24.1, 46.3)	37.70 (17.1)	0.776
FEV_1 (Z-score)	-3.73 (0.97)	-3.68 (0.99)	0.844
FEV_1/FVC (%)	0.56 (0.19)	0.56 (0.20)	0.864
FEV_1/FVC (Z-score)	-2.22 (-4.1, -1.1)	-2.39 (1.96)	0.811

Continuous variables shown as mean ± SD (if normally distributed) or median (IQR) if not normally distributed.

Table 9: *Spirometric data by clinical diagnosis for the combined cohort data*

	COPD (n=49)	**OHVS** (n=34)	**CWD** (n=8)	**NMD** (n=4)
FVC (L)	1.59 (1.3, 1.9)	2.0 (0.8)	1.1 (0.5)	1.69 (0.6)
FVC predicted (%)	51.7 (14.5)	55.4 (16.1)	32.5 (27.3, 35.5)	40.0 (5.5)
FVC (Z-score)	-3.1 (1.1)	-3.0 (1.1)	-4.3 (1.3)	-4.0 (-4.5, -4.0)
FEV_1 (L)	0.7 (0.3)	1.4 (0.6)	0.6 (0.5,0.8)	1.3 (0.4)
FEV_1 predicted (%)	28.6 (19.7, 35.2)	49.2 (15.9)	26.6 (23.1, 29.5)	38.4 (3.2)
FEV_1 (Z-score)	-4.00 (0.8)	-3.24 (1.0)	-3.97 (1.3)	-3.94 (0.3)
FEV_1/FVC (%)	38 (32,52)	69 (11)	70 (20)	76 (8)

FEV_1/FVC (Z-score)	-3.9 (-4.6, -2.8)	-1.1 (-1.3)	-0.9 (2.38)	-0.3 (1.1)

Continuous variables shown as mean ± SD (if normally distributed) or median (IQR) if not normally distributed.

The spirometric data comparing in-patient initiation versus outpatient NIV initiation (Table 8) indicates that the two groups are not statistically different. The spirometric values by clinical condition were in keeping with the reported clinical diagnosis; patients with COPD demonstrated clinically significant airflow obstruction indicated by the Z-score for FEV_1/FVC that was < -1.645; patients with OHVS, CWD and NMW had restrictive spirometry, indicated by Z-scores < -1.645 for FVC, FEV_1 with an FEV_1/FVC above the lower limit of normal. The morphology of the flow volume curves (data available, but not included within the body of this study) supported the numerical data.

Clinically significant airflow obstruction, defined as Z-score < -1.645 for FEV_1/FVC, was observed in 13 (38.2%) patients (of 34 measured) with OHVS as their primary diagnosis, indicating probable overlap between these two conditions. Smoking history, calculated in pack years, is available for all patients that performed spirometry but is not included within the body of this study.

4.2.3 Patient anthropometric data by Route of NIV initiation

To provide comparative data for the in-patient and outpatient NIV initiation groups, Table 10 presents the baseline anthropometric characteristics of the study cohort described by their route of NIV initiation.

Table 10: *Anthropometric data by method of NIV initiation*

		Method of NIV initiation		
		In-patient n=92	**Outpatient n=21**	**p value**
Diagnosis	**COPD**	52 (56.5%)	9 (42.9%)	0.640
	OHVS	29 (31.5%)	8 (38.1%)	
	CWD	7 (7.6%)	3 (14.3%)	
	NMD	4 (4.3%)	1 (4.8%)	
Male sex		41 4 (44.6%)	8 (38.1%)	0.589
Prescribed LTOT		36 (39.1%)	12 (57.1%)	0.134
BMI		33.1 (22.6, 40.7)	37.0 (10.1)	0.191
Age		68 (62, 75)	64 (11)	0.298
Pre-NIV treatment $PaCO_2$		10.2 (9.0, 11.5)	7.4 (0.8)	<0.001*

Mann Whitney U Test is used to test for differences between continuous variables and Pearson's chi squared test for categorical variables.

The number of patients in the in-patient NIV initiation group was significantly higher than that of the outpatient NIV initiation group. Despite the difference in patient numbers between the two groups, they were similar in terms of their sex (p = 0.589), age (p = 0.298) and the proportion of patients with COPD (p = 0.640). A greater percentage of patients in the outpatient NIV group were prescribed LTOT; the difference between the groups did not reach statistical significance. The baseline mean pre-NIV $PaCO_2$ value for the in-patient NIV initiation group was 2.8kPa higher than that for the outpatient NIV initiation group; this difference was statistically significant (<0.001), suggesting that this group had poorer alveolar ventilation at the point of NIV initiation. It may also reflect the recovery period from the acute event that precipitated their admission to hospital.

4.3 PRIMARY OUTCOME: $PaCO_2$ VALUES AT FIRST, SECOND AND THIRD REVIEW

4.3.1 $PaCO_2$ FIRST REVIEW DATA:

Following initiation of home long-term NIV, all patients were scheduled to attend a NIV first review after approximately 6 weeks. The blood gas data ($PaCO_2$), compliance data, pressure support and days from initiation of NIV are presented in Table 11.

From the initial study cohort of 113 patients commenced on nocturnal home NIV, 102 patients attended for their first review of NIV treatment and had data on blood gases pre and post NIV (baseline and first follow up). Two data sets were missing from the compliance data, 1 data set was missing from pressure support. Overall, this represented an attrition rate of 9.73% of patients from the baseline cohort.

4 patients (3 COPD; 1 OHVS) failed to attend follow up and did not notify the service they would not attend (DNA). 2 patients (2 OHVS) reported that they were unable to attend (UTA) for review, 4 patients (3 COPD; 1 NMD) were deceased before their first review and 1 patient (COPD) had ceased NIV treatment as he was unable to tolerate. In Table 10, the Pre-NIV treatment $PaCO_2$ was re-analysed to reflect the total number of patients that attended for review (n = 102); the Pre-NIV treatment $PaCO_2$ values therefore differ from Table 7, where n = 113.

Table 11: *$PaCO_2$ at first review following NIV initiation*

Measurements at first NIV review	Method of NIV initiation		
	In-patient (n = 82)	**Outpatient** (n = 20)	**p value**
Pre-NIV treatment $PaCO_2$	10.1 (9.0, 11.5)	7.1 (6.8, 8.0)	<0.001*
1st review $PaCO_2$	6.2 (1.1)	6.5 (0.9)	0.21
Pressure support	14.1 (2.7)	10.5 (3.1)	<0.001*
Compliance	6.9 (5.3, 8.4)	5.8 (4.2, 7.3)	0.54
Normalised $PaCO_2$	35 (42.7)	6 (30)	0.218
Days from initiation to 1st review	56.5 (43.0, 78.0)	39.0 (32.5, 59.5)	0.008*

Values shown as mean (SD) or median (IQR) for continuous variables, and frequency (%) for categorical variables. Normalised $PaCO_2$ defined as $PaCO_2$ at first follow up <6.0kPa.

The pre-NIV treatment $PaCO_2$ demonstrated a statistically significant difference (p = <0.001) in the baseline pre NIV $PaCO_2$ values between those patients set up on NIV as an in-patient ($PaCO_2$ = 10.2 (9.0 – 11.5)) and those set up as an outpatient ($PaCO_2$ = 7.4 (0.8)). However, the mean $PaCO_2$ at first review was slightly lower for patients established on NIV as an in-patient compared to patients established on NIV as an outpatient; the difference was not statistically significant (p = 0.21) and absolute difference (0.3kPa) was less than the level defined as conferring a clinical beneficial (0.4kpa). Both patient groups were equally likely to present with normalised $PaCO_2$ at the first review. Compliance with treatment was not statistically different between the groups (p = 0.54), but there were statistically significant differences observed in the amount of pressure support (the difference between IPAP and EPAP) for the in-patient NIV set up group (p = <0.001), with the in-patient NIV group receiving higher mean pressures. This was almost certainly a function of the higher pre-NIV treatment $PaCO_2$ in the in-patient NIV set up group requiring increased pressure support to

normalise their $PaCO_2$. The time to first review following initiation of NIV was also statistically significantly different between the two groups (p = 0.008), with the in-patient set up group attending for 1st review significantly longer following initiation of NIV than those set up via the outpatient pathway.

4.3.2 $PaCO_2$ Second Review data

Following their first review of home long-term NIV, all patients were scheduled to attend a NIV second review after approximately 6 months (182 days). The blood gas data ($PaCO_2$), compliance, pressure support and days from initiation of NIV are presented in Table 12. From the cohort of 102 patients that attended for their first review following NIV initiation, 84 patients attended for their second NIV review and had paired data for blood gases and compliance; 1 dataset for pressure support was absent. This difference at second review represented a patient attrition rate of 17.64% from the first review and 25.66% overall from baseline. 3 patients failed to attend follow up (DNA); 1 patient reported that they were unable to attend (UTA), 7 patients were deceased or following a palliative care pathway and 7 patients had ceased NIV treatment.

In Table 12, the pre-NIV treatment $PaCO_2$ was re-analysed to reflect the total number of patients that attended for review (n = 84); the Pre-NIV treatment $PaCO_2$ values therefore differ from Table 7 (n = 113) and Table 10 (n = 102).

Table 12: *$PaCO_2$ at second review following NIV initiation*

Measurements at second review	Method of NIV initiation		
	In-patient (n = 67)	**Outpatient** (n = 17)	p value
Pre-NIV treatment $PaCO_2$	9.9 (8.7, 11.3)	7.1 (6.8, 7.9)	<0.001
2^{nd} review $PaCO_2$	5.8 (5.5, 6.4)	6.5 (6.1, 7.4)	0.004*
Pressure support	13.1 (2.8)	11.1 (2.6)	<0.001
Compliance	7.5 (6.2, 8.6)	5.6 (3.6, 6.8)	0.003*
Normalised $PaCO_2$	38 (56.7)	3 (17.6)	0.004*
Days from set up	264 (236, 300)	224 (202, 252)	0.007*

Values shown as mean (SD) or median (IQR) for continuous variables, and frequency (%) for categorical variables. Normalised $PaCO_2$ defined as $PaCO_2$ measured at second review <6.0kPa.

At NIV first review, there was no statistical difference (p= 0.21) or clinical difference ($PaCO_2$ difference = 0.3kPa) in the $PaCO_2$ between the 2 groups. However, at second review (approximately 6 months post NIV initiation) the mean $PaCO_2$ was higher for patients established on NIV as an outpatient; this difference is statistically significant (p = 0.004) and clinically significant ($PaCO_2$ difference = 0.7kPa). Patients established on NIV as an in-patient were statistically more likely to maintain a normalised $PaCO_2$ at their second review. The difference in compliance between the 2 groups was also statistically significant (p = 0.003) at second NIV review. Patients established on home NIV as an in-patient used their NIV for almost 2 hours more each day than those established as an outpatient, which may be a contributing factor to the higher mean $PaCO_2$ values observed in the outpatient initiation group. At second review, there remained a statistically significant differences in pressure support received by the 2 groups (p = <0.001), with patients initiated as in-patients

continuing to receive greater pressure support. The time to second review also remained statistically significantly different between the two groups (p = 0.007), with the in-patient NIV initiation group attending for 2nd review later than those set up via the outpatient pathway.

4.3.3 $PaCO_2$ Third Review data

Following their second review of their home long-term NIV, patients were scheduled to attend a NIV third review after approximately 12 months (365 days); this was the end-point of the study. The blood gas data ($PaCO_2$), compliance, pressure support and days from initiation of NIV are presented in Table 13.

From the cohort of 84 patients that attended for their second review following NIV initiation, 67 patients attended for their third NIV review and had paired data for blood gases and compliance; 1 dataset for compliance was missing. At third review, this represented a patient attrition rate of 20.23% from the second review and 40.71% overall from baseline.

4 patients failed to attend follow up (DNA); 1 patient reported that they were unable to attend (UTA), 10 patients were deceased or following a palliative care pathway and 2 patients had ceased NIV treatment.

In Table 13, the Pre-NIV treatment $PaCO_2$ was re-analysed to reflect the total number of patients that attended for review (n = 67); the Pre-NIV treatment $PaCO_2$ values therefore differ from Table 7 (n = 113), Table 10 (n = 102) and Table 11 (n = 84).

Table 13: *$PaCO_2$ at third review following NIV initiation*

Measurements at third review	Method of NIV initiation		
	In-patient NIV (n = 52)	**Outpatient NIV** (n = 15)	**p value**
Pre-NIV treatment $PaCO_2$	9.4 (8.6, 11.3)	7.1 (6.8, 8.3)	<0.001*
3rd review $PaCO_2$	5.9 (5.3, 6.4)	6.2 (5.7, 6.4)	0.164
Pressure support	13.2 (3.1)	11.7 (3.6)	0.113
Compliance	7.5 (2.4)	6.1 (2.5)	0.059
Normalised $PaCO_2$	34 (64.1)	6 (40.0)	0.084
Days from set up	496 (434, 586)	426 (379, 500)	0.022*

Values shown as mean (SD) or median (IQR) for continuous variables, and frequency (%) for categorical variables. Normalised $PaCO_2$ defined as $PaCO_2$ measured at third review <6.0kPa.

Whilst the mean $PaCO_2$ at the end point of the study remained modestly higher for patients established on NIV as an outpatient, the difference compared to the in-patient group was neither statistically significant (p = 0.164) or clinically significant ($PaCO_2$ difference = 0.3kPa) and both groups were equally likely to present with normalised $PaCO_2$ at the third review. There were no statistically significant differences in compliance (p = 0.059) or pressure support received (p = 0.113) between the 2 groups. The time to third review remained statistically significantly different between the two groups (p = 0.022), with the in-patient set up group attending their 3rd review significantly later after NIV initiation than those set up via the outpatient pathway.

The daytime $PaCO_2$ values during spontaneous breathing without NIV at baseline, first review, second review and third review are illustrated graphically in Figure 5 (individual

values for in-patient NIV initiation group) and Figure 6 (individual values for outpatient NIV initiation group).

Figure 5: *Change in daytime $PaCO_2$ values for in-patient NIV initiation group*

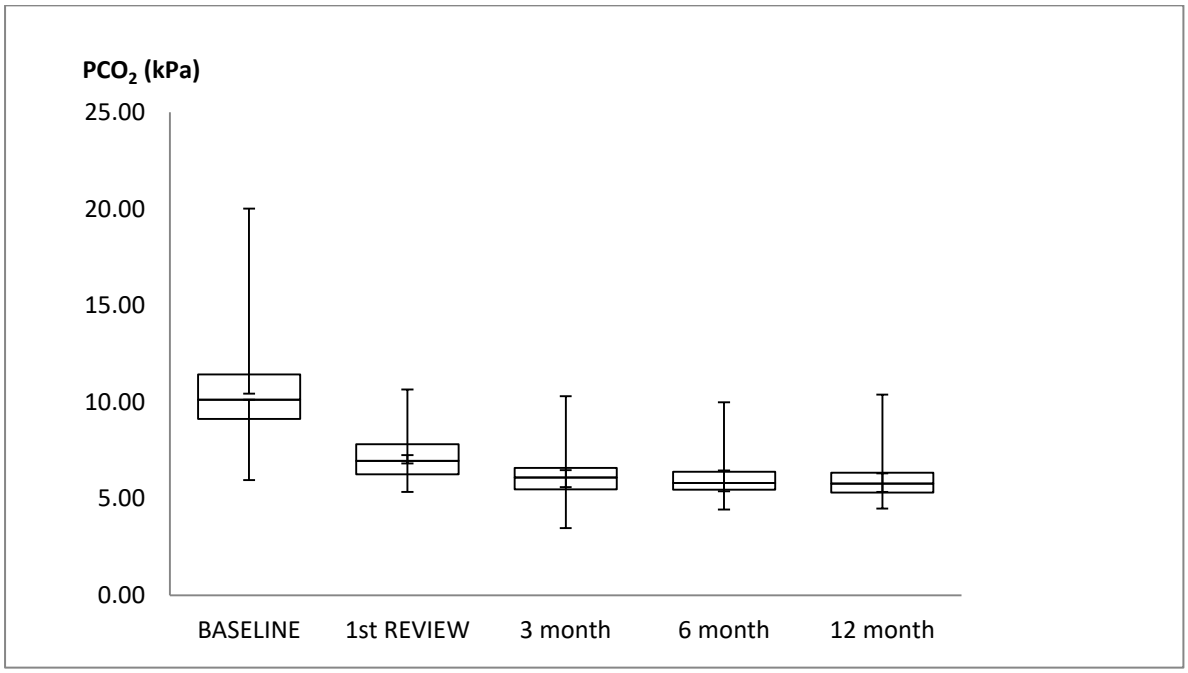
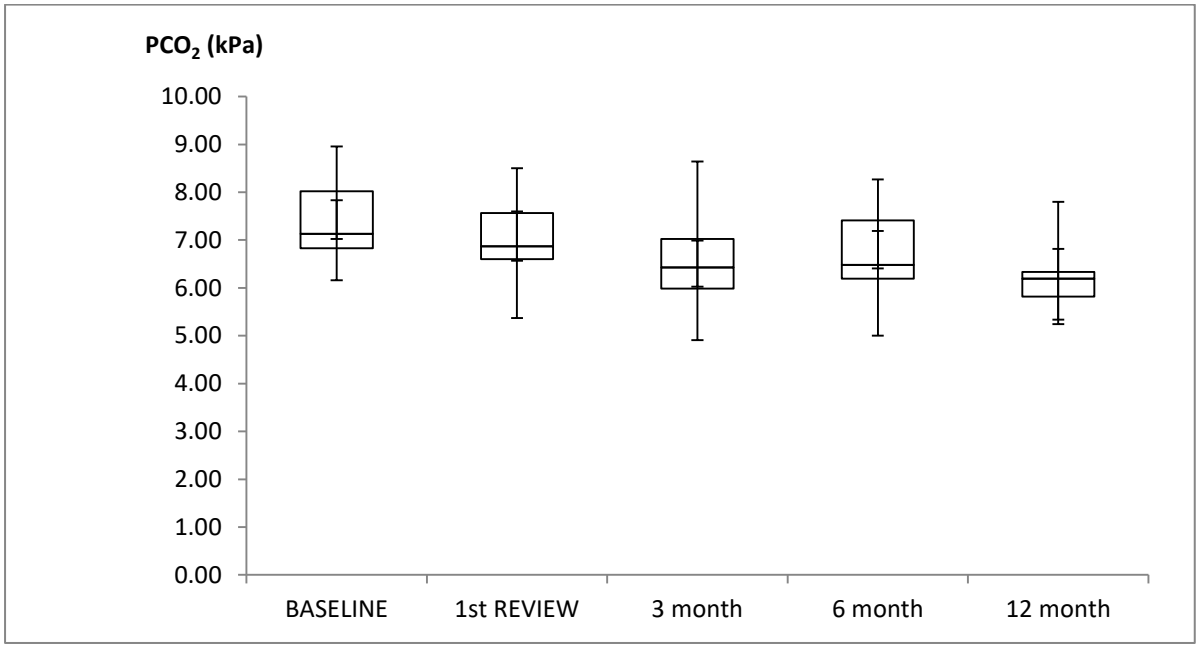


Figure 6: *Change in daytime $PaCO_2$ values for outpatient NIV initiation group*



For both study groups, the $PaCO_2$ values were reduced at first review compared to baseline and for those patients that remained in the study at 12 months, remained below the baseline value at the end-point of the study. The reduction in $PaCO_2$ from baseline to first review was more profound for the in-patient group, but this must be considered in the context of their baseline $PaCO_2$ values being significantly higher than the outpatient NIV group.

For both groups, the change in $PaCO_2$ from baseline was clinically significantly at the end of the 12-month study period (in-patient $PaCO_2$ difference = -3.5kPa; outpatient $PaCO_2$ difference = -0.9kPa); the mean $PaCO_2$ values at 12 months between the groups were not statistically different (p = 0.164). The difference between the 2 groups at 12- months post NIV was below the threshold (0.4kPa) where clinical benefit would be conferred ($PaCO_2$ difference = 0.3kPa)

4.4 PART A: SECONDARY OUTCOMES

4.4.1 OUTCOME 1: FREQUENCY AND LENGTH OF STAY FOR RESPIRATORY RELATED ADMISSIONS

To assess the impact of the introduction of home long-term NIV on frequency and length of respiratory related admissions by route of initiation of NIV (in-patient versus outpatient), the total number of respiratory related admissions and total bed days in the 12 month period prior to initiation and the 12 month period following initiation of NIV (Table 14) were compared. Patients who were still using long-term home NIV and were still alive at one year post NIV initiation were included (n = 88) in the analysis. From the baseline cohort (n = 113), 16 patients were deceased at < 12 months, 6 patients were no longer on NIV, and 3 patients

had moved out of the area and were no longer followed up by the Good Hope Home NIV service.

Table 14: *Admissions and bed days pre and post initiation of NIV between groups (in-patient vs. outpatient)*

	In-patient NIV (n = 71)	Outpatient NIV (n = 17)	p value
Admissions 1 year prior to NIV	2 (1-3)	1 (0-2)	0.016*
Admissions 1 year post NIV	0 (0-1)	0 (0-1)	0.510
Bed days 1 year prior to NIV	23 (13-33)	1 (0-8)	<0.001*
Bed days 1 year post NIV	0 (0-6)	0 (0-4)	0.437

Non-parametric data – Median (IQR); Mann Whitney U (unpaired) test used.

**signifies significant result.*

The in-patient NIV initiation group had a greater number of hospital admissions 1-year prior to commencing NIV compared to the outpatient NIV initiation group; the difference is statistically significant (p =0.016). Bed days in the 1-year prior to NIV were significantly higher for the in-patient NIV initiation group compared to the outpatient NIV initiation group and the difference was statistically significant (p = <0.001). Following initiation of home NIV, the number of admissions and bed days were reduced for the in-patient NIV initiation group. There was no statistically significant difference between the 2 groups in terms of either admissions (p= 0.510) or bed days (p =0.437) following 12-months of home NIV.

Within groups analysis of the frequency and length of respiratory related admission data (Table 14) demonstrates that for the outpatient NIV initiation group, there is not a statistically significant difference in either admissions (p = 0.475) or bed days (p = 0.878) following initiation of NIV i.e. introduction of NIV neither improves or worsens admissions or

bed days. However, for the in-patient NIV initiation group, the reduction in in-patient admissions (p = <0.001) and bed-days (p = <0.001) is statistically significant following 12-months of home NIV.

Table 15: *Admissions and bed days pre and post initiation of NIV within groups*

	1 year pre-NIV	1 year post NIV	p value
Admissions (OP NIV set up)	1 (0-2)	0 (0-1)	0.475
Bed days (OP NIV set up)	1 (0-8)	0 (0-4)	0.878
Admissions (IP NIV set up)	2 (1-3)	0 (0-1)	<0.001*
Bed days (IP NIV set up)	23 (13-33)	0 (0-6)	<0.001*

*Non-parametric data – Median (IQR); Wilcoxon signed rank test (paired) test used. *signifies significant result.*

The data indicated that for patients that required long-term home NIV as an in-patient following an acute admission with decompensated Type II respiratory failure, the introduction of home NIV reduced the frequency of admissions and the number of bed-days at 1-year post NIV; this difference was not observed for patients commenced on NIV as an outpatient.

4.4.2 OUTCOME 2: WAS POOR COMPLIANCE WITH NIV ASSOCIATED WITH RE-ADMISSION?

Compliance data for the 12-month periods was available for 82 patients from the original cohort of n = 133. The data was not stratified by route of NIV admission due to the small numbers in the outpatient initiation group, and sought only to assess if there was an association between poor compliance with NIV and re-admission to hospital with decompensated Type II respiratory failure

Cross tabulation of compliance data against re-admission was performed to assess correlation; Chi-Square Test for statistical significance. Cross tabulation suggests that a higher number of patients that are compliant with NIV are re-admitted to hospital compared to those that are not compliant. The data was combined for both groups, thus the outcome may be skewed by the greater number of patients who were initiated with NIV as an in-patient. The in-patient group consistently showed higher levels of compliance with NIV, but conversely tend to have poorer alveolar ventilation (as indicated by level of $PaCO_2$) and thus are more likely to be re-admitted to hospital with decompensated type II respiratory failure. From statistical analysis of the data, the corresponding p-value (0.989) indicates that there was insufficient evidence of an association between poor compliance with NIV and re-admission to hospital.

4.4.3 Outcome 3: All-Cause Mortality at 12-months following initiation of NIV

Assessment of all-cause mortality of the grouped NIV subject data at the end point of the study (12 months), along with a comparison of in-patient versus outpatient NIV initiation groups was performed (Table 17; Table 18) and Kaplan- Meier survival curves plotted (Figure 7). 6 patients were excluded (counted in censored) as they were no longer on NIV at 12 months.

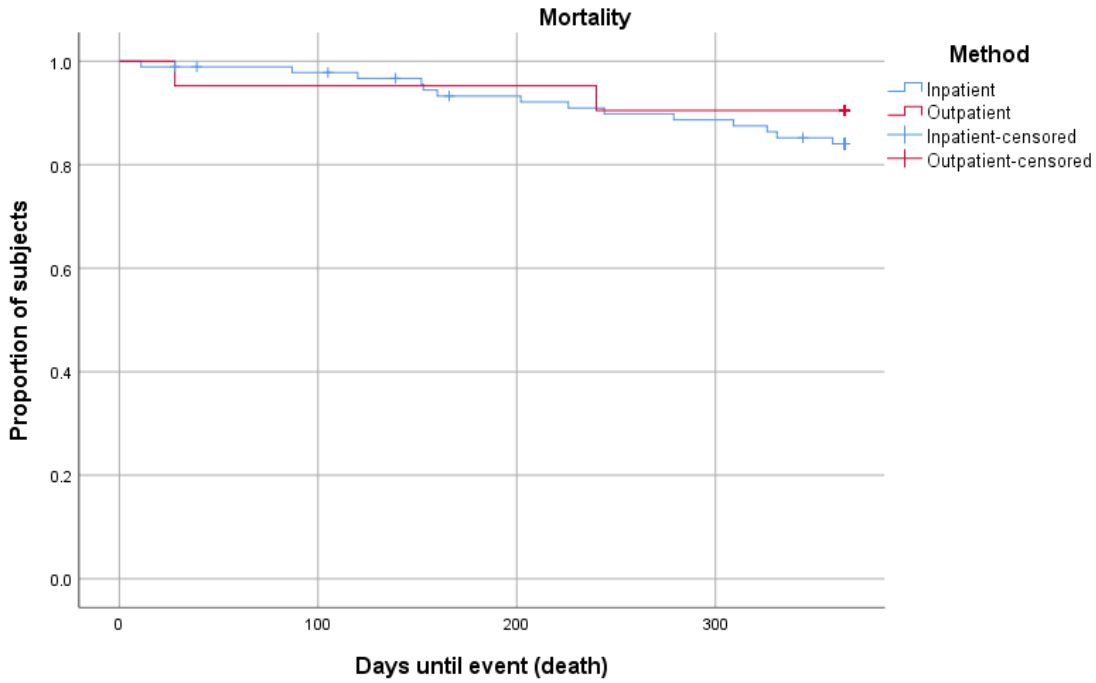
***Table 16**: Mortality at 1-year (in-patient initiation vs. outpatient initiation of NIV)*

Mortality at 1 year				
Method	Total	Events (death)	Censored	
	N		N	Percent
Inpatient	92	14	78	84.8%
Outpatient	21	2	19	90.5%
Overall	113	16	97	85.8%

Excluding the 6 patients who were no longer on home NIV at the 12 month review, all cause mortality at 1-year for all patients commenced on long-term home NIV was 15.0%.

Visual assessment of the Kaplan- Meier Survival curves at 1-year (Figure 7), comparing the in-patient and outpatient NIV initiation group, suggests that mortality in the in-patient NIV initiation group may be slightly higher. However, statistical analysis of the data produced a p value of 0.523, indicating that there was no statistical difference in mortality associated with initiation of NIV as an outpatient compared to NIV initiation as an in-patient.

Figure 7: *Kaplan- Meier Survival curve at 1-year (in-patient initiation vs. outpatient initiation of NIV)*



4.4.4 Outcome 4: Was poor-compliance with NIV associated with death before the end-point of the study?

Analysis of patient NIV compliance data (where compliance is defined as > 5 hours NIV use, every night) against death at <12 months (end-point of study) for correlation and statistical significance was performed for the combined cohort data (n = 100). The data was not stratified by route of NIV admission due to the small numbers in the outpatient initiation group, and sought only to assess if there was an association between poor compliance with NIV and death (any cause) before the end-point of the study.

From the statistical analysis, the corresponding p-value (0.055) indicates that there was insufficient evidence of an association between poor compliance with NIV and death before 12 months for patients receiving long-term home NIV.

4.4.5 Outcome 5: Admission free survival at 12 months following initiation of NIV (in-patient versus outpatient NIV initiation)

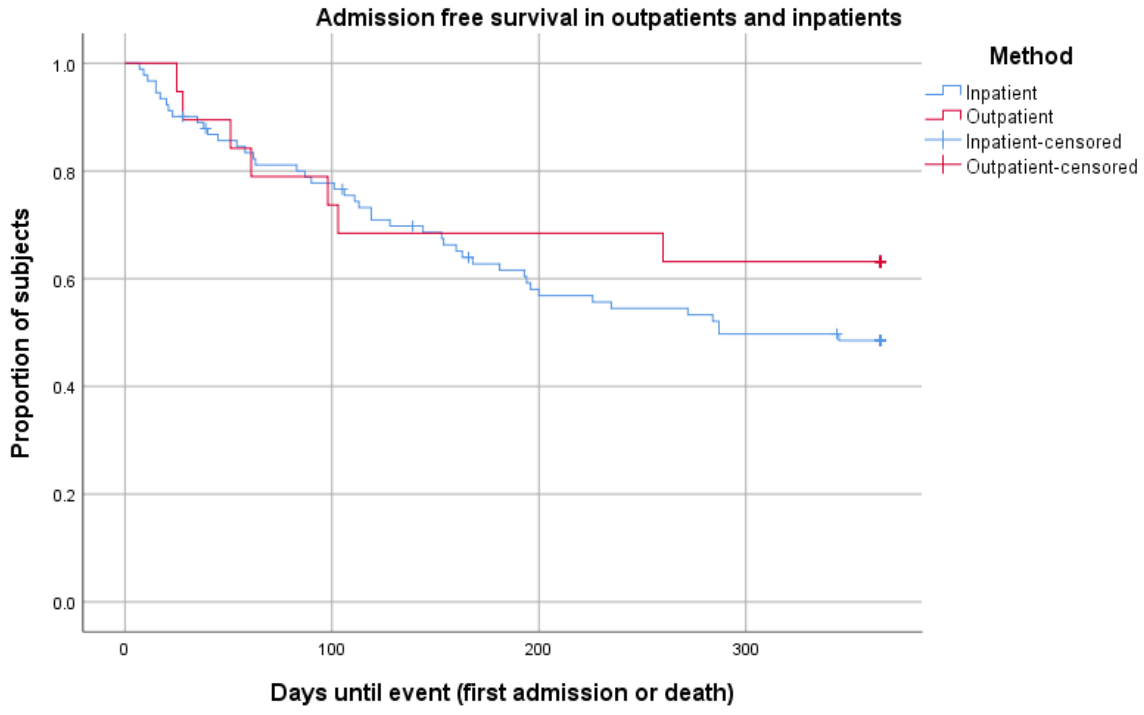
Assessment of admission free survival of the combined patient cohort at the end-point of the study (12 months), along with a comparison between in-patient and outpatient NIV initiation was performed (Table 17) and Kaplan- Meier admission free survival curves were plotted (Figure 8). 3 patients were excluded from analysis (included in censored) as their secondary care provider was 'out of area' and hospital admissions data was not accessible.

***Table 17**: Admission free survival at 1-year (in-patient initiation vs. outpatient initiation of NIV)*

Admission free survival at 1 year				
Method	Total	Events (death or readmission)	Censored	
	N		n	Percent
Inpatient	91	45	46	50.5%
Outpatient	19	7	12	63.2%
Overall	110	52	58	52.7%

Analysis of the data, with patients who ceased NIV < 12 months removed, provides an admission free survival estimate of 50% at 12 months.

***Figure 8:** Kaplan- Meier admission free survival curve at 1-year (in-patient initiation vs. outpatient initiation of NIV)*



Visual inspection of the Kaplan- Meier admission free survival curves (Figure 8) comparing in-patient and outpatient NIV initiation groups suggests that the in-patient NIV group had lower admission free survival at 12 months compared to the outpatient NIV group. Statistical comparison of the data produced a p value of 0.346, indicating that there was no statistical difference in admission free survival associated with initiation of NIV as an in-patient compared to an outpatient.

PART B: QUALITY OF LIFE DATA

4.5 PRIMARY OUTCOME: COMPARING THE SRI SCORE BETWEEN GROUPS OVER A 12 MONTH PERIOD

4.5.1 SRI SCORES PRE AND POST INITIATION OF NIV BETWEEN GROUPS (POOLED DATA)

For the pooled data for each group (sum of sample size >15), statistical analysis demonstrated no significant differences in the mean summative SRI score between groups at baseline and at subsequent visits (Table 18) for the study period.

Table 18: *SRI summative score comparison pre and post initiation of NIV between groups (in-patient versus outpatient)*

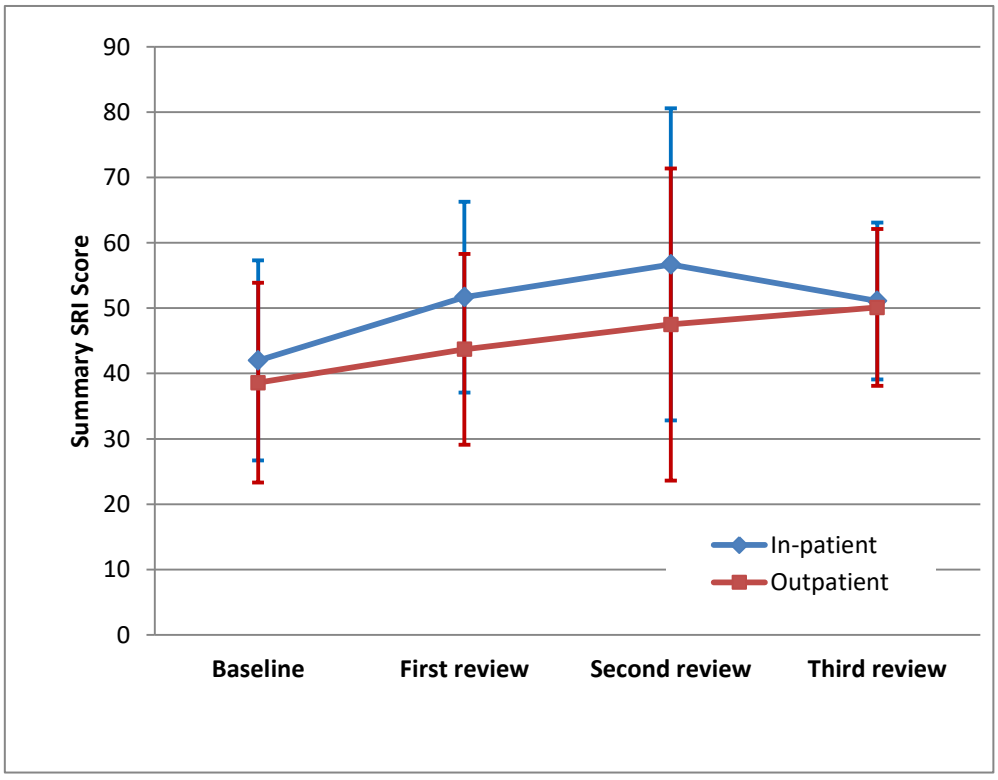
	Inpatient NIV initiation		**Outpatient NIV initiation**		
		(n)		**(n)**	**p value**
Baseline Summary Score	42.0 (17.9)	47	38.6 (15.3)	16	0.502
First review summary score	51.7 (22.1)	41	43.7 (14.6)	15	0.200
Days until first review	65 (29)	41	48 (28)	15	0.046*
Second review summary score	56.7 (23.9)	26	47.5 (11.9)	7	0.334
Days until second review	256 (46)	26	242 (51)	7	0.390

Third review summary score	51.1 (21.2)	24	50.1 (12.0)	9	0.894
Days until third review	521 (444, 657)	24	430 (375, 497)	9	0.016*

Higher SRI scores reflect better self-reported quality of life

At baseline, the mean SRI score was higher for the in-patient NIV initiation group (42.0 (17.9)) compared to the outpatient NIV initiation group (38.6 (15.3)); this difference was not statistically significant (p = 0.502) and was not greater than the MCID (difference = 3.4 points). This indicated that the 2 groups reported similar HRQoL prior to the introduction of long-term home NIV. The mean SRI score for both study groups at first review increased by greater than the MCID from baseline (in-patient NIV = 9.7 points; outpatient NIV = 5.1 points); improvement in mean SRI from baseline was sustained throughout the study for both patient groups (Figure 9) but the difference between the groups at each review was not statistically significant.

Figure 9: *Change in SRI over 12 months for in-patient and outpatient NIV initiation*



At the end-point of the study (third review) for the pooled data for each group, both the in-patient and outpatient NIV initiation groups demonstrated a significant improvement in HRQoL from baseline that was greater than the MCID for SRI (in-patient NIV = 9.1 points; outpatient NIV = 11.5 points); the difference between groups was not statistically significant. This indicates that there were no differences in self-reported HRQoL at 12-months comparing in-patient and outpatient initiation of long-term home NIV.

4.5.2 SRI SCORES PRE AND POST INITIATION OF NIV WITHIN GROUPS AT FIRST REVIEW (PAIRED DATA)

Change in mean SRI at first review from baseline within the two study groups was compared. Only paired data was included for each time point such that if there was not a pair of 'baseline SRI score' and 'follow up SRI score' those patients were excluded from the sub analysis. An absolute change in SRI value of 5 points was considered clinically significant. The data for baseline summary SRI score compared to first review is presented in Table 19.

***Table 19**: Baseline summary SRI versus first review summary SRI Score within groups (in-patient and outpatient)*

Outpatient NIV initiation				
N	Baseline	First review	p value	Absolute change in mean SRI
13	38.4 (13.2)	42.3 (13.9)	0.277	3.9 (12.2)
In patient NIV initiation				
N	Baseline	First review	p value	
31	40.6 (17.6)	48.7 (22.8)	0.016*	8.1 (17.8)

The change in mean SRI observed between baseline and mean SRI at first review was statistically significant for patients commenced on NIV during an in-patient admission (p = 0.016), but not for those commenced on NIV as an outpatient (p = 0.277). Absolute change in mean SRI for patients commenced on NIV as an in-patient was greater than SRI MCID (8.1 points). However, a clinically important difference in SRI was not observed for those patients commenced on NIV as an outpatient (3.9 points).

4.5.3 SRI SCORES PRE AND POST INITIATION OF NIV WITHIN GROUPS AT SECOND REVIEW

Change in mean summative SRI at second review from baseline within the two study groups was compared. Only paired data was included for each time point and non-paired data was excluded from the sub analysis. The data for baseline summary SRI score compared to second review is presented in Table 20.

***Table 20**: Baseline summary SRI versus second review summary SRI Score within groups (in-patient and outpatient)*

Outpatient NIV initiation				
N	Baseline	Second review	p value	Absolute change in mean SRI
6	41.2 (8.6)	48.4 (12.8)	0.269	7.2 (14.2)
In patient NIV initiation				
N	Baseline	Second review	p value	
19	46.5 (16.0)	53.0 (25.2)	0.180	6.5 (20.5)

Change observed between baseline mean summative SRI and SRI at second review was not statistically significant for either group (outpatients p= 0.269; inpatients p = 0.180). However, the absolute change in mean SRI for patients in both groups was greater than SRI

MCID (in-patient NIV = 8.1 points; outpatient NIV = 7.2 points) and indicated a clinically important improvement in HRQoL at second review.

4.5.4 SRI SCORES PRE AND POST INITIATION OF NIV WITHIN GROUPS AT THIRD REVIEW

Change in mean summative SRI at the end-point of the study (third review) from baseline within the two study groups was compared and the data is presented in Table 21. Only paired data was included for each time point and non-paired data was excluded from the sub analysis.

Table 21: *Baseline summary SRI versus third review summary SRI Score within groups (in-patient and outpatient)*

		Outpatient NIV initiation		
N	Baseline	Third review	p value	Absolute change in mean SRI
8	44.1 (14.3)	49.8 (12.8)	0.450	5.7 (14.1)
		In patient NIV initiation		
N	Baseline	Third review	p value	
17	44.5 (18.4)	50.3 (23.4)	0.345	5.8 (24.7)

Comparing the baseline mean SRI and SRI at the end-point of the study, there was no statistically significant change in HRQoL for either group in the study (outpatient NIV p= 0.450; in-patient NIV p = 0.345). However, absolute change in mean SRI for patients in both groups was greater than the SRI MCID (in-patient NIV = 5.8 points; outpatient NIV = 5.7 points) and indicates a clinically important improvement in HRQoL at the end-point of the study for both in-patient and outpatient initiation of NIV.

4.6 Part B: Secondary Outcomes

4.6.1 Outcome 1: Are there Differences within SRI Domains between groups at First Review compared to BASELINE

To identify differences within each group in terms of change for each SRI domain at review during the study period, analysis for in-patient NIV initiation compared to outpatient NIV initiation was made for each of the 7 SRI domains. The comparison of baseline and first review SRI domain score for in-patient (Table 22), outpatient (Table 23) NIV initiation is tabulated, and the absolute change is presented graphically (Figure 10).

***Table 22**: Comparison of baseline and first review SRI domains for in-patient NIV initiation*

In-patient NIV initiation	Baseline	First review	N	p value
Respiratory complaints	40.8 (22.5)	48.8 (24.6)	43	0.024*
Physical Function	25.0 (12.5, 45.8)	25.0 (12.50, 54.2)	41	0.382
Sleep Quality	44.3 (19.4)	52.8 (23.2)	43	0.017*
Social Relationships	62.2 (18.6)	63.0 (22.2)	41	0.780
Anxiety	20.0 (10.0, 52.5)	46.8 (30.0)	40	0.002*
Psychological well-being	48.3 (21.9)	51.4 (24.0)	43	0.342
Social Functioning	39.1 (31.3, 59.4)	50.4 (28.0)	34	0.163

***Table 23**: Comparison of baseline and first review SRI domains for outpatient NIV initiation*

Outpatient NIV initiation	Baseline	First review	N	p value
Respiratory complaints	36.8 (29.7, 18.8)	43.5 (21.6)	15	0.166
Physical Function	31.9 (14.2)	34.7 (15.9)	15	0.339
Sleep Quality	37.5 (20.3)	42.4 (20.3)	14	0.421
Social Relationships	59.2 (11.8)	59.2 (17.7)	15	1.000
Anxiety	27.7 (27.6)	39.0 (29.5)	15	0.132
Psychological well-being	46.3 (14.8)	45.7 (15.7)	15	0.879
Social Functioning	40.9 (16.5)	50.5 (20.2)	14	0.115

Patients commenced on NIV as an in-patient self-reported statistically significant improvements in respiratory complaints (p = 0.024), sleep quality (p = 0.017) and anxiety (p = 0.002) at first review compared to baseline. For patients commenced on NIV as an outpatient, no statistically significant improvements in any SRI domain at first review compared to baseline were observed.

Figure 10: *Absolute change in SRI domain score from baseline to first review for in-patient and outpatient NIV initiation*

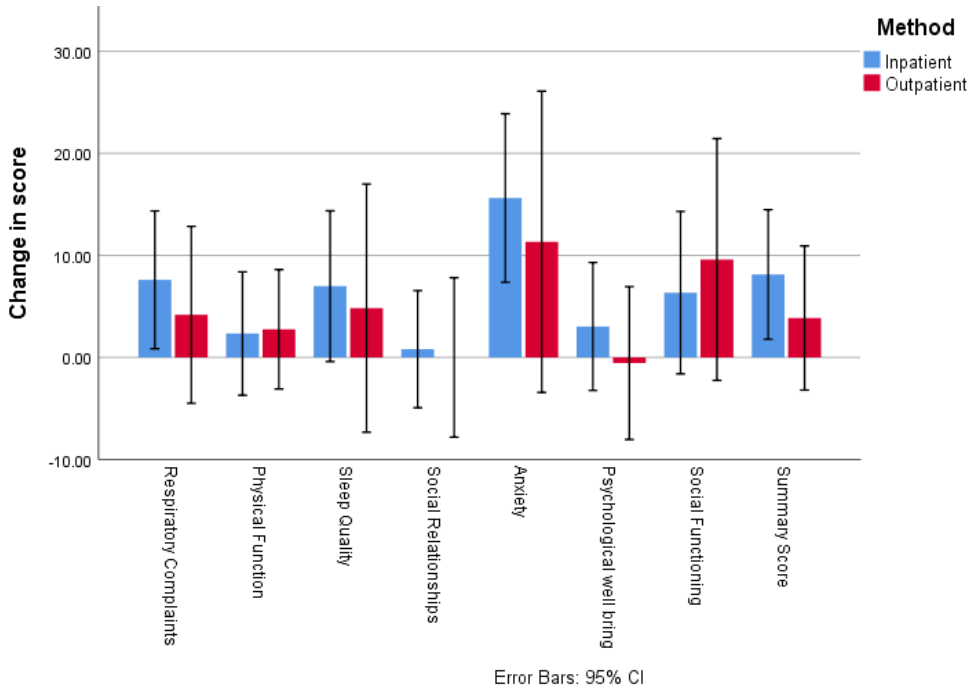


Figure 10 shows an increase in SRI domain score from baseline for both groups at first review for all domains with the exception of the psychological well-being SRI domain score for the outpatient NIV initiation group.

The average (or median) change in each SRI domain was compared across the in-patient and outpatient NIV initiation groups to assesses if the magnitude of change for each subdomain was similar. The data for baseline to first follow up for both groups is summarised in Table 24.

***Table 24**: Comparison of the absolute change in SRI domain scores between in-patient and outpatients NIV initiation groups from baseline to first review*

	Inpatient NIV initiation	N	Outpatient NIV initiation	N	p value
Respiratory complaints	7.6 (22.3)	44	4.2 (16.1)	13	0.589
Physical Function	2.3 (19.5)	41	2.8 (10.9)	13	0.937
Sleep Quality	10.7 (-5.4, 21.4)	44	4.8 (21.8)	13	0.465
Social Relationships	0.8 (18.5)	41	0.0 (14.5)	13	0.880
Anxiety	15.6 (26.3)	40	11.3 (27.4)	13	0.596
Psychological well-being	3.0 (20.7)	43	-0.6 (13.9)	13	0.537
Social Functioning	6.3 (23.4)	34	9.6 (21.3)	13	0.655

The outpatient NIV initiation group produced smaller absolute changes in each of the SRI domain scores at first review. However, there are no statistically significant differences in the magnitude of change in each domain comparing NIV initiation as an in-patient and an outpatient from baseline to first review.

4.6.2 Comparison of SRI domains between groups at Second Review compared to Baseline

The comparison of baseline and second follow up SRI domains for in-patient (Table 25) and outpatient NIV initiation (Table 26) is tabulated and absolute change is presented graphically (Figure 11).

***Table 25**: Comparison of baseline and second review SRI domains for in-patient NIV initiation*

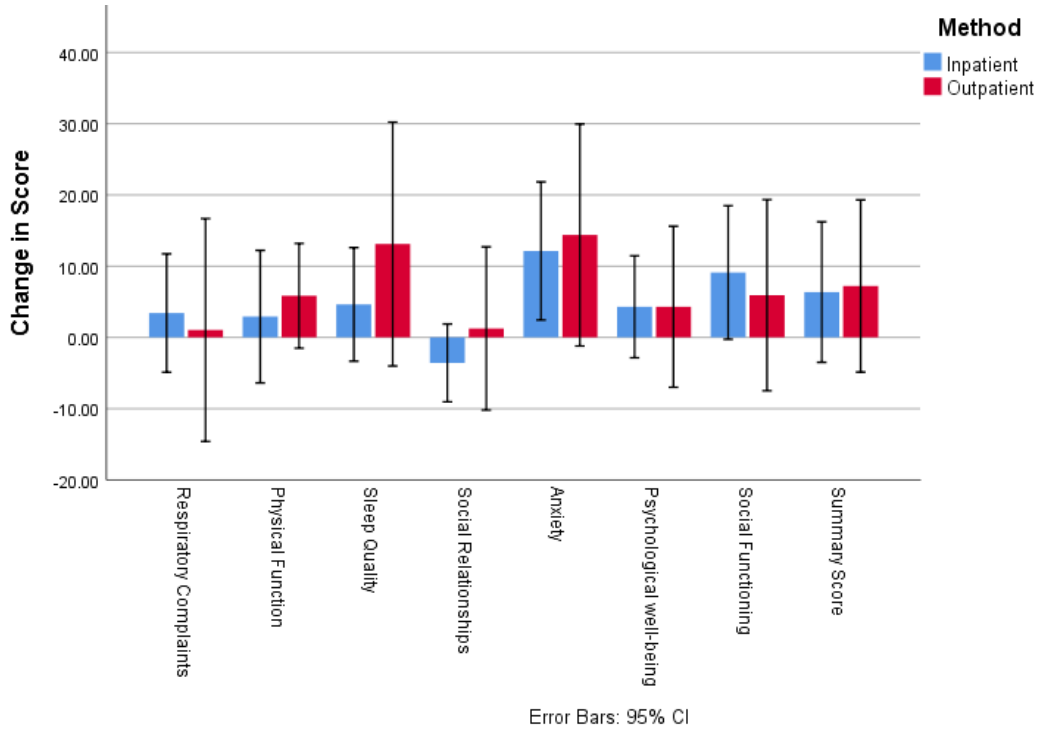
In-patient NIV initiation	Baseline	Second review	N	p value
Respiratory complaints	47 .7 (22.5)	51.1 (26.5)	32	0.420
Physical Function	35.0 (24.4)	38.0 (27.7)	27	0.537
Sleep Quality	49.2 (17.2)	53.8 (24.4)	30	0.257
Social Relationships	65.5 (19.2)	61.9 (23.4)	28	0.205
Anxiety	27.5 (20.0, 55.0)	40.0 (15.0, 85.0)	28	0.015*
Psychological well-being	52.4 (20.4)	56.7 (25.0)	31	0.242
Social Functioning	47.2 (22.6)	56.3 (26.8)	23	0.067

***Table 26:** Comparison of baseline and second review SRI domains for outpatient NIV initiation*

Outpatient NIV initiation	Baseline	Second review	N	p value
Respiratory complaints	44.5 (31.1)	45.6 (14.1)	9	0.893
Physical Function	29.2 (29.2, 41.7)	38.3 (12.1)	10	0.141
Sleep Quality	40.9 (19.9)	54.0 (20.9)	9	0.149
Social Relationships	66.7 (54.2, 70.8)	63.3 (16.4)	10	0.779
Anxiety	22.5 (19.5)	36.9 (21.2)	8	0.096
Psychological well-being	47.2 (44.4, 58.3)	55.6 (55.6, 55.6)	9	0.483
Social Functioning	42.8 (13.6)	48.8 (15.7)	10	0.380

Patients commenced on NIV as an in-patient continued to report statistically significant improvements in anxiety domain score (p = 0.015) at second review compared to baseline. They reported a reduction in SRI domain score for social relationships at second review (-3.6) but this was not statistically significant (p = 0.779). No statistically significant improvements in any SRI domain score from baseline were observed for patients commenced on NIV as an outpatient at second review.

Figure 11: *Absolute change in SRI domain score from baseline to second review for in-patient and outpatient NIV initiation*



Assessment of the absolute change in SRI domain score for the in-patient and outpatient NIV initiation groups from baseline to second review is summarised in Table 27.

Table 27: *Comparison of the absolute change in SRI domain scores between in-patient and outpatients NIV initiation groups from baseline to second review*

	Inpatient NIV initiation	Outpatient NIV initiation	p value
Respiratory complaints	3.4 (23.6)	1.0 (22.5)	0.788
Physical Function	2.9 (24.3)	5.8 (11.2)	0.719
Sleep Quality	4.6 (22.0)	13.1 (24.6)	0.330
Social Relationships	-3.6 (14.6)	1.3 (17.4)	0.397
Anxiety	12.1 (25.8)	14.4 (21.1)	0.825
Psychological well-being	4.3 (21.0)	4.3 (16.3)	0.999
Social Functioning	9.1 (22.6)	5.9 (20.3)	0.705

There no statistically significant differences in the magnitude of change in each SRI domain between NIV initiation as an in-patient and as an outpatient from baseline to second review.

4.6.3 COMPARISON OF SRI DOMAINS BETWEEN GROUPS AT THIRD REVIEW COMPARED TO BASELINE

The comparison of baseline and third follow up SRI domains score for in-patient (Table 28) and outpatient (Table 29) NIV initiation was tabulated; absolute change is presented graphically (Figure 12).

Table 28: *Comparison of baseline and third review SRI domains in in-patients*

In-patient NIV initiation	Baseline	Third review	N	p value
Respiratory complaints	44.6 (24.5)	47.1 (26.2)	25	0.677
Physical Function	29.5 (20.3)	31.1 (23.6)	24	0.684
Sleep Quality	45.9 (19.2)	44.1 (23.2)	26	0.707
Social Relationships	63.5 (18.9)	60.8 (27.3)	25	0.607
Anxiety	35.6 (27.3)	48.4 (34.6)	25	0.046*
Psychological well-being	49.4 (22.6)	52.8 (24.5)	26	0.454
Social Functioning	47.4 (22.8)	54.3 (29.1)	18	0.328

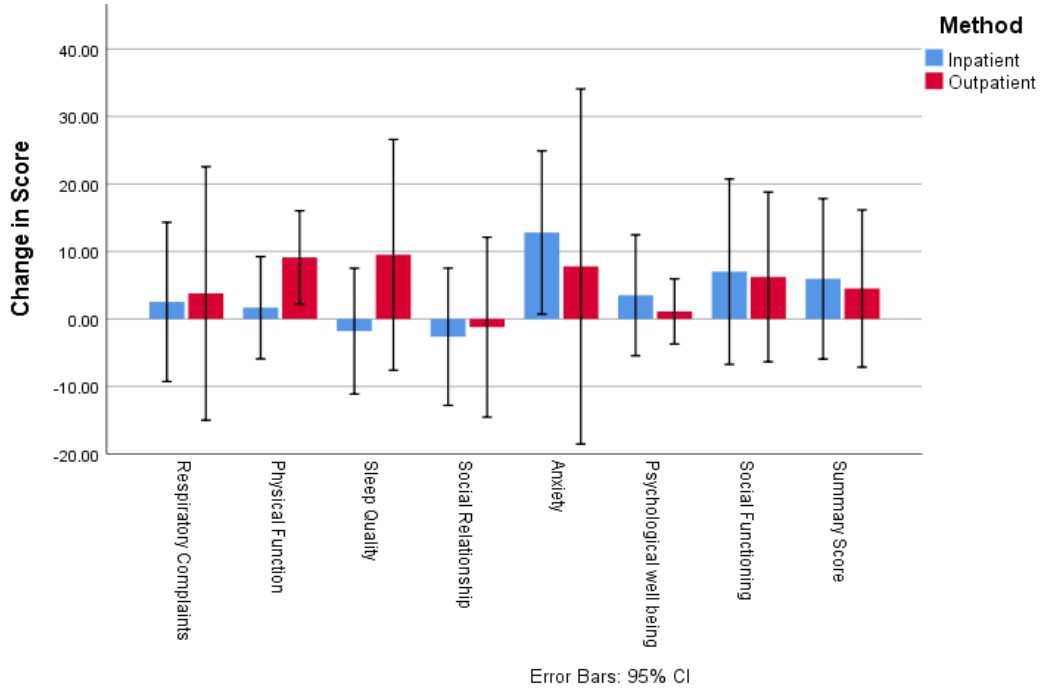
Table 29: Comparison of baseline and third review SRI domains in outpatients

Outpatient NIV initiation	Baseline	Third review	N	p value
Respiratory complaints	44.5 (29.7)	48.3 (15.3)	9	0.682
Physical Function	34.3 (16.2)	43.5 (19.1)	9	0.023*
Sleep Quality	44.6 (20.5)	54.0 (16.6)	8	0.293
Social Relationships	59.7 (11.8)	58.3 (15.9)	9	0.833
Anxiety	35.0 (30.3)	42.8 (23.6)	9	0.555
Psychological well-being	47.5 (12.8)	48.8 (14.2)	9	0.601
Social Functioning	48.3 (17.8)	54.5 (13.8)	9	0.329

At the end-point of the study (third review), patients commenced on NIV as an in-patient continued to report statistically significant improvements in anxiety (p = 0.015) compared to baseline. They reported a slightly lower sleep quality score compared to baseline, but the difference is not significant (p= 0.707). Patients commenced on NIV as an outpatient reported a statistically significant improvement in SRI domain score for their physical functioning (p = 0.023) at 12-months following NIV.

Both groups reported a reduced SRI domain score for social relationships compared to baseline; this difference is not statistically significant (in-patient p =0.607; outpatient p =0.833).

Figure 12: *Absolute change in SRI domain score from baseline to third review up for in-patient and outpatient NIV initiation*



Absolute change in SRI domain score for the in-patient and outpatient NIV initiation groups from baseline to third review is summarised in Table 30.

***Table 30**: Comparison of absolute change in SRI domain scores between in-patient and outpatients NIV initiation groups from baseline to third review*

	Inpatient NIV initiation	Outpatient NIV initiation	p value
Respiratory complaints	2.5 (29.7)	3.8 (27.0)	0.912
Physical Function	1.7 (18.7)	9.1 (9.9)	0.267
Sleep Quality	-1.8 (23.9)	9.5 (23.2)	0.248
Social Relationships	-2.6 (25.6)	-1.2 (19.2)	0.881
Anxiety	12.8 (30.5)	7.8 (37.8)	0.693
Psychological well-being	3.5 (23.0)	1.1 (7.0)	0.763
Social Functioning	7.0 (29.3)	6.2 (18.1)	0.943

Both groups reported improvements from baseline in 'respiratory complaints', 'physical function', 'anxiety', 'psychological well-being' and 'social functioning' domains. The outpatient group reported larger domain improvement scores for each of these domains with the exception of anxiety and social functioning. The in-patient NIV group reported poorer sleep quality than that recorded at baseline and both groups reported lower scores for social functioning following 12-months of home NIV.

At the end-point of the study (12 months), there are no statistically significant differences between the domain scores reported by the in-patient NIV initiation group compared to the scores reported by the outpatient NIV initiation group. This indicates that outpatient NIV initiation is not inferior to in-patient NIV initiation in terms of the specific quality of life domains scored by the SRI.

4.6.4 OUTCOME 2: ARE THERE DIFFERENCES IN THE DOMAINS OF SRI THAT ARE DISEASE SPECIFIC?

From the combined (in-patient and outpatient NIV initiation) data pool for this study, there were insufficient baseline SRI scores with paired data sets for first, second or third review for patients with chest wall disease and slowly progressive neuromuscular disease; these clinical groups have not been included in this sub-analysis.

For patients with COPD and OHVS, the baseline SRI domain scores were compared (Table 31).

Table 31: *Comparison of baseline SRI domain scores in COPD and OHVS*

	OHVS	COPD	p value
Respiratory complaints	54.6 (29.1)	38.1 (21.1)	0.089
Physical Function	44.7 (18.3)	25.0 (17.1)	0.007*
Sleep Quality	52.7 (21.7)	42.4 (18.2)	0.179
Social Relationships	68.3 (17.7)	58.3 (15.1)	0.115
Anxiety	49.2 (31.2)	21.9 (16.9)	0.006*
Psychological well-being	55.3 (17.7)	46.1 (21.9)	0.224
Social Functioning	59.9 (23.3)	37.8 (13.1)	0.011*

Prior to commencing long-term home NIV, all of the domain scores for patients with COPD were lower than those reported by patients with OHVS and the differences were greater than the SRI MCID, indicating that there were clinically significant differences in HRQoL between the groups prior to commencing NIV. The differences in SRI domain scores for physical function (p = 0.007), anxiety (p = 0.06) and social functioning (p = 0.011) between the 2 groups reached statistical significance.

4.6.5 Outcome 3: Are there Differences in SRI Domain Score Change Over Time Comparing COPD with OHVS?

From the combined (in-patient and outpatient NIV initiation) data pool for this study, there were insufficient baseline SRI scores with paired data sets for first, second or third review for patients with CWD and slowly progressive NMD; these clinical groups have not been included in this sub-analysis.

To assess within group (COPD and OHVS) changes in SRI domain score at each review during the study, baseline SRI domain data for both patient clinical groups were compared with SRI domain data at first, second and third review. Data is presented in Tables 32 - 40 and Figures 13-15.

***Table 32**: Comparison of baseline and first review SRI domain data in OHVS*

OHVS	Baseline	First review	N	p value
Respiratory complaints	47.5 (27.4)	59.1 (24.2)	20	0.028*
Physical Function	39.1 (22.1)	45.6 (26.6)	18	0.148
Sleep Quality	44.9 (22.6)	53.8 (19.1)	19	0.097
Social Relationships	69.8 (18.1)	66.7 (22.5)	20	0.325
Anxiety	41.3 (30.5)	59.8 (27.9)	20	0.019*
Psychological well-being	55.6 (17.0)	56.7 (19.9)	20	0.791
Social Functioning	54.0 (25.4)	63.0 (23.1)	18	0.065

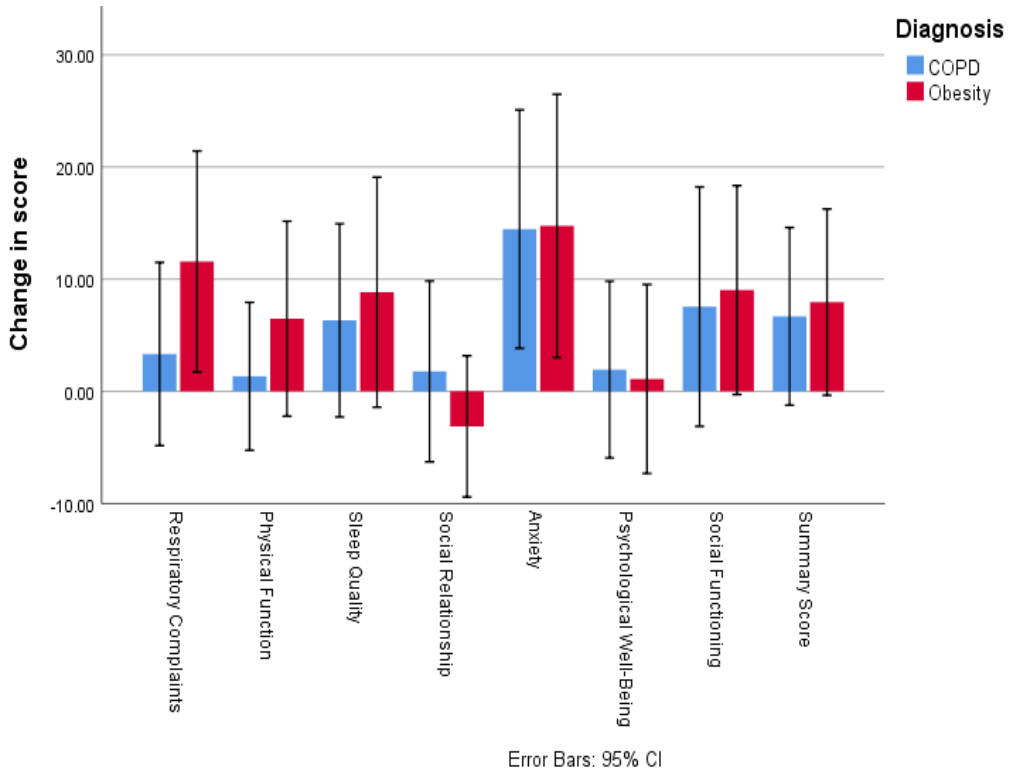
***Table 33**: Comparison of baseline and first review SRI domain data in COPD*

COPD	Baseline	First Review	N	p value
Respiratory complaints	38.9 (20.8)	42.2 (21.9)	31	0.182
Physical Function	28.1 (17.9)	29.4 (19.2)	31	0.359
Sleep Quality	42.0 (17.8)	48.6 (25.8)	30	0.137
Social Relationships	57.4 (15.7)	59.2 (22.1)	28	0.484
Anxiety	23.6 (21.3)	39.1 (30.0)	28	0.008*
Psychological well-being	46.3 (22.3)	48.2 (24.7)	30	0.840
Social Functioning	37.1 (16.6)	44.7 (26.4)	24	0.292

***Table 34**: Comparison of absolute change in SRI domain score between OHVS and COPD from baseline to first review*

	OHVS	COPD	p value
Respiratory complaints	11.6 (21.7)	3.3 (22.8)	0.204
Physical Function	6.5 (18.2)	1.3 (18.4)	0.348
Sleep Quality	8.8 (22.0)	6.3 (24.0)	0.713
Social Relationships	-3.1 (13.9)	1.8 (21.3)	0.374
Anxiety	14.8 (25.8)	14.5 (28.1)	0.972
Psychological well-being	1.1 (18.5)	1.9 (21.6)	0.888
Social Functioning	9.0 (19.5)	7.6 (26.2)	0.842

Figure 13: *Absolute change in SRI domain score from baseline to first follow up in patients with COPD and OHVS*



Patients reported increased domain scores at first review compared to baseline, suggesting an overall improvement in HRQoL with the exception of OHVS, who reported a reduction in the social relationships domain; the change was not statistically significant ($p = 0.325$). Patients with OHVS reported statistically significant improvements in respiratory complaints ($p = 0.028$) and anxiety ($p = 0.019$); patients with COPD reported statistically significant improvements in anxiety ($p = 0.008$) at first review following initiation of long-term home NIV.

Table 35: *Comparison of baseline and second review SRI domains in OHVS*

OHVS	Baseline	Second review	N	p value
Respiratory complaints	54.7 (29.2)	60.0 (24.1)	16	0.485
Physical Function	41.4 (22.0)	44.7 (29.8)	15	0.626
Sleep Quality	47.9 (19.7)	60.7 (42.9, 67.9)	15	0.414
Social Relationships	71.9 (17.1)	65.1 (23.7)	15	0.410
Anxiety	36.5 (27.5)	57.3 (30.2)	13	0.018*
Psychological well-being	56.4 (17.5)	60.6 (23.4)	16	0.450
Social Functioning	56.0 (24.7)	63.4 (26.1)	14	0.319

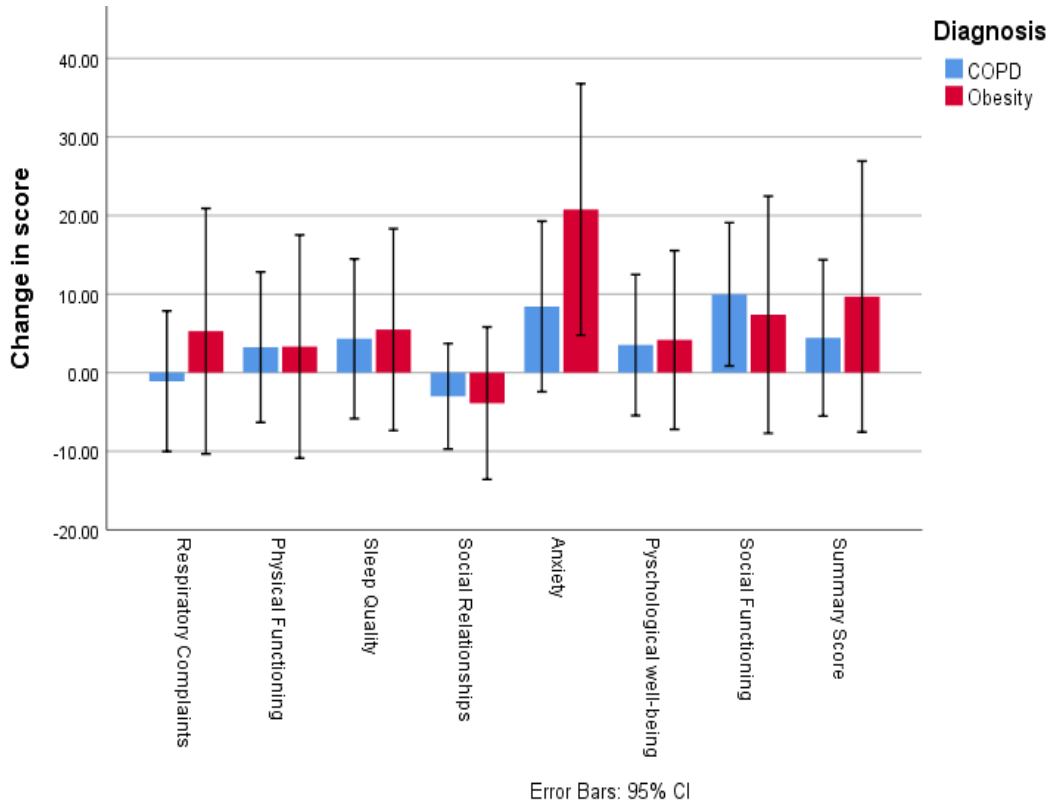
Table 36: *Comparison of baseline and second review SRI domains in COPD*

COPD	Baseline	Second review	N	p value
Respiratory complaints	40.5 (19.6)	39.4 (18.6)	20	0.801
Physical Function	31.0 (21.7)	34.3 (20.1)	18	0.489
Sleep Quality	45.5 (17.2)	49.8 (19.1)	19	0.385
Social Relationships	58.8 (15.5)	55.8 (19.8)	18	0.361
Anxiety	26.1 (20.7)	34.5 (28.7)	19	0.122
Psychological well-being	50.3 (19.6)	53.8 (23.7)	19	0.424
Social Functioning	37.3 (12.5)	47.3 (21.4)	16	0.037*

Table 37*: Comparison of absolute change in SRI domain score between OHVS and COPD from baseline to second review*

	OHVS	COPD	p value
Respiratory complaints	5.3 (29.5)	-1.1 (19.1)	0.438
Physical Function	3.3 (25.9)	3.2 (19.4)	0.991
Sleep Quality	5.5 (23.5)	4.3 (21.2)	0.880
Social Relationships	-3.9 (17.7)	-3.0 (13.6)	0.874
Anxiety	20.8 (27.2)	8.4 (22.6)	0.173
Psychological well-being	4.2 (21.5)	3.5 (18.7)	0.925
Social Functioning	7.4 (26.6)	10.0 (17.4)	0.751

Figure 14: *Absolute change in SRI domain score from baseline to second review in patients with COPD and OHVS*



At second review, both groups reported a reduction from baseline in absolute SRI domain score for social functioning (OHVS = -3.9 points; COPD = -3.0 points); the difference within groups (OHVS p = 0.410; COPD p = 0.361) and between groups (p = 0.874) was not statistically significant. Patients with OHVS reported a statistically significant improvement in anxiety (p = 0.018) at second review and patients with COPD reported improved social functioning (p = 0.037), but there were no statistical differences between groups.

Table 38: *Comparison of baseline and third review SRI domain score in OHVS*

	Baseline	Third review	N	p value
Respiratory complaints	54.6 (29.1)	55.8 (26.5)	13	0.905
Physical Function	44.7 (18.3)	48.5 (21.9)	11	0.512
Sleep Quality	52.7 (21.7)	52.4 (21.8)	12	0.968
Social Relationships	68.3 (17.7)	65.1 (23.4)	13	0.643
Anxiety	49.2 (31.2)	55.0 (29.9)	13	0.618
Psychological well-being	55.3 (17.7)	57.1 (21.1)	13	0.787
Social Functioning	59.9 (23.4)	59.4 (28.7)	12	0.951

Table 39: *Comparison of baseline and third review SRI domain score in COPD*

	Baseline	Third review	N	p value
Respiratory complaints	38.1 (21.1)	41.6 (19.8)	15	0.630
Physical Function	25.0 (17.1)	28.9 (20.9)	16	0.367
Sleep Quality	42.4 (18.2)	40.3 (18.2)	16	0.739
Social Relationships	58.3 (15.1)	56.0 (26.8)	15	0.738
Anxiety	21.9 (16.9)	41.6 (32.7)	15	0.011*
Psychological well-being	46.1 (21.9)	49.2 (24.4)	16	0.536
Social Functioning	27.8 (13.1)	50.9 (24.8)	10	0.113

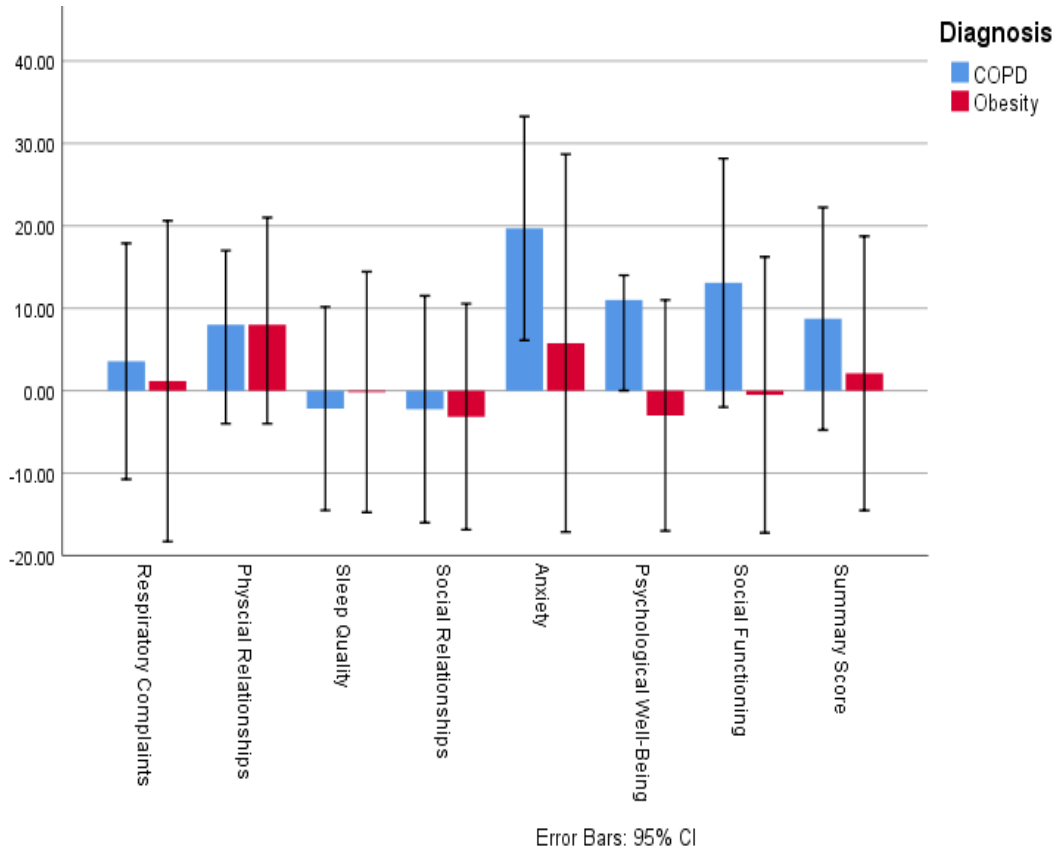
At the end-point of the study, patients with COPD reported a statistically significant improvement in anxiety compared to baseline (p = 0.011). No other statistically significant improvements in SRI domains were observed for either group.

Table 40: *Comparison of the absolute change in SRI domain score between OHVS and COPD from baseline to third review*

	OHVS	COPD	p value
Respiratory complaints	1.2 (34.5)	3.6 (28.6)	0.834
Physical Function	8.0 (0.0, 13.0)	8.0 (-4.0, 17.00)	0.853

Sleep Quality	-0.2 (24.9)	-2.2 (25.5)	0.927
Social Relationships	-3.2 (24.3)	-2.3 (27.5)	0.834
Anxiety	5.8 (40.7)	19.7 (27.2)	0.280
Psychological well-being	-3.0 (-8.0, 6.0)	11.0 (0.0, 14.0)	0.229
Social Functioning	-0.5 (28.5)	13.1 (25.0)	0.240

Figure 15: *Absolute change in SRI domain score from baseline to third review in patients with COPD and OHVS*



At the end-point of the study, both clinical groups reported lower SRI domain scores for sleep quality and social functioning compared to baseline; comparison between the 2 groups did not yield any statistically significant differences in SRI domain scores comparing OHVS with COPD at 12 months post NIV initiation. This suggests that whilst there may be

statistically significant changes for SRI domains within each clinical condition, there are no significant differences in individual absolute domain SRI scores between the clinical groups.

4.7 Comparison of costs of in-patient NIV initiation versus outpatient NIV initiation

4.7.1 Equipment Costs

In-patient NIV initiation versus outpatient NIV equipment costs are summarised in Table 41 and are based on the cost per device (including hose) and interface from the current block contract for the organisation with the equipment provider.

Table 41: *In-patient NIV initiation versus outpatient NIV equipment costs*

		In-patient n= 92		Outpatient n= 21	
Devices	**Unit cost (£)**	**Units**	**Units**	**Cost (£)**	**Cost(£)**
Lumis ST150	1,600	19	21	33,600	30,400
Stellar ST150	2,300	73	0	0	167,900
Interfaces		**Units**	**Units**	**Cost (£)**	**Cost(£)**
ResMed AirFit™ F20	80	44	12	960	3,520
Fisher & Paykel Simplus™	81	31	9	729	2,511
Philips Amara View™	73	17	0	0	1,241
Cost per patient (£)				**1,680.43**	**2,234.48**

Overall, the equipment costs, NIV initiation via an in-patient route were 32.97% more costly that initiation as an outpatient. This was primarily due to the selection of a more costly NIV device (Stellar ST150) for this patient group.

4.7.2 Time taken to initiate NIV

The time taken for in-patient compared to outpatient initiation of long-term home NIV was estimated and is summarised in Table 42

Table 42: *Time required for initiation of NIV (in-patient versus outpatient)*

	Time taken to establish on NIV (days)
Inpatient initiation* ***(median, interquartile range)***	3 (2,5)
Outpatient initiation	0.5

** Calculated from decision to treat with home NIV to discharge from NIV service*

Based on when the decision to initiate on long-term home NIV was made and the time to discharge from the in-patient NIV service, patients established on home NIV as an inpatient required a significantly greater amount of time to be established on NIV than those who were established via an outpatient pathway. However, there is no information available of the time elapsed from when the decision to initiate on long-term home NIV via an outpatient was made and when the patient received an appointment for this.

4.7.3 Estimate of Procedure Costs Based on NHS HRG Codes

Using HRG code DZ37A, the total costs were compared between use of the 'Combined day case/ordinary elective spell' tariff versus the 'Non-elective spell' tariff for in-patients and 'Combined day case/ordinary elective spell' tariff versus the 'Non-elective spell' tariff for outpatients (Table 43)

Table 43: *Comparison of in-patient and outpatient NIV costs based on HRG tariff*

In-patient NIV n =92	**HRG Tariff**	**Total Cost (£)**
Non-elective spell	1,188	109,296
Combined day case / ordinary elective spell	712	65,504
Outpatient NIV N =21	**HRG Tariff**	**Total Cost (£)**
Combined day case / ordinary elective spell	712	14,952
Outpatient procedure	170	3,570

There were significant differences in the 'cost' of initiation of NIV depending on the HRG code selected, irrespective of whether this was as an in-patient or outpatient. In reality, this 'cost' reflects only the income received by the Trust per patient, rather than the actual costs associated with the individual procedure per patient in the study.

4.7.4 Costs associated with admissions Before and after commencing NIV

Using the HRG tariff associated with a non-elective spell, the costs associated with hospital admissions before and after initiation of NIV were calculated, comparing the in-patient initiation group with the outpatient initiation group (Table 44).

Following initiation of long-term home NIV, there was a reduction in respiratory related admissions comparing 1-year pre NIV to 1-year post NIV for both groups; a reduction in costs associated with in-patient admissions following initiation of NIV was therefore demonstrated for both groups. The reduction in cost associated with in-patient admissions pre NIV were greater for the in-patient NIV initiation group. However, at 1-year post NIV,

the admissions and bed days and thus the costs for both groups were similar. This would suggest that NIV reduces admissions and therefore costs irrespective of the route of initiation.

Table 44: *Cost of NIV 1-year pre and post NIV initiation (in-patient versus outpatient initiation)*

	1 year pre-NIV	Cost (£)	1 year post NIV	Cost (£)
Admissions (IP NIV set up)	2 (1-3)	2,376 (1,188-3,564)	0 (0-1)	0 (0-1,188)
Bed days (IP NIV set up)	23 (13-33)	5,198 (2,938-7,458)*	0 (0-6)	0 (0-1,356)
Total cost inc. excess bed days (IP NIV set up)		**7,574 (4,126-11,022)**		**0 (0-2,544)**
Admissions (OP NIV set up)	1 (0-2)	1,188 (0–2,376)	0 (0-1)	0 (0-1,188)
Bed days (OP NIV set up)	1 (0-8)	0 (0–1,808)*	0 (0-4)	0 (0-904)
Total cost inc. excess bed days (OP NIV set up)		**1,188 (0-4,184)**		**0 (0-2,093)**

** Based on a trim point of 5-days, with' long stay' at a cost of £226/day*

5 DISCUSSION AND CONCLUSION

5.1 DISCUSSION

5.1.1 PRIMARY OUTCOMES

The aim of this study was to demonstrate that initiation of long-term home NIV as an elective outpatient produces equivalent outcomes compared to an in-patient NIV initiated service following an acute admission. At the end-point of the study (12 months), both patient study groups demonstrated a reduction in $PaCO_2$; both groups were equally likely to demonstrate a normalised $PaCO_2$. There was neither a statistically significant nor clinically important difference in $PaCO_2$ between the two groups, suggesting that in a mixed cohort of patients the initiation of long-term home NIV as an elective outpatient produces equivalent outcomes in terms of $PaCO_2$, compared to NIV initiated as an in-patient following an acute admission.

Previously, it has been suggested that improvements in physiological variables may come at the cost of quality of life (McEvoy et al., 2009). In this study, the improvements observed in gas exchange did not appear to come at the cost of reduced quality of life; patients in both groups reported an improvement from baseline in mean SRI score at the end-point of the study that was greater than the minimal clinically important difference. There was no statistically significant difference in the mean SRI score between the groups at the end of the study. The difference between the two groups was less than the MCID, implying that in a mixed cohort of patients (COPD, OHVS, CWD and NMD), initiation of long-term home NIV as an elective outpatient via a non-specialist NIV service does not produce inferior outcomes in terms of HRQoL compared to NIV initiated as an in-patient following an acute admission.

5.1.2 PART A: SECONDARY OUTCOMES

It has been established previously that the introduction of long-term home NIV following a hospital admission requiring acute NIV has been shown to reduce subsequent hospital admissions and length of stay for persistently hypercapnic COPD patients (Murphy, P.B., et al., 2017) and for a mixed cohort of patients (Livesey, A., et al., 2018). In line with previous research, the introduction of long-term home NIV reduced the frequency of hospital admissions and the length of stay in the 12-months following its introduction for both patient groups within the current study. For patients commenced on home NIV following an acute admission this improvement was statistically significant for both admissions (p= <0.001) and bed days (p= <0.001). However, statistical significance was not achieved for patients commenced on NIV as an outpatient. This finding was unsurprising, as it can be observed from the baseline data for both groups (Table 9) that the in-patient NIV group had significantly higher $PaCO_2$ at baseline. Severity of hypercapnia is associated with a longer time to clinical stability (Iqbal, N., et al., 2017) and more frequent and longer hospitalisation (Yassin, Z., et al., 2016). In addition, NIV is often not considered unless patients have had two or more hospital admissions requiring NIV, or they have had difficulty being weaned off invasive ventilation (Agency for Clinical Innovation Respiratory Network, 2012). It is very likely that the outpatient NIV cohort were identified earlier in their disease progression than the in-patient group, as they were already known to the Lung Function and Sleep service either as home oxygen patients via the HOS-AR clinics or as CPAP patients via the Sleep service. Thus, this group of patients were being more closely monitored than the in-patient group and NIV was commenced earlier, and before the frequency of acute in-patient admissions had increased.

Whilst statistical analysis indicates that there is insufficient evidence of an association between poor compliance and re-admission, cross-tabulation of the data comparing the association between two would seem to suggest that patients that are more compliant are more likely to be re-admitted to hospital. If this were correct, it would be in direct contradiction to the findings of previous studies, which found that poor compliance with NIV was associated with more frequent re-admissions (Funk, G.C., et al., 2011; Ankjærgaard, K.L., et al., 2016; Cheng, L., et al., 2011). However, the data from this study must be considered in the context of the numbers of patients in each treatment group, with significantly more patients who were initiated on NIV as an in-patient compared to outpatient initiation. At all points throughout the study period, the in-patient NIV group demonstrated higher compliance with NIV therapy than those initiated as an outpatient (tables 10 -12). The factors that affect patient therapeutic compliance are complex and varied and include age, ethnicity, sex, marital status and the patients' beliefs and motivation about the therapy (Jin, J., et al., 2008). It has been identified that if a patient believes that an illness or its complications could pose severe consequences for their health (McLane, C.G., et al., 1995; Sirey, J.A., et al., 2001; Löffler, W., et al., 2003) or if they believe that the therapy will be effective or perceive benefits from the therapy (Wild, M.R., et al., 2004; Aloia, M.S., et al., 2005) they are more likely to be compliant with treatment. It may be hypothesised that patients initiated as an in-patient have experienced a life-threatening event and are more aware of the severe consequences of their illness; outpatients initiated on NIV before an acute life-threatening event may be less cognizant of the severity of their disease and thus do not have as great a desire to comply with treatment.

Several good quality RCTs have shown that if adequate ventilatory settings are applied, aimed at a substantial reduction in $PaCO_2$, home NIV provides survival benefits in patients with severe chronic hypercapnic respiratory failure (Duiverman, M.L., 2018). For patients in this current study there was no statistical difference in all-cause mortality associated with initiation of NIV as an outpatient compared to an in-patient at 12 months, suggesting that outpatient initiation of NIV is not inferior to inpatient initiation in terms of mortality. Whilst the Kaplan Meier survival curve does suggest increased mortality for the in-patient initiation group (Figure 5) and the overall attrition rate for this group is higher, this may be a function of censored data within the larger dataset (n= 92 vs. n= 21); there is no statistical difference between the 2 groups. In addition, it is probable that the in-patient group were more severely ill than the outpatient cohort by definition of having multiple previous admissions. The all-cause mortality for the whole NIV patient cohort at one year was 15.0%; this compares very favourably with previous studies (Ansari, Z., et al., 2014; Chu, C.M., et al., 2004; Ankjærgaard, K.L., et al., 2016). The higher mortality figure of 30.8% reported by Ansari, Z., et al. (2014) was for a mixed cohort of subjects. This may be explained by data collection over a 4-year period, in what many may consider as palliative care in end-stage disease. The studies by Chu, C.M., et al. (2004), who reported mortality at 1-year of 49.1% and Ankjærgaard, K.L., et al. (2016), who reported a 1-year mortality of 20% were in patients with COPD that had been admitted with an episode of AHRF. Clearly, the severity of disease in the populations being studied greatly influences these outcome measures. The patients in this study were a mixed clinical group; they were mainly COPD and OHVS patients. The data from Ansari, Z., et al. (2014) for a mixed patient cohort suggests that patients with COPD have a shorter mean duration between home NIV initiation and death than patients with OHVS and NMD, which may account for the differences observed

between this study and those studies with an exclusively COPD patient cohort. The cause of death for the patients in this current study was not recorded, as it fell outside the original scope of the data collection.

5.1.3 PART B OUTCOMES

This study has inferred that that initiation of long-term home NIV as an elective outpatient service in a mixed cohort of patients does not produce inferior outcomes in health related quality of life at 12-months when compared to NIV initiated as an in-patient following an acute admission. The patients in this study demonstrated improvements in SRI at the first, second and third review post NIV initiation; improvement in SRI reached statistical significance only in the in-patient initiation group between baseline and first review. The improvement in SRI at first review observed in the outpatient NIV initiation group was less than the MCID, suggesting that at first review, this group felt no clinically important improvement following initiation of NIV. This finding is disappointing, but not unexpected. The outpatient cohort was naïve to NIV, although a small number of patients had previously used continuous positive airway pressure (CPAP); the in-patient cohort were commenced on to long-term home NIV following an acute admission with AHRF and prior to discharge, thus they were more accustomed to NIV treatment and had received intensive one-to-one support to facilitate their use. There is a considerable literature to support that view that acceptance of long-term positive pressure support is a lengthy process, which involves gradual orientation with the machine (Lindahl, B., et al., 2005; Sawyer, A.M., et al., 2010; Ando, H., et al., 2015; Fung, C.H., et al., 2015). Evident throughout all the studies was the fact that when patients are started on NIV treatment, they usually have difficulties and troubles in becoming accustomed to the treatment. These difficulties are related to

significant air leaks, feelings of claustrophobia, aerophagia, presence or risk of facial injuries and respiratory distress (Ngandu, H., et al., 2016).

However, at the second review (6 months post NIV initiation), both groups had achieved an improvement in their summative SRI score that was greater than the MCID; this improvement was sustained at the third review, and end of the study, at 12 months.

The summative baseline SRI score reported for this study cohort (in-patient initiation 42.0 (17.9); outpatient initiation 38.6 (15.3)) was lower than that reported in similar studies; it was lower at the study end-point at 12 months, using the same HRQoL tool (Table 45) as comparable studies. In addition, the absolute changes in mean SRI observed at 12 months were not as large (in-patient initiation absolute change 5.8); outpatient initiation absolute change 5.7) as reported in the studies below.

***Table 45**: Baseline SRI reported in HRQoL studies in home NIV*

Authors	Study aim	Cohort	Main SRI findings
Storre, J.H., et al., 2006	AVAPS in OHVS	10 OHVS patients starting NIV	63 ± 15 (baseline) 78 ± 14 (6 weeks BPV-S/T) 76 ± 16 (6 weeks BPV-S/T-AVAPS)
Windisch, W., et al., 2008	HRQoL improvement during HMV	85 stable NIV patients	49 ± 15 (baseline) 61 ± 15 (1 month) 61 ± 16 (1 year)
Struik, F.M., et al., 2014	NIV vs. standard treatment	108 COPD patients after acute exacerbation	47.9 ± 15.1 (baseline) 55.0 ± 15.4 (12 months)
Valko, L., et al., 2020.	HRQoL improvement during HMV	74 hypercapnic patients commencing home IV or NIV	57.7 ±14.4 (baseline) 68.2 ± 15.8 (6 months)

The reasons for these discrepancies in reported SRI between this study and comparable studies are unclear; the patients in this study do not differ significantly anthropometrically or physiologically from those in previous studies. The patient cohort in this study are a mixed clinical group, as were the cohorts in the studies by Windisch, W., et al (2008) and Valko, L., et al., 2020. However, the cohort was biased towards patients with COPD (54%) and absolute improvements in SRI at 12 months in the study by Struik, F.M., et al. (2014) of COPD patients were more modest (7.1 points).

A further consideration is that the concept of HRQoL is understood differently in different cultures (Haraldstad, K., et al., 2019) or in different healthcare systems. The SRI was originally developed in German. It has been translated and validated in to a number of languages including English (Ghosh, D., et al., 2012). This required translation and back-translation of the original German SRI by two independent professional translators. Items with incongruence or discrepancies between the original and back-translated version required modification in the definitive UK English version. This requirement may contribute to the differences observed in the reported HRQoL from a cohort of predominantly white, English speaking patients using a tool developed in and translated from the original German version.

Each of the studies described in Table 45 are controlled prospective studies rather than retrospective studies and it is possible the data obtained may be of better quality and was more selective than that obtained in this study, due to the limitations associated with retrospective data analysis. In a prospective study, there is a degree of control as to who administers the HRQoL tool with the patient and when in the pathway it is administered. Mercieca-Bebber, R., et al. (2018) found that whilst healthcare professionals often feel

confident about administering patient related outcome questionnaires, there are challenges and inconsistencies in day-to-day practices that can adversely affect the quality and value of the data obtained. This is a retrospective study, and therefore the timing of when the baseline SRI was administered to the patient and who administered it was not controlled; this may have directly affected the SRI score that was reported. However, this current work represents the "real world" clinical situation rather than a carefully selected, but potentially less representative research cohort.

When analysing the individual domains within the SRI, the domains of respiratory complaints, physical functioning, anxiety and social functioning were the aspects that were reported as most diminished at baseline SRI for the in-patient and outpatient initiation groups. The reduced SRI score reported in the respiratory complaints domain would be anticipated in a cohort of patients that have chronic respiratory failure and contains a high proportion of patients with severe COPD. Impaired physical capacity and low-level daily physical activity are common features in patients with COPD (Watz, H., et al., 2014) and OHVS (Dreher, M. and Kabitz, H.J., 2012). The thematic synthesis of NIV experiences in adults with hypercapnic respiratory failure by Ngandu, H., et al. (2016) found that in all but four studies from the thirty two reviewed, participants expressed a fear of being on NIV. The perceptions of anxiety and fear are intrinsically linked, but as noted by Sarnoff, I. and Zimbardo, P.G. (1961), as fear increases so does the desire to affiliate with others, but the opposite is true for anxiety; this self-isolation may contribute to the patients reported feelings of reduced social functioning.

The SRI domain in the current study that demonstrated the greatest improvement across both groups was anxiety (in-patients 12.8 (30.5); outpatients 7.8 (37.8)), with the in-patient

NIV group having the greatest improvements in this domain score. The standard deviation for both groups is wide, particularly for the outpatient group, primarily due to the small number of paired data sets in the analysis. Patients discharged on long-term home NIV as an in-patient following hospitalisation for acute exacerbation have a high prevalence of anxiety and depression and a poor health status (Gudmundsson, G., et al., 2006; Piggin, L.H. (2011). The study by Piggin identified that patients who received NIV for the treatment of CHRF regarded the NIV machine as a “lifesaver” and therefore its use may reduce their feelings of anxiety about their breathing. This finding may also contribute to the observation that the in-patient group in the current study demonstrates higher compliance with NIV at all points during the study period. Patients commenced on NIV as an in-patient also reported improved psychological well-being and social functioning at the end of the study compared to baseline; these improvements may be a consequence of their reduced perceived levels of anxiety but would require further work to explore any association. The outpatient NIV initiation group reported robust improvements in their physical function, sleep quality and social function. This finding is in keeping with previous work that has demonstrated that the introduction of long-term home NIV improves physical function in a cohort of patients with COPD and OHVS (Valko, L., et al., 2020). The differences observed in the domains of SRI for the 2 groups in the current study may also reflect that the outpatient and in-patients NIV cohorts are a continuum of disease severity but at different time points on the same timescale.

Whilst the study by Valko, L., et al. (2020) described improvements in physical function domain with NIV for COPD and OHVS patients, there are also differences between these 2 patient cohorts at baseline and 12-months for the patients in the current study. Patients

with OHVS report higher baseline domain scores for physical function, anxiety and social functioning compared with the COPD; despite the higher baseline domain score for anxiety, patients with OHVS reported improvements in anxiety that are greater than the MCID but do not show similar improvements in physical function or social functioning. A significant improvement in physical function following the introduction of NIV would not be anticipated in patients with OHVS. Fleming, J., et al. (2016) found that in patients referred for weight management, patient reported physical function was progressively lower in a dose-dependent fashion with increasing levels of obesity, independent of gender, age, education and Charlson Comorbidity Index (CCI).

Table 7 demonstrates that 52.5% of the patients with COPD required long-term oxygen therapy compared to 24.3% of patients with OHVS , implying that this group of patients may have received home NIV relatively late in their course of disease progression.

5.1.4 Analysis of Costs

Luján, M., et al. (2007) demonstrated that initiation of NIV as an outpatient demonstrated a 50% saving on the direct costs generated in the case of conventional initiation in a mixed cohort of patients. Subsequent studies in patients with OHVS (Murphy, P.B., et al., 2019) and COPD (Duiverman, M.L., et al., 2020) have demonstrated similar cost savings when initiation NIV as an outpatient compared to an in-patient admission. It proved challenging to calculate accurately the costs associated with initiating long-term home NIV as an in-patient compared to an outpatient using a retrospective methodology. This was due to the obstacles outlined in the study methodology. However, even when using as crude a tool as the HRG code associated with the procedure, this study clearly demonstrates that outpatient initiation of NIV produces cost savings in terms of equipment utilised and

healthcare professional time; a more granular assessment of cost would almost certainly produce significantly greater cost benefits of initiating NIV as an outpatient.

The Eurovent study from 2005 (Lloyd-Owen, S.J., et al., 2005) and the systemic review by MacIntyre et al. (2016) confirmed that the number of patients receiving home NIV continues to grow. Given that the prevalence of COPD is expected to rise in the future (Rayner, et al., 2017; Terzikhan, et al., 2016) and the growing levels of obesity (Hales, et al., 2017), it is reasonable to conclude the number of patients that will benefit from home NIV will also continue to increase. Given the increasing burden that this will place upon healthcare in the UK, the utilisation of outpatient initiation of home NIV in appropriately selected patients and the associated cost savings that can be made would be advantageous to the system. The historic precedent has been that initiation and titration of home NIV targeted at a substantial arterial carbon dioxide reduction requires a hospital admission (Dreher, M., et al., 2010; Duiverman, M.L., et al., 2008). However, there are no specific evidence based guidelines that indicate where this should take place within the hospital, who should undertake this procedure and what monitoring should take place in order to ensure the desired outcomes. There is an increasing body of evidence that demonstrates that long-term home NIV can be established safely in carefully selected patients in an outpatient setting or even in the patients home (Newnham, M., et al., 2014; Hazenberg, A., et al., 2014; Tai, C., et al., 2018; Duiverman, M.L., et al., 2020). This study, whilst not definitive, adds to this growing body of evidence.

With the exception of the study by Tai, C., et al. (2018) the majority of studies demonstrating the feasibility and outcomes for NIV initiation performed outside an in-patient setting were performed by large specialist NIV centres. This may reduce how the

outcomes from the study can be applied and replicated by smaller, non-specialist services. Each of the studies targeted a specific clinical group such as COPD (Schwarz, S.B., et al., 2018; Duiverman, M.L., et al., 2020) or NMD and CWD (Luján, M., et al., 2007; Chatwin, M., et al., 2008; Hazenberg, A., et al., 2014) for their study population.

In line with previously published work, this study demonstrates the cost savings that may be achieved by initiating home NIV as an outpatient in terms of both initiation time and the reduction in hospital bed-days that can be achieved by initiating NIV in this way. The outpatient NIV initiation service described in this study is healthcare scientist led, without direct supervision by another healthcare professional. Developing a new service under the control of a non-medical professional has presented a number of challenges and required the support and agreement of our medical colleagues to allow it to succeed. In the NHS (UK), the increasing pressures on resources, particularly chronic shortages of medical consultants, can act as a driver for the development of services such as this. Given the pressures currently faced by all health economies across the globe due to the COVID 19 pandemic, any service that provides a reduction in healthcare utilisation and hospital bed-days with the opportunity to ease pressure on medical consultants should be considered.

5.2 Critique of the Study

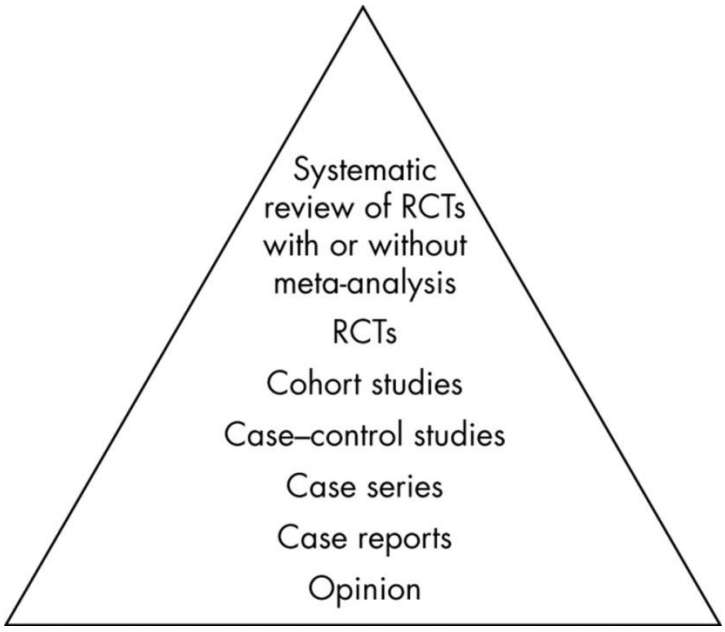
5.2.1 Study design

Despite providing evidence to support the assertion that patients initiated on long-term home NIV as an outpatient have non-inferior outcomes in terms of $PaCO_2$ and HRQoL at 12 months following initiation, it is clear that this study has a number of significant limitations. The study was retrospectively performed and hence needs further validation by prospective

RCTs; however, the utility of this study is that the findings may help to design future prospective trials.

With respect to study design, randomized controlled trials (RCTs) as well as analysis of quantitatively synthesized RCT data are considered the gold standard for evaluating efficacy in clinical research and constitute evidence for medical treatment. (Spieth, P.M., et al., 2016).

Figure 16: *Hierarchy of evidence for questions about the effectiveness of an intervention or treatment (Taken from Akobeng, A.K., 2005)*



This opinion has given rise to the concept of '*hierarchy of evidence'*; the hierarchy (Figure 16) provides a framework for ranking evidence that evaluates health care interventions and indicates which studies should be given most weight in an evaluation where the same question has been examined using different types of study (Rychetnik, L., et al., 2004).

The processes used during the conduct of an RCT minimise the risk of confounding factors influencing the results; thus, the findings generated by RCTs are likely to be closer to the

"true" effect than the findings generated by other research methods (Evans, D., 2003). However, such trials are difficult to deliver due to the costs in terms of time and money. They may also lead to results that are difficult to apply to a real world setting due to either the rigor or complexity of the intervention or the selection process for participants that yields a population dissimilar from that seen in general clinical practice (Boyko, E.J., 2013). There is evidence to suggest that adequately controlled observational studies produce results similar to randomized controlled trials (Concato, J., et al., 2000; Benson, K. and Hartz, A.J., 2000).

In reality, daily practice as a clinician is primarily based on the understanding of the pathophysiology of disease, and how a given interventions may influence that pathophysiology to improve outcomes (Vincent, J.L., 2010). In the management of patients with decompensated type II respiratory failure, it is clear that to assess the long-term effect of NIV versus placebo or 'sham' NIV would be considered highly unethical, and in reality would not be performed. Thus, observational studies such as this, which provide real-world evidence (RWE), are sometimes the only option to obtain data on specific scientific questions. Broadly speaking, RWE refers to information obtained from the analysis of data from a healthcare intervention, typically from clinical practice, that has not been collected as part of an RCT. It may be considered to represent more closely routine practice when compared with the highly controlled conditions of an RCT (Garrison Jr, L.P., et al., 2007; McDonald, L., et al., 2016; Blonde, L., et al., 2018). This study used a mixed cohort of patients, which may enhance the external validity (i.e., the generalizability) of the findings, however because the data cohort is constructed for the routine review of NIV patients rather than specifically for the purposes of research, it may not be perfectly suited to the

testing of the hypothesis. This may ultimately affect the internal validity of the study, but makes findings more realistic and relevant to others trying to establish similar services.

A retrospective study methodology was selected for this study for a number of reasons. A primary driver was the ready availability of a database of long-term home NIV patients. The use of previously collected data is efficient and comparatively inexpensive; this reduced the funding issues associated with undertaking the study. The original database was developed for those patients initiated on long-term home as an in-patient to allow their on-going follow up as an outpatient. The NIV database was developed solely for the review and clinical management of NIV patients within the service to allow access to information on NIV settings, treatment hours and efficacy of treatment. The in-patient NIV service was introduced following publication of the NICE Quality Standard for COPD (QS10) in 2011 (NICE, 2011); the outpatient NIV service was developed from work following an feasibility study as part of the HSST C1 Innovation project in 2018.

This was a single centre study and as such, the findings may not be generalizable to other centres with different work practices. There is evidence to suggest that single centre studies may provide larger treatment effect estimates than multi-centre trials (Unverzagt, S., et al., 2013) and many positive single-centre trials have been contradicted when tested in other settings and, in one case, the subsequent definitive multi-centre trial has found a previously recommended intervention associated with active harm (Bellomo, R., et al., 2009). Therefore, whilst it does provide important information of the “real world” initiation of outpatient NIV in a smaller hospital setting compared with much of the published data from large, often academic centres, the findings can only be applied after careful consideration of the context of the study with an individual’s own situation.

5.2.2 SAMPLE SIZE

There are significant differences in the number of patients initiated on home NIV as an in-patient compared to those initiated as an outpatient. Since the outpatient NIV initiation service was commenced a significant period of time after the in-patient service, the number of patients in the outpatient NIV initiation group was less than a quarter of those initiated on NIV as an inpatient.

The relatively smaller sample size for the outpatient NIV initiation groups must raise the possibility of a Type II statistical error; it is concluded that there is not a significant difference between the 2 groups, when actually there really is. A longer data collection period may have been helpful to increase the number of patients in the outpatient NIV initiation arm of the study. However, the number of patients initiated by the service as an outpatient is governed by the number of patients that present to the service with decompensated Type II respiratory failure or who cannot be adequately oxygenated due to their Type II failure; greater patient numbers cannot guaranteed by a longer data collection period for a non-specialist NIV service.

Despite the relatively small number of outpatients included in the study, it is reassuring that the previous studies that have concluded that outpatient NIV initiation is equivalent to in-patient NIV initiation do not have significantly larger numbers of patients in their study cohort (Table 46).

Table 46: *Number of subjects in outpatient versus in-patient NIV initiation studies*

Authors	Cohort	Route of NIV initiation	Study Duration
Luján, M., et al., 2007	19 NMD patients	9 outpatients 10 in-patients	3 months

Chatwin, M., et al., 2008	28 NMD and CWD patients	14 outpatients 14 in-patients	2 months
Hazenberg, A., et al., 2014	77 NMD and CWD patients	38 outpatients 39 in-patients	6 months
Duiverman, M.L., et al., 2020.	67 COPD patients	33 outpatients 334 in-patients	6 months

The relatively smaller number of subjects in the outpatient initiation group (n = 21) of this study compared to the in-patient group (n = 92) may mean that interpretation of the results, particularly the confidence intervals and p values, may be less reliable. Unequal sample sizes can lead to:

- Unequal variances between samples, which affects the assumption of equal variances in tests like ANOVA.
    - Having both unequal sample sizes and variances dramatically affects statistical power and Type I error rates (Rusticus, S.A. and Lovato, C.Y., 2014.).
- A general loss of power
    - Equal-sized groups maximize statistical power.
- Issues with confounding variables.

However, it is unclear how unequal the sample sizes need to be for heterogeneity of variance to be a problem (Wickens, T.D. and Keppel, G., 2004).

The data in this current study was tested for normality and the means were tested to ensure that appropriate statistical analysis was used. It has been suggested that the Welch's t-test should be selected routinely, instead of Student's t-test, because Welch's t-test performs

better than Student's t-test whenever sample sizes and variances are unequal between groups, and gives the same result when sample sizes and variances are equal (Delacre, M., et al., 2017). However, when the sample size is small, Student's t-test is able to form uniform p-value distributions, whereas Welch's t-test exacerbates the type II error rate. Thus for the purposes of this study, the Student's t-test was the preferred statistical test.

5.2.3 DATA COLLECTION

The data recorded within the NIV database was collected by specialist respiratory physiologists and respiratory clinical scientists directly involved in the routine review and care of patients treated with home NIV and completely independently of this study. They were unaware that the data would be used for research and thus any hypothesis proposed; this has the advantage of diminishing observer bias because the outcome of current interest was not the original reason for the data to be collected (Mann, C.J., 2003). The retrospective use of this NIV database allows for the examination of medical care utilisation as it occurs in routine clinical care (Motheral, B., et al., 2003); clinical safety and effectiveness can be assessed using a RWE study methodology.

Retrospective comparisons are prone to multiple biases, including sampling bias, recall bias, confounding by indication and changes in practice and/or disease biology (Cohen, A.T., et al., 2015; Mann, C.J., 2003). In accordance with the standard operating procedure (SOP) developed for undertaking an outpatient review of an NIV patient, it is expected that patient data is collected in a standardised way for each patient. If this process occurs as it should, it has the potential to increase the number of data points available for analysis. However, whilst there is an expectation of standardised data collection, there remains the very real

risk that the data is incomplete and it is unlikely that all the relevant information will have been rigorously collected for a number of reasons.

It is well recognised that one of the most common issues with RWE studies is the quality and consistency of data collection. Inferences drawn from retrospective RWE studies should be done with caution, and interpretations need to take account of the design, robustness and quality assurance in each study (Camm, A.J. and Fox, K.A., 2018). Missing data points in a number of areas significantly reduced the amount of available data points for this study. Mercieca-Bebber, R., et al. (2018) reported that participants would often question the need for, and in some cases refuse to complete, questionnaires due to their excessive burden. In a prospective study, patients will have provided informed consent and will been prepared for this administrative burden via the Patient Information Sheet (PIS). For this retrospective study, data was often incomplete. In some cases, patients declined to complete the paperwork. In others, the healthcare professional reviewing the patient did not have adequate time to complete it in the context of their conflicting clinical workloads. The percentage of missing data points may be a proxy for study quality and risk of bias, although not necessarily bias due to missing data (Groenwold, R.H. and Dekkers, O.M., 2020).

5.2.4 Utilisation of Arterial and Arterialised Blood Gas sampling within the study

It is widely accepted that the 'gold standard' sample for blood gas analysis is arterial blood obtained via an indwelling arterial catheter or by arterial puncture. Placing an arterial catheter is an invasive, painful and technically difficult procedure (Eisen, L.A., et al., 2007) that is associated with risk of serious complications including systemic infection, haemorrhage, thrombosis and ischemia (Wallach, S.G., 2004). For radial artery sampling, the number of failures at the first attempts is reported to be approximately 10% (Giner, J., et al.,

1996; Laursen, C.B., et al., 2015), and the procedure frequently results in multiple punctures. Furthermore, repeated punctures of the radial artery have important long-term effects on radial artery patency (Costa, F., et al., 2016).

There has been prejudice against utilising arterialised capillary samples in routine practice as there have been studies to suggest that there is poor agreement between PaO_2 measured in this way compared to arterial sampling (Sauty, A., et al., 1996; Fajac, I., et al., 1998; Eaton, T., et al., 2001). However, the seminal paper by Pitkin, A.D., et al. (1994) and a subsequent meta-analysis by Zavorsky, G.S., et al. (2007) have demonstrated that arterialised blood gases accurately reflect true arterial oxygen level when PaO_2 values are below 8.0kPa. Despite these potential differences, patients within the study were known to have respiratory failure with PaO_2 values < 8.0kPa. Therefore, the use of arterialised blood gases would have had only a marginal impact on the study outcomes, and thus can be considered largely irrelevant.

5.3 Improvements to the Study Design

On reflection, the design of this study could have been significantly improved to provide a more robust data set to support the effectiveness of outpatient initiation of domiciliary NIV when compared to in-patient initiation. These changes include, but are not limited to:

- The utilisation of a multi-centre approach to provide a larger sample size.
    - This would reduce the 'small-study effect' in studies with a sample size that is too small to detect a clinically plausible effect (Sterne, J.A., et al., 2000).
- Use of a prospective rather than retrospective study methodology to allow greater control of the outcomes of interest and to ensure matched sample size. A

prospective study design would have potentially reduced the incidence of 'missing' data points, as participants would have been prepared for the burden of data collection and the clinical team would have planned to ensure data was collected. Whilst a prospective methodology would have almost certainly improved the accuracy of data collection with regard to exposures, confounders, and endpoints, this would have to have been balanced against the increased cost and expensive and time required to complete the study (Euser, A.M., et al., 2009).

- Estimation of an appropriate sample size required to ensure that the study was capable of detecting clinically relevant differences prior to commencement. An appropriate sample would have rendered the research more efficient and the data generated would have been more reliable.

- Reduction in the duration of the study from 12 to 6 months to minimise the effects of losses to follow up. Similar studies collected data over a period of 3 or 6 months; thus, a study duration of 12 months may have inadvertently introduced 'loss to follow up' bias, which can severely compromise a study's validity. This is particularly important when either the dropout rates are different between the groups or the patients who drop out are different from those who do not drop out (Dettori, J.R., 2011). This was not explored during analysis of this study. On reflection, this may have influenced the conclusions drawn from the data reported.

5.4 Impact of the Study and Future Research

Several international guidelines for long-term home mechanical ventilation recommend that the initiation and control of NIV therapy should not be performed in an outpatient setting

(Windisch, W., et al., 2018). The potential advantages of outpatient initiation of home NIV are described earlier and include reduction in treatment delays, increased bed availability, reduction in risks associated with hospitalisation and potential reductions in cost. However, to confer any true advantage, the outcomes for outpatient NIV initiation must not be inferior to those for in-patient NIV initiation.

Using real world data, this study has provided evidence to support the assertion that outpatient initiation of NIV produces outcomes that are not inferior to in-patient NIV initiation in carefully selected patients. In terms of the physiological outcomes, it builds on the evidence base of previous studies and has demonstrated similar outcomes. Locally, this work has led to the establishment of a dedicated outpatient NIV initiation service for patients that require long-term home NIV to optimise their oxygenation, in accordance with BTS guidelines (Hardinge, M., et al., 2015). Complete analysis of the financial impact of outpatient NIV initiation was not completed at the time of submission of this work. However, using a median length of stay of 9 days for an NIV patient (BTS National Audit Report: Adult NIV Audit, 2019) and an average 'bed-day' total cost of £ 799.17 (Manoukian, S., et al., 2021), the study demonstrates a potential cost saving of up to £7,192.53 per patient initiated on NIV as an outpatient. This does not take in to account the reduction in in-patient admission costs produced by commencing home NIV prior to the threshold of two previous in-patient admissions requiring NIV being achieved.

For this study, the number of patients initiated on NIV as an outpatient is small when compared to in-patient initiation; further work is required to increase the data pool. The study cohort was principally comprised of COPD and OHVS patients; larger numbers of patients with CWD and slowly progressive NMD would increase the reliability and

generalisability of the conclusions drawn in the study. Since the initiation of this retrospective study, the site where the study was completed has become part of a group of three major hospitals across the West Midlands region. Data from additional sites, who also offer in-patient and outpatient NIV, could be included or compared with this current data to strengthen the conclusions drawn.

A key element of this study was the effect of long-term home NIV on HRQoL; HRQoL has been shown to be a strong predictor of survival (Fayers, P.M. and Machin, D., 2015). This study was unable to demonstrate the improvements in summative SRI seen in previous studies and potential reasons for this have been discussed. SRI score was completed at 4 points during the study: baseline, first review, second review and third review. These brief 'snapshots' in to the patients' quality of life may not fully describe the true effects of an intervention such as NIV. Further research is necessary to identify how frequently HRQoL tools should be administered to reflect change accurately and to identify how healthcare professionals can more reliably monitor change in quality of life over a longer period.

In this study, the utilisation and effectiveness of home NIV was reviewed at patient follow up visits; remote monitoring of NIV was not used. The principal reason was the lack of availability of an appropriate internet connectivity module for a large number of the NIV machines used. Anecdotally, accessing data stored by the ventilator is not common practice in the UK within sleep and ventilation services (Mansell, S.K., et al., 2020).

Over the last 20 years, the number of parameters that can be monitored remotely from a home ventilator has grown steadily. Remote monitoring of patients established on long-term home NIV as an outpatient may provide objective data on patient compliance, mask fit and the opportunity to intervene and provide solutions should problems with treatment

arise. Possible benefits of data from remote monitoring may include reduced requirements for outpatient appointments, earlier identification of exacerbations and more personalised and timely interventions by healthcare professionals. However, whilst the availability of such data seems intuitively useful and, for the majority of variables, appears reliable, there is a paucity of evidence to support their effectiveness in improving outcomes in patients receiving home NIV (Borel, J.C., et al., 2019). The potential benefits and challenges of using remote monitoring technology in home NIV services have yet to be established (Mansell, S.K., et al., 2020) and further understanding of how we use digital solutions to support patients is required. The statement by the European Respiratory Society on tele-monitoring of ventilator dependent patients (Ambrosino, N., et al., 2016) concludes that '*much more research is needed before considering tele-monitoring a real improvement in the management of these patients*'.

5.5 CONCLUSION

The evidence from this study supports the assertion that, for outpatient NIV initiation in carefully selected patients, the outcomes in terms of $PaCO_2$ and HRQoL are not inferior to those of in-patient NIV initiation. Furthermore, the study also suggests that this can be achieved safely in a mixed patient cohort and delivered by a non-specialist NIV service. Using an outpatient set-up methodology produces measurable cost savings when compared to in-patient initiation. This appears to be achieved without an associated negative impact on quality of care in terms of healthcare professional time and utilisation of health resources. Given the challenges due to the COVID 19 pandemic faced by healthcare across the globe, outpatient initiation of long-term home NIV in carefully selected patients

potentially provides significant benefits with the added advantage of reducing the risks associated with in-patient admission.

APPENDICES

APPENDIX 1 – SEVERE RESPIRATORY INSUFFICIENCY QUESTIONNAIRE

Severe Respiratory Insufficiency Questionnaire

SRI

General Health Questionnaire for patients with Severe Respiratory Insufficiency

Dear patient!

We are treating you for your respiratory disorder. Please fill in this questionnaire so that we can assess your current state of general health. Please answer every question by marking the appropriate answer once with a cross. Participation is, of course, voluntary. All data is bound by the rules of patient/doctor confidentiality and will be treated in strict confidence. Your attending physician will be pleased to answer any questions you may have.

Code number:

© W. Windisch, University Hospital Freiburg, Germany

SRI

The following question relate to your general condition. You will see statements related to various aspects of daily life.

How did you feel ***last week?*** For EVERY statement please mark the answer that best applies to you.

	completely untrue -2	mostly untrue -1	sometimes true 0	mostly true 1	always true 2
1. I find it difficult to climb stairs.	-2	-1	0	1	2
2. I suffer from breathing problems when I eat.	-2	-1	0	1	2
3. I can go out in the evening.	-2	-1	0	1	2
4. I often feel miserable.	2	1	0	1	2
5. I suffer from breathing problems even without physical exertion.	-2	-1	0	1	2
6. I often have a headache.	-2	-1	0	1	2
7. I have many friends and acquaintances.	-2	-1	0	1	2
8. I worry that my illness might worsen.	2	1	0	1	2
9. I go to sleep easily.	-2	-1	0	1	2
10. I can deal with other people easily.	-2	-1	0	1	2
11. I sometimes feel dizzy.	-2	-1	0	1	2
12. I wake up at night with breathing difficulties	2	1	0	1	2
13. I am afraid of having breathing difficulties at night.	-2	-1	0	1	2
14. I often have neck pain.	-2	-1	0	1	2
15. I am largely confined to the house.	-2	-1	0	1	2
16. Housework is difficult for me.	2	1	0	1	2

© W. Windisch, University Hospital Freiburg, Germany

SRI

How did you feel ***last week?*** For EVERY statement please mark the answer that best applies to you.

	completely untrue 2	mostly untrue 1	sometimes true 0	mostly true 1	always true 2
17. I often wake up at night.	2	1	0	1	2
18. I sleep through the night easily	-2	-1	0	1	2
19. I am often short of breath.	-2	-1	0	1	2
20. I am optimistic about the future.	-2	-1	0	1	2
21. I feel lonely.	2	1	0	1	2
22. I have trouble breathing when I speak.	-2	-1	0	1	2
23. Visitors exhaust me.	-2	-1	0	1	2
24. I cough a lot.	-2	-1	0	1	2
25. There is often mucus in my airways.	2	1	0	1	2
26. I avoid situations where my breathing problems might embarrass me	-2	-1	0	1	2
27. I feel good when I am with friends/ acquaintances.	-2	-1	0	1	2
28. I am afraid of having a bout of difficult breathing.	-2	-1	0	1	2
29. I have difficulties breathing during physical exertion.	2	1	0	1	2
30. I am irritated by the limitations caused by my illness.	-2	-1	0	1	2
31. My marriage/relationship is suffering because of my illness.	-2	-1	0	1	2
32. I can go shopping.	-2	-1	0	1	2
33. I can pursue all hobbies that interest me.	2	1	0	1	2

© W. Windisch, University Hospital Freiburg, Germany

SRI

How did you feel ***last week?*** For EVERY statement please mark the answer that best applies to you.

	completely untrue	mostly untrue	sometimes true	mostly true	always true
	2	1	0	1	2
34. I am often irritable.	2	1	0	1	2
35. My contact with friends/acquaintances is limited by my illness.	- 2	- 1	0	1	2
36. I am enjoying life.	- 2	- 1	0	1	2
37. I can take part in social events.	2	1	0	1	2
38. I am often sad.	2	1	0	1	2
39. My breathing difficulties bother me in public situations.	- 2	- 1	0	1	2
40. I am often nervous.	- 2	- 1	0	1	2
41. I can dress myself.	- 2	- 1	0	1	2
42. I am tired during the day.	2	1	0	1	2
43. I feel isolated.	- 2	- 1	0	1	2
44. I can cope well with my illness.	- 2	- 1	0	1	2
45. My breathing difficulties impair me in everyday activities.	- 2	- 1	0	1	2
46. My family life is suffering because of my illness.	2	1	0	1	2
47. I have broken off contact to other people because of my breathing problems.	2	1	0	1	2
48. My free-time opportunities are limited	2	1	0	1	2
49. I am satisfied with life in general	- 2	- 1	0	1	2

Thank you!

© W. Windisch, University Hospital Freiburg, Germany

APPENDIX 1A – SEVERE RESPIRATORY INSUFFICIENCY QUESTIONNAIRE SCORING GUIDANCE

Severe Respiratory Insufficiency Questionnaire

SRI

General Health Questionnaire for patients with Severe Respiratory Insufficiency

Guidance for scoring

Please provide the following values for each item:

completely untrue	=>	1
mostly untrue	=>	2
sometimes true	=>	3
mostly true	=>	4
always true	=>	5

The majority of items need to be recoded following the instructions given below:

value		recoded value
1	→	5
2	→	4
3	→	3
4	→	2
5	→	1

Items which need to be recoded:

1, 2, 4, 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 19, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 34, 35, 38, 39, 40, 42, 43, 45, 46, 47, 48.

Next, the scales need to be calculated as indicated below. For this purpose at least 50% of the items per scale must be correctly addressed. Please find the item number indicated in brackets [a, b, c.....]. This process of transformation produces a score between 0 and 100 with higher values indicating a better health-related quality of life according to content of the scale.

1

Respiratory Complaints

$$SRI - RC = \frac{Mean\ [2,5,12,19,22,24,25,29] - 1}{4} * 100$$

Physical Functioning

$$SRI - PF = \frac{Mean\ [1,16,32,33,41,45] - 1}{4} * 100$$

Attendant Symptoms and Sleep

$$SRI - AS = \frac{Mean\ [6,9,11,14,17,18,42] - 1}{4} * 100$$

Social Relationships

$$SRI - SR = \frac{Mean\ [7,10,21,27,43,46] - 1}{4} * 100$$

Anxiety

$$SRI - AX = \frac{Mean\ [8,13,26,28,39] - 1}{4} * 100$$

Psychological Well-Being

$$SRI - WB = \frac{Mean\ [4,20,30,34,36,38,40,44,49] - 1}{4} * 100$$

Social Functioning

$$SRI - SF = \frac{Mean\ [3,15,23,31,35,37,47,48] - 1}{4} * 100$$

Summary Scale

The Summary Scale (*SRI-SS*) can be calculated by the mean of the values for the subscales (SRI-RC, SRI-PF, SRI-AS, SRI-SR, SRI-AX, SRI-WB, SRI-SF). The SRI-SS should not be calculated if one subscale is missing.

2

APPENDIX 2 – SEMI-STRUCTURED INTERVIEW INFORMATION SHEET

Interview Information Overview

1. Participants and interviewers

    a. Interviewer: all patient interviews will be carried out by Julie Lloyd, Clinical Scientist/Service Lead, Lung Function and Sleep, Good Hope Hospital (GHH)

    b. Participants: participants will be patients who are domiciliary NIV users, who were commenced on NIV from GHH either via an acute in-patient admission or via an elective outpatient set up, and are attending for a routine NIV review.

    c. Interviews will generally be conducted on a one-to-one basis but caregivers, relatives or friends will be present as requested by the patient

2. Consent:

    a. Patients will be provided with an information leaflet about the study to accompany their appointment letter. This will inform them that participation is voluntary and will not affect their care in any way. There will be a contact number available for any questions prior to attending their appointment.

    b. Consent forms will be provided on the day and will be completed and signed. Copies will be provide to the patient, retained in the patient notes and stored with the study materials.

    c. If during the interview the patient discloses information that suggests that they are at risk of harm, this will be escalated to the safeguarding team immediately and appropriate action taken to maintain patient safety.

3. Recording devices:

    a. Each interview will be recorded on a Dictaphone, with patient consent.

    b. They will be transcribed and typed in to a password protected Word document by a named medical secretary employed by University Hospitals, Birmingham.

4. Session Structure:

    a. Introduce self, explain the research and obtain participant's written consent

    b. Point out the recording device to the participant and ensure sure that it is working.

c. Ask warm-up or demographic questions first; then, using the interview guide, move on to more focused questions. Allow flexibility for dialogue.

d. Interview length is estimated to be 30-45 minutes

Patient Perception of Non-Invasive Ventilation: Interview guide

Interviewee: Patient / carer / both

Sex: M / F

Age:

Clinical Group: COPD / OHS / both

Initiated: In-patient acute / Outpatient elective

1. Qualitative interview introduction

'*I would like to talk to you about how you felt about your experience with home NIV and how it has affected your life. However, firstly, I must make it clear that giving your honest answers to my questions will not affect your care, your treatment or your on-going care in any way. This also applies if you decide not to talk to me*.

Secondly, what you say will not be used to criticise any members of the team involved in your NIV care. He/she/they is/are happy that I am talking to you. By agreeing to talk to me, you are providing useful information that we hope will improve all patients' care.'

2. Consent

Consent was obtained from the study participant

Consent was NOT obtained from the study participant (interview terminated at this point)

3. Background Information

Overview:

Invite interviewee to tell interviewer briefly about him/herself: General information about respiratory and general health prior to introduction of home Non-Invasive Ventilation (NIV).

Explore how much their breathing affected their life, frequency of hospital admissions and input from healthcare teams prior to initiation of NIV.

If the interviewee indicates that they have required NIV prior to commencing long-term NIV, probe with questions describing their experience of acute NIV.

4. Acute NIV – experience

Aim of Section: to establish patient perspective of initiation of acute NIV

Thinking of a/the time when you were admitted to hospital because you were feeling unwell, can you tell me a little bit about your experience of NIV?

- Where was the NIV started?
- Can you remember who put the machine on for you?
- What were your first feelings about this?
- Can you describe how the NIV affected on your breathing?
- Would you describe this as a positive or negative experience?
    - Can you give me some reasons for your answer?
- Is there anything that could have been done differently to improve your experience?

5. Initiation of home NIV – experience

Aim of Section: to establish patient perspective of potential long-term NIV

When long-term NIV was suggested for your breathing, what were your thoughts?

Did you have a chance to discuss home NIV with your family or people who support you at home before you decided? If yes,

- What were their feelings about it?
- How did this affect your decision?

Did you feel that the NIV team listened to you and understood what was important to you?

- [Whether 'yes' or 'no'] Can you give an example?

If the interviewee has used NIV previously, explore this further: Did any previous experience with NIV affect how you felt about having home NIV?

Did you feel you were involved in the decision to have NIV at home?

- Would you want more or less involvement?
    - Can you explain why?

Can you tell be a bit about how the staff explained the information about the home NIV to you?

- Did the staff explain why they wanted you to have NIV at home?
- Did you understand the information that you were given?
    - What format was this information given to you e.g. verbal/leaflet/email
- Did they discuss what might happen if you did not have the NIV at home?
- Did they discuss any alternatives with you?

After receiving this information, did you have enough time to think about having home NIV before you made your decision?

- [Whether 'yes' or 'no'] Can you tell me a little more about why you felt this way?

Once you decided to have at home NIV, did you receive any further information?

- Did you feel that you were given enough information about using NIV at home when you were set up with your machine?
    - [Whether 'yes' or 'no'] Can you give explain a little more?
- Do you have any comments on how helpful the information booklets you received were?
- Can you think of anything that could have been done differently to help you cope with starting home NIV?

6. Continuing home NIV – experience

Aim of Section: to establish patient perspective of NIV at home

Since staring home NIV, can you describe what is a typical day is like for you?

- What time do you get up?

- How long does it take you to get washed/dressed?
- What sort of things do you do each day?
    - At home tasks e.g. cooking, cleaning
    - Going out e.g. shopping, visiting friends
    - Hobbies
- How does your breathing affect your day?

Thinking about your daily activities and your breathing, when do you use your NIV?

- Can you describe how it feels to use your NIV machine?
    - Comfort/like/dislike/anxiety/inconvenience/sleep position/pressure
- How do you feel that the NIV has affected your life in general?
    - Do you feel that NIV has helped your breathing?
        - [Whether 'yes' or 'no'] Can you give an example?
    - Do you feel that your daily activities have changed?
- Are there any challenges to using your NIV?
        - Comfort/like/dislike/anxiety/inconvenience/sleep position/pressure/synchronisation
- Do you feel that NIV has affected your quality of life?
    - [Whether 'yes' or 'no'] Can you give an example?

How would you describe the support you have received since starting with NIV at home?

- Who have you received support from?
- How regular is this support?
- Ease of accessing support when needed?
- How useful has this support been?

Overall, how satisfied have you been with the support you have received for at home NIV?

How satisfied have you been with your experience of at home NIV?

- What worked well for you?
- What did not work well for you?

7. Close of interview

Finally, can you think of anything that could have been done differently to help you cope with continuing home NIV?

Thank patient/carer for participation, check if there are any questions or issues raised from the interview that they wish to address.

Close interview, prepare and code recording and send for transcription.

APPENDIX 3 – GUIDELINES FOR THE USE OF NON-INVASIVE VENTILATION (HGS)

University Hospitals Birmingham NHS
NHS Foundation Trust

CONTROLLED DOCUMENT

[Guidelines for the use of Non-Invasive Ventilation (HGS)]

CATEGORY:	Policy
CLASSIFICATION:	Clinical Guideline
Controlled Document Number:	[insert same number as previous version or if new obtain from Risk and Compliance Unit]
Version Number:	6
Controlled Document Sponsor:	CSL for Respiratory Medicine
Controlled Document Lead:	HGS Clinical Lead
Approved By:	HGS Respiratory department
On:	14 September 2018
Review Date:	31 Aug 2021

Contents

Paragraph		Page
1	Executive Summary & Overview	3
2	Indications	3
3	The consideration for Acute NIV	3
4	Inclusion criteria for Acute NIV application	3
5	Exclusion criteria for Acute NIV application	4
6	Accessing the Acute NIV service	4
7	Location	5
8	Set-up	5
9	Monitoring	5
10	Duration of treatment	6
11	Escalation & Flow charts	6-8
12	Pressure area monitoring and care	9
13	Weaning	9
14	Palliation	9
Appendices		
Appendix 1	Hospital Admissions Policy of people on Domiciliary NIV	10
Appendix 2	Domiciliary Non-Invasive Ventilation Assessment proforma	11
Appendix 3	BHH Acuity-based nursing staffing level scoring system	12
Appendix 4	GHH Acuity-based nursing staffing level scoring system	13
Appendix 5	Non-invasive Ventilation in people with Highly Transmissible Airborne Diseases	14
Appendix 6	Weaning patients from Acute Non-invasive ventilation	15
Appendix 7	NIV Transfer Policy - Solihull Hospital	16
Appendix 8	Critical Care Transfer Proforma	17
Appendix 9	Critical care Transfer Criteria	18
Appendix 10	Critical care Transfer Pathway	19-20
Appendix 11	NIV Tissue Viability Flowchart	21
Appendix 12	NIV Application Record	22-23
Appendix 13	NIV Weaning Record	24
Appendix 14	Physiotherapist guidance on Managing Patients where an NIV bed unavailable	25
Appendix 15	NIV Withdrawal Checklist	26-27
Appendix 16	Capacity Flow Chart	28

Executive Summary & Overview

NIV refers to ventilatory support through the patient's upper airway using a mask or similar device (BTS 2002 and RCP 2008). NIV is indicated for Type II respiratory failure. AHRF results from an inability of the respiratory pump, in concert with the lungs, to provide sufficient alveolar ventilation to maintain a normal arterial PCO2. Co-existent hypoxaemia is usually mild and easily corrected. Conventionally, a pH <7.35 and a PCO2 >6.5 kPa define acute respiratory acidosis. (BTS 2016) NIV is not indicated for patients with Type I respiratory failure, or pneumonia, metabolic acidosis, acute asthma, pulmonary embolism, ARDS or pulmonary oedema.

Indications

Acute Non-Invasive Ventilation (NIV) **is indicated** for acute hypercapnic respiratory failure (AHRF) with acidosis (pH <7.35 and/or [H+]>45) in exacerbation of COPD, obesity-related respiratory failure, neuromuscular disorders, thoracic cage deformities (e.g. Post-Polio Syndrome, thoracoplasty for TB or other chest wall surgery, kyphoscoliosis), Cystic Fibrosis non-CF Bronchiectasis and any combination of these conditions. NIV **is not indicated** for Type 1 respiratory failure or pneumonia, metabolic acidosis, acute asthma, pulmonary embolism, ARDS or pulmonary oedema.

Note: Type 1 Respiratory Failure is pO_2 < 8 kPa ON AIR, pCO_2 < 6.5 kPa
Acute Hypercapnic Respiratory Failure (Type 2) is pO_2 < 8 kPa ON AIR, pCO_2 > 6.5 kPa
If no pO_2 on air is available: pO_2: F_iO_2 ratio<33.3 kPa constitutes respiratory failure where the "Type" depends on the pCO_2 after the pO_2: F_iO_2 criterion is met [F_iO_2=Fraction of inspired oxygen] (Where F_iO_2 is expressed in decimals not percentage, i.e. F_iO_2 of 28% is expressed as 0.28)

The consideration for Acute NIV

The medical registrar, of ST3 level or above, will initially assess all patients considered for NIV. All patients with any of the above mentioned indications with persistent respiratory acidosis, despite maximal standard treatment on controlled oxygen therapy no more than 1 hour should be considered for NIV. All patients with AHRF should target Spo2 88-92% including COPD, obesity-related respiratory failure, neuromuscular disorders, thoracic cage deformities (e.g. Post-Polio Syndrome, thoracoplasty for TB or other chest wall surgery, kyphoscoliosis), The maximal standard medical treatment for COPD exacerbation also includes: Nebulised Salbutamol 2.5-5mg; Nebulised ipratropium 500µg; Prednisolone 30mg (for COPD exacerbations only); Antibiotic agent (when indicated). A combination of causes of acute respiratory failure including drug overdose and possible causes of metabolic acidosis, particularly acute kidney injury, should be considered and treated. Hypovolemia and coexistent uncontrolled heart failure should be considered and treated, prior to the commencement of NIV

Inclusion criteria for Acute NIV application

PCO_2 > 6.5 **AND** pH <7.35 (or H+ >45) following immediate medical therapy.

Note- NIV should now also be considered for patients who have reduced conscious level, but are unsuitable for endotracheal intubation, *only* if NIV is provided in critical care. Patients who are unable to protect their airway due to hypoxaemia caused by pneumonia or ARDS are excluded from ward based NIV but may be considered for NIV on an individual basis in Critical Care. **Note-** pH <7.25 can still be treated with NIV but may need critical care due to higher risk of mortality if not transferred to HDU/ITU.
(See Inpatient NIV Referral Pathway Flowchart ON PAGES 7 & 8)
Note- NIV should almost always be considered in NMD or CWD when acutely unwell with hypercapnia (Pc02 >6.50kPa) or where Vital Capacity is known to be <1L and RR >20 with normocapnia.

Exclusion criteria for Acute NIV application

Absolute: Cardiac/ Respiratory Arrest within the last 24hours, Severe Facial Deformity, Facial Burns and Fixed Upper Airway Obstruction, Imminent cardiac arrest

Other exclusion criteria include:

PH <7.15,
<GCS less than 8 (Hypercapnia may be the cause of reduced consciousness, which may improve with NIV)
Confusion/agitation/severe cognition impairment
Inability to protect the airway
Life threatening hypoxaemia
Severe co-morbidity
Recent facial, upper airway or upper gastrointestinal surgery
Vomiting
Undrained pneumothorax
Copious respiratory secretions
Haemodynamically unstable requiring inotropes/vasopressors (unless in critical care unit) Patient moribund
Bowel obstruction
Primary diagnosis of heart failure or pneumonia, but may be used in COPD patients with these complications if escalation to intubation and ventilation is deemed inappropriate.

Any of the above excluding the absolute contraindications NIV, **may** be considered where appropriate, however should be monitored in a HDU/ITU environment. A patient's wish or advance directive not to have NIV should be respected and anyone with mental capacity who expresses such a wish or has an advance directive not to have NIV is automatically excluded ***even if*** the healthcare professional thinks that is an unreasonable decision.

Accessing the Acute NIV service:

For patients fulfilling the inclusion criteria, the medical officer (ST3 or above) should contact the NIV physiotherapist for the respective hospital.
Good Hope on bleep 8224 Monday-Friday 8am-4:30pm,
Heartlands on bleep 2718 Monday to Friday 8am-4:00pm
Solihull on bleep 2050/1039 Monday-Friday 8am - 4:30pm
Or the 'out of hours' on call physiotherapist for the respective hospital via switchboard after these times.

The initiating medical officer (if below the ST3 grade) must also contact the following:
At Heartlands: on call Respiratory Registrar (between 9am and 9pm) and RMO1 at night
At Solihull: On call Medical Registrar in the day and at night
At Good Hope: On call Medical Registrar in the day and at night.

The medical registrar must decide and document at the time of consideration for NIV, the resuscitation status and whether intubation and ventilation should be attempted in treatment failure. If NIV is regarded as the "ceiling" of care, the medical officer (ST3 or above) should know and document what escalation of treatment is necessary if the need arises. In cases of uncertainty, the on call Registrar/RMO1 should discuss with the responsible clinical consultant as per on call rota. Under **ALL** circumstances, the plan if NIV fails should be documented at the time of commencement of NIV.

Location

NIV can be initiated in any area of the hospital. However, a patient should be transferred to the appropriate area as soon as a bed is available and the patient is stable to transfer. Patients in respiratory failure (single organ system failure) should be transferred to **Good Hope** ward 10 NIV bay, at **Heartlands** to ward 24 unit C, and at **Solihull** to the High Dependency Unit. The medical officer (ST3 or above) on call must liaise with bed manager/on call sister and ward nurse in charge to facilitate an available bed. Patients in acute multi-organ failure or who may need critical care due to the severity of respiratory failure should be discussed with critical care outreach and the on call ITU Consultant/Registrar for transfer to critical care. Patients with pH <7.25 may need to be considered for critical care.
Note- OHS patients may have an increased risk of failure and intubation may be more difficult therefore consider treatment in Critical Care

The physiotherapist can discuss any concerns with the following:
BHH site- Respiratory Registrar on call (9am – 9pm) or the Respiratory Consultant on call after 9pm
GHH and Solihull Site – the RMO on call

Set-up

Administering and monitoring of patients on NIV will only be performed by staff with specific up to date training in this practice. Initial minimum IPAP of 15cmH2O (In COPD/OHS/Kyphoscoliosis Minimum IPAP 10cmH2O in NMD) and EPAP of 3cmH2O (Greater if OSA is known or suspected) IPAP increased over the next 10-30minutes until therapeutic response is achieved, patient tolerance is reached and Respiratory Rate has reduced. Pressure target is 20- 30cmH2O, IPAP greater than 25cmH2O and EPAP greater than 8cmH2O then the On Call Physiotherapist to liaise with the Respiratory Consultant (BHH) or Registrar (GHH & SHH)The medical officer (ST3 or above) must prescribe oxygen for both on and off NIV. Aim target oxygen saturations of 88-92% for all patients in AHRF Based on available data from previous admissions, if any, the on call physiotherapist can use their discretion to increase the initial pressures at set up. (See site specific NIV Database)
Note: Patients on Continuous NIV for greater than 12hours, a high NRS or inadequate oral intake should be considered for Nasogastric (NG) feeding.
If NG Feeding is required then the following needs to be considered:

- Enteral feeding must be stopped whilst NIV is initiated/established.
- Consider feeding around NIV usage.
- If the patient feeds whilst on NIV, they must be positioned in an upright position at a minimum of 45° during feeding and for 1 hour after feeding.
- Ideally, patients would be transferred to a nasal NIV mask if tolerated.
- If NIV is used with a nasogastric tube in situ, it should be a fine bore tube to minimise mask leakage (RCP 2008).

Please refer to the most recent editions of following Trust Guidelines for full details:
- Guideline for Nasogastric Feeding in Patients Requiring Non-Invasive Ventilation.
- Guideline for Enteral Feeding Patients Requiring Non-Invasive Ventilation who have an Existing Gastrostomy.

Monitoring

Observations should be recorded prior to NIV initiation. Frequent clinical monitoring of patients should be performed every 15 minutes in the first hour, every 30 minutes in the 1-4 hour period, and hourly in the 4-12 hour period. Observations to be recorded are indicated on the monitoring

chart. Pulse oximetry and electrocardiogram recordings should be continuous during the first 24 hours, then if clinically warranted after this time. Any patient triggering a MEWS of more than 4 (unless documented by the medical team otherwise) should be discussed with the critical care outreach service. If in agreement with critical care outreach, it is jointly felt that there is no need for the outreach team to review the patient at that time, this decision must be documented in the medical notes. However, the patient must be re-discussed with outreach if their condition deteriorates. Arterial blood gases (ABGs) should be taken 1 hour post NIV commencement, following any deterioration in condition, any subsequent change of settings and at 4 hours or earlier if the patient is not improving clinically. Once NIV has corrected the acidosis, further evaluation and ABGs should be taken based on clinical judgement.

Urine output and temperature will be charted by physiotherapy staff as competent/ adequately informed to do so; otherwise nursing staff caring for the patient must chart these observations.

Duration of treatment

If NIV is being beneficial then this should continue as long as possible during the first 24 hours. Hours and times of NIV and rest periods should be documented. All patients should be reviewed by the daytime NIV physiotherapist and the respiratory consultant/registrar every morning as cover allows. During the weekend, the respiratory registrar will review these patients. The physiotherapist will review patients at the weekend based upon their weekend criteria of who is suitable for the out of hour's service.

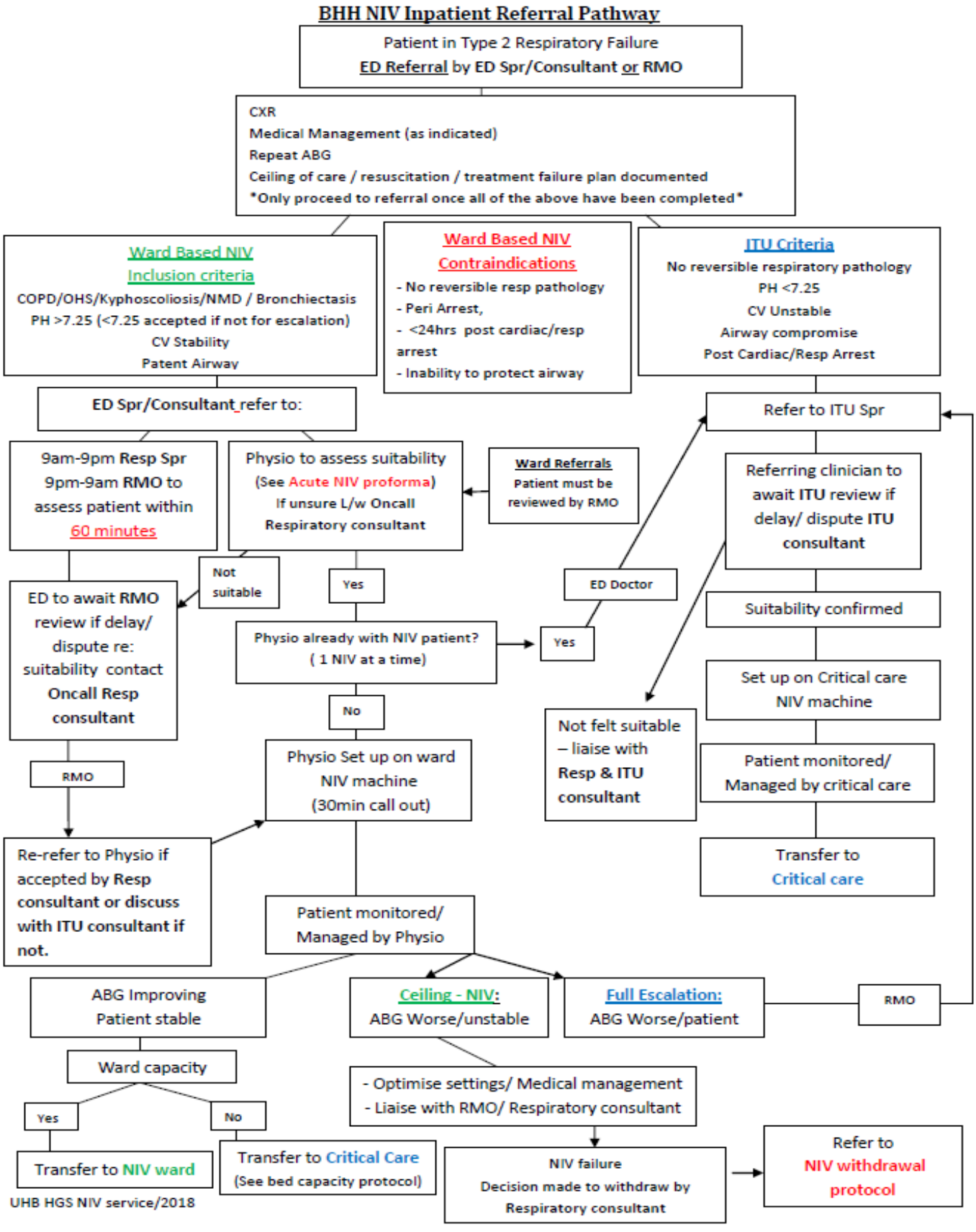
Escalation

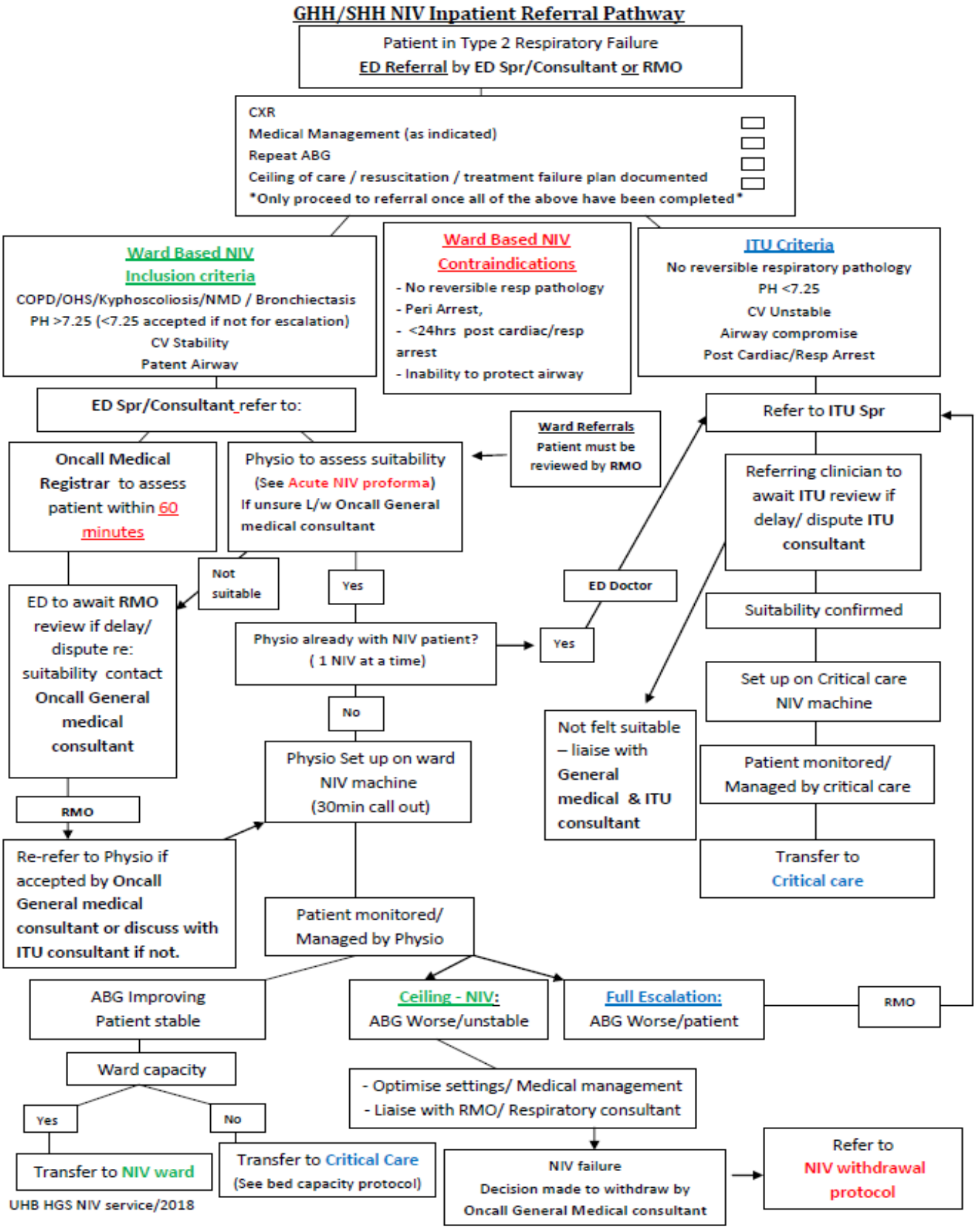
Decisions not to proceed to invasive mechanical ventilation should be taken by a RMO/Specialist Registrar and/or Consultant. Treatment failure includes:

- Patients intolerant to NIV,
- Worsening acidosis and hypercapnia despite appropriate settings,
- Worsening clinical condition e.g. pneumothorax or cardio respiratory arrest
- Inability to maintain adequate pO2 +/or Spo2 <85-88%(unless specified otherwise) despite high flow O2 on NIV (consider NIV on BIPAP Vision machine/V60 on HDU at BHH/SHH)
- Continuing acidosis after 48 hours of NIV should be considered for intubation, and not continued NIV. If the decision is not to proceed to invasive mechanical ventilation, this should be decided by a ST3 or above and / or Consultant.

NIV treatment failure should be conveyed to the medical officer (ST3 or above) immediately and candidates for intubation should proceed without delay. Those not suitable for intubation (after discussion with the ST3 or above / Consultant) should continue with maximal treatment. Decision on whether or not to proceed to endotracheal intubation should be made at commencement of Acute NIV and reconfirmed within 4 hours of starting NIV, as improvements in ABGs, Respiratory Rate and Heart Rate should be expected within this time. The physiotherapist can discuss any concerns with the following:
BHH site- Respiratory Registrar on call (9am – 9pm) or the Respiratory Consultant on call after 9pm
GHH and Solihull Site – the RMO (Medical Registrar) on call.

SEE FLOW CHARTS ON PAGES 7 & 8


BHH NIV Inpatient Referral Pathway
Patient in Type 2 Respiratory Failure
ED Referral by ED Spr/Consultant or RMO
CXR
Medical Management (as indicated)
Repeat ABG
Ceiling of care / resuscitation / treatment failure plan documented
Only proceed to referral once all of the above have been completed
Ward Based NIV
Inclusion criteria
COPD/OHS/Kyphoscoliosis/NMD / Bronchiectasis
PH >7.25 (<7.25 accepted if not for escalation)
CV Stability
Patent Airway
Ward Based NIV
Contraindications
- No reversible resp pathology
- Peri Arrest,
- <24hrs post cardiac/resp arrest
- Inability to protect airway
ITU Criteria
No reversible respiratory pathology
PH <7.25
CV Unstable
Airway compromise
Post Cardiac/Resp Arrest
ED Spr/Consultant refer to:
9am-9pm Resp Spr
9pm-9am RMO to assess patient within 60 minutes
Physio to assess suitability
(See Acute NIV proforma)
If unsure L/w Oncall Respiratory consultant
Ward Referrals
Patient must be reviewed by RMO
Refer to ITU Spr
Referring clinician to await ITU review if delay/ dispute ITU consultant
Not suitable
Yes
ED to await RMO review if delay/ dispute re: suitability contact Oncall Resp consultant
Physio already with NIV patient?
(1 NIV at a time)
Yes
ED Doctor
Suitability confirmed
No
Set up on Critical care NIV machine
Not felt suitable – liaise with Resp & ITU consultant
Patient monitored/ Managed by critical care
RMO
Physio Set up on ward NIV machine
(30min call out)
Transfer to Critical care
Re-refer to Physio if accepted by Resp consultant or discuss with ITU consultant if not.
Patient monitored/ Managed by Physio
ABG Improving
Patient stable
Ceiling - NIV:
ABG Worse/unstable
Full Escalation:
ABG Worse/patient
RMO
Ward capacity
- Optimise settings/ Medical management
- Liaise with RMO/ Respiratory consultant
Yes
No
Transfer to NIV ward
Transfer to Critical Care
(See bed capacity protocol)
NIV failure
Decision made to withdraw by Respiratory consultant
Refer to NIV withdrawal protocol
UHB HGS NIV service/2018


GHH/SHH NIV Inpatient Referral Pathway
Patient in Type 2 Respiratory Failure
ED Referral by ED Spr/Consultant or RMO
CXR
Medical Management (as indicated)
Repeat ABG
Ceiling of care / resuscitation / treatment failure plan documented
Only proceed to referral once all of the above have been completed
Ward Based NIV
Inclusion criteria
COPD/OHS/Kyphoscoliosis/NMD / Bronchiectasis
PH >7.25 (<7.25 accepted if not for escalation)
CV Stability
Patent Airway
Ward Based NIV
Contraindications
- No reversible resp pathology
- Peri Arrest,
- <24hrs post cardiac/resp arrest
- Inability to protect airway
ITU Criteria
No reversible respiratory pathology
PH <7.25
CV Unstable
Airway compromise
Post Cardiac/Resp Arrest
ED Spr/Consultant refer to:
Oncall Medical Registrar to assess patient within 60 minutes
Physio to assess suitability
(See Acute NIV proforma)
If unsure L/w Oncall General medical consultant
Ward Referrals
Patient must be reviewed by RMO
Refer to ITU Spr
Referring clinician to await ITU review if delay/ dispute ITU consultant
Not suitable
Yes
ED to await RMO review if delay/ dispute re: suitability contact Oncall General medical consultant
Physio already with NIV patient?
(1 NIV at a time)
Yes
ED Doctor
Suitability confirmed
Set up on Critical care NIV machine
No
Physio Set up on ward NIV machine
(30min call out)
Not felt suitable – liaise with General medical & ITU consultant
Patient monitored/ Managed by critical care
Transfer to Critical care
RMO
Re-refer to Physio if accepted by Oncall General medical consultant or discuss with ITU consultant if not.
Patient monitored/ Managed by Physio
ABG Improving
Patient stable
Ceiling - NIV:
ABG Worse/unstable
Full Escalation:
ABG Worse/patient
RMO
Ward capacity
- Optimise settings/ Medical management
- Liaise with RMO/ Respiratory consultant
Yes
No
Transfer to NIV ward
Transfer to Critical Care
(See bed capacity protocol)
NIV failure
Decision made to withdraw by Oncall General Medical consultant
Refer to NIV withdrawal protocol
UHB HGS NIV service/2018

Pressure area monitoring and care

- Waterlow scoring should be completed by nursing staff as part of Tissue Viability Assessment on admission. Patients scoring 10 or above are considered at risk and should have pressure areas monitored and recorded daily by trained nursing staff (including facial areas beneath NIV interface, which should be checked at intervals set out on NIV MEWS Observation Chart).
- Barrier dressings should be applied from the outset, as appropriate e.g. over bridge of nose, to minimise risk of skin ulceration. (See NIV Tissue Viability Flowchart).
- In patients with red or broken pressure areas, advice should be sought promptly from the Tissue Viability Team and alternative interfaces considered to relieve pressure areas.
- Patients who have been on continuous NIV for 48hours and are unable to wean should be considered for an alternative interface to relieve pressure from the bridge of the nose and forehead

Weaning

Weaning should commence 24 hours after initiation of NIV if it has been successful; PH >7.35, underlying cause and symptoms resolved and RR normalised. This will be initiated by the NIV physiotherapist or the Weekend Respiratory physiotherapy team. Weaning should generally commence during normal daylight hours. Although some patients may wean more quickly/self-wean/need domiciliary support, the aim would be to discontinue NIV by day 4. A proforma charting physiological indices may aid successful weaning (See NIV weaning proforma – Appendix 13.

Note- Consider referral to Home Ventilation services on discharge from hospital following 1-2 admissions for AHRF (See Domiciliary NIV Screening Proforma – Appendix 2)

Palliation

Palliation of symptoms (with help from the Palliative Care Team) may be appropriate when there is a decision not for ITU ventilation, standard medical treatment or NIV fails, or when a patient chooses not to have NIV or further treatment. On occasions where NIV is used for palliation of breathlessness only, the Palliative Care team should be informed and the Supportive Care Pathway (available in the intranet) should be initiated. (See NIV Withdrawal Checklist – Appendix 15) NIV for symptom palliation should be considered only after these measures are instituted and such a service is subject to the availability of machines, life-prolonging treatment with NIV (e.g. acute hypercapnic acidosis in respiratory failure) taking priority over palliative use.

Rahul Mukherjee, Lead Consultant for NIV

NIV Appendix 1

Hospital Admissions Policy of people on Domiciliary NIV/ Home Mechanical Ventilation (HMV)

Patients discharged with NIV for domiciliary use will broadly fall into two categories: Non ventilator dependent and ventilator-dependent. For the purpose of this policy ventilator dependent patients are defined as those who require more than 14 hours use of NIV per day. Ventilator dependent patients would be expected to be supplied with two ventilators (as a back up to prevent equipment failure preventing use of NIV). Irrespective of which category the patient falls into the policy remains the same.

- Where patients are admitted to hospital who are capable of using their NIV machine they should continue to do so as at home. There should be no specific need for admission to ward 24 or other NIV competent area to facilitate this unless they are admitted with a respiratory condition/progression of respiratory failure.

Assessment of deterioration in patients on Domiciliary NIV/ HMV

- Deterioration with associated acidosis/hypercapnia should be reviewed by the medical team. Usage of NIV should be ascertained in case deterioration is secondary to insufficient time on NIV.
- If the patient is not currently using NIV it should be started and an ABG taken after an hour to establish progress. During normal working hours referral should be made to the NIV physiotherapy team for review/monitoring. As long as the patient remains competent to manage their own NIV, this need not involve referral to the on call physiotherapist outside of normal working hours but should be at the discretion of the reviewing senior doctor/respiratory consultant. In either case, transfer to ward 24 or other NIV competent area for continued management may be advisable.
- Where deterioration occurs despite consistent NIV use the patient should be referred to the ward based NIV service in the same manner of an acute referral. Review should consist of adjustment of ventilator settings as necessary and change to a standard NIV machine used in the Trust if the physiotherapist is unfamiliar with the patient's own ventilator. This will apply both for normal working hours and on call working.

Equipment Failure

- Where domiciliary patients experience problems with their equipment this should be managed via respiratory physiology (9am-5pm Monday to Friday), for problems outside of these times the patient should stop using NIV until they can have the problem investigated by respiratory physiology. Provided the patient does not become acidotic/hypercapnic, no input from on call physiotherapy services are required.
- If the patient becomes acidotic/hypercapnic during admission following a failure of equipment they should be reviewed by the medical team with a view to referral to physiotherapy team (as per an acute setup of NIV) – within normal working hours this would fall to the ward NIV team, outside of normal working hours this will fall to the on call physiotherapist via switchboard

- If a patient is in a critical care environment and experiences an out-of-hours equipment failure with resultant acidosis/hypercapnia, the patient should be managed with critical care input/equipment in the first instance. Only if there is no available equipment within critical care to provide the patient with NIV, should the on call physiotherapist be contacted with a view to using ward based equipment for treatment.

Weaning / Step down Care

- Weaning and step down care for patients on domiciliary machines admitted to critical care would be carried out during normal working hours with the involvement of the specialist NIV consultants and NIV physiotherapy team.

NIV Appendix 2

Domiciliary Non-invasive Ventilation Assessment

This form is designed to assess patient suitability for safe/appropriate provision of domiciliary NIV.
This decision to commence Home NIV is a multidisciplinary decision led by a physician as per PLCV regulations.

Affix Patient PID Label

Name: _____
PID: _____ DOB: ____/_____/_____
Date of referral: ____/_____/_____ Weight/BMI: _____ / _____

Current Patient Location _____ Referring Physician _____

Diagnosis and medical problems

_____

_____

Pre-admission functional Status/Clinical Frailty Score/ Previous occupation

_____

_____

Home NIV Criteria:

Daytime hypercapnia ☐
≥ 3 Acute NIV episodes ☐

_____

Inability to wean from acute nocturnal NIV ☐
Patient consents to use Home NIV ☐

ReSPECT status:

CPR ☐ No CPR ☐
Ceiling of care

Exclusion Criteria:

- Inability to remove mask independently (with no waking night carer) ☐
- Cognitive/behavioural limitation affecting ability to comply safely with NIV ☐
- Intolerance of acute NIV ☐
- Multiple co-morbidities limiting utility of NIV ☐

Physiotherapy Assessment: (for mode of ventilation)

COPD/significant airways disease ☐ Obesity-related respiratory failure ☐

Neuromuscular disorder ☐ Thoracic cage deformity ☐

Symptomatic relief for admission prevention (in conjunction with any of the above) ☐

Chest/Cough Assessment (if applicable)

Auscultation: …… Palpation: ……
Cough:…… Peak Cough Flow:……
Sputum:…….. FEV1…… FVC……
Overnight oximetry……..

>360L/min = monitor

<270L/min = Teach cough augmentation techniques

<160L/min = Establish airway clearance device

NIV Appendix 3

BHH SITE Ward Based NIV:
ACUITY-BASED NURSING STAFFING LEVEL SCORING SYSTEM

Physiotherapist and Senior Nurse for NIV Unit will update the scoring system daily prior to end of Physio day shift.

5	ACUTE NIV (requiring continuous NIV) NEUROMUSCULAR ACUTE TRACHEOSTOMY (Without NIV)
4	POST 4 HR WEAN
3	POST 6 HR TO FULL DAY WEAN PALLIATIVE NIV
2	OVERNIGHT WEAN
1	DOMICILIARY NIV LONG TERM TRACHEOSTOMY (Self caring)

NURSE STAFFING FOR ACUITY SCORES

SCORING	**NIV NURSE**	**TOTAL NUMBER OF QUALIFIED NURSES NEEDED IN BHH NIV UNIT**
0-15	1 NURSE	2
16-30	2 NURSES	3
31-45	3 NURSES	4
46-60	4 NURSES	4

1. Use clinical bank for requesting additional nurses.

2. There is always 1 bank shift already allocated for LD/N against NIV cost code to allow 3 qualified nurses in the unit.

3. This will be permanently recruited into to allow an acuity score of up to 30.

4. If additional staff is required: use clinical bank via POD/on-call matron/Senior Sister and use NIV cost code.

Louise Wood, Ward manager, Ward 24 BHH
Joanne Hartland, Ward manager, Ward 24 BHH
Amy Oakes, Acute NIV Physiotherapy lead
Debbie Williams, Matron for Respiratory Medicine

NIV Appendix 4

GHH SITE Ward Based NIV:

ACUITY-BASED NURSING STAFFING LEVEL SCORING SYSTEM

Physio and Senior Nurse for NIV Unit will update the scoring system daily prior to end of Physio day shift.

5	ACUTE NIV (requiring continuous NIV) NEUROMUSCULAR ACUTE TRACHEOSTOMY (Without NIV)
4	POST 4 HR WEAN
3	POST 6 HR TO FULL DAY WEAN PALLIATIVE NIV
2	OVERNIGHT WEAN
1	DOMICILIARY NIV LONG TERM TRACHEOSTOMY (Self caring)

STAFFING FOR ACUITY SCORES

SCORING	**NIV NURSE**	**TOTAL NUMBER OF QUALIFIED NURSES NEEDED IN UNIT (Ward 10)**	
0-15	1 NURSE	Early	5
		Late	4
		Night	4
		+ co-ordinator daytime	
16 - 20	1 / 2 NURSES	Early	5
		Late	5
		Night	5
		+ co-ordinator daytime	
21 - 25	2 NURSES	Early	6
		Late	5
		Night	5
		+ co-ordinator daytime	
26 - 30	3 NURSES	Early	6
		Late	6
		Night	5
		+ co-ordinator daytime	

NIV Appendix 5

Non-invasive Ventilation in people with Highly Transmissible Airborne Diseases

The use of non-invasive ventilation (NIV) poses an enhanced risk to the airborne transmission of disease. Standard NIV circuit has no filtration of the expired gases which are vented from the mask at volume and flow rates higher than normal respiration.

During the SARS outbreaks in Canada and Hong Kong management of highly transmissible diseases with NIV was discussed, studies have shown that NIV can be used effectively and safely in such situations if infection control procedures are strictly followed.

General principles of infection control will apply to use of NIV in all situations but in highly transmissible airborne diseases including: coronavirus, influenza, smear positive/multibacillary TB; additional precautions will need to be taken. General principles of current suggested best practice for delivery of non-invasive ventilation (NIV) in highly transmissible airborne disease are:

a) Staff should be trained in infection control;
b) A gown, gloves and eye protection should be worn for all aerosol-generating procedures; use of an FFP3 respirator instead of a surgical mask may be prudent until data are available that allow better assessment of the risk associated with different procedures;
c) Ideally, patients should be managed in negative pressure single rooms with anterooms, where these are available. If such facilities are not available, they should be cared for in standard single rooms or, if there is no other option, in cohorted groups;
d) A non-vented patient mask should be used if available;
e) Although bi-level pressure support NIV (bi-level positive airway pressure) is likely to be the preferred method of NIV support, in certain circumstances continuous positive pressure ventilation may also be used;
f) NIV masks should be applied to the patient's face and secured before the ventilator is turned on;
g) Ventilators that function with double-hose tubing (an inspiratory and an expiratory limb) may be advantageous;
h) The ventilator should be turned off before removal of the close-fitting mask or when lifting the mask away from the face, e.g. for mouth care or sips of fluid;
i) Humidification with water should be avoided.

BHH Site Specific Guidance

Ward 24 NIV unit does not have negative pressure side rooms. Negative pressure side rooms within the site are available on ward 26 and ward 28. Discussion needs to occur at a bed management/consultant level about the best use of clinical resource in this situation, options include:

- Housing the patient on ward 26 negative pressure side rooms, with additional staffing in line with normal NIV capacity management.
- Housing the patient on ward 28 negative pressure side rooms. Ward 28 staff is not clinically competent to manage acute NIV so trained staffing will need to be supplied (either from ward 24 or critical care pools).
- Housing the patient on ward 24 in side room (will not be negative pressure and so will have increased risk of transmission.
- Cohorted groups.

Patients should be considered for critical care admission where appropriate; however, there is no facility for negative pressure room isolation within Heartlands critical care.

NIV Appendix 6:

Weaning patients from Acute Non-invasive ventilation

Approach to weaning

Weaning NIV for patients with chronic lung conditions is based around gradually increasing time off NIV, interspersed with appropriate rest periods on the NIV. Gradual reduction in the duration of NIV should be determined by clinical improvement of ABG's and as medical management of their respiratory illness takes effect. Initially weaning should take place during the day prior to nocturnal weaning, as patients with long-term respiratory conditions are more susceptible to developing respiratory failure during sleep.

Assessing a patient's suitability to commence weaning

Patients benefitting from NIV in the first few hours of treatment should receive NIV for a minimum of 6hrs during the first 24hours (with appropriate rest breaks for meals, medications etc.). Weaning should commence when arterial blood gas analysis demonstrates pH >7.35 and pCO2 within desirable range for the patient. Clinical observations must be stable (e.g. HR, RR, SpO_2) and the patient's work of breathing be controlled.

Duration of wean

Determining the duration of wean must be made by clinical assessment of the patient. Typically patients will begin by completing 1hr off the mask. This can then be extended to 4hrs and 8hrs if the patient is stable. After successfully weaning in the day, most patients will require an additional night on NIV prior to commencing an overnight wean, unless chronic ventilatory failure indicates trial of domiciliary NIV. (See Domiciliary NIV screening proforma – appendix2)

Monitoring during weaning

Clinical monitoring of the patient, to include MEWs scoring and subjective assessment of a patient's perceived breathlessness, must be recorded during the weaning period. An arterial blood gas is taken at the end of the planned weaning period and documented in the NIV weaning proforma (see appendix 13)

Determining whether to extend duration of wean

Duration of wean can be extended if, at the end of the weaning period, the patients ABG shows pH >7.35 and pCO_2 within desirable range. Clinical parameters (e.g. HR, SpO_2, RR) must be stable and the patient's work of breathing be controlled.

If the ABG shows pH <7.35 and or pCO2 higher than desired the patient must recommence NIV. The patient may re-attempt weaning the following day and once they meet the criteria outlined above. Once the patient has successfully weaned nocturnally, subsequent monitoring of arterial blood gases may only be indicated depending on the patient's presentation.

Long-term nocturnal NIV

Long-term NIV therapy may be indicated in a select group of patients following assessment by the specialist respiratory and NIV teams. (See Domiciliary NIV screening proforma – appendix 2)

NIV & Ward 'Step-down'

A 'step-down' in the patients Level of Care may be considered once the patient has successfully completed a night off NIV and arterial blood gases are stable.

Documentation

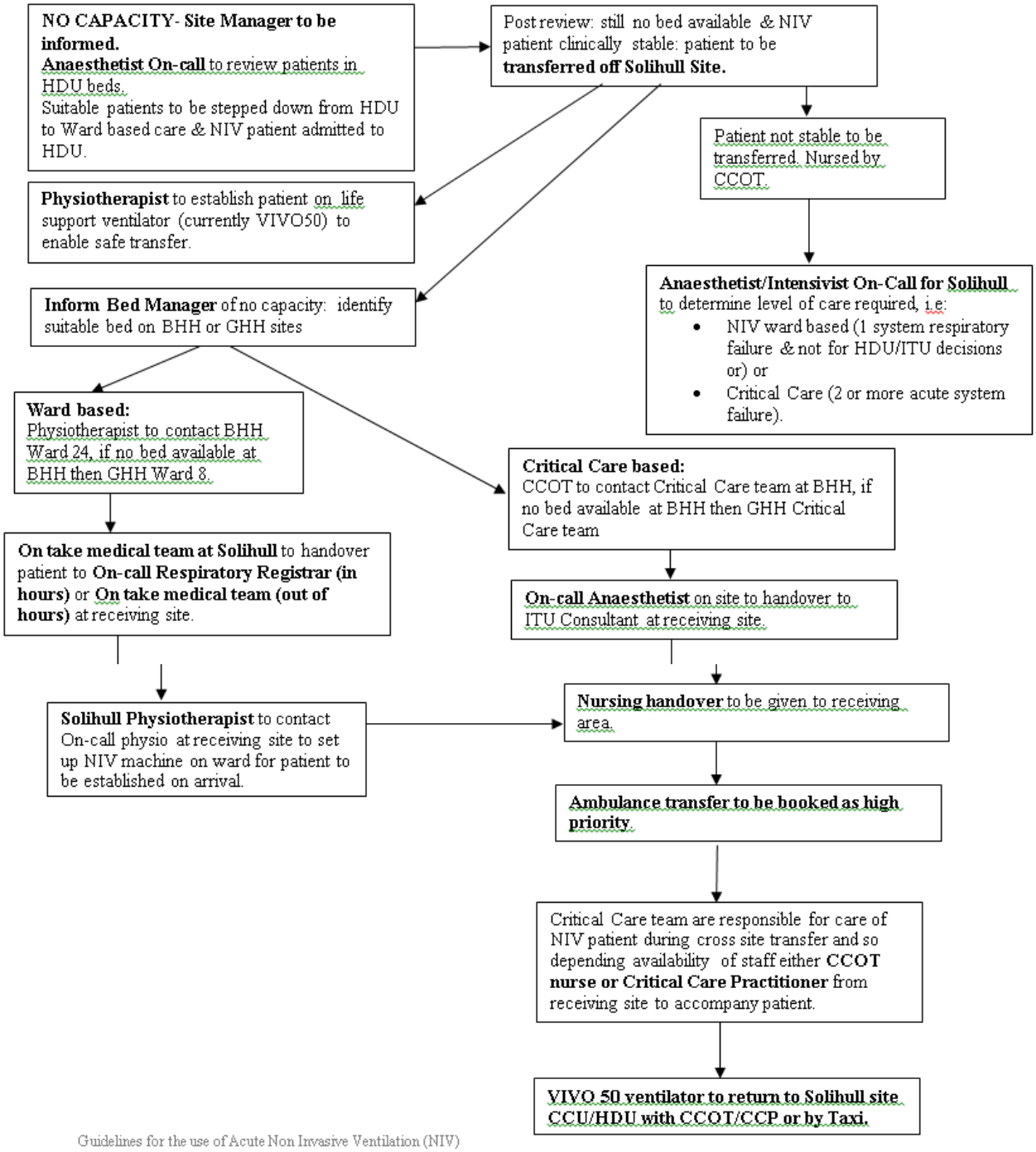
The weaning strategy must be documented in the patient's NIV weaning proforma (see appendix 13). This will include planned duration of weans, analysis of arterial blood gases, outcome of weaning periods and a detailed plan for ongoing management. The weaning plan will then be handed over to nursing staff and the NIV acuity score updated as appropriate (See NIV nursing acuity score – appendix 3+4)

NIV Appendix 7

NIV Transfer Policy Solihull Hospital

Physiotherapist to contact CCOT to begin plans for patient movement: Bleep CCOT (2071) and contact Anaesthetist On-call: Bleep 0205/ via switchboard.
CCOT or physiotherapist to contact HDU/CCU to ascertain bed capacity.

Capacity (nursing & bed) on HDU/CCU available: patient to be transferred by physiotherapist, nurse and porter, +/- CCOT (if available) once clinically stable, preferably after NIV established and first ABG taken at 1 hour on NIV.



Guidelines for the use of Acute Non Invasive Ventilation (NIV)

NIV Appendix 8

Critical Care NIV Transfer Proforma

Name: _____ **PID**: _____
Date:_____
Named Nurse: _____
Handover taken by: _____ **Time**: _____
Date: _____
Patient accepted by Respiratory Consultant ☐ Yes ☐ No

Patient ID Label

History of Presenting Condition

Past Medical History

Patient known and reviewed by NIV Physiotherapy Team ☐ Yes ☐ No

ABG prior to NIV: pH
PCO2
PO2
BE
HCO3

Commenced on NIV: Date: Time:

Initial Settings: IPAP
EPAP
Oxygen

Mask type and size:

Current NIV Settings: IPAP
EPAP
Oxygen

Current NIV regime:

Passed Weans: (e.g. 1, 2, 4 hours)

ABG prior to transfer: pH
PCO2
PO2
BE
HCO3

Time transferred to ward 24:

ABG on NIV: pH
PCO_2
PO_2
BE
HCO_3

NIV Appendix 9

Critical Care Transfer Criteria – BHH/GHH

Inclusion Criteria:

- Patient no longer requires critical care support – decision made by the critical care medical team;
- Transfer agreed by critical care team/Ward Respiratory consultant /NIV physiotherapy team;
- Patient able to protect own airway;
- Single organ failure/organ failure needs can be met at ward level;
- FiO2 $\leq$ 0.4;
- Arterial line removed;
- CVC removed unless discussed with/requested by ward team:
- Clear plan for escalation/palliation in the event of further deterioration:
- Clear resuscitation decision - DNAR form completed where appropriate;
- Patient established on ward NIV machine prior to transfer.

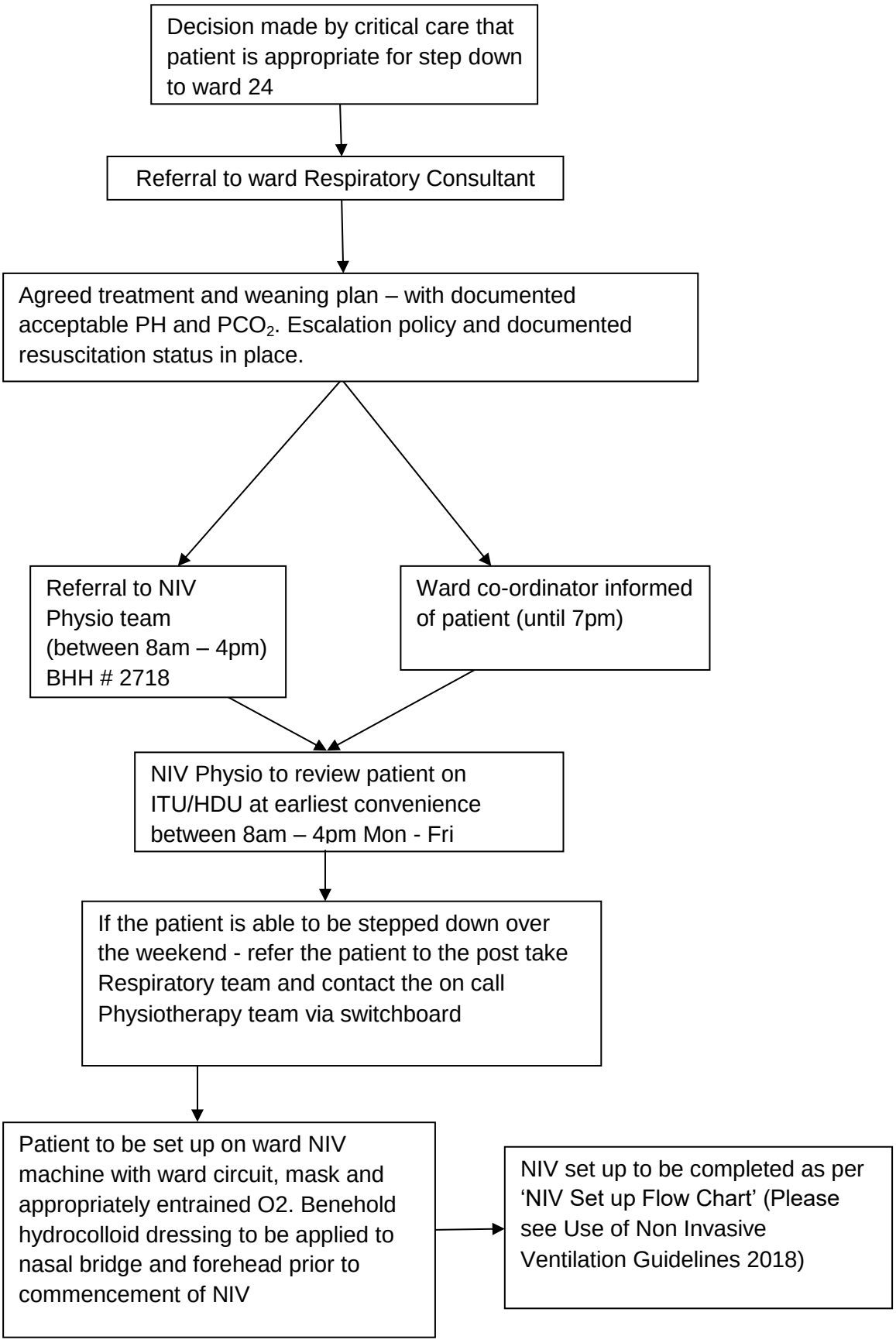
NB Step down at the weekend is to be avoided where possible, however if necessary and the above criteria are met it can be actioned with agreement from the on call respiratory consultant and on call physiotherapy team.

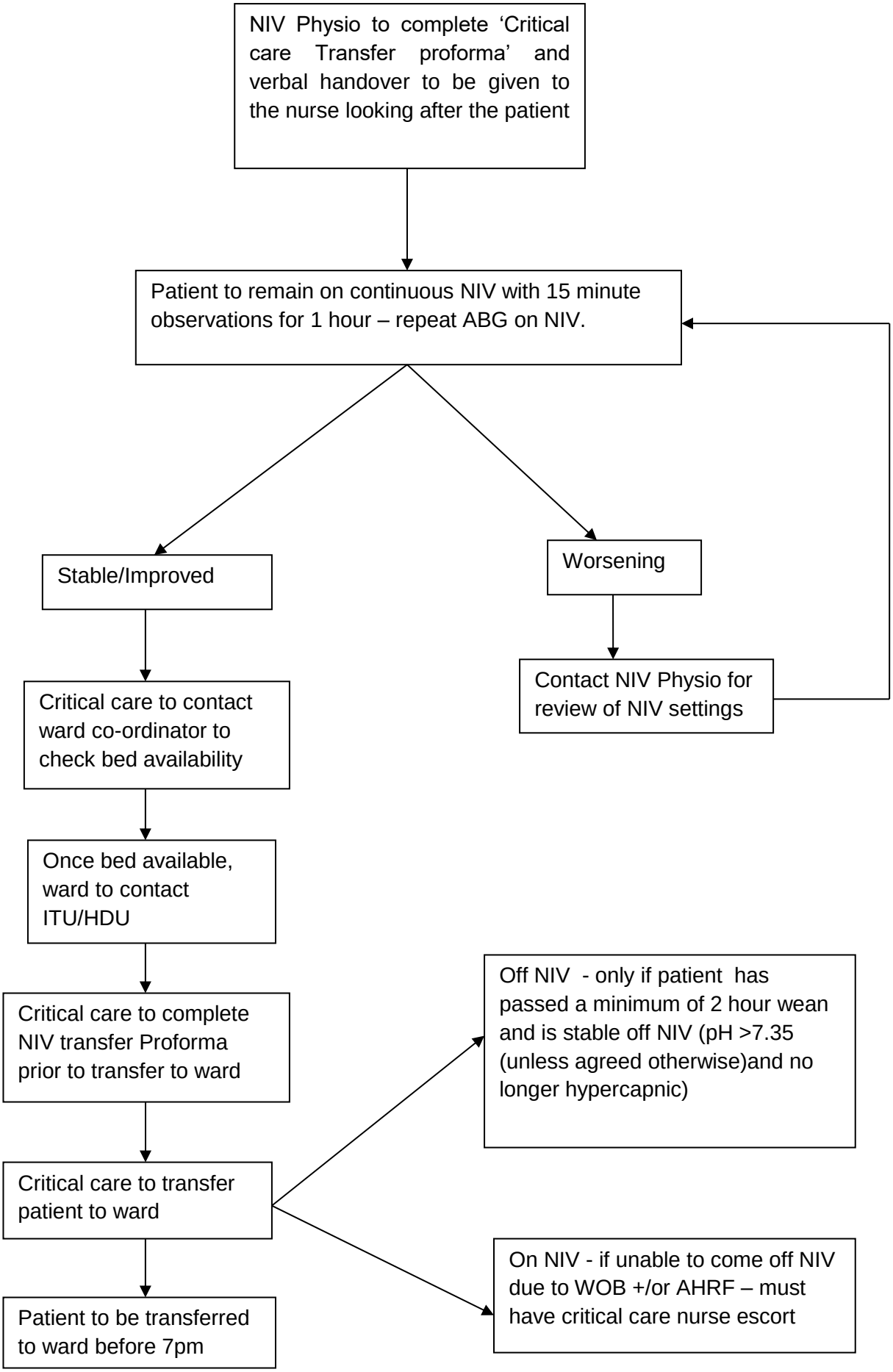
NB Patients are not to be set up for NIV transfers after 20.00 as this is not a provision provided by the overnight On Call Physiotherapy service. The NIV team are to be contacted from 08.00 the following day.

NB If the patient remains on continuous NIV but is appropriate for step down; they should still be set up on the ward NIV machine by the NIV Physiotherapy team however, they should remain on HDU for the next 24 hours for continuous monitoring. If during that time, the patient requires any setting changes or the patient deteriorates after 20.00 Critical Care should return the patient to an NIV machine they are trained to use and contact the NIV Physiotherapy team at 08.00 the following day.

NIV Appendix 10

Critical Care Transfer Pathway – BHH/GHH




NIV Physio to complete 'Critical care Transfer proforma' and verbal handover to be given to the nurse looking after the patient
Patient to remain on continuous NIV with 15 minute observations for 1 hour – repeat ABG on NIV.
Stable/Improved
Worsening
Contact NIV Physio for review of NIV settings
Critical care to contact ward co-ordinator to check bed availability
Once bed available, ward to contact ITU/HDU
Critical care to complete NIV transfer Proforma prior to transfer to ward
Off NIV - only if patient has passed a minimum of 2 hour wean and is stable off NIV (pH >7.35 (unless agreed otherwise)and no longer hypercapnic)
Critical care to transfer patient to ward
On NIV - if unable to come off NIV due to WOB +/or AHRF – must have critical care nurse escort
Patient to be transferred to ward before 7pm

NIV Appendix 11

NIV Tissue Viability Flow Chart

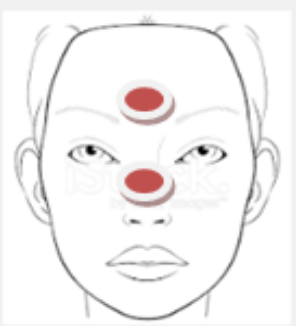
Prevention **Initial NIV Set up**

- Hydrocolloid dressings + full face mask from initial set up →Forehead + Nasal bridge
- In T.V box behind nursing desk
- Please trim to appropriate size

Documentation

N. Staff →Daily skin check in SKIN Bundle

Physio's →use of dressings/ mask changes in Medical notes



If not passed 1hr wean at

24hr continuous NIV

Prevention

- Convert to **Amara Mask** (or shield mask as appropriate). Contact physios to trial suitability

Documentation

N. Staff →Daily skin check + complete skin check in SKIN Bundle

Physio's → use of dressings/ mask changes in Medical notes

Treatment Grade >1 sore

- If unsuitable for Amara mask trial and grade >1 sore develops:

- Cover wound with **non- adhesive dressing**

- 2 Brands of facemask + alternate usage day + night

- Advise patient not to alter mask fitting / pull down onto lower part of nose

Documentation

N. Staff →Grade wound daily+ complete skin check in SKIN Bundle

NIV Appendix 12

NIV Application Record

Name: _____

PID: _____

Date of referral: ____/_____/_____ Time NIV requested: _____
Time attended Ward: _____

Referral Source –
RMO / ED SpR (ST3 Level or above only) ☐ Bleep .....
Resp/ ED/ AMU Consultant ☐.....

Inclusion Criteria: (**Must** tick at least one - otherwise contact consultant)
COPD/significant smoking history ☐ Obesity hypoventilation/obstructive sleep apnoea ☐
Neuromuscular disorder ☐ Thoracic cage deformity ☐ Bronchiectasis ☐

Conditions Excluded:
Primary Heart failure / Asthma / Pneumonia with no co-existing inclusion criteria
HPC: _____
_____

PMH: _____
_____ ***Home Oxygen:*** Y / N Prescription_____L/min__ ***Nebs*** Y / N

Medical Management:
(PH<7.25 – Ref to ITU for consideration if for escalation)
(As Indicated)
☐ *Controlled O2 (SpO2 88-92%)*
☐ *Salbutamol Nebs*
☐ *Ipratropium Nebs*
☐ *Prednisolone/Hydrocortisone*
☐ *Antibiotics*

*Other:*_____

Arterial Blood Gases:

	First T2RF ABG	Pre NIV T2RF ABG
Date:		
Time:		
pH: (<7.35)		
pCO2: (>6.5)		
pO2:		
HCO3:		
SpO2:		
O2 :		

ABG Interpretation: _____
E.g. Decompensated type 2 respiratory failure +/- Hypoxia

***Resuscitation*:** Yes ☐ DNAR ☐
***Ceiling of care*:** Level 3/ITU/Intubation ☐ NIV ceiling of care Level 2/HDU ☐ Ward based NIV only ☐
***Treatment failure plan*:** _____
Pre NIV observations:
RR:_____ SpO2:_____Fi02:_____HR:_____BP_____AVPU_____
Chest X-ray findings:_____ **Pneumothorax** No Yes ☐ ☐

Contraindications: (x those that do **not** apply)
Imminent cardiac or respiratory arrest or need for intubation ☐
Inability to protect airway ☐
CV instability requiring inotropes/vasopressors (BP systolic <80mmHg) ☐

Print name: _____Signed:_____Date:_____/_____/_____

NIV set up:

Verbal Consent: ☐ Implied Consent: ☐ Best Interest: ☐
Pressure areas checked: ☐ Concerns:_____
Prophylactic pressure care in situ _____
Date:_____Time:_____Machine:_____No:_____
Mask Size **S M L**
IPAP:_____(cmH20) **EPAP:**_____(cmH20) **O2 entrained:**_____L/min **Back-up rate:**_____

Measured or estimated weight of patient:_____(Kg) Targeted tidal volumes: _____(ml) to_____(ml)
Any settings changed from default (e.g. Pressures/Trigger/ Ti / Rise + Fall):

_____

_____

Baseline Observations on NIV:

RR:_____ SpO2:_____Fi02:_____HR:_____BP_____AVPU_____Temp_____MEWS=
Tidal Volumes (Vt) :_____(ml) Mask LK:_____(L/min) *Aim 0 mask leak. Acceptable <20L/min*

Tolerance: Yes ☐ No ☐ If intolerant of NIV, Escalate back to referring doctor for urgent review.
Chest Wall movement: Yes ☐ No ☐ If no CW movement, escalate back to referring doctor for urgent review.

NIV Settings: IPAP: ..... EPAP: ..... Time:.....

	ABG 1hr post NIV set up:	**Analysis** ↑ ↓ normal
PH:		
pCO2:		
pO2:		
HCO3		
O2 Entrained		

→

Improving ABG =

Routine ABG in 4-6 hours

Worsening ABG=

Increase/ Optimise settings

Optimise Medical management

Contact RMO/Resp cons

repeat ABG in 1-2 hours

Interpretation:_____
_____
_____

Plan: Any settings changes: Yes ☐ No ☐ If *yes*, please document:_____

_____

Breaks from NIV: *(i.e. Short breaks <10mins)*_____
Oxygen requirements on NIV:_____L/min Oxygen requirements off NIV:(*if assessed*) _____L/min
ABG due at:_____*Target sp02 88-92% documented and MEWS chart adjusted* ☐

Transfer

Time Suitable to transfer: (i.e. improving ABG's) _____
Reason for delay: Bed not available ☐ Insufficient Nurse Capacity ☐ Patient not stable to transfer ☐
Time arrived to ward _____

Print name: _____Signed:_____Date:_____/_____/_____

NIV Appendix 13

NIV Weaning Record

Date:_____

Time:_____

Name:_____

PID:_____

Subjective Assessment

Patient verbally consents to treatment/ ABG ☐ Treated in best interests ☐

Comments

:.....

.....

.....

.....

Objective Assessment (complete as indicated)

RR -

BP -

HR -

Amara)

SpO2 -

O_2 –

Amara)

AVPU –

Clinical presentation –

ABG Results

pH	
pCO2	
pO2	
HCO3	
Spo2	
FiO2	

Nasal pressure care:

Hydrocolloid dressing (preventative) ☐

Aquacel Dressing (non-adhesive) ☐

(use for > Grade 1+ if unable to tolerate

Interface:

F+P Mask (>24hr continuous NIV change to ☐

Amara Mask ☐

Shield Mask

Other Wean (No of hrs) …….

Current NIV settings if taken on NIV:

IPAP

Analysis/Intervention (including changes in settings / interface changes) ** If acidotic replace NIV

_____

_____

Today's Plan:

_____

_____

ABG due at: .....

Name (Sign and print) _____

NIV Appendix 14

General guidance on Managing Patients where an NIV bed unavailable Physiotherapist Information

- **Only one NIV patient should be set up at any one time to ensure patient safety**.
- A second patient may only be commenced by CCOT or by the on call physiotherapist once the first is located within an NIV competent area i.e. Respiratory ward/Critical care

(See inpatient NIV referral flowchart)

- The on call physiotherapist:
  - May leave the patient if waiting for bed availability/ transfer off site after 4hours only if the patient is clinically stable and the 1 hour ABG shows improvement in pH/pCO_2. Observations can be taken by nursing staff as per NIV MEWS chart instructions.
  - May treat only a chest patient during this time
  - Must remain on site and leave contact details for review in the event of deterioration in MEWS/ABGs or persistent machine alarms.

- On site accommodation is available at short notice for on-call physiotherapists to remain on site and come and review the patient urgently – contact Security.

NIV Appendix 15: NIV Withdrawal Checklist

Summary Checklist for the Management of Withdrawal of NIV care when end-of-life care expected {DRAFT 2}	Name: PiD: NHS No. DoB
GUIDANCE: ➢ Use this document for patients choosing to withdraw from NIV care and for patients lacking capacity for this decision ➢ Ensure ceiling of care excludes intubation and CPR ➢ Aim to plan withdrawal in NORMAL WORKING HOURS	

1. Indicate available supporting documentation which discusses **shared decisions** regarding withdrawal from NIV

ADRT	Other Advance Care Plan	GP Records	Community Palliative Care records

Current case notes: See discussion dated_____

2. Indicate who is involved in discussions concerning NIV withdrawal, **and if these persons are aware of the deterioration expected from underlying life-limiting illness (including trauma), irrespective of NIV use**

			Involved in discussion about NIV withdrawal	Aware deterioration expected with or without NIV
Patient (18 years old or older; no reason to doubt capacity)			*	
Legal proxy (*copy of registration in casenotes)				
Family/Friend (supply names here) or IMCA (if no NOK & patient lacks capacity)				
Healthcare team	Hospital site_____ Ward_____	Consultant_____		
		Registrar/STr_____		
		Ward sister_____		
		Staff Nurse_____		
		NIV Physiotherapist_____		
		Occupational Therapist_____		
	Critical Care Outreach Team_____			
	Palliative Care team	CNS_____		
		Registrar/STr_____		
		Consultant_____		
	Healthcare Chaplaincy Team_____			

GUIDANCE:
- ➢ Starred box to be ticked ONLY if patient has requested NIV withdrawal
- ➢ If patient has not requested NIV withdrawal, proceed in best interests: the main clinical team should discuss **rationale for expected deterioration** with family/friend, or appoint Independent Mental Capacity Advocate (IMCA) if no next of kin
- ➢ If disagreement, obtain a second opinion

3. Identify responsibilities and roles (select and individualise as needed)

Communication		Leading discussions with patient & family/friend, and allowing time to process
		Withdrawing telemetry and other continuous live/cycling monitoring
NIV Equipment		Alteration of NIV settings, alarms and modes; mask removal where requested
Medication		Prescribing of EOL medication: injectable strong opioid and injectable sedation
		Signing out of Controlled Drugs
		Administration of oxygen (e.g. nasal specula after mask removal)
Supportive care		Providing comfort
		Providing religious/spiritual support
Care after death		Verification of death
		Provision of personal care after death
		Completion of death certificate and/or cremation form

4. Identify approach to managing end-of-life symptoms (e.g. breathlessness, anxiety, terminal restlessness or agitation) and aim to reduce consciousness level with use of strong opioids and sedation prior to withdrawal – seek NIV physiotherapy & specialist palliative care advice			
A. Best interests decision agreed to withdraw NIV level of care when AVPU is "U"		**B. Patient requests withdrawal of NIV care**	
iv route available	i) Use of continuous strong opioid +/- sedation ☐	i) Gradual weaning: reduction in ventilator pressure settings +/- increase in sedation level prior to mask withdrawal...	...with use of IV PRN +/- continuous medication ☐
iv route available	ii) Use of PRN (bolus) strong opioid +/- sedation ☐		...with use of SC PRN +/- continuous medication ☐
sc route available	iii) Use of continuous strong opioid +/- sedation ☐	ii) Use of continuous IV strong opioid +/- sedation followed by mask removal when patient sedated ☐	
sc route available	iv) Use of PRN (bolus) strong opioid +/- sedation ☐	iii) Use of continuous SC strong opioid +/- sedation followed by mask removal when patient sedated ☐	

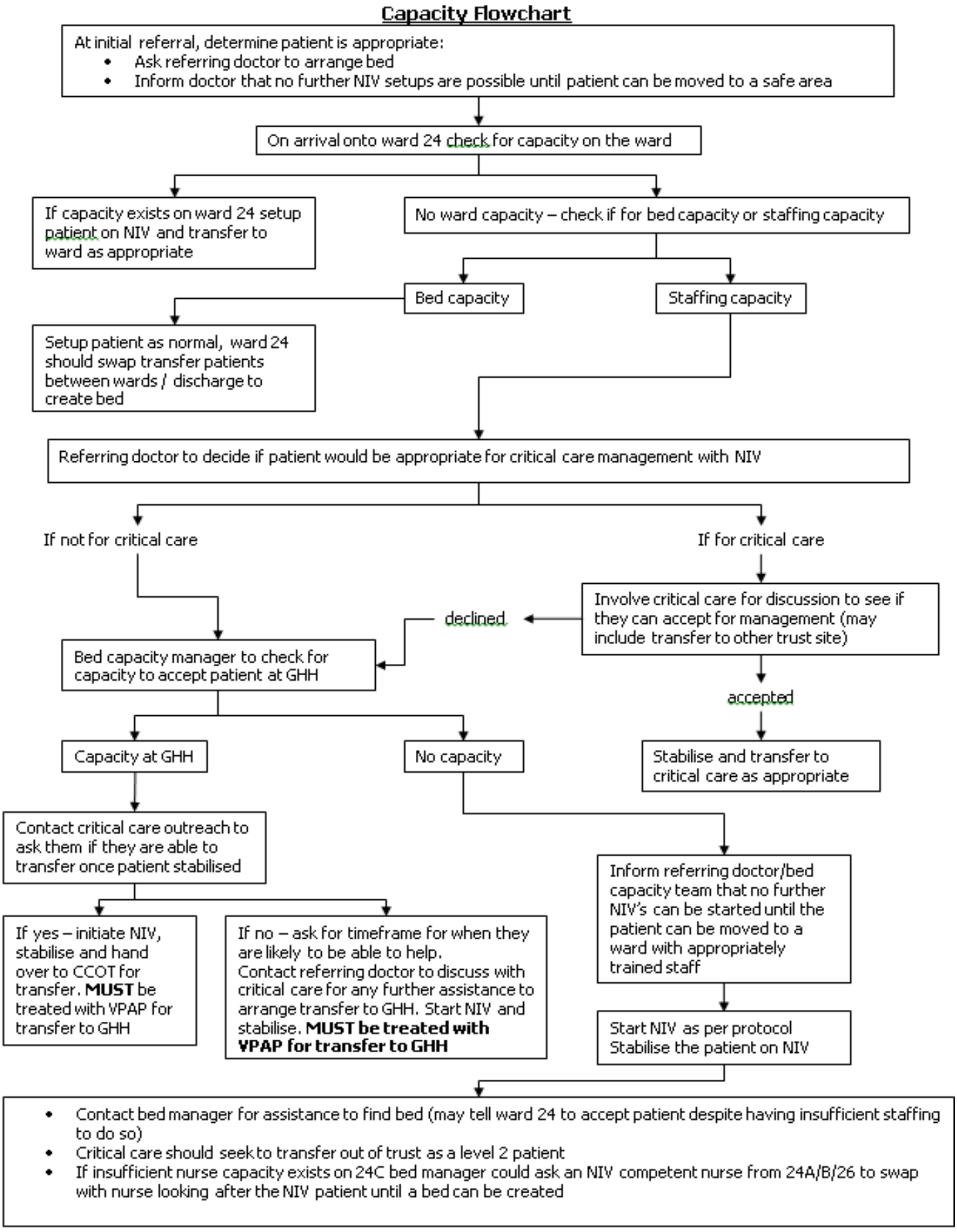
5. Document administration record and process here

ALLERGIES:

Date: Time	On examination: AVPU/motor activity/ restless	If oxygen is in use (FiO_2 or L/min)	Respiratory Rate	Who is present with patient	NIV pressure setting [Check alarms silenced and in 'spont mode'] Write "OFF" when mask withdrawn	Drugs administered [Indicate doses in continuous infusion if commenced]	Signature & PRINT NAME

M.Arolkar/ K.Stygall 2018

NIV Appendix 16



APPENDIX 4: OUTPATIENT NIV TRIAL FOR CHRONIC HYPERCAPNIC RESPIRATORY FAILURE IN PATIENTS REQUIRING NON-COMPLEX NIV (GOOD HOPE HOSPITAL)

CONTROLLED DOCUMENT

University Hospitals Birmingham NHS Foundation Trust

Outpatient NIV Trial for chronic hypercapnic respiratory failure in patients requiring non-complex NIV (Good Hope Hospital)

CATEGORY:	Clinical Guidelines
CLASSIFICATION:	Clinical
Controlled Document Number:	
Version Number:	
Controlled Document Sponsor:	
Controlled Document Lead (Author):	Richard Glover Clinical Scientist
Approved By:	Julie Lloyd Service Lead/Clinical Scientist
On:	
Review Date:	

STATEMENT OF NEED/ INTRODUCTION

Non-invasive Ventilation (NIV) is ventilatory support delivered to the upper airway via a facial mask. Mechanically it is similar to invasive ventilation delivered in the ITU, the main difference is the state of the patient, with NIV the' alert, awake and cooperative whereas those on ITU are usually sedated and totally dependent upon others.

There are many instances where NIV is useful and can often be implemented to stop patients being intubated who would ordinarily be difficult to wean once the acute episode is past.

The principle use of NIV within the context of this document is to treat hypercapnic respiratory failure. This SOP refers only to NIV trials performed within the OP setting on stable patients.

EQUIPMENT PREPARATION

NIV machine:

- ResMed Stellar 150
- Lumis 150

Consumables:

- Mask
- External disk filter
- Tubing
- Oxygen bubble tubing
- Oxygen connector
- Concentrator
- Pulse oximeter
- Humidifiers

INDICATIONS

Trial of long term domiciliary NIV must be recommended and authorised by a respiratory physician and usually (not limited to) the following selection criteria is applied:

- Hypercapnic respiratory failure with:
    - Associated symptoms
    - Suboptimal oxygenation due to hypercapnic respiratory failure,
    - Frequent admissions and/or exacerbations,
    - Persistent hypercapnia despite clinical stability
    - Failure of CPAP (or CPAP trial deemed inappropriate) in the context of obesity related hypoventilation found in conjunction with obstructive sleep apnoea
- Nocturnal hypoventilation

CONTRAINDICATIONS

Absolute

- Acute hypercapnic respiratory failure (pH < 7.35, PCO_2 >6.5kPa)
- Facial trauma
- Life threatening event
- Multi-organ failure
- Severe fixed upper airway obstruction
- Inability to cooperate
- No cough reflex – risk of aspiration

Relative

- Highly uncooperative
- Multiple pathologies
- Recent Pneumothorax

PROCEDURE

Test preparation and set up:

- Prepare paperwork
- Explain procedure and why the patient has been referred for NIV trial
- Perform ELCS/ABG according to ELCS SOP

- If patient is in acute (decompensated) hypercapnic respiratory failure, case should be escalated for acute intervention and outpatient set up is not appropriate.

- Size mask and allow the patient to hold the mask on the face with the NIV machine running at IPAP 12 EPAP 4 to acclimatize patient / alternatively affix mask, using strapping.
- Follow the NIV set up flow chart (appendix 1)
  - The aim of NIV set up is to:
    - Provide at least a minimally effective level of NIV pressure support (≥8cmH_2O)
    - Ensure that the patient is able to tolerate the pressure prescribed
    - Correct blood gases*
      - *Blood gas derangement is unlikely to be satisfactorily corrected without a prolonged period of time spent using NIV (ideally overnight)
      - *Prescribing significantly higher than current O2 flow rates should be considered a risk until the effectiveness (compliance and improvement in hypercapnia) of NIV is confirmed; subsequently LTOT requirements should be managed in line with BTS guidelines and Trust guidelines on home oxygen.
      - As a result of these points, NIV titration should aim to be *at least* minimally effective and to facilitate comfort; secondary changes to NIV settings can be considered at a later date once good tolerance and compliance with NIV has been accomplished to maximise therapeutic effectiveness.
- Once satisfactory settings have been established repeat ELCS

Review results:

- If titration is successful, confirm the NIV prescription with Respiratory Physician and complete Appendix 2.
- Issue short term loan NIV for a period of 2-4 weeks
- Give the patient an NIV leaflet and explain that they will need to contact Lung Function & Sleep with any issues regarding their NIV machine. Highlight we are

an outpatient department open between 08:30 – 17:00 for enquiries or appointments, weekdays only.

- Any weekend emergencies should be dealt with via A+E or their community team (if a clinical concern, such as exacerbation) or Ward 10 (if a functional NIV issue). If not an emergency the patient should be advised to wait until Monday before calling the department.

Provide education:

- Mask fit
  - Can the patient fit and remove the mask independently?
- Machine
  - Can the patient turn the machine on and off independently?
- Cleaning of mask
- Alarms of machine
- How to use the 'Home' settings e.g. alarm, noise, back light etc.
- Explain they must bring their NIV machine with them if they get admitted to the ward
- Humidifier - if utilising a humidifier, do not use an external filter with the circuit
- Arrange to phone the patient within a few days to check how they are progressing
- Complete Competency assessment checklist (Appendix 2).
- Add the patient to the NIV database and comment temporary loan
- Log machine on sleep database
- Complete 'summary of sleep pathway'

2-week review appointment

- Download compliance
- Perform ELCS
- If results are satisfactory re compliance and blood gas results issue long term loan and arrange for a clinic follow up.
- Complete funding request
- Reaffirm education regarding:
  - Machine operation

  - Filters for machine - Provide 3 external filters with the instruction to change when they become discoloured. The internal filter is disposable and should be changed regularly once discoloured, the grey washable filter must be changed every 6-12 months.
  - Mask fitting and cleaning
  - Humidifier cleaning if appropriate
- Complete outpatient proforma
  - Change comments on NIV database to long term loan
  - Sign long term loan agreement
  - Complete clinical letter

Downloading NIV machine compliance

- Stellar 100/150,
  - Insert USB stick/ SD card into the machine
  - On the machine choose:
    - Write set/log
    - Detailed and summary data
    - Select relevant dates
    - Write
    - Overwrite existing data
- Run Rescan software
  - Remove the USB stick from the NIV and insert into the PC
  - On the PC choose:
    - Select new patient and insert details or open patient details if existing patient
    - Download data selecting all available data
- Review data
- Choose all available data report ensuring the correct dates are selected and print.

Note: No patient identifiable information is transferred onto the memory sticks only compliance data from the device.

CRITERIA FOR COMPETENCE

In house training that includes shadowing Band 6+ performing NIV trials and progressing to performing NIV trials under direct and indirect supervision until competence assessment is successful.

Attendance at recognised lectures, conferences and courses e.g. ARTP NIV course

REPORTING OF RESULTS/ PREPARATION OF REPORT

NIV set up should be documented on clinical letters using the appropriate report template. This correspondence must be copied to the G.P referring clinician and the patient.

The NIV commencement documentation (see Appendix 2) should be completed and filed in the clinical notes, and scanned onto the patients file within the Lung Function and Sleep departments network drive.

PROTOCOL SUBMISSION DETAILS

Protocol Prepared by:	Richard Glover (Adapted from UHB QE protocol)
Date:	06/08/2018
Protocol submitted to and approved by:	Julie Lloyd
Protocol review date:	06/08/2020

REFERENCES

BTS NIV guidelines

S Baudouin, S Blumenthal, B Cooper, C Davidson, A Davison, M Elliot, W Kinnear, R Paton, E Sawicka, L Turner.

Non-invasive ventilation in acute respiratory failure

Thorax 2002;57:192-211 doi:10.1136/thorax.57.3.192 .

Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet1993;341:1555–7.

Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease.

N Engl J Med1995;333:817–22.

Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure.

Am J Respir Crit Care Med1995;151:1799–806.

Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet2000;355:1931–5.

Plant PK, Owen J, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbation of COPD; implications for the provision of non-invasive ventilation and oxygen administration. Thorax2000;55:550–4.

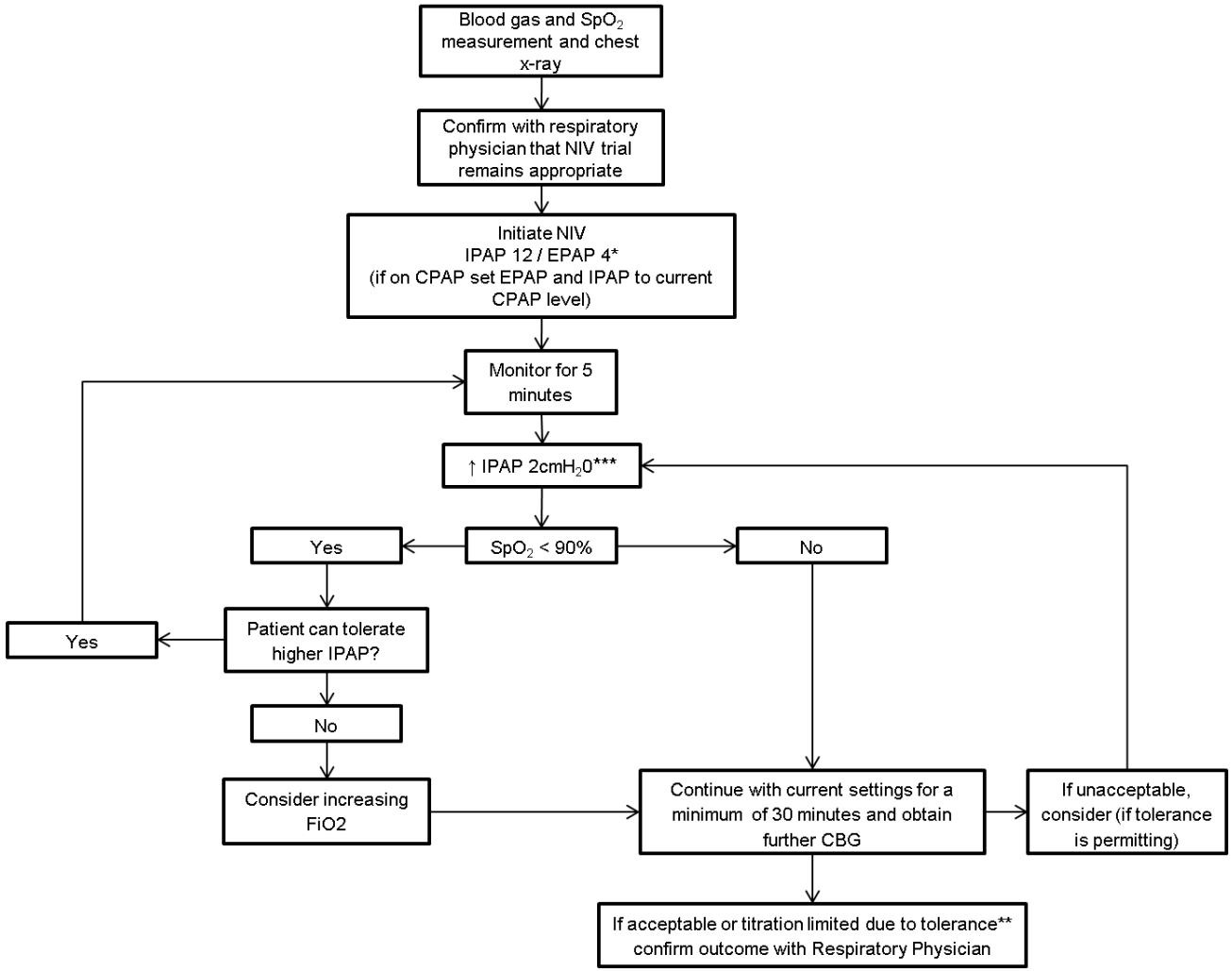
Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax2001;56:708–12.

Mark W Elliott

Editorial: Domiciliary non-invasive ventilation in stable COPD?

Thorax 2009;64:553-556 doi:10.1136/thx.2009.113423

Appendix 1: NIV titration protocol



*Consider increases to EPAP during the procedure as clinically appropriate / indicated, ensuring a minimal difference in PS is maintained ≥8cmH_2O

**Further pressure increases may be considered following a period of acclimatisation ***ensure a minimal difference in PS is maintained ≥8cmH_2O

Appendix 2: Domiciliary Non-invasive Ventilation Assessment

This form is designed to assess patient suitability for safe/appropriate provision of domiciliary NIV.
This decision to commence Home NIV is a multidisciplinary decision led by a physician as per PLCV regulations.

Name:
PID: DOB:
Date of referral: Weight/BMI: _____ / _____

Affix Patient PID Label

Current Patient Location: Outpatient (home) Referring Physician: Dr Ismail

Diagnosis and medical problems

_____

Pre-admission functional Status/Clinical Frailty Score/ Previous occupation

_____

Home NIV Criteria:

Daytime hypercapnia ☐
≥ 3 Acute NIV episodes ☐
Inability to wean from acute nocturnal NIV ☐
Patient consents to use Home NIV ☐

ReSPECT status:

CPR ☐ No CPR ☐
Ceiling of care: _____

Exclusion Criteria:

- Inability to remove mask independently (with no waking night carer) ☐
- Cognitive/behavioural limitation affecting ability to comply safely with NIV ☐
- Intolerance of acute NIV ☐
- Multiple co-morbidities limiting utility of NIV ☐

Physiotherapy Assessment: (for mode of ventilation)

COPD/significant airways disease ☐ Obesity-related respiratory failure ☐

Neuromuscular disorder ☐ Thoracic cage deformity ☐

Symptomatic relief for admission prevention (in conjunction with any of the above) ☐

Chest/Cough Assessment (if applicable)

Auscultation: ..... Palpation: .....
Cough:..... Peak Cough Flow:.....
Sputum:..... FEV1..... FVC.....
Overnight oximetry.....

>360L/min = monitor
<270L/min = Teach cough augmentation techniques
<160L/min = Establish airway clearance device

Arterial Blood Gases (with Max and discharge CO_2 at time of deciding home NIV):

Date:		**Date:**	
Time:		**Time:**	
pH:		**pH:**	
pCO_2:		**pCO_2:**	
pO_2:		**pO_2:**	
HCO_3:		**HCO_3:**	
SpO_2:		**SpO_2:**	
FiO_2:		**FiO_2:**	

Reported symptoms:

- Excessive daytime somnolence ☐
- Headache ☐
- Confusion ☐
- Increased shortness of breath ☐
- Resting Tremor ☐

Non- Invasive Ventilation physician Review:

Name :…… Suitability: Yes ☐ No ☐

Yes ☐ Further discharge planning for increased care needs

Further Comments:

……

……

Domiciliary NIV Settings:

Machine	
Serial Number	
Headgear	
Interface and Size	**S M L**
IPAP (cmH20)	
PS min/max	
EPAP (cmH20)	
Mode	
Back up rate	
Trigger	
Rise / Fall	
Ti Min	
Ti Max	
Oxygen On NIV	
Oxygen Off NIV	

Domiciliary NIV regime:
Daytime……
Overnight……

Ambulatory Oxygen: Yes ☐ No ☐
If YES, prescription……

Long Term Oxygen Therapy: Yes ☐ No ☐
If YES, prescription……

ABG on LTOT
prescription……

CCG……
CHC Funded **Yes No** PHB **Yes No**

Print name:_____Signed:_____Date:_____/_____/_____

NIV AGREEMENT

Name: ……
PID: ……
DOB: …../…../……

Address: ……
……

……

Affix Patient ID Label

Contact Telephone number: ……..

I, the above named, have received treatment with NIV. My treatment centre is the Lung Function & Sleep Department at Good Hope Hospital and I agree to bring my machine for servicing on an annual basis. I understand that it is my responsibility to arrange a mutually convenient date and time for this through the Lung Function & Sleep Department on 0121 424 7229.

I also acknowledge that the CCG funds the machine, masks and equipment, and that only a certain amount of masks and equipment can be provided. I agree that if I exceed what the CCG have funded to provide, that it is my responsibility to purchase further masks and equipment independently.

I understand that failure to comply with this agreement will result in my service and maintenance contract with my Primary Care Trust being cancelled. The Lung Function & Sleep Department will then no longer be able to service my machine or provide me with consumables.

Signed: ……

Date: ……

Competency / Teaching

	Before Discharge	Date & Initialled
1.	Provided with patient information booklet	
2.	Indications and benefits explained	
3.	Minimal frequency of use for clinical effectiveness and advised on increasing frequency and other action if the patient is unwell	
4.	Seek assistance via GP/ Lung Function & Sleep if they suffer side effects	
5.	Bring the machine with them for any overnight stay in hospital	
6.	Taught on/off buttons, visual screen explanation and an instruction manual given	
7.	Practical demonstration how to attach the circuit and detach it from the machine	
8.	Taught how to clean the circuit and mask, and how to reassemble them	
9.	It is not the responsibility of HEFT to train carers or care agencies	
10.	NIV machine is hospital property and should be returned if not used. Insurance is required if the machine is taken abroad.	
11.	Servicing should be arranged annually by the patient with the Lung Function & Sleep Department	
12.	Lung Function & Sleep Department details provided for any problems with machine/mask	
	Once patient Discharged home	
13.	Follow up appointment arranged in clinic to assess the efficacy of the machine and daily routine/usage will be discussed. If the machine is not in regular use, the continuing issue of the machine may be ceased.	

Issuing HCP Signed …… Date ……

Print ……

Patient or Family Signed …… Date ……

Print ……

APPENDIX 5: Domiciliary NIV Service Proposal Consultant Feedback

The aim of this survey was to assess the Respiratory Consultants perception of the service proposal to develop a local domiciliary NIV Service.

Initially, it had been planned to conduct 1:1 meetings with each consultant using a semi-structured interview format. However, given the pressures on their time and following several cancellations of interview sessions, a simple questionnaire consisting of three questions was used and their responses are summarised below:

Q1 Do you feel that an elective outpatient domiciliary NIV Service would be beneficial to the patient population served by Good Hope Hospital?

The responses are displayed in Table 1

1	Significant patient benefit	4
2	Some patient benefit	0
3	About the same	0
4	No perceived patient benefit	0
5	Negative effect on patient care	0

All of the Respiratory Consultants indicated that they felt that the proposed service would have a significant beneficial effect on patients living close to Good Hope Hospital.

Q2 Do you feel that an elective outpatient domiciliary set up NIV Service will impact on your existing patient workload?

The responses are displayed in Table 2

1	No significant effect on workload	3
2	Some effect on workload	1*
3	Significant increase in workload	0

* The consultant that responded that there would be some effect on their workload has agreed to take the role of site Clinical Lead for the proposed domiciliary NIV Service.

Q3 Do you feel confident that non-complex patients can be safely managed by a local domiciliary NIV Service?

The responses are displayed in Table 3

1	Very confident	4
2	Somewhat confident	0
3	Uncertain	0
4	Not confident at all	0

The consultants were provided with a 'free text' section to highlight if there were any further concerns or queries about the proposal. There were 2 responses recorded to this section:

'My only concern about this proposal is whether the scientific staff will be able to absorb this in to the current workload, given the conflicting pressures they are under. I would not like other areas of service, such as lung function testing, to suffer at the expense of NIV.'

'This service should offer a real benefit to patients living locally and is a much needed addition the Respiratory Medicine Service at Good Hope site. '

It was reassuring that the Consultants were considering the impact of an additional service. This additional work has been factored in to the recent respiratory physiology staffing review, and staff roles have been adjusted to allow for this. It is clear than there is strong Consultant support for this service in terms of the perceived benefits it will provide for patients living geographically closer to Good Hope hospital.

APPENDIX 6: GHH HOME NIV SERVICE ENGAGEMENT MEETING AGENDA

GHH Home NIV Service Engagement Meeting Agenda

29/09/2017 13:50 – 15:00,

Venue: Outpatients seminar room – 1st Floor

Attended: Dr Iyad Ismail (Consultant Physician), Julie Lloyd (Service Lead), Richard Glover (Senior Clinical Physiologist), Dr R Rajput (GP/SES Clinical Lead), Anna Redpath (Community Matron, SES), Tim Owen (Sutton Coldfield Breath Easy Group), Iona Belgrove (PALS)

1. **Minutes from previous meeting 08/07/2015**
2. **Local Outpatient Domiciliary NIV Proposal**

2.1. The outline proposal had previously been circulated and a short PowerPoint presentation was given to expand on the service proposal. The floor was opened to questions about the proposed NIV service.

2.2. Anna Redpath (AR) raised some concerns about how much involvement would be expected from Community Matrons in terms of management; Dr Rajput (RR) echoed this concern about community support. Julie Lloyd (JL) and Dr Ismail (II) reassured them that there was no expectation that the community teams would take on the management of newly established NIV patients. The clinical responsibility for managing the NIV would remain with the GHH NIV Team and the community teams would continue to provide their current level of support.

2.2.1. JL outlined the education and training that would be provided for the patients receiving NIV and for the community teams supporting this group of patients.

2.3. Iona Belgrove (IB) asked if the proposed NIV service at GHH would be the same as patients would receive at a Tertiary Centre. II stated that the GHH service would only take on

patients that met the 'non-specialist' NIV criteria and he described which patients would be suitable for the GHH service. Patients requiring more complex ventilation would continue to be referred on to the Tertiary Centres based at Birmingham Heartlands hospital or North Staffs Hospital. The pathway and agreed standards of care were in line with those established at the Tertiary Centre and equivalent across all sites.

2.4. IB asked how it was planned to monitor that the care that the patients received would be 'equivalent' to the current care received. JL described that we planned to undertake a service review over a 12-month period, comparing the current model of in-patient initiation with the new model of outpatient initiation. The service review would compare outcomes in terms of physiological measures and also quality of life; IB asked if it was planned to share this data and JL advised that publication was planned.

2.5. Tim Owen (TO) stated that he was pleased that this new service was being brought closer for local patients. He reported that following review and discussion within the Breathe Easy group, members of the local group were pleased that they would potentially have to travel less for their care.

2.5.1. TO asked if carers would receive education and support with NIV. JL advised that this formed part of the service proposal.

2.5.2. TO asked how patients would be involved with the service. JL advised that it was planed to conduct individual patient interviews to gain a deeper understanding of patients perceptions and feelings around home NIV in addition to measuring quality of life outcomes. TO thanked JL for this information.

2.6. No further questions were raised and all participants were asked if they felt that they would support the service proposal. The proposal was accepted unanimously and all

participants in the meeting were advised that if they had any further questions or queries, they could contact JL by email or telephone (details provided)

3. **AOB**

3.1. NIV Polices and guidelines: the service pathway documents were distributed to the attendees and queries could be directed as above.

3.2. The research proposal was also circulated to the group for dissemination and comments; no comments received to date.

The meeting was closed and the attendees thanked for their helpful participation. The minutes of the meeting will be distributed to all attendees; no further meetings were planned at this time.

APPENDIX 7: SIGNED SPONSORSHIP LETTER

NHS
University Hospitals Birmingham
NHS Foundation Trust

18/04/2019

Dear Julie Lloyd,

Confirmation of University Hospitals Birmingham NHS Foundation Trust Sponsorship:

"The impact of domiciliary NIV on physiological and QoL parameters in a cohort of patients." (2019005STU)

Thank you for submitting your project for consideration of UHB Sponsorship. Your proposal was reviewed by the R&D Management Team and I am writing to confirm that the decision was made that University Hospitals Birmingham NHS Foundation Trust, of Birmingham Heartlands Hospital, is able to take on the duty and responsibility of Sponsor for the above named study from the date of this letter.

University Hospitals Birmingham NHS Foundation Trust, of Birmingham Heartlands Hospital will fulfil its Sponsorship duties in accordance with the legislative requirements as detailed in the UHB Sponsorship of a Research Study standard operating procedure (SOP), which is available from the Trust policies and procedures intranet site: http://sharepoint/policies/Procedures/Forms/

As part of our processes, Nick Denyer (Project & Sponsorship Co-ordinator) will work directly with you as the Trust's Sponsor representative for the duration of your project. Please refer to the "UHB Sponsorship of a Research Study" SOP for further details on the role of the link person and the support they will provide you during the study.

We would like to wish you all the best for your project and we look forward to hearing of your progress in the near future.

Yours sincerely

Dr. Sarah Pountain
Interim Head of Research

V3.0, 01/02/2019

Chair: Rt Hon Jacqui Smith

Chief Executive: Dr David Rosser

APPENDIX 8: NIV REVIEW (LUNG FUNCTION AND SLEEP, GOOD HOPE HOSPITAL)

CONTROLLED DOCUMENT

University Hospitals Birmingham NHS Foundation Trust

NIV Review (Lung Function and Sleep, Good Hope Hospital)

CATEGORY:	Clinical Guidelines
CLASSIFICATION:	Clinical
Controlled Document Number:	
Version Number:	
Controlled Document Sponsor:	
Controlled Document Lead (Author):	Richard Glover Clinical Scientist
Approved By:	Julie LLOYD, Service Lead/Clinical Scientist
On:	
Review Date:	

STATEMENT OF NEED/ INTRODUCTION

Non-invasive Ventilation (NIV) is ventilatory support delivered to the upper airway via a facial interface (mask). Mechanically it is similar to invasive ventilation delivered in the ITU, the main difference is the state of the patient, with NIV patients alert, awake and cooperative whereas those on ITU are usually sedated and totally dependent upon others.

There are many instances where domiciliary NIV has uses. The principle use of NIV is to improve oxygenation and reduce inspiratory muscle load in patients who have a history of type II respiratory failure. Patients treated with domiciliary NIV have met certain criterion that demonstrated that the treatment would be beneficial, in terms of reducing the likelihood and frequency of admission and exacerbation (COPD), improve and control symptoms, and effectively treat sleep disordered breathing (obesity related hypoventilation)

This SOP refers only to NIV reviews performed in the Good Hope Hospital Respiratory Physiology department, and covers patients previously established on domiciliary term non-invasive ventilation.

EQUIPMENT PREPARATION

The following equipment is required:

- Calibrated Blood Gas Analyser,
- ResScan (software)
- Back up NIV devices, to include:
    - Lumis ST-A 150
    - Stellar 150

Consumables:

- An appropriate range of NIV/CPAP masks.
- Circuit tubing,
- Ventilator filters,
- Blood gas sampling equipment.

INDICATIONS

Patients attending the Good Hope Hospital Lung Function and Sleep NIV review service and previously established on home NIV.

CONTRAINDICATIONS

The Good Hope Hospital service is appropriate for patients who require non-complex NIV.

A concise definition for non-complex NIV is not formally defined but in relation to the local service, patient groups excluded include:

- Motor Neurone Disease,
- Muscular Dystrophy,
- Other rapidly progressive neuromuscular conditions,
- NIV dependant (NIV usage >14 hours)

Patients presenting to the service with these conditions should be referred to a specialist centre for home NIV.

PROCEDURE

Health and Safety

- Patient-operator and patient-patient cross-contamination can occur if the use of gloves, hand washing, and equipment-decontamination procedures are not adhered to correctly.
- Operators routinely use Standard Precautions (see Infection Control chapter) as a protective precaution when caring for all patients if there is any possibility of direct contact with blood, body fluid, mucous membrane, non-intact skin or secretions.

Patient Preparation and Pre-test considerations

Prior to the appointment, the subject should be asked to avoid:

- Smoking for 24 hours prior to the test
- Consuming alcohol for at least 4 hours
- Vigorous exercise for at least 30 minutes prior to the test
- Wearing clothes or surgical appliances that restrict chest movement

Process:

The NIV review service offers a combined approach to long-term oxygen therapy and domiciliary NIV management. There is no capacity or funding for home visitations and all instances of NIV reviews are performed in the Treatment Centre at Good Hope Hospital.

Patient education:

Patients should be provided with appropriate education with respect to their NIV therapy and respiratory condition, which includes:

- Contacting their community team in the event of deterioration,
- Contacting the emergency services in the event of significant deterioration,
- Contacting the Lung function and Sleep department (GHH) if they have issues with their current therapy, including oxygen or NIV.
- Provided with the 'Long-term NIV' patient information booklet.
- Provided with oxygen alert cards

Oxygen therapy:

Oxygen therapy is managed in line with BTS guidelines and is formally outlined in a separate operating procedure (Please see: LTOT assessment)

NIV therapy:

The management of NIV in the local service includes the following aspects:

- Issuing and recording the SRI (Severe Respiratory Insufficiency) quality of life questionnaire.
- Download data from NIV device (Stellar 100/150, Lumis 100/150)
    - Insert USB stick/ SD card into the machine
    - On the machine choose:
        - Write set/log
        - Detailed and summary data
        - Select relevant dates
        - Write
        - Overwrite existing data
        - (Note no patient information is transferred onto the memory sticks only compliance data from the device.)
    - Run Rescan software
    - Remove the USB stick/ SD card from the NIV and insert into the PC
    - On the PC choose:
        - Select new patient and insert details or open patient details if existing patient
        - Download data selecting all available data

    - Review data
        - Choose all available data report ensuring the correct dates are selected
- Obtain a limited clinical history to identify acute/chronic deterioration and recommend medical input where appropriate.
- Assessing and improving the effectiveness of NIV settings and interface, to include
    - Control of hypercapnic respiratory failure in relation to previous blood gases and expected blood gases.
        - ****Decompensated hypercapnic respiratory failure**:**
            - Patients presenting with decompensated hypercapnic respiratory failure should be escalated for acute medical input with either a review in the respiratory medical clinic, or attendance at the Acute Medical Assessment unit if recommended by a respiratory physician or registrar.
    - Adequacy of tidal volumes and minute ventilation in relation to the individual patient.
    - Mask fit in terms of air leakage.
    - Making appropriate changes to NIV settings to provide effective ventilation.
- Assessing and improving synchrony and comfort with current NIV settings,
- Identify any side effects of NIV and take appropriate action, which includes:
    - Aerophagia and associated risk of abdominal distension (bloating)
    - Facial skin trauma,
    - Pain / discomfort
- Performing or requesting sleep studies (Overnight oximetry and Limited polysomnography) as necessary and as indicated by the patient's clinical presentation or reported symptoms (tests should be performed in line with the relevant standard operating procedure for each test (Please see Overnight oximetry / Overnight limited channel sleep study).
- Making recommendations to attend Pulmonary Rehab (and arranging a referral) where appropriate and where consent is obtained.
- Referring the patient for medical input on the day, or as a follow up as clinically indicated

Spirometry:

Patients attending for a NIV review should undergo spirometry 1-2 times per year. Spirometry should be performed in line with the relevant standing operating procedure (Please see: Spirometry SOP).

Machine servicing

NIV devices require an annual service. The process to facilitate this is as follows:

- The NIV device service month should be pre-registered on the appointments system (NIV service OPA type) and booked to coincide with the patients NIV physiology review
- The day preceding the service date, a job to service the device should be logged with EBME (electrical and biomedical engineering).
- When the patient attends for the test, and following any machine related activities, EBME should be called and notified that the machine is ready for service.
- Following the OPA, the NIV device should be pre-registered for a repeat service in 12 months' time when the process repeats.

Follow up procedure

Following the attendance the physiologist reviewing the patient should make a recommendation for the patient's next review. Patients undergoing changes to their ventilator may need to be reviewed again within 4-8 weeks to re-assess the success of the change. Patients with controlled blood gases and who are clinically stable without frequent admissions should be considered for once yearly reviews. All other patients should be reviewed biannually.

CRITERIA FOR COMPETENCE

Physiology staff undertaking routine NIV reviews should be trained to Band 6 level. The following competencies and skills are required:

- Ability to competently obtain and interpret blood gases using arterial and/or capillary blood gas measurements.
- Trained (in house) and competent in the assessment and prescription of long-term oxygen therapy.

- Trained (in house) in the use and application of NIV
- Trained (n house) in the issuing and interpretation of overnight oximetry studies.
- Attendance at recognised lectures, conferences and courses; ARTP/BTS NIV course.

REPORTING OF RESULTS/ PREPARATION OF REPORT

Following the attendance a clinical letter should be prepared describing the action taken and discussions had during the review. This should be attached to clinical letters and copied to the G.P and the patients referring clinician.

Any changes to oxygen prescriptions should be made via OxyShop and recorded on the clinical letter.

Any changes to ventilator settings and/or interface should be recorded on the clinical letter.

In the event where the NIV device is changed this should be noted on the NIV database by changing the model and serial number where appropriate.

PROTOCOL SUBMISSION DETAILS

Protocol Prepared by: Richard Glover **Date**: 06/08/2018

Protocol submitted to and approved by:

Clinical Service Lead: Julie Lloyd **Protocol review date:** August 2020

REFERENCES

- BTS NIV guidelines
- S Baudouin, S Blumenthal, B Cooper, C Davidson, A Davison, M Elliot, W Kinnear, R Paton, E Sawicka, L Turner.
- Non-invasive ventilation in acute respiratory failure
- Thorax 2002;57:192-211 doi:10.1136/thorax.57.3.192 .
- Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet1993;341:1555–7.
- Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease.
- N Engl J Med1995;333:817–22.
- Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure.
- Am J Respir Crit Care Med1995;151:1799–806.
- Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet2000;355:1931–5.
- Plant PK, Owen J, Elliott MW. One year period prevalance study of respiratory acidosis in acute exacerbation of COPD; implications for the provision of non-invasive ventilation and oxygen administration. Thorax2000;55:550–4.
- Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. Thorax2001;56:708–12.
- Mark W Elliott
- Editorial: Domiciliary non-invasive ventilation in stable COPD?
- Thorax 2009;64:553-556 doi:10.1136/thx.2009.113423

REFERENCES

Agency for Clinical Innovation Respiratory Network, 2012. Domiciliary Non-invasive Ventilation in Adult Patients: A Consensus Statement.

Akobeng, A.K., 2005. Understanding randomised controlled trials. Archives of disease in childhood, 90(8), pp.840-844.

Ali, S. and Kabir, Z., 2007. Domiciliary non-invasive ventilation and the quality of life outcome of patients suffering from chronic respiratory failure. Irish medical journal, 100(1), pp.336-338.

Aloia, M.S., Arnedt, J.T., Stepnowsky, C., Hecht, J. and Borrelli, B., 2005. Predicting treatment adherence in obstructive sleep apnea using principles of behavior change. Journal of Clinical Sleep Medicine, 1(04), pp.346-353.

Ambrosino, N., Vitacca, M., Dreher, M., Isetta, V., Montserrat, J.M., Tonia, T., Turchetti, G., Winck, J.C., Burgos, F., Kampelmacher, M. and Vagheggini, G., 2016. Tele-monitoring of ventilator-dependent patients: a European Respiratory Society Statement. European respiratory journal, 48(3), pp.648-663.

Ando, H., Williams, C., Angus, R.M., Thornton, E.W., Chakrabarti, B., Cousins, R., Piggin, L.H. and Young, C.A., 2015. Why don't they accept non-invasive ventilation?: Insight into the interpersonal perspectives of patients with motor neurone disease. British journal of health psychology, 20(2), pp.341-359.

Ankjærgaard, K.L., Maibom, S.L. and Wilcke, J.T., 2016. Long-term non-invasive ventilation reduces readmissions in COPD patients with two or more episodes of acute hypercapnic respiratory failure. European Clinical Respiratory Journal, 3(1), p.28303.

Ansari, Z., Sahal, A., Sharma, P., Das, J., Herath, S. and Nathani, N., 2014. Review of mortality in patients on domiciliary non-invasive ventilation for type 2 respiratory failure. European Respiratory Journal, 44(Suppl 58).

Antonelli, M., Conti, G., Rocco, M., Bufi, M., De Blasi, R.A., Vivino, G., Gasparetto, A. and Meduri, G.U., 1998. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. New England Journal of Medicine, 339(7), pp.429-435.

Arellano-Maric, M.P., Hamm, C., Duiverman, M.L., Schwarz, S., Callegari, J., Storre, J.H., Schmoor, C., Spielmanns, M., Galetke, W. and Windisch, W., 2020. Obesity hypoventilation syndrome treated with non-invasive ventilation: Is a switch to CPAP therapy feasible?. Respirology, 25(4), pp.435-442.

Bach, J.R., Alba, A.S. and Saporito, L.R., 1993. Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users. Chest, 103(1), pp.174-182

Bach, P.B., Brown, C., Gelfand, S.E. and McCrory, D.C., 2001. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Annals of Internal Medicine, 134(7), pp.600-620.

Barger, S., Sullivan, S.D., Bell-Brown, A., Bott, B., Ciccarella, A.M., Golenski, J., Gorman, M., Johnson, J., Kreizenbeck, K., Kurttila, F. and Mason, G., 2019. Effective stakeholder engagement: design and implementation of a clinical trial (SWOG S1415CD) to improve cancer care. *BMC medical research methodology*, *19*(1), pp.1-7.

Basch, E., Aronson, N., Berg, A., Flum, D., Gabriel, S., Goodman, S.N., Helfand, M., Ioannidis, J.P., Lauer, M., Meltzer, D. and Mittman, B., 2012. Methodological standards and patient-centeredness

in comparative effectiveness research: the PCORI perspective. JAMA-Journal of the American Medical Association, 307(15), pp.1636-1640.

Bellomo, R., Warrillow, S.J. and Reade, M.C., 2009. Why we should be wary of single-center trials. Critical care medicine, 37(12), pp.3114-3119.

Benson, K. and Hartz, A.J., 2000. A comparison of observational studies and randomized, controlled trials. New England Journal of Medicine, 342(25), pp.1878-1886

Berg, G., Delaive, K., Manfreda, J., Walld, R. and Kryger, M.H., 2001. The use of health-care resources in obesity-hypoventilation syndrome. Chest, 120(2), pp.377-383

Bertella, E., Banfi, P., Paneroni, M., Grilli, S., Bianchi, L., Volpato, E. and Vitacca, M., 2017. Early initiation of night-time NIV in an outpatient setting: a randomized non-inferiority study in ALS patients. European Journal of Physical and Rehabilitation Medicine, 53(6), pp.892-899

Blonde, L., Khunti, K., Harris, S.B., Meizinger, C. and Skolnik, N.S., 2018. Interpretation and impact of real-world clinical data for the practicing clinician. Advances in therapy, 35(11), pp.1763-1774.

Blouet, S., Sutter, J., Fresnel, E., Kerfourn, A., Cuvelier, A. and Patout, M., 2018. Prediction of severe acute exacerbation using changes in breathing pattern of COPD patients on home noninvasive ventilation. *International Journal of Chronic Obstructive Pulmonary Disease*, *13*, p.2577.

Borel JC, Borel AL, Monneret D, Tamisier R, Levy P, Pepin JL. Obesity hypoventilation syndrome: from sleep-disordered breathing to systemic comorbidities and the need to offer combined treatment strategies. Respirology. 2012; 17: 601–10

Borel, J.C., Burel, B., Tamisier, R., Dias-Domingos, S., Baguet, J.P., Levy, P. and Pepin, J.L., 2013. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. PLoS One, 8(1), p.e52006.

Borel, J.C., Palot, A. and Patout, M., 2019. Technological advances in home non-invasive ventilation monitoring: Reliability of data and effect on patient outcomes. Respirology, 24(12), pp.1143-1151.

Borel, J.C., Pelletier, J., Taleux, N., Briault, A., Arnol, N., Pison, C., Tamisier, R., Timsit, J.F. and Pepin, J.L., 2015. Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof-of-concept study. *Thorax*, *70*(3), pp.284-285.

Bott, J., Carroll, M.P., Conway, J.H., Keilty, S.E.J., Ward, E.M., Brown, A.M., Paul, E.A., Elliott, M.W., Godfrey, R.C., Wedzicha, J.A. and Moxham, J., 1993. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. The Lancet, 341(8860), pp.1555-1557

Boyko, E.J., 2013. Observational research—opportunities and limitations. Journal of Diabetes and its Complications, 27(6), pp.642-648

British Lung Foundation, 2018. Chronic obstructive pulmonary disease (COPD) statistics. Available via: https://statistics.blf.org.uk/copd . Accessed 14th February 2019.

British Thoracic Society National Audit Report: Adult NIV Audit (2019). National Audit Period: 1 February – 31 March 2019 Available via: https://www.brit-thoracic.org.uk/document-library/quality-improvement/audit-reports/adult-niv-audit-report-2019/. Accessed 4th January 2022.

British Thoracic Society Standards of Care Committee, 2002. Non-invasive ventilation in acute respiratory failure. Thorax; 57:192–211

Brochard, L., Isabey, D., Piquet, J., Amaro, P., Mancebo, J., Messadi, A.A., Brun-Buisson, C., Rauss, A., Lemaire, F. and Harf, A., 1990. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. New England Journal of Medicine, 323(22), pp.1523-1530

Brochard, L., Mancebo, J., Wysocki, M., Lofaso, F., Conti, G., Rauss, A., Simonneau, G., Benito, S., Gasparetto, A., Lemaire, F. and Isabey, D., 1995. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. New England Journal of Medicine, 333(13), pp.817-822

Bruno, C.M. and Valenti, M., 2012. Acid-base disorders in patients with chronic obstructive pulmonary disease: a pathophysiological review. BioMed Research International, 2012

Budin, C.E., Maierean, A.D., Ianosi, E.S., Socaci, A., Buzoianu, A.D., Alexescu, T.G., Olteanu, M., Rusu, E., Moldovan, C.A. and Nemes, R.M., 2019. Nocturnal Hypoxemia, a Key Parameter in Overlap Syndrome. Rev. Chim.(Bucharest), 70(2), pp.449-54.

Budweiser, S., Hitzl, A.P., Jörres, R.A., Heinemann, F., Arzt, M., Schroll, S. and Pfeifer, M., 2007. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. International journal of clinical practice, 61(9), pp.1516-1522

Budweiser, S., Hitzl, A.P., Jörres, R.A., Schmidbauer, K., Heinemann, F. and Pfeifer, M., 2007. Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. Respiratory research, 8(1), p.92.

Budweiser, S., Riedl, S.G., Jörres, R.A., Heinemann, F. and Pfeifer, M., 2007. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. Journal of internal medicine, 261(4), pp.375-383

Burholt, V. and Nash, P., 2011. Short form 36 (SF-36) health survey questionnaire: normative data for Wales. Journal of Public Health, 33(4), pp.587-603

Buss, A.S. and Silva, L.M., 2009. Comparative study of two quality of life questionnaires in patients with COPD. J Bras Pneumol, 35(4), pp.318-24

Bwika, J., Ali, A., O'Sullivan, O., Beauchamp, B., D'Cruz, R., Morley, K., Vaughan, M. and Mukherjee, R., 2013. Changing trends in domiciliary non-invasive ventilation (NIV) set-up. European Respiratory Journal, 42 (Suppl 57) P2467

Camm, A.J. and Fox, K.A., 2018. Strengths and weaknesses of 'real-world'studies involving non-vitamin K antagonist oral anticoagulants. Open Heart, 5(1).

Carone, M., Antoniu, S., Baiardi, P., Digilio, V.S., Jones, P.W., Bertolotti, G. and QuESS Group, 2016. Predictors of mortality in patients with COPD and chronic respiratory failure: the quality-of-life evaluation and survival study (QuESS): a three-year study. COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(2), pp.130-138.

Carone, M., Bertolotti, G., Anchisi, F., Zotti, A.M., Donner, C.F. and Jones, P.W., 1999. Analysis of factors that characterize health impairment in patients with chronic respiratory failure. European Respiratory Journal, 13(6), pp.1293-1300

Carone, M., Donner, C.F. and Jones, P.W., 2001. Health Status measurement: an increasingly important outcome evaluation in COPD patients. Monaldi Archives for Chest Disease, 56(4), pp.297-298. Med 2001; 163: A13

Carone, M., Patessio, A., Ambrosino, N., Baiardi, P., Balbi, B., Balzano, G., Cuomo, V., Donner, C.F., Fracchia, C., Nava, S. and Neri, M., 2007. Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): The Maugeri Study. Respiratory medicine, 101(12), pp.2447-2453.

Casanova, C., Celli, B.R., Tost, L., Soriano, E., Abreu, J., Velasco, V. and Santolaria, F., 2000. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. CHEST Journal, 118(6), pp.1582-1590

Castro-Añón, O., de Llano, L.A.P., De la Fuente Sánchez, S., Golpe, R., Marote, L.M., Castro-Castro, J. and Quintela, A.G., 2015. Obesity-hypoventilation syndrome: increased risk of death over sleep apnea syndrome. PLoS One, 10(2), p.e0117808

Çelikel, T., Sungur, M., Ceyhan, B. and Karakurt, S., 1998. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest, 114(6), pp.1636-1642

Celli, B.R., Cote, C.G., Lareau, S.C. and Meek, P.M., 2008. Predictors of Survival in COPD: more than just the FEV1. Respiratory medicine, 102, pp.S27-S35

Cerveri, I., Corsico, A.G., Accordini, S., Niniano, R., Ansaldo, E., Antó, J.M., Künzli, N., Janson, C., Sunyer, J., Jarvis, D. and Svanes, C., 2008. Underestimation of airflow obstruction among young adults using FEV1/FVC< 70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. Thorax, 63(12), pp.1040-1045

Chailleux, E., Fauroux, B., Binet, F., Dautzenberg, B. and Polu, J.M., 1996. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation: a 10-year analysis of ANTADIR Observatory. Chest, 109(3), pp.741-749

Chaouat, A.R.I., Weitzenblum, E., Krieger, J., Ifoundza, T., Oswald, M. and Kessler, R., 1995. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. American journal of respiratory and critical care medicine, 151(1), pp.82-86

Chatwin, M., Hawkins, G., Panicchia, L., Woods, A., Hanak, A., Lucas, R., Baker, E., Ramhamdany, E., Mann, B., Riley, J. and Cowie, M.R., 2016. Randomised crossover trial of telemonitoring in chronic respiratory patients (TeleCRAFT trial). Thorax, pp.thoraxjnl-2015

Chatwin, M., Heather, S., Hanak, A., Polkey, M.I. and Simonds, A.K., 2010. Analysis of home support and ventilator malfunction in 1,211 ventilator-dependent patients. European Respiratory Journal, 35(2), pp.310-316

Chatwin, M., Nickol, A.H., Morrell, M.J., Polkey, M.I. and Simonds, A.K., 2008. Randomised trial of inpatient versus outpatient initiation of home mechanical ventilation in patients with nocturnal hypoventilation. Respiratory medicine, 102(11), pp.1528-1535

Chediak, A., Brown, L.K., Finder, J., Gozal, D., Iber, C., Kushida, C.A., Morgenthaler, T., Rowley, J.A. and Davidson-Ward, S.L., 2010. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. Journal of Clinical Sleep Medicine, 6(05), pp.491-509

Chen, R., Guan, L., Wu, W., Yang, Z., Li, X., Luo, Q., Liang, Z., Wang, F., Guo, B., Huo, Y. and Yang, Y., 2017. The Chinese version of the Severe Respiratory Insufficiency questionnaire for patients with

chronic hypercapnic chronic obstructive pulmonary disease receiving non-invasive positive pressure ventilation. BMJ open, 7(8), p.e017712

Cheng, L., Chan, V. and Chu, C.M., 2011. A pilot study of treatment compliance in home non-invasive ventilation.

Cheung, A.P.S., Chan, V.L. and Chu, C-M., 2010. Home noninvasive ventilation in COPD. Breathe, Volume 6, No 32

Chevrolet, J.C., Jolliet, P., Abajo, B., Toussi, A. and Louis, M., 1991. Nasal positive pressure ventilation in patients with acute respiratory failure: difficult and time-consuming procedure for nurses. Chest, 100(3), pp.775-782

Chu, C.M., Chan, V.L., Lin, A.W.N., Wong, I.W.Y., Leung, W.S. and Lai, C.K.W., 2004. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. Thorax, 59(12), pp.1020-1025.

Ciccarella, A., Staley, A.C. and Franco, A.T., 2018. Transforming research: engaging patient advocates at all stages of cancer research. Annals of translational medicine, 6(9)

Clini, E., Sturani, C., Rossi, A., Viaggi, S., Corrado, A., Donner, C.F. and Ambrosino, N., 2002. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. European Respiratory Journal, 20(3), pp.529-538

Cohen, A.T., Goto, S., Schreiber, K. and Torp-Pedersen, C., 2015. Why do we need observational studies of everyday patients in the real-life setting?. European Heart Journal Supplements, 17(suppl_D), pp.D2-D8.

Concato, J., Shah, N. and Horwitz, R.I., 2000. Randomized, controlled trials, observational studies, and the hierarchy of research designs. New England journal of medicine, 342(25), pp.1887-1892.

Conway, J.H., Hitchcock, R.A., Godfrey, R.C. and Carroll, M.P., 1993. Nasal intermittent positive pressure ventilation in acute exacerbations of chronic obstructive pulmonary disease—a preliminary study. Respiratory medicine, 87(5), pp.387-394

Costa, F., van Leeuwen, M.A., Daemen, J., Diletti, R., Kauer, F., van Geuns, R.J., Ligthart, J., Witberg, K., Zijlstra, F., Valgimigli, M. and Van Mieghem, N.M., 2016. The Rotterdam radial access research: ultrasound-based radial artery evaluation for diagnostic and therapeutic coronary procedures. Circulation: Cardiovascular Interventions, 9(2), p.e003129

Cournand, A., Motley, H.L., Werko, L. and Richards JR, D.W., 1947. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. American Journal of Physiology-Legacy Content, 152(1), pp.162-174

Crawford, A., 2004. An audit of the patient's experience of arterial blood gas testing. British journal of nursing, 13(9), pp.529-532.

Crimi, C., Noto, A., Princi, P., Cuvelier, A., Masa, J.F., Simonds, A., Elliott, M.W., Wijkstra, P., Windisch, W. and Nava, S., 2016. Domiciliary non-invasive ventilation in COPD: an international survey of indications and practices. COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(4), pp.483-490

Criner, G.J., Brennan, K., Travaline, J.M. and Kreimer, D., 1999. Efficacy and compliance with noninvasive positive pressure ventilation in patients with chronic respiratory failure. Chest, 116(3), pp.667-675.

Dar, K., Williams, T., Aitken, R., Woods, K.L. and Fletcher, S., 1995. Arterial versus capillary sampling for analysing blood gas pressures. Bmj, 310(6971), pp.24-25.

Davidson, A.C., Banham, S., Elliott, M., Kennedy, D., Gelder, C., Glossop, A., Church, A.C., Creagh-Brown, B., Dodd, J.W., Felton, T. and Foëx, B., 2016. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax, 71(Suppl 2), pp.ii1-ii35

Davies, J.D. and Gentile, M.A., 2009. What does it take to have a successful noninvasive ventilation program?. Respiratory Care, 54(1), pp.53-61

de Miguel, J., Cabello, J., Sánchez-Alarcos, J.M. and Espinós, D., 2002. Long-term effects of treatment with nasal continuous positive airway pressure on lung function in patients with overlap syndrome. Sleep and Breathing, 6(1), pp.3-10.

Delacre, M., Lakens, D. and Leys, C., 2017. Why psychologists should by default use Welch's t-test instead of Student's t-test. International Review of Social Psychology, 30(1)

Dettori, J.R., 2011. Loss to follow-up. *Evidence-based spine-care journal*, *2*(01), pp.7-10.

Diaz, O., Begin, P., Andresen, M., Prieto, M.E., Castillo, C., Jorquera, J. and Lisboa, C., 2005. Physiological and clinical effects of diurnal noninvasive ventilation in hypercapnic COPD. European Respiratory Journal, 26(6), pp.1016-1023.

DiMarco, A.F. and Renston, J.P., 1999. Noninvasive mechanical ventilation. Rehabilitation of the patient with respiratory disease. Nueva York: McGraw-Hill, pp.387-400

Domecq, J.P., Prutsky, G., Elraiyah, T., Wang, Z., Nabhan, M., Shippee, N., Brito, J.P., Boehmer, K., Hasan, R., Firwana, B. and Erwin, P., 2014. Patient engagement in research: a systematic review. BMC health services research, 14(1), pp.1-9.

Dreher, M. and Kabitz, H.J., 2012. Impact of obesity on exercise performance and pulmonary rehabilitation. Respirology, 17(6), pp.899-907.

Dreher, M., Storre, J.H., Schmoor, C. and Windisch, W., 2010. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax, 65(4), pp.303-308

Dretzke, J., Blissett, D., Dave, C., Mukherjee, R., Price, M., Bayliss, S., Wu, X., Jordan, R., Jowett, S., Turner, A.M. and Moore, D., 2015. The cost-effectiveness of domiciliary non-invasive ventilation in patients with end-stage chronic obstructive pulmonary disease: a systematic review and economic evaluation. Health Technol Assess (Winch Eng), 19, pp.1-246

Duiverman, M.L., 2018. Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? ERJ open research, 4(2), pp.00012-2018.

Duiverman, M.L., Arellano-Maric, M.P. and Windisch, W., 2016. Long-term noninvasive ventilation in patients with chronic hypercapnic respiratory failure: assisting the diaphragm, but threatening the heart?. Current opinion in pulmonary medicine, 22(2), pp.130-137

Duiverman, M.L., Maagh, P., Magnet, F., Claudia, S., Arellano-Maric, M.P., Storre, J.H., Wijkstra, P.J., Windisch, W. and Callegari, J., 2016. Impact of high-intensity non-invasive ventilation on cardiac function in stable hypercapnic COPD: A randomised cross-over trial. European Respiratory Journal, 48 (suppl 60)

Duiverman, M.L., Vonk, J.M., Bladder, G., van Melle, J.P., Nieuwenhuis, J., Hazenberg, A., Kerstjens, H.A., van Boven, J.F. and Wijkstra, P.J., 2020. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. Thorax, 75(3), pp.244-252

Duiverman, M.L., Wempe, J.B., Bladder, G., Jansen, D.F., Kerstjens, H.A., Zijlstra, J.G. and Wijkstra, P.J., 2008. Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. Thorax, 63(12), pp.1052-1057.

Duiverman, M.L., Wempe, J.B., Bladder, G., Vonk, J.M., Zijlstra, J.G., Kerstjens, H.A. and Wijkstra, P.J., 2011. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respiratory research, 12(1), p.112.

Duke, G.J., 1999. Cardiovascular effects of mechanical ventilation. Critical Care and Resuscitation, 1(4), p.388.

Eaton, T., Rudkin, S. and Garrett, J.E., 2001. The clinical utility of arterialized earlobe capillary blood in the assessment of patients for long-term oxygen therapy. Respiratory medicine, 95(8), pp.655-660.

Eisen, L.A., Minami, T., Berger, J.S., Sekiguchi, H., Mayo, P.H. and Narasimhan, M., 2007. Gender disparity in failure rate for arterial catheter attempts. Journal of intensive care medicine, 22(3), pp.166-172.

Elliott, M.W., 2009. Domiciliary non-invasive ventilation in stable COPD?. Thorax, 64(7), pp.553-556

Ellis, E.R., Bye, P.T., Bruderer, J.W. and Sullivan, C.E., 1987. Treatment of respiratory failure during sleep in patients with neuromuscular disease: positive-pressure ventilation through a nose mask. American Review of Respiratory Disease, 135(1), pp.148-152

England, N.H.S., 2019. The NHS long-term plan. Available via: https://www.longtermplan.nhs.uk/.Accessed 29th December 2019.

Engström, C.G., 1954. Treatment of severe cases of respiratory paralysis by the Engström universal respirator. British medical journal, 2(4889), p.666

Ergan, B., Oczkowski, S., Rochwerg, B., Carlucci, A., Chatwin, M., Clini, E., Elliott, M., Gonzalez-Bermejo, J., Hart, N., Lujan, M. and Nasilowski, J., 2019. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. European respiratory journal, 54(3), p.1901003.

Esquinas, A.M., Scala, R. and Nasiłowski, J., 2013. Inspiratory pressure during noninvasive ventilation in stable COPD: help the lungs, but do not forget the heart. European Respiratory Journal, 41(3), pp.764-765.

Euser, A.M., Zoccali, C., Jager, K.J. and Dekker, F.W., 2009. Cohort studies: prospective versus retrospective. *Nephron Clinical Practice*, *113*(3), pp.c214-c217.

Evans, D., 2003. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. Journal of clinical nursing, 12(1), pp.77-84.

Fajac, I., Texereau, J., Rivoal, V., Dessanges, J.F., Dinh-Xuan, A.T. and Dall'Ava-Santucci, J., 1998. Blood gas measurement during exercise: a comparative study between arterialized earlobe sampling and direct arterial puncture in adults. European Respiratory Journal, 11(3), pp.712-715.

Farré Ventura, R., Navajas Navarro, D., Prats, E., Marti, S., Guell, R., Canal, M., Ma, J., Tebé, C. and Escarrabill Sanglas, J., 2006. Performance of mechanical ventilators at the patient's home: a multicentric quality control study. Thorax, 2006, vol. 61, num 5, p. 400-404

Farrero, E., Antón, A., Egea, C.J., Almaraz, M.J., Masa, J.F., Utrabo, I., Calle, M., Verea, H., Servera, E., Jara, L. and Barrot, E., 2013. Guidelines for the management of respiratory complications in patients with neuromuscular disease. Archivos de Bronconeumología (English Edition), 49(7), pp.306-313

Fayers, P.M. and Machin, D., 2015. Quality of life: the assessment, analysis and reporting of patient-reported outcomes. John Wiley & Sons.

Ferrer, M., Esquinas, A., Leon, M., Gonzalez, G., Alarcon, A. and Torres, A., 2003. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. American journal of respiratory and critical care medicine, 168(12), pp.1438-1444

Filley, G.F., Beckwitt, H.J., Reeves, J.T. and Mitchell, R.S., 1968. Chronic obstructive bronchopulmonary disease: II. Oxygen transport in two clinical types. The American journal of medicine, 44(1), pp.26-38.

Fleming, J., Wood, G.C., Seiler, C., Cook, A., Lent, M.R., Still, C.D., Benotti, P.N. and Irving, B.A., 2016. Electronically captured, patient-reported physical function: an important vital sign in obesity medicine. Obesity science & practice, 2(4), pp.399-406.

Flenley, D.C., 1985. Sleep in chronic obstructive lung disease. Clinics in chest medicine, 6(4), pp.651-661.

Fletcher, S.V., Ewles, S. and Wilkinson, J.E., 2012. P226 The changing face of home NIV (non invasive ventilation). Thorax, 67(Suppl 2), pp.A163-A164.

Foglio, C., Vitacca, M., Quadri, A., Scalcini, S., Marangoni, S. and Ambrosino, N., 1992. Acute exacerbations in severe COLD patients: treatment using positive pressure ventilation by nasal mask. Chest, 101(6), pp.1533-1538

Fung, C.H., Igodan, U., Alessi, C., Martin, J.L., Dzierzewski, J.M., Josephson, K. and Kramer, B.J., 2015. Human factors/usability barriers to home medical devices among individuals with disabling conditions: in-depth interviews with positive airway pressure device users. Disability and health journal, 8(1), pp.86-92.

Funk, G.C., Breyer, M.K., Burghuber, O.C., Kink, E., Kirchheiner, K., Kohansal, R., Schmidt, I. and Hartl, S., 2011. Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. Respiratory medicine, 105(3), pp.427-434.

Garratt, A.M., Ruta, D.A., Abdalla, M.I., Buckingham, J.K. and Russell, I.T., 1993. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS?. Bmj, 306(6890), pp.1440-1444.

Garrison Jr, L.P., Neumann, P.J., Erickson, P., Marshall, D. and Mullins, C.D., 2007. Using real-world data for coverage and payment decisions: The ISPOR real-world data task force report. Value in health, 10(5), pp.326-335.

Ghosh, D., Rzehak, P., Elliott, M.W. and Windisch, W., 2012. Validation of the english severe respiratory insufficiency questionnaire. European Respiratory Journal, 40(2), pp.408-415.

Giner, J., Casan, P., Belda, J., González, M., Miralda, R.M. and Sanchis, J., 1996. Pain during arterial puncture. Chest, 110(6), pp.1443-1445

Goldberg, A., 1999. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation. A Consensus conference report. Chest, 116(2), p.521-534

Groenwold, R.H. and Dekkers, O.M., 2020. Missing data: the impact of what is not there. European Journal of Endocrinology, 183(4), pp.E7-E9.

Gudmundsson, G., Gislason, T., Janson, C., Lindberg, E., Ulrik, C.S., Brøndum, E., Nieminen, M.M., Aine, T., Hallin, R. and Bakke, P., 2006. Depression, anxiety and health status after hospitalisation for COPD: a multicentre study in the Nordic countries. Respiratory medicine, 100(1), pp.87-93.

Guideline, B.T.S., 2002. Non-invasive ventilation in acute respiratory failure. Thorax, 57(3), pp.192-21

Guyatt, G.H., Berman, L.B., Townsend, M., Pugsley, S.O. and Chambers, L.W., 1987. A measure of quality of life for clinical trials in chronic lung disease. Thorax, 42(10), pp.773-778.

Guyatt, G.H., Van Zanten, S.V., Feeny, D.H. and Patrick, D.L., 1989. Measuring quality of life in clinical trials: a taxonomy and review. CMAJ: Canadian Medical Association Journal, 140(12), p.1441.

Hajiro, T. and Nishimura, K., 2002. Minimal clinically significant difference in health status: the thorny path of health status measures?. The European respiratory journal, 19(3), p.390.

Hajiseyedjavady, H., Saeedi, M., Eslami, V., Shahsavarinia, K. and Farahmand, S., 2012. Less painful arterial blood gas sampling using jet injection of 2% lidocaine: a randomized controlled clinical trial. The American journal of emergency medicine, 30(7), pp.1100-1104.

Hales, C.M., Carroll, M.D., Fryar, C.D. and Ogden, C.L., 2017. Prevalence of obesity among adults and youth: United States, 2015–2016.

Hannan, L.M., Rautela, L., Berlowitz, D.J., McDonald, C.F., Cori, J.M., Sheers, N., Chao, C., O'Donoghue, F.J. and Howard, M.E., 2019. Randomised controlled trial of polysomnographic titration of noninvasive ventilation. European Respiratory Journal, 53(5), p.1802118.

Haraldstad, K., Wahl, A., Andenæs, R., Andersen, J.R., Andersen, M.H., Beisland, E., Borge, C.R., Engebretsen, E., Eisemann, M., Halvorsrud, L. and Hanssen, T.A., 2019. A systematic review of quality of life research in medicine and health sciences. Quality of Life Research, pp.1-10.

Hayes, H., Buckland, S. and Tarpey, M., 2012. INVOLVE briefing notes for researchers: involving the public in NHS. Public Health and Social Care Research Eastleigh: INVOLVE.

Hazenberg, A., Kerstjens, H.A., Prins, S.C., Vermeulen, K.M. and Wijkstra, P.J., 2014. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs. Respiratory medicine, 108(9), pp.1387-1395.

Heinemann, F., Budweiser, S., Dobroschke, J. and Pfeifer, M., 2007. Non-invasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. Respiratory medicine, 101(6), pp.1229-1235

Higgins, C., 2008. Capillary blood gases: To arterialize or not. MLO Med Lab Obs, 40(42), pp.4-7.

Hill, N.S. and Braman, S.S., 1999. Noninvasive ventilation in neuromuscular disease. Rehabilitation of the patient with respiratory disease. Nueva York: McGraw-Hill, pp.587-604

Howard, M., Piper, A., Stevens, B., Holland, A., Yee, B., Dabscheck, E., Mortimer, D., Burge, A., Flunt, D., Buchan, C. and Rautela, L., 2014. A randomised controlled trial of CPAP vs non-invasive

ventilation for initial treatment of obesity hypoventilation syndrome. European Respiratory Journal, 44(Suppl 58), p.4868

Huttmann, S.E., Windisch, W. and Storre, J.H., 2015. Invasive home mechanical ventilation: living conditions and health-related quality of life. Respiration, 89(4), pp.312-321.

Iqbal, N., Irfan, M., Zubairi, A.B.S., Awan, S. and Khan, J.A., 2017. Association of hypercapnia on admission with increased length of hospital stay and severity in patients admitted with community-acquired pneumonia: a prospective observational study from Pakistan. BMJ open, 7(6), p.e013924.

Jaeschke, R., Singer, J. and Guyatt, G.H., 1989. Measurement of health status: ascertaining the minimal clinically important difference. Controlled clinical trials, 10(4), pp.407-415

Janssens, J.P., Derivaz, S., Breitenstein, E., de Muralt, B., Fitting, J.W., Chevrolet, J.C. and Rochat, T., 2003. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest, 123(1), pp.67-79

Javaheri, S. and Simbartl, L.A., 2014. Respiratory determinants of diurnal hypercapnia in obesity hypoventilation syndrome. What does weight have to do with it? Annals of the American Thoracic Society, 11(6), pp.945-950

Jin, J., Sklar, G.E., Oh, V.M.S. and Li, S.C., 2008. Factors affecting therapeutic compliance: A review from the patient's perspective. Therapeutics and clinical risk management, 4(1), p.269.

Jones, P.W. and Bosh, T.K., 1997. Quality of life changes in COPD patients treated with salmeterol. American journal of respiratory and critical care medicine, 155(4), pp.1283-1289.

Jones, P.W., 2002. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. European Respiratory Journal, 19(3), pp.398-404.

Jones, P.W., Quirk, F.H. and Baveystock, C.M., 1991. The St George's respiratory questionnaire. Respiratory medicine, 85, pp.25-31.

Juniper, E.F., Guyatt, G.H., Willan, A. and Griffith, L.E., 1994. Determining a minimal important change in a disease-specific quality of life questionnaire. Journal of clinical epidemiology, 47(1), pp.81-87.

Juniper, M.C., Ellis, G., Protopapa, K.L. and Smith, N.C.E., 2017. Inspiring Change: a report on acute non-invasive ventilation. British Journal of Hospital Medicine, 78(9), pp.497-502

Kent, Surrey and Sussex Non-Invasive Ventilation network. Available via: http://www.kssahsn.net/what-we-do/better-quality-and-safer-care/KSS-respiratory-programme/Pages/Non-invasive--ventilation.aspx Accessed 13th February 2018.

Kerby, G.R., Mayer, L.S. and Pingleton, S.K., 1987. Nocturnal positive pressure ventilation via nasal mask. American review of respiratory disease, 135(3), pp.738-740

Kessler, R., Chaouat, A., Schinkewitch, P., Faller, M., Casel, S., Krieger, J. and Weitzenblum, E., 2001. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest, 120(2), pp.369-376

Köhnlein, T., Windisch, W., Köhler, D., Drabik, A., Geiseler, J., Hartl, S., Karg, O., Laier-Groeneveld, G., Nava, S., Schönhofer, B. and Schucher, B., 2014. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. The Lancet Respiratory Medicine, 2(9), pp.698-705

Kort, J., Bladder, G. and Duiverman, M., 2018. The minimal clinically important difference of the Severe Respiratory Insufficiency questionnaire. European Respiratory Journal 2018 52: Suppl. 62, PA2371

Kramer, N., Meyer, T.J., Meharg, J., Cece, R.D. and Hill, N.S., 1995. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. American journal of respiratory and critical care medicine, 151(6), pp.1799-1806

Kushida, C.A., Littner, M.R., Morgenthaler, T., Alessi, C.A., Bailey, D., Coleman Jr, J., Friedman, L., Hirshkowitz, M., Kapen, S., Kramer, M. and Lee-Chiong, T., 2005. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep, 28(4), pp.499-523.

Lane, A., Harlow, S. and Murray, P., 2015. P196 A Local Domiciliary Non-invasive Ventilation (NIV) Service Reduces Length of Hospital Stay for Patients Unable to Wean From NIV. Thorax, Volume 70, Issue Suppl 3

Laursen, C.B., Pedersen, R.L. and Lassen, A.T., 2015, December. Ultrasound guided puncture of the radial artery for blood gas analysis: a prospective, randomized controlled trial. In Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine (Vol. 23, No. 1, pp. 1-1). BioMed Central.

Lightowler, J.V., Wedzicha, J.A., Elliott, M.W. and Ram, F.S., 2003. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. Bmj, 326(7382), p.185

Lindahl, B., Sandman, P.O. and Rasmussén, B.H., 2005. On becoming dependent on home mechanical ventilation. Journal of Advanced Nursing, 49(1), pp.33-42.

Livesey, A., Oakes, A., Antoine-Pitterson, P., Gallagher, E., Chakraborty, B. and Mukherjee, R., 2018. The effect of Post-acute domiciliary non-invasive ventilation (NIV) on hospital admissions and length of stay (LOS).

Lloyd-Owen, S.J., Donaldson, G.C., Ambrosino, N., Escarabill, J., Farre, R., Fauroux, B., Robert, D., Schoenhofer, B., Simonds, A.K. and Wedzicha, J.A., 2005. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. European Respiratory Journal, 25(6), pp.1025-1031

Löffler, W., Kilian, R., Toumi, M. and Angermeyer, M.C., 2003. Schizophrenic patients' subjective reasons for compliance and noncompliance with neuroleptic treatment. Pharmacopsychiatry, 36(03), pp.105-112.

Luján, M., Moreno, A., Veigas, C., Montón, C., Pomares, X. and Domingo, C., 2007. Non-invasive home mechanical ventilation: effectiveness and efficiency of an outpatient initiation protocol compared with the standard in-hospital model. Respiratory medicine, 101(6), pp.1177-1182.

Lukácsovits, J., Carlucci, A., Hill, N., Ceriana, P., Pisani, L., Schreiber, A., Pierucci, P., Losonczy, G. and Nava, S., 2012. Physiological changes during low-and high-intensity noninvasive ventilation. European Respiratory Journal, 39(4), pp.869-875.

Machado, M.L., Vollmer, W.M., Togeiro, S.M., Bilderback, A.L., Oliveira, M.C., Leitão, F.S., Queiroga, F., Lorenzi-Filho, G. and Krishnan, J.A., 2010. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. European Respiratory Journal, 35(1), pp.132-137.

MacIntyre, E.J., Asadi, L., Mckim, D.A. and Bagshaw, S.M., 2016. Clinical outcomes associated with home mechanical ventilation: a systematic review. Canadian respiratory journal, 2016.

Mandal, S., Arbane, G., Murphy, P., Elliott, M.W., Janssens, J.P., Pepin, J.L., Muir, J.F., Cuvelier, A., Polkey, M., Parkin, D. and Douiri, A., 2015. Medium-term cost-effectiveness of an automated non-invasive ventilation outpatient set-up versus a standard fixed level non-invasive ventilation inpatient set-up in obese patients with chronic respiratory failure: a protocol description. BMJ open, 5(4), p.e007082.

Mandal, S., Suh, E., Davies, M., Smith, I., Maher, T.M., Elliott, M.W., Davidson, A.C. and Hart, N., 2013. Provision of home mechanical ventilation and sleep services for England survey. Thorax, pp.thoraxjnl-2013

Mandal, S., Suh, E.S., Harding, R., Vaughan-France, A., Ramsay, M., Connolly, B., Bear, D.E., MacLaughlin, H., Greenwood, S.A., Polkey, M.I. and Elliott, M., 2018. Nutrition and Exercise Rehabilitation in Obesity hypoventilation syndrome (NERO): a pilot randomised controlled trial. Thorax, 73(1), pp.62-69

Mann, C.J., 2003. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency medicine journal, 20(1), pp.54-60.

Manoukian, S., Stewart, S., Graves, N., Mason, H., Robertson, C., Kennedy, S., Pan, J., Kavanagh, K., Haahr, L., Adil, M. and Dancer, S.J., 2021. Bed-days and costs associated with the inpatient burden of healthcare-associated infection in the UK. *Journal of Hospital Infection*, *114*, pp.43-50.

Mansell, S.K., Cutts, S., Kanakaraj, R., Jose, R., Mackay, A., Moonsie, I. and Mandal, S., 2017. S39 An outreach service for domiciliary non-invasive ventilation (niv) improves access for patients. Thorax, Volume 72, Issue Suppl 3

Mansell, S.K., Kilbride, C., Wood, M.J., Gowing, F. and Mandal, S., 2020. Experiences and views of patients, carers and healthcare professionals on using modems in domiciliary non-invasive ventilation (NIV): a qualitative study. BMJ Open Respiratory Research, 7(1), p.e000510.

Mansfield, D. and Naughton, M.T., 1999. Effects of continuous positive airway pressure on lung function in patients with chronic obstructive pulmonary disease and sleep disordered breathing. Respirology, 4(4), pp.365-370.

Manuel, A.R., Hart, N. and Stradling, J.R., 2015. Is a raised bicarbonate, without hypercapnia, part of the physiologic spectrum of obesity-related hypoventilation? Chest, 147(2), pp.362-368

Marin, J.M., Soriano, J.B., Carrizo, S.J., Boldova, A. and Celli, B.R., 2010. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. American journal of respiratory and critical care medicine, 182(3), pp.325-331.

Markussen, H., Lehmann, S., Nilsen, R.M. and Natvig, G.K., 2015. The Norwegian version of the Severe Respiratory Insufficiency Questionnaire. International journal of nursing practice, 21(3), pp.229-238.

Markussen, H., Lehmann, S., Nilsen, R.M. and Natvig, G.K., 2019. Health-related quality of life as predictor for mortality in patients treated with long-term mechanical ventilation. BMC pulmonary medicine, 19(1), p.13.

Masa, J.F., Celli, B.R., Riesco, J.A., Hernaéndez, M., de Cos, J.S. and Disdier, C., 2001. The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. Chest, 119(4), pp.1102-1107

Masa, J.F., Corral, J., Alonso, M.L., Ordax, E., Troncoso, M.F., Gonzalez, M., Lopez-Martínez, S., Marin, J.M., Marti, S., Díaz-Cambriles, T. and Chiner, E., 2015. Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick study. American journal of respiratory and critical care medicine, 192(1), pp.86-95

McDonald, L., Lambrelli, D., Wasiak, R. and Ramagopalan, S.V., 2016. Real-world data in the United Kingdom: opportunities and challenges. BMC medicine, 14(1), pp.1-3.

McEvoy, R.D., Pierce, R.J., Hillman, D., Esterman, A., Ellis, E.E., Catcheside, P.G., O'Donoghue, F.J., Barnes, D.J. and Grunstein, R.R., 2009. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax, 64(7), pp.561-566.

McGhan, R., Radcliff, T., Fish, R., Sutherland, E.R., Welsh, C. and Make, B., 2007. Predictors of rehospitalization and death after a severe exacerbation of COPD. Chest, 132(6), pp.1748-1755.

McKim, D.A., Avendano, M., Abdool, S., Côté, F., Duguid, N., Fraser, J., Maltais, F., Morrison, D.L., O'Connell, C., Petrof, B.J. and Rimmer, K., 2011. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Canadian Respiratory Journal, 18.

McLane, C.G., Zyzanski, S.J. and Flocke, S.A., 1995. Factors associated with medication noncompliance in rural elderly hypertensive patients. American Journal of Hypertension, 8(2), pp.206-209.

McMillan, S.S., Kendall, E., Sav, A., King, M.A., Whitty, J.A., Kelly, F. and Wheeler, A.J., 2013. Patient-centered approaches to health care: a systematic review of randomized controlled trials. Medical Care Research and Review, 70(6), pp.567-596.

McNicholas, W.T., 2009. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. American journal of respiratory and critical care medicine, 180(8), pp.692-700.

McNicholas, W.T., 2017. COPD-OSA overlap syndrome: evolving evidence regarding epidemiology, clinical consequences, and management. Chest, 152(6), pp.1318-1326.

Meduri, G.U., Conoscenti, C.C., Menashe, P. and Nair, S., 1989. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest, 95(4), pp.865-870

Meecham Jones, D.J., Paul, E.A., Jones, P.W. and Wedzicha, J.A., 1995. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. American Journal of Respiratory and Critical Care Medicine, 152(2), pp.538-544

Mehta, S. and Hill, N.S., 2001. Noninvasive mechanical ventilation. Am J Respir Crit Care Med, 163, pp. 540-77

Meltzer, E.O., Wallace, D., Dykewicz, M. and Shneyer, L., 2016. Minimal clinically important difference (MCID) in allergic rhinitis: Agency for Healthcare Research and Quality or anchor-based thresholds?. The Journal of Allergy and Clinical Immunology: In Practice, 4(4), pp.682-688.

Mercieca-Bebber, R., Calvert, M., Kyte, D., Stockler, M. and King, M.T., 2018. The administration of patient-reported outcome questionnaires in cancer trials: Interviews with trial coordinators regarding their roles, experiences, challenges and training. Contemporary clinical trials communications, 9, pp.23-32.

Miller, M.R., Hankinson, J.A.T.S., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., Van Der Grinten, C.P.M., Gustafsson, P. and Jensen, R., 2005. Standardisation of spirometry. European respiratory journal, 26(2), pp.319-338.

Mirza, S., Clay, R.D., Koslow, M.A. and Scanlon, P.D., 2018, October. COPD guidelines: a review of the 2018 GOLD report. In Mayo Clinic Proceedings (Vol. 93, No. 10, pp. 1488-1502). Elsevier.

Mokhlesi, B., 2010. Obesity hypoventilation syndrome: a state-of-the-art review. Respiratory Care, 55(10), pp.1347-1365

Mokhlesi, B., Kryger, M.H. and Grunstein, R.R., 2008. Assessment and management of patients with obesity hypoventilation syndrome. Proceedings of the American Thoracic Society, 5(2), pp.218-225

Motheral, B., Brooks, J., Clark, M.A., Crown, W.H., Davey, P., Hutchins, D., Martin, B.C. and Stang, P., 2003. A checklist for retrospective database studies—report of the ISPOR Task Force on Retrospective Databases. Value in health, 6(2), pp.90-97.

Motley, H.L. and Werko, L., 1947. Observations on the clinical use of intermittent positive pressure. The Journal of aviation medicine, 18(5), p.417

Mullins, C.D., Abdulhalim, A.M. and Lavallee, D.C., 2012. Continuous patient engagement in comparative effectiveness research. Jama, 307(15), pp.1587-1588.)

Mulloy, E. and McNicholas, W.T., 1996. Ventilation and gas exchange during sleep and exercise in severe COPD. Chest, 109(2), pp.387-394.

Murphy, P., Arbane, G., Bourke, S., Calverley, P., Dowson, L., Duffy, N., Gibson, G.J., Hughes, P., Hurst, J.R., Lewis, K. and Mukherjee, R., 2016. Improving admission free survival with home

mechanical ventilation (HMV) and home oxygen therapy (HOT) following life threatening COPD exacerbations: HoT-HMV UK Trial NCT00990132. Eur. Respir. J, 48, p.OA3527.

Murphy, P.B. and Hart, N., 2014. Trials of home mechanical ventilation in COPD: what have we learnt? Thorax 2014;69:787-788.

Murphy, P.B. and Janssens, J.P., 2016. NIV for OHS without severe OSAS: is it worth it? Thorax; Volume 17, issue 10

Murphy, P.B., Arbane, G., Bourke, S., Calverley, P., Crooks, A., Dowson, L., Duffy, N., Gibson, G.J., Hughes, P., Hurst, J.R. and Lewis, K., 2016. S115 Hot-hmv uk trial secondary outcome analysis: early readmission is reduced by the addition of home mechanical ventilation to home oxygen therapy in copd patients with chronic respiratory failure following a life-threatening exacerbation.

Murphy, P.B., Brignall, K., Moxham, J., Polkey, M.I., Davidson, A.C. and Hart, N., 2012. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. International journal of chronic obstructive pulmonary disease, 7, p.811.

Murphy, P.B., Davidson, C., Hind, M.D., Simonds, A., Williams, A.J., Hopkinson, N.S., Moxham, J., Polkey, M. and Hart, N., 2012. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax, pp.thoraxjnl-2011

Murphy, P.B., Patout, M., Flach, C., Arbane, G., Cuvelier, A., Douiri, A., Elliott, M., Kaltsakas, G., Mandal, S., Pepin, J.L. and Polkey, M.I., 2019. Late Breaking Abstract-Cost-effectiveness of outpatient (OP) vs. inpatient (IP) setup of home non-invasive ventilation (NIV) in obesity hypoventilation syndrome (OHS): A Randomised Clinical Trial.

Murphy, P.B., Rehal, S., Arbane, G., Bourke, S., Calverley, P.M., Crook, A.M., Dowson, L., Duffy, N., Gibson, G.J., Hughes, P.D. and Hurst, J.R., 2017. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. Jama, 317(21), pp.2177-2186.

Nallamothu, B.K., Hayward, R.A. and Bates, E.R., 2008. Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies. Circulation, 118(12), pp.1294-1303.

National Institute for Health and Care Excellence, 2008. Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. Technology appraisal guidance [TA139]. Available via: https://www.nice.org.uk/guidance/ta139. Accessed 29th January 2018

National Institute for Health and Clinical Excellence (Great Britain), 2011. Quality Standard for Chronic Obstructive Pulmonary Disease in adults (QS10). Available via: https://www.nice.org.uk/guidance/qs10/resources/chronic-obstructive-pulmonary-disease-in-adults-pdf-2098478592709. Accessed February 13th 2020.

National Institute of Clinical Excellence, 2010. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Clinical guideline [CG101 chronic-obstructive-pulmonary-diseasecg101]. Available via: https://www.nice.org.uk/guidance/cg101. Accessed 14th February 2018

National Institute of Clinical Excellence, 2010. Motor neurone disease: assessment and management. NICE guideline [NG42]. Available via: https://www.nice.org.uk/guidance/ng42. Accessed 15th February 2018.

Nava, S. and Ergan, B., 2013. Long-term non-invasive ventilation (NIV) for COPD patients with chronic respiratory failure. EMJ Respir, 1, pp.54-62

Nava, S., Evangelisti, I., Rampulla, C., Compagnoni, M.L., Fracchia, C. and Rubini, F., 1997. Human and financial costs of noninvasive mechanical ventilation in patients. Chest, Volume 111, Issue 6, Pages 1631–1638

Netter, F.H., 1979. The Ciba Collection of Medical Illustrations. Vol. 7. Respiratory System. Ciba Pharmaceutical Company, Medical Education Division.

Newnham, M., Stone, H., Ahmed, M., Knowles, G., Mountford, M. and Mustfa, N., 2014. In or out? initiating a clinic NIV service. European Respiratory Journal, 44(Suppl 58).

Ngandu, H., Gale, N. and Hopkinson, J.B., 2016. Experiences of noninvasive ventilation in adults with hypercapnic respiratory failure: a review of evidence. European Respiratory Review, 25(142), pp.451-471.

NHS Birmingham and Solihull CCG & NHS Sandwell and West Birmingham CCG. Policy for use of domiciliary Non-Invasive Ventilation Version 2.0. Available via: https://www.birminghamandsolihullccg.nhs.uk/about-us/publications/policies/3513-policy-for-use-of-domiciliary-non-invasive-ventilation/file. Accessed 26th February 2020.

NHS Digital, 2016. Statistics on Obesity, Physical Activity and Diet - England, 2016. Available via: https://digital.nhs.uk/catalogue/PUB20562. Accessed 3rd February 2018.

NHS Digital. HRG4+ 2020/21 Consultation Grouper. Available via: https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/hrg4-2020-21-consultation-grouper. Accessed 3rd January 2020.

NHS England, 2013/14. A14/S/a NHS STANDARD CONTRACT FOR RESPIRATORY: COMPLEX HOME VENTILATION (ADULT). PARTICULARS, SCHEDULE 2- THE SERVICES, A- SERVICE SPECIFICATIONS. Available via: https://www.england.nhs.uk/wp-content/uploads/2013/06/a14-respiratory-comp-home-vent.pdf. Accessed 3rd January 2018

NHS England. Improving care for older people. Available via https://www.england.nhs.uk/ourwork/clinical-policy/older-people/improving-care-for-older-people/ . Accessed January 19th 2020.

NHS Modernisation Agency, 2002. Critical Care Programme. Weaning and Long Term Ventilation. London (archived)

Niewoehner, D.E., 2006. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. The American journal of medicine, 119(10), pp.38-45.

Nishiyama, O., Taniguchi, H., Kondoh, Y., Kimura, T., Ogawa, T., Watanabe, F. and Arizono, S., 2005. Factors in maintaining long-term improvements in health-related quality of life after pulmonary rehabilitation for COPD. Quality of life research, 14(10), pp.2315-2321

O'driscoll, B.R., Howard, L.S., Earis, J. and Mak, V., 2017. BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax, 72(Suppl 1), pp.ii1-ii90

Oga, T., Taniguchi, H., Kita, H., Tsuboi, T., Tomii, K., Ando, M., Kojima, E., Tomioka, H., Taguchi, Y., Kaji, Y. and Maekura, R., 2017. Validation of the Japanese Severe Respiratory Insufficiency Questionnaire in hypercapnic patients with noninvasive ventilation. Respiratory investigation, 55(2), pp.166-172.

Patout, M., Arbane, G., Cuvelier, A., Muir, J.F., Hart, N. and Murphy, P.B., 2019. Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial. Thorax, 74(1), pp.83-86.

Pépin, J.L., Timsit, J.F., Tamisier, R., Borel, J.C., Lévy, P. and Jaber, S., 2016. Prevention and care of respiratory failure in obese patients. The Lancet Respiratory medicine, 4(5), pp.407-418

Peter, J.V., Moran, J.L., Phillips-Hughes, J. and Warn, D., 2002. Noninvasive ventilation in acute respiratory failure—a meta-analysis update. Critical care medicine, 30(3), pp.555-562

Pierson, D.J., 1990. Complications associated with mechanical ventilation. Critical care clinics, 6(3), pp.711-724

Piggin, L.H., 2011. The experience of non-invasive ventilation in motor neurone disease: a qualitative exploration (Doctoral dissertation, University of Liverpool).

Pinto, A., Almeida, J.P., Pinto, S., Pereira, J., Oliveira, A.G. and De Carvalho, M., 2010. Home telemonitoring of non-invasive ventilation decreases healthcare utilisation in a prospective controlled trial of patients with amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry, pp.jnnp-2010

Piper, A.J., Wang, D., Yee, B.J., Barnes, D.J. and Grunstein, R.R., 2008. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax, 63, pp. 387-387

Pitkin, A.D., Roberts, C.M. and Wedzicha, J.A., 1994. Arterialised earlobe blood gas analysis: an underused technique. Thorax, 49(4), pp.364-366.

Postma, D.S., Burema, J., Gimeno, F., May, J.F., Smit, J.M., Steenhuis, E.J., Weele, L.T.V. and Sluiter, H.J., 1979. Prognosis in severe chronic obstructive pulmonary disease. American Review of Respiratory Disease, 119(3), pp.357-367.

Priou, P., Hamel, J.F., Person, C., Meslier, N., Racineux, J.L., Urban, T. and Gagnadoux, F., 2010. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest, 138(1), pp.84-90.

Purnell, J.Q., 2018. Definitions, classification, and epidemiology of obesity. In Endotext [Internet]. MDText. com, Inc.

Quint, J.K., Ward, L. and Davison, A.G., 2007. Previously undiagnosed obesity hypoventilation syndrome. Thorax, 62(5), pp.462-463

Raherison, C. and Girodet, P.O., 2009. Epidemiology of COPD. European Respiratory Review, 18(114), pp.213-221.

Ramalho, M.F.J., Alvarenga, M., Aguiar, M., Sacramento, V. and Furtado, S., 2019. Home non-invasive ventilation (NIV) adherence for chronic respiratory failure treatment of obesity hypoventilation syndrome (OHS) vs. chronic obstructive lung disease (COPD).

Raveling, T., Kort, J., Bladder, G., Windisch, W., Wijkstra, P.J. and Duiverman, M.L., 2020. The minimal clinically important difference of the Severe Respiratory Insufficiency questionnaire in severe COPD. European Respiratory Journal.

Rayner, L., Sherlock, J., Creagh-Brown, B., Williams, J. and DeLusignan, S., 2017. The prevalence of COPD in England: An ontological approach to case detection in primary care. Respiratory medicine, 132, pp.217-225.

Rejón-Parrilla, J.C., Garau, M. and Sussex, J., 2014. Obstructive sleep apnoea health economics report. London: British Lung Foundation, Office for Health Economics.

Ribeiro, C., Ferreira, D., Conde, S., Oliveira, P. and Windisch, W., 2017. Validation of the Portuguese severe respiratory insufficiency questionnaire for home mechanically ventilated patients. Revista Portuguesa de Pneumologia (English Edition), 23(3), pp.139-145.

Rodger, M.A., Gagné-Rodger, C., Howley, H.E., Carrier, M., Coyle, D. and Wells, P.S., 2003. The outpatient treatment of deep vein thrombosis delivers cost savings to patients and their families, compared to inpatient therapy. Thrombosis research, 112(1-2), pp.13-18.

Rusticus, S.A. and Lovato, C.Y., 2014. Impact of sample size and variability on the power and type I error rates of equivalence tests: A simulation study. *Practical Assessment, Research, and Evaluation*, *19*(1), p.11.

Rychetnik, L., Hawe, P., Waters, E., Barratt, A. and Frommer, M., 2004. A glossary for evidence based public health. Journal of Epidemiology & Community Health, 58(7), pp.538-545.

Sahn, S.A., Nett, L.M. and Petty, T.L., 1980. Ten year follow-up of a comprehensive rehabilitation program for severe COPD. Chest, 77(2), pp.311-314.

Sarnoff, I. and Zimbardo, P.G., 1961. Anxiety, fear, and social isolation. The Journal of Abnormal and Social Psychology, 62(2), p.356.

Sauty, A., Uldry, C., Debetaz, L.F., Leuenberger, P. and Fitting, J.W., 1996. Differences in PO2 and PCO2 between arterial and arterialized earlobe samples. European Respiratory Journal, 9(2), pp.186-189.

Sawyer, A.M., Deatrick, J.A., Kuna, S.T. and Weaver, T.E., 2010. Differences in perceptions of the diagnosis and treatment of obstructive sleep apnea and continuous positive airway pressure therapy among adherers and nonadherers. Qualitative health research, 20(7), pp.873-892.

Schwarz, E.I., Mackie, M., Weston, N., Tincknell, L., Beghal, G., Cheng, M.C., Ramsay, M., Suh, E.S., Kaltsakas, G., Pattani, H. and Marino, P., 2020. Time-to-death in chronic respiratory failure on home mechanical ventilation: a cohort study. *Respiratory medicine*, *162*, p.105877.

Schwarz, S.B., Callegari, J., Hamm, C., Windisch, W. and Magnet, F.S., 2018. Is outpatient control of long-term non-invasive ventilation feasible in chronic obstructive pulmonary disease patients? Respiration, 95(3), pp.154-160.

Shneerson, J.M. and Simonds, A.K., 2002. Noninvasive ventilation for chest wall and neuromuscular disorders. European Respiratory Journal, 20(2), pp.480-487.

Simonds, A.K., 2006. Risk management of the home ventilator dependent patient. London: Arnold, 282–91

Simonds, A.K., 2016. Home mechanical ventilation: an overview. Annals of the American Thoracic Society, 13(11), pp.2035-2044

Sirey, J.A., Bruce, M.L., Alexopoulos, G.S., Perlick, D.A., Friedman, S.J. and Meyers, B.S., 2001. Stigma as a barrier to recovery: Perceived stigma and patient-rated severity of illness as predictors of antidepressant drug adherence. Psychiatric services, 52(12), pp.1615-1620.

Slutsky, A.S., 2005. Ventilator-induced lung injury: from barotrauma to biotrauma. Respiratory care, 50(5), pp.646-659

Snell, N., Strachan, D., Hubbard, R., Gibson, J., Limb, E., Gupta, R., Martin, A., Laffan, M. and Jarrold, I., 2016. Burden of lung disease in the UK; findings from the British Lung Foundation's' respiratory health of the nation'project.

Spelta, F., Pasini, A.F., Cazzoletti, L. and Ferrari, M., 2017. Body weight and mortality in COPD: focus on the obesity paradox. Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, pp.1-8

Spieth, P.M., Kubasch, A.S., Penzlin, A.I., Illigens, B.M.W., Barlinn, K. and Siepmann, T., 2016. Randomized controlled trials–a matter of design. Neuropsychiatric disease and treatment, 12, p.1341.

Srinivasan, S., Doty, S.M., White, T.R., Segura, V.H., Jansen, M.T., Ward, S.L.D. and Keens, T.G., 1998. Frequency, causes, and outcome of home ventilator failure. Chest, 114(5), pp.1363-1367

Sterne, J.A., Gavaghan, D. and Egger, M., 2000. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *Journal of clinical epidemiology*, *53*(11), pp.1119-1129.

Storre, J.H., Matrosovich, E., Ekkernkamp, E., Walker, D.J., Schmoor, C., Dreher, M. and Windisch, W., 2014. Home mechanical ventilation for COPD: high-intensity versus target volume noninvasive ventilation. Respiratory care, 59(9), pp.1389-1397.

Storre, J.H., Seuthe, B., Fiechter, R., Milioglou, S., Dreher, M., Sorichter, S. and Windisch, W., 2006. Average volume-assured pressure support in obesity hypoventilation: a randomized crossover trial. Chest, 130(3), pp.815-821

Struik, F.M., Kerstjens, H.A., Bladder, G., Sprooten, R., Zijnen, M., Asin, J., van der Molen, T. and Wijkstra, P.J., 2013. The Severe Respiratory Insufficiency Questionnaire scored best in the assessment of health-related quality of life in chronic obstructive pulmonary disease. Journal of clinical epidemiology, 66(10), pp.1166-1174.

Struik, F.M., Lacasse, Y., Goldstein, R.S., Kerstjens, H.A.M. and Wijkstra, P.J., 2014. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. *Respiratory medicine*, *108*(2), pp.329-337.

Struik, F.M., Sprooten, R.T.M., Kerstjens, H.A.M., Bladder, G., Zijnen, M., Asin, J., Cobben, N.A.M., Vonk, J.M. and Wijkstra, P.J., 2014. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax, 69(9), pp.826-834.

Strumpf, D.A., Millman, R.P., Carlisle, C.C., Grattan, L.M., Ryan, S.M., Erickson, A.D. and Hill, N.S., 1991. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis, 144(6), pp.1234-1239.

Suh, E.S., Murphy, P.B. and Hart, N., 2019. Home mechanical ventilation for chronic obstructive pulmonary disease: What next after the HOT-HMV trial?. Respirology, 24(8), pp.732-739.

Suissa, S., Dell'Aniello, S. and Ernst, P., 2012. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax, 67(11), pp.957-963.

Sullivan, C., Berthon-Jones, M., Issa, F. and Eves, L., 1981. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. The Lancet, 317(8225), pp.862-865

Suntharalingam, J., Wilkinson, T., Annandale, J., Davey, C., Fielding, R., Freeman, D., Gibbons, M., Hardinge, M., Hippolyte, S., Knowles, V. and Lee, C., 2017. British Thoracic Society quality standards for home oxygen use in adults. BMJ open respiratory research, 4(1).

Swanney, M.P., Ruppel, G., Enright, P.L., Pedersen, O.F., Crapo, R.O., Miller, M.R., Jensen, R.L., Falaschetti, E., Schouten, J.P., Hankinson, J.L. and Stocks, J., 2008. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. Thorax, 63(12), pp.1046-1051.

Swigris, J.J., Brown, K.K., Behr, J., du Bois, R.M., King, T.E., Raghu, G. and Wamboldt, F.S., 2010. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respiratory medicine, 104(2), pp.296-304.

Tai, C., Madhi, N., Whitlow, G., Martin, K. and Banerjee, S., 2018. The cost benefit of initiating domiciliary Non-invasive Ventilation (NIV) as an outpatient is accompanied by good clinical outcomes for hypercapnic Chronic Obstructive Pulmonary Disease (COPD) patients.

Terzikhan, N., Verhamme, K.M., Hofman, A., Stricker, B.H., Brusselle, G.G. and Lahousse, L., 2016. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. European journal of epidemiology, 31(8), pp.785-792.

Testa, M.A. and Simonson, D.C., 1996. Assessment of quality-of-life outcomes. New England journal of medicine, 334(13), pp.835-840.

Titlestad, I.L., Lassen, A.T. and Vestbo, J., 2013. Long-term survival for COPD patients receiving noninvasive ventilation for acute respiratory failure. International journal of chronic obstructive pulmonary disease, 8, p.215.

Tremblay, L.N. and Slutsky, A.S., 2006. Ventilator-induced lung injury: from the bench to the bedside. Intensive care medicine, 32(1), pp.24-33

Tsara, V., Michailidis, V., Perantoni, E., Nena, E., Moysiadis, N., Windisch, W. and Steiropoulos, P., 2017. Validation of the Greek version of the Severe Respiratory Insufficiency questionnaire. Hippokratia, 21(4), p.186.

Tuggey, J.M., Plant, P.K. and Elliott, M.W., 2003. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. Thorax, 58(10), pp.867-871

Unverzagt, S., Prondzinsky, R. and Peinemann, F., 2013. Single-center trials tend to provide larger treatment effects than multicenter trials: a systematic review. Journal of clinical epidemiology, 66(11), pp.1271-1280.

Valko, L., Baglyas, S., Gyarmathy, V.A., Gal, J. and Lorx, A., 2020. Home mechanical ventilation: quality of life patterns after six months of treatment. BMC Pulmonary Medicine, 20(1), pp.1-13.

Valko, L., Baglyas, S., Kunos, L., Terray-Horvath, A., Lorx, A., Gal, J. and Windisch, W., 2020. Validation of the Hungarian version of the SRI Questionnaire. BMC pulmonary medicine, 20, pp.1-9.

Van Belle, G., Fisher, L.D., Heagerty, P.J. and Lumley, T., 2004. Biostatistics: a methodology for the health sciences (Vol. 519). John Wiley & Sons.

Vesalius, A., 1998. De humani corporis fabrica (No. 4). Norman Publishing

Vincent, J.L., 2010. We should abandon randomized controlled trials in the intensive care unit. Critical care medicine, 38(10), pp.S534-S538.

Wallach, S.G., 2004. Cannulation injury of the radial artery: diagnosis and treatment algorithm. American Journal of Critical Care, 13(4), pp.315-319.

Walterspacher, S., July, J., Kohlhäufl, M., Rzehak, P. and Windisch, W., 2016. The Severe Respiratory Insufficiency Questionnaire for subjects with COPD with long-term oxygen therapy. Respiratory care, 61(9), pp.1186-1191.

Ware Jr, J.E. and Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical care, pp.473-483.

Watz, H., Pitta, F., Rochester, C.L., Garcia-Aymerich, J., ZuWallack, R., Troosters, T., Vaes, A.W., Puhan, M.A., Jehn, M., Polkey, M.I. and Vogiatzis, I., 2014. An official European Respiratory Society statement on physical activity in COPD.

Weir, M., Marchetti, N., Czysz, A., Hill, N., Sciurba, F., Strollo, P. and Criner, G.J., 2015. High Intensity Non-Invasive Positive Pressure Ventilation (HINPPV) for Stable Hypercapnic Chronic Obstructive Pulmonary Disease (COPD) Patients. Chronic Obstructive Pulmonary Diseases, 2(4), p.313

Wickens, T.D. and Keppel, G., 2004. Design and analysis: A researcher's handbook. Upper Saddle River, NJ: Pearson Prentice-Hall.

Wijkstra, P.J., Lacasse, Y., Guyatt, G.H., Casanova, C., Gay, P.C., Jones, J.M. and Goldstein, R.S., 2003. A meta-analysis of nocturnal noninvasive positive pressure ventilation in patients with stable COPD. CHEST Journal, 124(1), pp.337-343

Wijkstra, P.J., Lacasse, Y., Guyatt, G.H., Goldstein, R.S. and Struik, F., 2002. Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 3

Wild, M.R., Engleman, H.M., Douglas, N.J. and Espie, C.A., 2004. Can psychological factors help us to determine adherence to CPAP? A prospective study. European Respiratory Journal, 24(3), pp.461-465.

Wilt, T.J., Niewoehner, D., MacDonald, R. and Kane, R.L., 2007. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. Annals of internal medicine, 147(9), pp.639-653.

Windisch, W., 2008. Impact of home mechanical ventilation on health-related quality of life. European respiratory journal, 32(5), pp.1328-1336.

Windisch, W., Budweiser, S., Heinemann, F., Pfeifer, M. and Rzehak, P., 2008. The Severe Respiratory Insufficiency Questionnaire was valid for COPD patients with severe chronic respiratory failure. Journal of clinical epidemiology, 61(8), pp.848-853.

Windisch, W., Dreher, M., Storre, J.H. and Sorichter, S., 2006. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. Respiratory physiology & neurobiology, 150(2-3), pp.251-260.

Windisch, W., Freidel, K., Schucher, B., Baumann, H., Wiebel, M., Matthys, H. and Petermann, F., 2003. The Severe Respiratory Insufficiency (SRI) Questionnaire A specific measure of health-related quality of life in patients receiving home mechanical ventilation. Journal of clinical epidemiology, 56(8), pp.752-759.

Windisch, W., Geiseler, J., Simon, K., Walterspacher, S., Dreher, M. and Guideline Commission, 2018. German national guideline for treating chronic respiratory failure with invasive and non-invasive ventilation: revised edition 2017–part 1. Respiration, 96(1), pp.66-97.

Windisch, W., Geiseler, J., Simon, K., Walterspacher, S., Dreher, M. and Guideline Commission, 2018. German national guideline for treating chronic respiratory failure with invasive and non-invasive ventilation–revised edition 2017: part 2. Respiration, 96(2), pp.171-203.

Windisch, W., Kostić, S., Dreher, M., Virchow Jr, J.C. and Sorichter, S., 2005. Outcome of patients with stable COPD receiving controlled noninvasive positive pressure ventilation aimed at a maximal reduction of PaCO2. Chest, 128(2), pp.657-662.

Windisch, W., Walterspacher, S., Siemon, K., Geiseler, J. and Sitter, H., 2010. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Pneumologie, 64(10), pp.640-652

Wise, M.P., Hart, N., Davidson, C., Fox, R., Allen, M., Elliott, M., Winter, B., Morgan, M., Shovelton, H., Meadowcroft, R. and Campbell, J., 2011. Home mechanical ventilation. BMJ, 342, p.d1687

Wood, K.A., Lewis, L., Von Harz, B. and Kollef, M.H., 1998. The use of noninvasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. Chest, 113(5), pp.1339-1346

World Health Organisation. 'The Structure of the WHOQOL-100'. WHOQOL: Measuring Quality of Life. Available via http://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/index4.html. Accessed 29th January 2018

World Health Organization, 2014. Constitution of the world health organization. 2006. Available from: http://www.who.int/governance/eb/who_constitution_en.pdf

Yassin, Z., Saadat, M., Abtahi, H., Foroushani, A.R. and Peiman, S., 2016. Prognostic value of on admission arterial PCO2 in hospitalized patients with community-acquired pneumonia. Journal of thoracic disease, 8(10), p.2765.

Yazar, E.E., Özlü, T., Sarıaydın, M., Taylan, M., Ekici, A., Aydın, D., Coşgun, İ.G. and Koçak, N.D., 2018. Prospective cross-sectional multicenter study on domiciliary noninvasive ventilation in stable hypercapnic COPD patients. International journal of chronic obstructive pulmonary disease, 13, p.2367.

Zavorsky, G.S., Cao, J., Mayo, N.E., Gabbay, R. and Murias, J.M., 2007. Arterial versus capillary blood gases: a meta-analysis. Respiratory physiology & neurobiology, 155(3), pp.268-279.

Zwillich, C.W., Pierson, D.J., Creagh, C.E., Sutton, F.D., Schatz, E. and Petty, T.L., 1974. Complications of assisted ventilation: a prospective study of 354 consecutive episodes. The American journal of medicine, 57(2), pp.161-170